

ISSFAL 2008



8TH MEETING OF THE INTERNATIONAL SOCIETY FOR THE STUDY OF
FATTY ACIDS & LIPIDS *incorporating the 7TH INTERNATIONAL CONGRESS
ON ESSENTIAL FATTY ACIDS AND EICOSANOIDS and 4th PUFA IN
MATERNAL AND INFANT HEALTH SCIENTIFIC MEETINGS*



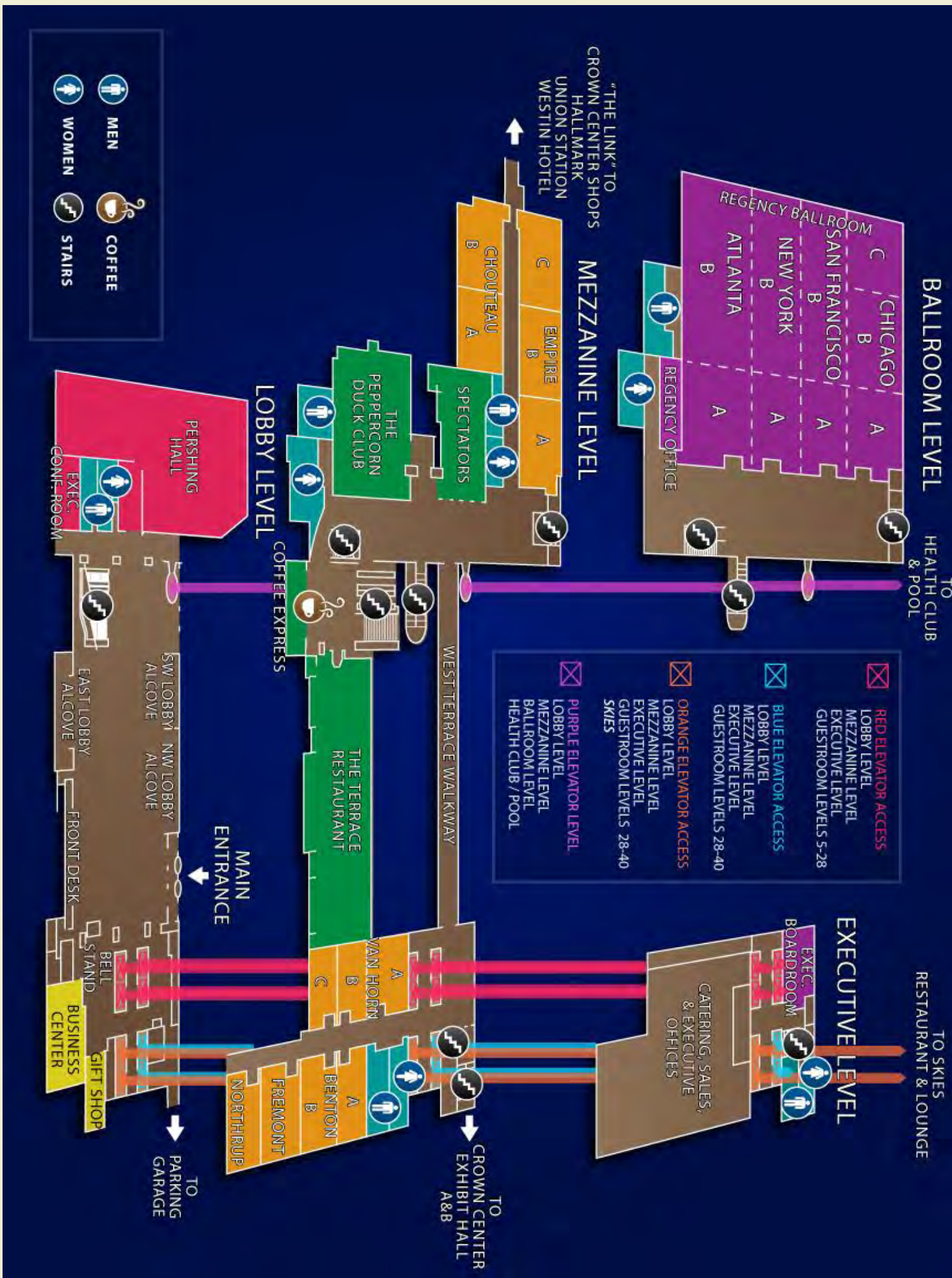
MAY 17-22, 2008

HYATT REGENCY CROWN CENTER

Kansas City, Missouri



PROGRAM & ABSTRACTS



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DETAILED PROGRAM

Sunday, May 17 I
 Monday, May 18 I
 Tuesday, May 19 I
 Wednesday, May 20 I
 Thursday, May 21 I

ABSTRACTS

Sunday, May 17 I
 Monday, May 18 I
 Tuesday, May 19 I
 Wednesday, May 20 I
 Thursday, May 21 I

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SPONORS

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WELCOME

ISSFAL 2008

Greetings from the Heartland!

Welcome to Kansas City! We hope that your trip, whether long or short, went smoothly and that your luggage arrived with you. This is a wonderful time of year to be here. Kansas City charms visitors with its warm-hearted, small-town graciousness. Yet plenty of culture and creativity are flowing from this pioneer town, which is sometimes called the City of Fountains because of the hundreds of beautiful fountains dotting its streets and parks. Kansas City, located in the center of the nation, was recognized as one of ten All-America Cities for 2006.

We are excited about the scientific program that we have put together for you. In keeping with the core mission of our society, an impressive group of leading scientists will provide plenary lectures on the many roles of dietary fatty acids and lipids in health and disease. Further, we have programmed over 300 scientific abstracts into four days of concurrent oral and poster sessions. Monday night four “courageous” scientists will attempt to present the evidence for and against changing current linoleic acid intake levels in the US and maybe elsewhere. (Separate tickets are required to attend this event.)

Relative to the social programming we believe that you will be pleasantly surprised by what Kansas City has to offer. We hope that most of you will make it in town in time to join us for a very special opening reception on Saturday, May 17th. This event will be held at the only national World War I museum in the U.S. Later in the week, you will get to experience an evening of jazz, Kansas City style. David Basse and City Light Orchestra along with Bobby Watson will be featured during dinner and dancing. For the past twenty years, Basse has been at the forefront of the music scene in this legendary jazz capitol. Watson headlined at Carnegie Hall, Lincoln Center and major U.S. and international jazz festivals. To quote Zan Stewart of the LA Times, David Basse is “a captivating singer who genuinely delights in a room full of happy people who are enjoying his danceable brand of jazz.” This will be an evening to remember. Don’t forget to wear your dance shoes.

Continuing the tradition of past meetings, we have worked hard to encourage the participation of students and new investigators. Thanks to the generosity of our sponsors, we’ve provided 63 free registrations as well as discounted hotel rooms to many of these young people. Nine of these 63 will be awarded a new laptop computer in recognition for “outstanding” posters and oral presentations. We will also have a competition to encourage attendees to visit the exhibits.

ISSFAL 2008 has been blessed with many very generous sponsors. In addition to enabling the organizers to provide many complimentary registrations, sponsors contributions have underwritten the social program and allowed us to provide many amenities that would otherwise result in a prohibitively high registration fee. Please be sure to thank the representatives of our sponsors and let them know they are appreciated.

We hope that you are ready to fully engage yourself in the world of fatty acids and lipids “From Lipidomics to Human Health” at this 8th biennial international meeting here in Kansas City. We hope that you will enjoy seeing old friends and make many new ones. While you are here be sure you take time to experience some of the local sights, sounds, and flavors of this charming Midwestern city.

Sincerely,

THE ISSFAL 2008 ORGANIZERS

Susan Carlson, William Harris, Margaret Craig-Schmidt, Jay Whelan, Kevin Fritsche, Ray Rice

Exhibitors Move-In & Setup

Sunday, May 18th	7:00am-10:00am
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Show Hours

Sunday, May 18th	9:45am-7:00pm
Monday, May 19th	7:00am-7:00pm
Tuesday, May 20th	7:00am-1:00pm
Wednesday, May 21st	7:00am-3:45pm
Thursday, May 22nd	7:00am-1:30pm

Exhibitor Teardown

Thursday, May 22nd	1:30pm-4:00pm
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Amarin Neuroscience Ltd.**Booth #?***Gold Sponsor*

Amarin is committed to improving the lives of patients suffering from central nervous system (CNS) and cardiovascular diseases. Our goal is to be a leader in the research, development and commercialization of novel drugs that address unmet patient needs.

Amarin's CNS development pipeline includes programs in myasthenia gravis, Huntington's disease, Parkinson's disease, epilepsy and memory. Amarin is initiating a series of cardiovascular preclinical and clinical programs to capitalize on the known therapeutic benefits of essential fatty acids in cardiovascular disease. Amarin also has two proprietary technology platforms: a lipid-based technology platform for the targeted transport of molecules through the liver and/or to the brain, and a unique mRNA technology based on cholinergic neuromodulation.

Amarin has its primary stock market listing in the U.S. on the NASDAQ Capital Market ("AMRN") and secondary listings in the U.K. and Ireland on AIM ("AMRN") and IEX ("H2E"), respectively.

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Avanti Polar Lipids, Inc.**Booth #?***Sponsor?*

Avanti. World Leader for lipids of unparalleled purity - phospholipids, sphingolipids, and sterols. Exciting new products for the Research Chemist and cGMP lipids for Pharmaceutical Production. Recent developments include Adjuvants, Glycosylated Sphingolipids, new Fluorescent and Deuterated lipids; plus Analytical Services.

Avanti Polar Lipids, Inc.
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BASF Corporation**Booth #?***Silver Sponsor*

BASF Nutrition Ingredients is a leading supplier of food ingredients including vitamins, carotenoids, omega-3s and others. BASF offers omega-3s from fish oil for applications in dietary supplements, infant formulas, functional foods and beverages. All omega-3 products from BASF contain fish oil of excellent quality and purity from strictly controlled marine sources. BASF's powder products have a pleasant smell and maintain the original food taste and aroma during final application. BASF Nutrition - the healthy decision.

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Tel: (800) 527-9881; Fax: 973-245-6843
E-mail: nutrition@basf.com
www.human-nutrition.basf.com

California Walnuts**Booth #?***Platinum Sponsor*

California walnuts are a leading source of alpha linolenic acid (ALA), the plant based omega-3 essential fatty acid. Walnuts are also rich in antioxidants and provide protein, fiber and more. The bottom line is that walnuts contribute nutrients essential to a healthy lifestyle. Best of all they taste great and are suited for inclusion in any diet. Visit our Web site for health research updates, nutrition information, recipes and more...www.walnuts.org.

Carlson Laboratories*Gold Sponsor*

Carlson Laboratories is a family owned and operated business dedicated to providing only the highest quality natural supplements. Since the beginning, in 1965, the product line includes many formulas designed to meet a wide variety of nutritional needs. Well known products include Super Omega-3, ACES, E-GEMS, and the Very Finest Fish Oil. Please stop by the booth and sample our outstanding liquid fish oils.

Kazia Bauer-Starz
Convention Manager
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Fax: 857-255-1605

Croda Health Care**Booth #?***Gold Sponsor*

Croda Health Care is the world's leading supplier of speciality lipids for pharmaceutical and nutritional applications. With new patented technologies such as PureMax™ (www.PureMax.info) and natural, sustainable raw material sourcing, Croda's Incromega, Crossential and Essentially range offer effective supplements for today's consumer health needs.

Highlights at ISSFAL include the newly launched Essentially range, clinically proven to protect against a number of disease states and Incromega V3, a sustainable, plant source of the omega 3 fatty acid SDA (C18:4 n-3), a highly effective precursor to the all important EPA.

www.croda.com/europe/hc
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www.puremax.info
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DSM Nutritional Products**Booth #?***Gold Sponsor*

Missing Information

E.I. du Pont de Nemours & Company Booth #?*Platinum Sponsor*

DuPont Applied BioSciences™ has leveraged its core competency in metabolic engineering to develop a yeast-based technology platform for producing mixtures of dietary fatty acids for use in nutritional products.

For information please contact:

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Business Development
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Efamol Ltd**Booth #?***Delegate Satchels Sponsor*

Efamol Ltd has for 30 years pioneered research, development, production and clinical testing of essential fatty acids. Current products include: EFALEX, specifically developed to provide the key fatty acids of the brain and central nervous system; a deficiency of which can adversely affect cognitive performance, behaviour and learning skills, EFALEX ACTIVE 50+, Omega-3 fatty acids combined with other key nutrients to prevent/slow down cognitive decline with age, and EFANATAL, providing the key fatty acids required in pregnancy and lactation.

Equateq Ltd

Dedicated to Fatty Acid Research and Production

A Centre of Excellence in the Western Isles of Scotland Equateq produces, to cGMP standards, up to 99% purity of all key fatty acids in the important Omega 3 and Omega 6 cascades; known as Ultra-RX, this range of fatty acid products can be delivered as FFA, EE or rTG depending on customer requirement.

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Vifor Pharma /Equazen**Booth #?***Platinum Sponsor*

Equazen's special interest is omega-3 and omega-6 long chain fatty acids. Our nutritional supplements: eye q, mumomega, cardiozen, equavision, and qarma, are made from high grade marine and botanical oils, and reflect some of the latest thinking in the field of lipid metabolism.

eye q has become one of the leading supplements in the UK and European markets for anyone with concerns about fatty acid deficiency in learning and behaviour. The formulation has been scientifically tested, most notably in the groundbreaking Oxford-Durham schools trial, which investigated how fatty acids may be of benefit in the classroom. Equazen eye q is suitable for children aged two years to adult, and comes in four formats - capsules, liquid, strawberry chews or a child-friendly fruity flavoured emulsion - to ensure convenient use by pretty much everybody.

Vifor Pharma highly encourages research to advance understanding of efficacy of fatty acids, and is excited to participate and contribute to ISSFAL Conference 2008.

www.equazen.com
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Phone: +41 58 851 65 11

Frito-Lay**Booth #?***Silver Sponsor*

Frito-Lay has a long-standing commitment to health and wellness and has led the food industry in many areas. Through improved products and new product introduction, Frito-Lay offers a wide variety of products that can fit into a healthy lifestyle. Through its commitment to well-being and by maintaining its tradition of providing great-tasting snacks, Frito-Lay is dedicated to meeting evolving needs of consumers. To help consumers understand the role of snacking and how favorite snacks can fit, visit snacksense.com and licensetosnack.com.

Fonterra**Booth #?***Silver Sponsor*

Fonterra is a multi-national dairy company and one of the world's leading dairy ingredients and consumer businesses. For generations, Fonterra has been leading the world in dairy innovation. As New Zealand's largest private sector investor in research and development, our commitment to innovation - from the farm to the factory - underpins our company vision to Lead in Dairy. Fonterra is dedicated to developing exciting technologies in a broad range of sciences, from forage and bovine genetics to nutrition, flavours, texturants and new ingredients that deliver health and nutritional benefits to the consumer.

GlaxoSmithKline**Booth #?***Platinum Sponsor*

GlaxoSmithKline is a leading research-based pharmaceutical company with a powerful combination of skills to discover and deliver innovative medicines. We offer a number of programs to support effective health management strategies and improve patient care. Please visit our exhibit to learn more about our products.

Three Franklin Plaza
1600 Vine Street
Philadelphia, PA 19101
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www.gsk.com

Martek**Booth #?**

Martek is a world leader in the research and development of docosahexaenoic acid (DHA), an omega-3 fatty acid that is important throughout life. DHA is a major structural fat in the brain and eyes and supports neurological and visual health. Martek's life'sDHA™, from a vegetarian source, is available in dietary supplements and functional foods.

Mead Johnson Nutritionals**Booth #?***Platinum Sponsor*

Mead Johnson Nutritionals is a world leader in nutrition, dedicated to helping provide infants and children around the world with the best start in life. Consistent with our support of breastfeeding as the gold standard in infant nutrition, we pattern our infant formulas after human milk. Our science-based products also include nutritional drinks and vitamins. For more information go to www.meadjohnson.com or contact MJMedicalAffairs@bms.com.

Minami Nutrition**Booth #?***Silver Sponsor*

Minami Nutrition are purveyors of the highest concentrated omega-3, fish oils supplement that are commercially available in the world. Ranging from 75% to 95% omega-3 concentrates, their oils are made with specific ratios of EPA:DHA that address specific health concerns. Minami does not use molecular distillation to make its oils, but rather uses a patented supercritical CO2 distillation process - at low temperature with no use of harsh solvents like hexane.

Minami Nutrition
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Mochida Pharmaceutical Co. Ltd.**Monsanto Company****Booth #?***Silver Sponsor*

Monsanto Company is a leading global provider of technology-based solutions and agricultural products that improve farm productivity and food quality. Using the tools of modern biology, we develop seeds that can improve the nutrition, taste and texture of consumer foods. Our line of Vistive soybeans provides food companies a solution to eliminate trans fats. Future products include improved soy protein, land-based sources of Omega-3's and more. For more information on Monsanto, see: www.monsanto.com.

Nordic Naturals*Silver Sponsor*

Nordic Naturals is dedicated to improving the overall health of our communities by providing awareness of the proper balance of essential fats, and stressing the importance of a healthy diet and lifestyle. Through our multi-patented manufacturing processes, accompanied by leading-edge technologies, we deliver fish oil with exceptional freshness, taste, and purity levels. All our fish oils are third party tested and show no detectable levels of environmental toxins. Nordic Naturals is committed to staying abreast with research in order to manufacture and provide the freshest and purest fish oils in the world.

NourishLife**Booth #?**

At NourishLife, our mission is to contribute to health and wellness by providing intelligent information, evidence-based products, collaboration and effective programs. We market direct to consumer and professionals exclusively through the internet. We provide very pure and concentrated EPA and DHA products through PharmaOmega and CardioNutrients brands.

Nu-Mega Ingredients**Booth #?***Poster Sessions Sponsor*

Nu-Mega Ingredients is a world leader in the supply of Omega-3 DHA as an ingredient to the food industry, through our range of refined fish oils (tuna) and Driphorm® HiDHA® microencapsulated tuna oil. Nu-Mega uses a patented microencapsulation technology that converts the HiDHA® tuna oil into a stable dry powder form (Driphorm®). This protects the tuna oil against oxidation and provides a form of taste barrier, such that manufacturers can increase the levels of Omega-3 DHA in a broad range of infant formulas and other everyday foods, with minimal flavor impact and often without any alterations to product formulations.

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Ocean Nutrition Canada**Booth #?***Silver Sponsor*

Ocean Nutrition Canada is a privately held company whose major shareholder is Clearwater Fine Foods Incorporated – the world's largest integrated shellfish harvester and processor. ONC is a global leading supplier of Omega-3 EPA and DHA ingredients from fish oil, marketed into the Dietary Supplement and Healthy Food markets. To date MEG-3® ingredients have been included in over 40 billion servings of food and supplement products world wide. For more information on the health benefits of MEG-3® ingredients please visit www.meg-3.com.

OmegaPure**Booth #?**

OmegaPure is made by Omega Protein, the world's largest producer of omega-3 fish oil, enriched with the essential nutrients EPA and DHA. Used in fortified food products, OmegaPure helps to support a lifetime of health for consumers.

Seven Seas**Booth #?**

Missing Information

sigma tau**Booth #?***Sponsor?*

Founded in 1957 by Emilio and Claudio Cavazza, sigma-tau has rapidly grown in to a leader in the Italian pharmaceutical industry. Based in Pomezia, just south of Rome, the group is now made up of several domestic and international companies. They include *Avantgarde*, a company led by Paolo Cavazza, which specializes in the production of pharmaceutical drugs for dermatological and gynecological applications. *sigma-tau HealthScience* develops nutritional supplements and medical foods that meet the same exacting standards as the company's pharmaceutical products. *Biosint SpA* is *sigma-tau's* manufacturer of L-carnitine and its derivatives. In 2001, *sigma-tau* launched *Biofutura Pharma*, a new subsidiary headquartered in Milan. *Biofutura* is developing pharmaceutical products designed to treat central nervous system problems and respiratory tract diseases.

The National Fisheries Institute (NFI)**Booth #?***Silver Sponsor*

The National Fisheries Institute (NFI) is a non-profit organization dedicated to education about seafood safety, sustainability, and nutrition. NFI promotes the USDA's Dietary Guidelines that Americans include fish and shellfish in their diets twice per week for longer, healthier lives. For the latest seafood science, fish facts, and tasty recipes, please call 703-752-8880 or visit aboutseafood.com.

Ther-Rx Corporation**Booth #?***Sponsor?*

Ther-Rx Corporation, a leader in women's healthcare, provides innovative products that are designed with women in mind to deliver high patient satisfaction. The diverse portfolio includes: the first transdermal spray for estrogen therapy; Clindesse® and Gynazole-1®, single-dose vaginal infection treatments; Repliva 21/7™, for anemia; and the PrimaCare® brand, the 'right for each mom' prenatal vitamins.

Heather Beggs

Ther-Rx Corporation

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Unilever/UFHRI**Booth #?***Silver Sponsor*

It is the Unilever mission to add Vitality to life. We meet everyday needs for nutrition, hygiene and personal care with brands that help people feel good, look good and get more out of life.

The Unilever Food and Health Research Institute brings this mission to life with science and technology innovations in foods. One of our science-based food brands is Becel/Flora, with a history of more than 45 years in the dietary management of risk factors of cardiovascular disease.

Wyeth Nutrition**Booth #?***Silver Sponsor*

Wyeth Nutrition is focused on the development and delivery of scientifically advanced, superior quality nutritional Products for Infants and Children.

Kathryn Pramuk

Wyeth Nutrition

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Christine Albert, MD, MPH received her MD at Harvard Medical School and did her Internal Medicine Residency at Mass General Hospital. She has completed fellowships in cardiology, preventive medicine and cardiac electrophysiology. She is currently at Brigham and Women's Hospital in Boston where she is Director of the Center for Arrhythmia Prevention. Dr. Albert has published seminal papers documenting the relations between omega-3 fatty acid intake or biomarkers and risk for sudden cardiac death.



Sonia Y. Angell, MD, MPH is Director of the Cardiovascular Disease Prevention and Control Program at the New York City Department of Health and Mental Hygiene. She is responsible for overseeing the development of citywide and targeted initiatives and policies designed to prevent cardiovascular morbidity and mortality in NYC residents and to eliminate related health disparities. Dr. Angell received her medical degree from the University of California, San Francisco, and completed Primary Care Internal Medicine residency training at Brigham and Women's Hospital in Boston. She has a Diploma in Tropical Medicine and Hygiene from the London School of Hygiene and Tropical Medicine, and a Masters in Public Health from the University of Michigan. She is a former Robert Wood Johnson Clinical Scholar.



Professor Nicolas Bazan, Nicolas Bazan is a medical graduate from Tucuman, Argentina. He has senior postings at Columbia University, and Harvard Medical School, the Clarke Institute, University of Toronto, Canada and Founding Director, Institute of Biochemical Research, University of South, Argentina. Since 1981 he has been Professor of the LSU School of Medicine and Founding Director, Neuroscience Center. His lab has reported major findings on brain ischemia or seizures on AA and DHA release, identification of supraenoic molecular species of phospholipids, liver derived DHA used during development of photoreceptors and brain, PAF synaptic and intracellular binding sites and PAF-mediated gene expression regulation, PAF as a retrograde messenger of LTP, they have identified neuroprotective docosanoids and defined their significance in muscular degeneration, stroke and Alzheimers disease.



Philippe Bougnoux, MD is head of the Inserm research Unit 921 « Nutrition, growth and Cancer », is professor of cancer biology at the university hospital of Tours (France). His research interests are to understand how diet and lipid nutrients influence the molecular alterations which result in malignant tumors and how they integrate to delay breast cancer occurrence or individual response to anticancer agents. As a medical oncologist, he does translational research in the field of dietary lipids in relation to breast cancer prevention and treatment. He is currently carrying out clinical trials of dietary intervention with omega-3 polyunsaturated fatty acids to enhance the sensitivity of tumors to radiation or chemotherapy. Web site www.n2c.univ-tours.fr. Email: bougnoux@med.univ-tours.fr.



Ingeborg Brouwer, PhD is an Assistant Professor in the Department of Nutrition and Health at the Institute for Health Sciences, Vrije Universiteit in Amsterdam. She studied Human Nutrition at Wageningen University (MSc, 1993). She received her PhD degree in Medical Sciences from the Catholic University Nijmegen in 1999. Her PhD research involved research on the effects of folate and folic acid on homocysteine. In 1999 she started to work as post-doc and later as project leader for the Wageningen Centre for Food Sciences (WCFS, currently named TI Food and Nutrition). Since 2006 she is Assistant Professor at the Institute of Health Sciences of the VU University Amsterdam. Her research focuses on nutrition and cardiovascular disease. She has more than 40 scientific publications.



Philip Calder, PhD is Professor of Nutritional Immunology at the University of Southampton, UK. His research interests are focused on understanding the influence of dietary fatty acids on aspects on cell function and human health, in particular in relation to cardiovascular disease, inflammation and immunity. He has served on committees of the Nutrition Society, the British Society of Immunology, the British Association for Parenteral and Enteral Nutrition and the European Society for Clinical Nutrition and Metabolism. He is Vice-President of ISSFAL. He is Editor-in-Chief of the British Journal of Nutrition and an Associate Editor of Clinical Science and of Lipids. He is a member of the nine other Editorial Boards including Annual Review in Nutrition, Biochimica et Biophysica Acta Molecular & Cell Biology of Lipids, Clinical Nutrition, Journal of Nutrition, Nutrition, and Prostaglandins Leukotrienes and Essential Fatty Acids. He is co-editor of the "Lipid Metabolism & Therapy" section of Current Opinion in Clinical Nutrition and Metabolism. He was overall chair of the 6th ISSFAL Congress.



Raffaele De Caterina, MD, PhD is currently Professor of Cardiology and Director of the University Cardiology Division "G. D'Annunzio" University, Chieti. In addition, Dr. De Caterina is the Director of the Laboratory for Thrombosis and Vascular Research, CNS Institute of Clinical Physiology, Pisa, Italy. He has scientific interests in the area of thrombosis, atherosclerosis, cardiovascular pharmacology, atrial fibrillation, and pathogenesis of coronary artery disease. He is the author of >250 peer-reviewed publications and an editor of 8 books. Currently he is a Visiting Lecturer on Medicine, Harvard Medical School and a Fellow of the European Society of Cardiology, Italian Association of Hospital Cardiologists (ANMCO), Italian Society of Cardiology (SIC). He is acting secretary for the Working Group on Arteriosclerosis, Thrombosis and Vascular Biology of the the Italian Society of Cardiology and a member of the Working Group on Thrombosis of the European Society of Cardiology. He is a member of the Cluster for Cardiovascular Pathology and Biology and Science Council, the European Society of Cardiology, the Council for Basic Cardiovascular Sciences, the European Society of Cardiology and the International Society for Nutrigenetics and Nutrigenomics.



John Colombo, PhD is a Professor of Psychology and Interim Director of the Schiefelbusch Institute for Life Span Studies at the University of Kansas. He has published numerous articles, chapters, and books on cognitive development in infancy and early childhood, and his research program pursues the topic of the development of attention and its relation to learning, intellectual development, and developmental disabilities. His work has been continuously funded by the National Institutes of Health and the National Science Foundation, and he is currently a co-investigator on the University of Kansas Center for the Behavioral Neurosciences in Communication Development. He sits on the editorial boards for *Infancy*, *Journal of Experimental Child Psychology*, *Infant Behavior and Development*, and the *Journal of Applied Developmental Psychology*, and he just began a three-year term as associate editor for *Child Development*. He has served as Chair of the Department of Psychology (2005-2006), and as Associate Dean for the Graduate School (2001-2004).



Andrew J. Dannenberg, MD is Director of the Cancer Center at The New York Presbyterian-Weill Cornell Medical Center. He is also the Henry R. Erle, M.D.-Roberts Family Professor of Medicine at Weill Cornell Medical College. Dr. Dannenberg received his medical degree from Washington University in St. Louis and served as a medical resident and gastroenterology fellow at The New York Hospital-Cornell Medical Center. His laboratory has focused on elucidating the mechanisms underlying the inflammation-cancer connection with an emphasis on prostaglandin biology. Dr. Dannenberg has authored more than 140 scientific articles, as well as edited several books and journals. He is a member of the American Society for Clinical Investigation, the American Association for Cancer Research, and the American Gastroenterological Association. He co-chaired the Keystone Symposium "Molecular Targets for Cancer Prevention" in 2006 and was Chairman of the Program Committee of the 2007 AACR "Frontiers in Cancer Prevention Research" meeting. He also serves on the editorial boards of several journals including *Cancer Research*, *Clinical Cancer Research* and *Journal of Clinical Oncology*.



Edward A. Dennis, PhD is Distinguished Professor of Chemistry and Biochemistry and of Pharmacology in the School of Medicine at the University of California at San Diego (UCSD). He received his BA from Yale in 1963 and a Ph.D. from Harvard in 1967. At UCSD he has served as Chair of the Department of Chemistry and Biochemistry, as Chair of the Faculty Academic Senate, and on the Board of Overseers. While at UCSD, he has also been a Visiting Professor at Harvard Medical School, a Visiting Scientist at Brandeis University, and currently serves as an Adjunct Professor at The Scripps Research Institute. Dr. Dennis' career research focus has been on the enzyme phospholipase A2 and inflammatory diseases as well as fat/lipid metabolism and he has authored over 280 original research publications and 11 patents, and has edited thirteen books. He is currently Editor-in-Chief of the *Journal of Lipid Research* and the Director of the LIPID MAPS Lipidomics Consortium. Dr. Dennis has been named a Fellow of the American Association for the Advancement of Sciences and received the Avanti Award in lipid enzymology from the American Society of Biochemistry and Molecular Biology in 2000 and the European Lipid Science Award from the European Federation for Lipid Science and Technology in 2007. Dr. Dennis serves on the Scientific Advisory Board and Board of Directors of both private and public companies. He also serves on the Council of the American Society for Biochemistry and Molecular Biology and the Board of Directors of the Keystone Symposia, ResMed Foundation, Eicosanoid Research Foundation, the Association of Yale Alumni, and the La Jolla Playhouse.



Klaus Gawrisch, PhD is a Senior Investigator and Acting Chief, Laboratory of Membrane Biochemistry and Biophysics and Chief of the Section of NMR at the National Institute on Alcohol Abuse and Alcoholism of the NIH. He is conducting NMR structural studies on biomembranes by solid state NMR. His interests include membrane biophysics, NMR, structure and function of membranes rich in polyunsaturated fatty acids, the role of cholesterol in domain formation, structural studies on G-protein coupled membrane receptors, and the effects of ethanol on membrane structure and function. He received the Avanti Award in Lipid Research at the Biophysical Society in 2007.



Ben de Kruijff, PhD is professor of Membrane Biochemistry at Utrecht University. His research interests are the role of different lipid classes in membrane structure and function, and the mode of action of membrane active toxins and antibiotics.



Maria Makrides, PhD is Director of the Child Nutrition Research Centre, a joint venture between the Women's & Children's Health Research Institute, Flinders Medical Centre & Children, Youth, and Women's Health Service, Adelaide Australia. Maria has served on the Board of Directors of the International Society for the Study of Fatty Acids and Lipids and currently leads 3 multi-centre, national trials investigating the potential health benefits of omega 3 fatty acids in the perinatal period. She is a Senior Research Fellow of the Australian National Health and Medical Research Council.



Dariush Mozaffarian, MD is an Assistant Professor of Medicine in the Division of Cardiovascular Medicine, Brigham and Women's Hospital and Harvard Medical School, and Co-Director of the Program in Cardiovascular Epidemiology (www.hsph.harvard.edu/research/cvdepi/) and Assistant Professor of Epidemiology at the Harvard School of Public Health. His research focuses on the effects of lifestyle, particularly dietary habits, on cardiovascular health and disease. Dr. Mozaffarian has authored more than 50 publications and research studies. He is a member of a number of committees that determine policy for lipid intake. Dr. Mozaffarian received his B.S. from Stanford University (with Honors, with Distinction, Phi Beta Kappa) and his M.D. from Columbia University College of Physicians and Surgeons (Alpha Omega Alpha). He also holds a Masters of Public Health from the University of Washington and a Doctorate of Public Health in Epidemiology from Harvard School of Public Health.



Jose M Ordovas, PhD, is Professor of Nutrition and a Senior Scientist at the USDA-Human Nutrition Research Center on Aging at Tufts University in Boston, Massachusetts where he also is the Director of the Nutrition and Genomics Laboratory. Dr. Ordovas' major research interests focus on the genetic factors predisposing to cardiovascular disease and obesity and their interaction with the environment and behavioral factors with special emphasis on diet. Dr. Ordovas is considered as one of the founders of Nutrigenomics. His current genetic studies involve populations and investigators from all continents. He has received many honors and serves on multiple editorial boards and is active with several peer review committees in the USA, UK, the Netherlands, New Zealand, France, Ireland, Italy, Qatar, Germany, Austria, Sweden and Singapore and the European Union.



Stanley Rapoport, PhD is Chief of the Brain Physiology Section at the National Institute on Aging (NIH) in the United States. He received his M.D. degree from Harvard Medical School, and did post-doctoral work at Uppsala University in Sweden. While at the NIH, he contributed to our understanding of the blood-brain barrier and directed a clinical program that used positron emission tomography (PET) to characterize healthy human aging and Alzheimer disease. In his recent lipid studies, he developed methods and models to quantify rates of brain PUFA metabolism in unanesthetized rodents and in humans. He demonstrated rapid energy-dependent recycling of PUFAs in brain phospholipids, and elucidated the role of arachidonic acid in neurotransmission. He also showed that drugs that are effective against bipolar disorder downregulate the brain arachidonic cascade in rodents, and was able to quantify exactly how brain PUFA metabolism depends on dietary PUFA content and liver PUFA metabolism.



Charles N. Serhan, PhD is the Director of the Center for Experimental Therapeutics and Reperfusion Injury at Brigham and Women's Hospital and Harvard Medical School, Boston. He is the Simon Gelman Professor of Anaesthesia (Biochemistry and Molecular Pharmacology) at Harvard Medical School, and is Professor in the Department of Oral Medicine, Infection and Immunity and an Affiliate Faculty Member of MIT. Dr. Serhan received degrees in Biochemistry from Stony Brook University, Experimental Pathology and Medical Sciences (New York University School of Medicine), as well as post-doctoral training in Physiological Chemistry at the Karolinska Institute Medical University with Prof. Bengt Samuelsson (1982 Nobel Laureate in Medicine). Dr. Serhan's research focuses on acute inflammation and on the structural elucidation of pathways and compounds with protective mechanisms operating in humans that prevent tissue injury and promote resolution. In July 2000, he received a MERIT Award from the National Institute of General Medical Sciences; an honorary degree in 1996 from Harvard University; a number of named-investigator awards, including a prestigious Pew Scholar in the biomedical sciences. In April 2000, he received the distinction of being named the first "Endowed Distinguished Scientist" at BWH. Dr. Serhan received the MacArthur Research Service Award in 2003, and the Outstanding Scientist Award in Inflammation Research at BioDefense 2004. He was the 2005 Kreshover Lecturer at NIH (NIDCR) and received the Dart/New York University Biotechnology Achievement Award in 2007.



Steven Watkins, PhD currently serves as the President and Chief Scientific Officer of Lipomics Technologies. Dr. Watkins received his Ph.D. in Food Science from UC Davis studying the effects of dietary lipids on mitochondrial energetics and lipid metabolism. After completing his Ph.D. he worked as a postdoctoral fellow at UC Davis and the Nestle Research Center in Lausanne Switzerland. In May of 2000 Dr. Watkins co-founded Lipomics and, along with Ryan Davis, developed the technology underpinning the Company's research and service capabilities. He has published many articles and chapters on lipids in peer-reviewed journals, is frequently sought as an invited speaker at conferences worldwide, and is a founding board member of the Metabolomics Society. Dr. Watkins received a B.S. with honors at Cornell University in 1993. E-mail: smwatkins@lipomics.com

DETAILED PROGRAM - Saturday - May 17, 2008

8:30 – 5:00	Maternal Infant Satellite Workshop (Requires Pre-registration)
6:00 – 9:00	Opening Reception (World War I Museum)

DETAILED PROGRAM - Sunday - May 18, 2008

7:00 – 8:15	Continental Breakfast
8:15 – 9:45	Plenary: Leaf Award Lecture <i>AA Cytochrome P450 Pathway: A New Target for Omega-3 Fatty Acids (Spector)</i>
9:45 – 10:30	Coffee/Poster Session I/Exhibits
10:30 – 12:00	Plenary: Lipid Networks <i>The LIPID MAPS Approach to Essential Fatty Acid and Eicosanoid Lipidomics (Dennis)</i> <i>Diet, Breast Cancer and the Lipidome (Bouhroux)</i>
12:00 – 1:30	Lunch/Poster Session I/Exhibits
1:30 – 3:00	Concurrent Sessions <i>Maternal Infant I</i> <i>Cardiovascular I</i> <i>Bioactive Lipids I</i> <i>Reffs</i>
3:00 – 3:45	Coffee/Poster Session I/Exhibits
3:45 – 5:15	Plenary: Lipid and Protein Biophysics <i>A Fresh Look at Lipid-Protein Interactions (Gawnisch)</i> <i>Lipids as Targets for Antibodies (de Kruijff)</i>
5:15 – 7:00	Poster Session I/Exhibits
	Evening at Leisure

DETAILED PROGRAM - Monday - May 19, 2008

7:00 – 8:15	Continental Breakfast
8:15 – 9:45	Plenary: Lipids in Aging Brain <i>In Vivo Brain Arachidonic Acid Metabolism as a New Therapeutic Targets (Rapoport)</i> <i>Neurodegenerative Diseases and the Bioactivity of Omega 3 Fatty Acids (Bazan)</i>
9:45 – 10:30	Coffee/Poster Session II/Exhibits
10:30 – 12:00	Concurrent Sessions <i>Neurological Repair and Protection</i> <i>Lipid Protein Interactions</i> <i>Developing US Recommendations for EPA and DHA</i> <i>PUFA Metabolism</i>
12:00 – 1:30	Lunch/Poster Session II/Exhibits
1:30 – 3:00	Concurrent Sessions <i>Maternal Infant II</i> <i>Metabolic Syndrome</i> <i>Gangliosides</i> <i>Dietary Arachidonic Acid</i>
3:00 – 3:45	Coffee/Poster Session II/Exhibits
3:45 – 5:15	Plenary: Lipid-Gene Interactions <i>Improving Human Health through Lipid Profiling (Watkins)</i> <i>Fats for Your Genes (Ordovas)</i>
5:15 – 7:00	Poster Session II/Exhibits
7:00 – 9:00	Dinner Program <i>Health Implications of Changing Linoleic Acid Intakes (Requires Pre-registration)</i>

DETAILED PROGRAM - Tuesday - May 20, 2008

7:00 – 8:15	Continental Breakfast (New Investigator Breakfast with Experts)
8:15 – 9:45	<p>Plenary: Cancer <i>Omega 3 PUFA: Good or Bad for Prostate Cancer (Brouwer)</i> <i>Prostaglandins, Cancer and the Clinic: From Bench to Bedside and Back (Dannenberg)</i></p>
9:45 – 10:30	Coffee/Exhibits
10:30 – 12:00	<p>Concurrent Sessions <i>Neuropsychology I</i> <i>Bioactive Lipids II</i> <i>Prostate Cancer</i> <i>Plant Omega-3 Biotech</i></p>
12:00 – 1:00	Box Lunch/Exhibits
1:30 – 2:30	<p>Plenary: Lipids in Developing Brain <i>DINO Trial: The Effect of DHA on the Development of Preterm Infants (Makrides)</i> <i>DHA and Early Biobehavioral Development (Colombo)</i></p>
2:30 – 6:30	Afternoon at Leisure
6:30 – 10:00	Jazz Night with Dave Base and Bobby Watson (Hyatt Ballroom)

DETAILED PROGRAM - Wednesday - May 21, 2008

7:00 – 8:15	Continental Breakfast
8:15 – 9:45	<p>Plenary: Fatty Acids and Cardiovascular Disease <i>Fatty Acids and CVD: Effects on Clinical Events (Albert)</i> <i>Fatty Acids and CVD: Molecular Mechanisms (De Caterina)</i></p>
9:45 – 10:30	Coffee/Poster Session III/Exhibits
10:30 – 12:00	<p>Concurrent Sessions <i>Maternal Child</i> <i>New Animal Models</i> <i>Cardiovascular II</i></p>
12:00 – 1:00	Lunch/Poster Session III/Exhibits
1:30 – 3:00	<p>Concurrent Sessions <i>CHD Megatrials</i> <i>Cancer</i> <i>Inflammation I</i></p>
3:00 – 3:45	Coffee/Poster Session III/Exhibits
3:45 – 5:15	<p>Plenary: Trans Fats - From NF-κB to NYC <i>CV effects, molecular mechanisms (Mozaffarian)</i> <i>CV effects, molecular mechanisms (Mozaffarian)</i></p>
6:30 – 10:00	Evening at Leisure

DETAILED PROGRAM - Thursday - May 22, 2008

7:00 - 8:15	Continental Breakfast
8:15 - 9:45	<p>Plenary: Lipids and Inflammation <i>PUFAs and the Immune System (Caldier)</i> <i>Resolvins and Protectins (Serhan)</i></p>
9:45 - 10:30	Coffee/Exhibits
10:30 - 12:00	<p>Concurrent Sessions <i>Aging</i> <i>Inflammation II</i> <i>Neuropsychology II</i></p>
12:00 - 1:30	Lunch
1:30 - 3:00	<p>New Investigator Awards and Early Career Award Lecture <i>Regulation of Brain PUFA Uptake and Turnover (Bazinet)</i></p> <p>Adjourn</p>

10:30 THE LIPID MAPS APPROACH TO ESSENTIAL FATTY ACID AND EICOSANOID LIPIDOMICS

DENNIS, EDWARD A.

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As part of the LIPID MAPS Consortium (www.lipidmaps.com) [Schmelzer et al. (2007) *Lipidomics Methods in Enzymology*, 432, 169-181], we have developed a robust and comprehensive approach to lipidomics analysis [Raetz et al. (2006) *J. Lipid Research*, 47, 1097-1111] of hundreds of fatty acids and eicosanoids, including their numerous metabolites arising from an array of cyclooxygenases, lipoxygenases, cytochrome P450s and non-enzymatic oxidation producing isoprostanes, as well as combinations thereof. The LC/MS approach to eicosanoid analysis [Deems et al. (2007) *Lipidomics Methods in Enzymology*, 432, 59-82] and GC/MS approach to fatty acid analysis will be summarized as well as the development of standards which facilitates widespread application of the LIPID MAPS approach. We will illustrate the use of these techniques in lipidomics analysis to: a) Discover novel lipids such as the family of dihomoprostaglandins [Harkewicz et al. (2007) *J. Biol. Chem*, 282, 2899-2910]; b) The application to characterize agonist stimulated RAW264.7 murine macrophages. Fifteen specific eicosanoids produced through COX and 5-LO were detected either intracellularly or in the media following stimulation with 16 different agonists including Toll-like receptors (TLR), G protein-coupled receptors, purinergic receptors and combinations thereof. Synergy between Ca²⁺ release and TLR pathways was detected and discovered to be independent of NF- κ B induced protein synthesis using lipidomics analysis [Buczynski et al. (2007) *J. Biol. Chem*, 282, 22834-22847]; c) We will illustrate the application of lipidomics analysis to the analysis of tissues with an example specifically of joint tissues from mice suffering Lyme Disease caused by *Borrelia burgdorferi* in which a comprehensive lipidomics analysis of the metabolites produced demonstrates the inflammatory profile resulting from infection. Supported by LIPID MAPS Glue Grant NIH U54 GM069338.

10:30 DIET, BREAST CANCER AND THE LIPIDOME

Bougnoux P

INSERM U 921, University Hospital Bretonneau, Tours, France

The potential for dietary fat to prevent breast cancer makes identification of defined molecules a mandatory step. In order to circumvent the limitations and/or bias of dietary exposure assessment tools, biomarkers of past lipid intake such as the fatty acid composition of white adipose tissue have been used. When considered separately, candidate fatty acids identified as favorable on the basis of their association with breast cancer risk have usually led to inconsistent results in animal intervention studies. This inconsistency indicates that any approach based on a single fatty acid should be abandoned for an integrated view over the complex lipid interactions, which finally determines the lipidome, the lipid profile that is found in individuals. We reappraised the role of the complete lipid profile through a comprehensive study of adipose tissue fatty acids obtained in patients with benign or malignant breast tumors as well as in experimental animals during dietary interventions. Rather than a single fatty acid, a composite indicator combining elevated monounsaturates and low n-6/n-3 fatty acid ratio was associated with breast cancer protection. This index offers the opportunity to quantify the part due to modifiable dietary factors in the risk of breast cancer. The lipidome may become the template for identifying proper dietary modifications to prevent breast cancer.

3:45 LIPIDS AS TARGETS FOR ANTIBIOTICS

de Kruijff, B.

Chemical Biology and Organic Chemistry, Utrecht University, Utrecht, the Netherlands

Membranes are vital structures essential for life. Therefore, it is not surprising that they form a target for many cell-killing agents of which the antibiotics form a special and important class in the fight against infectious diseases. Antibiotics and antimicrobials in general specifically target microorganisms and interfere with cellular functions specific for these microorganisms. In recent years it became clear that specific membrane lipids can play crucial roles in the killing of bacteria by members of the lantibiotic family. Antibiotics are antibiotics with a structure containing lantionine rings. They are produced by certain bacterial strains and are commonly used as food preservatives. Several members of that antibiotic family were shown to bind with high affinity to Lipid II the membrane lipid that shuttles the peptidoglycan building blocks across the bacterial membrane. Depending of the type of lantibiotic they kill by targeted pore formation or by removing lipid II out of its functional location. A parallel can be drawn between the mode action of the lantibiotics and the polyene antibiotics that kill fungi via different mechanisms using the membrane lipid ergosterol as receptor.

Selected references:

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3:45 A FRESH LOOK AT LIPID-PROTEIN INTERACTIONS

Gawrisch K

NIAAA, NIH, Bethesda, MD, USA

The composition of the lipid matrix is critical for function of membrane proteins. Perhaps one of the best studied examples is the function of the G-protein coupled membrane receptor (GPCR) rhodopsin which has a specific requirement for high concentrations of docosahexaenoic acid (DHA) to achieve functional properties similar those in rod outer segment disk membranes. Results that show the importance of lipids for stabilization of recombinant peripheral cannabinoid receptor CB2 will be presented as well. Technological advances in nuclear magnetic resonance spectroscopy applied to biomembranes as well as in sample preparation technology enabled a much more detailed analysis of lipid-protein interactions. It appears that GPCR adjust function in response to their lipid environment far more nimbly than classical continuum models with treat the lipid matrix like an elastic rubber band that deforms upon interaction with the more rigid protein would suggest. In particular, the concept of hydrophobic matching between the lipid matrix and rhodopsin was confirmed, but structural changes of rhodopsin itself appear to be more significant than changes in the lipid matrix surrounding the GPCR. Formation of photointermediates of rhodopsin does not result in adjustment of bilayer thickness. However, photoactivation had a measurable influence on interaction between rhodopsin and lipids with DHA hydrocarbon chains. The lipid-rhodopsin interface is heterogeneous with a limited number of sites on rhodopsin that preferentially interact with the polyunsaturated fatty acid. Surprisingly the polyunsaturated lipids in the first layer surrounding the protein maintained their high conformational freedom. The exchange of lipids between the lipid-protein interface and the bulk matrix is very rapid. Rhodopsin has some preference for collecting polyunsaturated phosphatidylethanolamines in its immediate vicinity. With increasing sophistication of investigative tools, there is now a growing appreciation for lipid diversity and for the role of individual lipids and specific lipid-protein interactions in membrane structure and function.

1:30 ETHNIC DIFFERENCES IN EARLY PREGNANCY MATERNAL N-3 AND N-6 FATTY ACID CONCENTRATIONS NOT EXPLAINED BY DIFFERENCES IN FISH CONSUMPTIONEijssden M van^{1,2}, Hornstra G³, Wal MF van der², Bonsel GJ^{1,4}¹Academic Medical Centre – University of Amsterdam, Amsterdam, The Netherlands; ²Municipal Health Service, Amsterdam, the Netherlands; ³Maastricht University, Maastricht, The Netherlands; ⁴Erasmus Medical Centre – Erasmus University, Rotterdam, The Netherlands.**Background:** Maternal nutrition has been proposed as an explanation of the world-wide existing ethnic disparities in birth weight. While n-3 and n-6 fatty acids (FA) may be relevant in this context, information on ethnic differences in intake or concentrations of these nutrients is limited.**Objectives:** **1)** to describe differences in early pregnancy maternal n-3 and n-6 plasma phospholipid-associated FA concentrations between white (Dutch), black (Ghanaian, Surinamese, Antillean) and Mediterranean (Turkish, Moroccan) women in Amsterdam, the Netherlands; and **2)** to assess the role of fish consumption in explaining differences in EPA (20:5n-3) and DHA (22:6n-3), as well as DGLA (20:3n-6) and AA (20:4n-6).**Procedure:** FA concentrations of 3284 participants of the multi-ethnic ABCD cohort were compared by general linear models, with ethnicity as primary independent variable and maternal age, parity, pregravid BMI, alcohol consumption and smoking habits as co-variables. For EPA, DHA, DGLA and AA, the role of fish consumption was determined by adding this variable to the model.**Results:** Compared to Dutch women (n=2459), Surinamese (n=292), Antillean (n=64), Turkish (n=168) and Moroccan (n=244) women had lower concentrations of n-3 FA but higher concentrations of n-6 FA except DGLA (p<0.001). Differences were most pronounced in Turkish women, who reported the lowest fish consumption. Ghanaian women (n=57) had the highest EPA and DHA concentrations but generally lower n-6 FA concentrations (p<0.001). Although they reported the highest fish consumption, adjustment for this variable attenuated differences in EPA, DHA, DGLA and AA concentrations only modestly.**Conclusions:** In this study, distinct differences in n-3 and n-6 FA patterns were observed between white, black, and Mediterranean women. The deviant pattern for Ghanaian women (compared to white as well as other black women) was largely unrelated to fish intake. Rather than intake variation, the observed differences may reflect metabolic variation, which warrants further research.**1:45** FACTORS AFFECTING THE STATUS OF LCP IN NEONATES AND INFANTS ASSESSED THROUGH A MICROMETHOD APPLIED TO WHOLE BLOOD FA ANALYSIS.Galli C¹, Agostoni C², Marangoni F¹, Risé P¹, Riva E² & Giovannini M².Department of Pharmacological Sciences and ²Department of Paediatrics San Paolo Hospital, University of Milan, Italy.**Background:** Long-chain polyunsaturated (LCP) fatty acids (FA) play relevant roles in infants' growth and development, but investigations have been limited by the ethical issue of blood collection in small infants and by the handling of samples.**Subjects and methods:** The role of LCP in large populations (from mildly premature to older infants) has been investigated by analysing FA in whole blood drops collected on a special adsorbent (Marangoni F et al, *Anal Biochem* 2004), and directly processed for analysis. Three different studies were carried out, 1, on preterm and term infants, either appropriate or small for gestational age (GA), 2, on infants born to smoking mothers, and, 3, in older infants in a developing Country (Cambodia), in order to check their FA status after supplementation of micronutrients to prevent iron-deficiency anaemia.**Results:** Study 1 confirmed that the FA pattern is associated to both GA and birthweight. The FA pattern of term small for GA infants suggests derangements in FA metabolism, resulting in high levels of 20:5n-3 vs 22:6n-3. In study 2 maternal smoking appeared to be associated with reduction of infants' LCP pools, especially DHA, in agreement with data in *in vitro* studies on mammary gland cells, showing that cigarette smoke inhibits desaturating enzymes. In study 3 in Cambodian infants, supplementation with micronutrients resulted in increase of linoleic acid and alpha-linolenic acid vs placebo, without significant changes in LCP.**Conclusions:** FA profiling in blood drops provide data allowing to establish correlations with anthropometric, nutritional and health parameters in infancy.**2:00** THE EFFECTS OF MATERNAL DHA SUPPLEMENTATION DURING PREGNANCY ON FETAL HEART RATE AND HEART RATE VARIABILITY.Gustafson KM¹, Carlson SE¹, Popescu EA¹, Popescu M¹, Colombo J², Cheatham CL¹¹University of Kansas Medical Center, Kansas City, KS, USA, ²University of Kansas, Lawrence, KS, USA**Background:** Pregnant women are being advised to supplement their diet with DHA-enriched foods or capsules containing algae oil or refined fish oil. Docosahexaenoic acid (DHA) has been shown to improve cardiovascular function in adults but little is known about how dietary DHA intake affects cardiac function in the fetus.**Objective:** We have been using a biomagnetometer to record fetal magnetocardiograms (fMCG) in the 2nd and 3rd trimesters of pregnancy to document fetal heart rate (HR), heart rate variability (HRV), fetal breathing and body movements from 20 weeks to term in uncomplicated pregnancies. We found a subset of women who were voluntarily taking DHA supplements.**Procedures:** 10 women took DHA supplements during the 2nd and 3rd trimesters. The average dose of DHA was 200 mg/day. fMCGs were recorded at 4 week intervals from 28 to 36 weeks GA. We compared the fMCG from DHA supplemented fetuses to age, sex and state-matched unsupplemented fetuses. Results: There was no difference in mean HR at 28 weeks GA between the two groups. At 32 and 36 weeks, the DHA supplemented fetuses had significantly lower HR. (32 weeks: DHA=140 bpm, Control=147 bpm p=.01, 36 weeks: DHA=137 bpm, Control=147 bpm p=.02). There was no difference in short-term HRV at 28 weeks. At 32 weeks, HRV was higher in the DHA supplemented group, reaching significance at 36 weeks (p=.02).**Conclusions:** We found lower fetal HR and higher short-term HRV in a small group of women who were taking commercial DHA supplements during pregnancy. This suggests that maternal DHA intake during pregnancy may have a positive effect on fetal cardiac autonomic control and merits the need for a larger, controlled study to determine the effects of maternal DHA supplementation during pregnancy on fetal and infant cardiac measures of rate and variability.**2:15** A MODEL TO ASSESS DOCOSAHEXAENOIC ACID REQUIREMENTS FOR BRAIN ACCRETION DURING EARLY CHILDHOOD

Hadley KB, Ryan AS, Nelson EB

Martek Biosciences Corporation, 6840 Dobbin Road, Columbia, Maryland 21045

Background: Adequate docosahexaenoic acid (DHA, 22:6n-3) is important for normal development of the central nervous system.**Objective:** To estimate the brain DHA accretion in early childhood**Procedure:** Using accretion, concentration, and turnover rates estimated from human and non-human primate studies, a model for brain DHA homeostasis is described. The model is based on physiological demands of the brain rather than on estimates derived from the DHA levels of human milk or the caloric contribution of alpha-linolenic acid (ALA, 18:3n-3).**Results:** It is estimated that approximately 3.75 mg of DHA per day is necessary to support total brain accretion in children 1-2 years of age.**Conclusion:** Sufficient data exist to develop a model for the requirements for DHA based upon brain metabolism. Future work is needed in order to establish dietary requirements for specific age groups and those populations at risk for low DHA intake.

2:45 PRENATAL DHA SUPPLEMENTS AND BIRTH OUTCOMES: DOUBLE-BLIND RANDOMIZED CONTROLLED TRIAL IN MEXICO

Ramakrishnan U,¹ Parra-Cabrera S², Stein AD¹, Juarez-Marquez S³, Rivera J², Martorell R¹.
¹Hubert Dept. of Global Health, Emory University, Atlanta, GA, USA, ²Instituto Nacional de Salud Pública, Cuernavaca, Mexico, ³Instituto Mexicano del Seguro Social, Cuernavaca, Mexico.

Objective: We conducted a double-blind randomized controlled trial to evaluate whether prenatal docosahexaenoic acid (DHA) supplements increase gestational age and birth size.

Procedures: We identified 1762 pregnant women (18–35 y) who sought prenatal care and intended to deliver at the Instituto Mexicano del Seguro Social, General Hospital I in Cuernavaca City, Mexico. Women who agreed to participate (n=1094) were randomized to receive daily supplements containing 400mg of DHA or placebo from 18–22 wk gestation through delivery. Supplements (provided by Martek Biosciences) were distributed weekly at the participants' home and/or work place. Birth outcomes were ascertained from hospital records within 24 hours of delivery. Gestational age (GA) was based on date of last menstrual period reported at recruitment.

Results: Maternal age (26.2 + 4.7 y), body mass index (26.0 + 4.2 kg/m²), and parity (38% primiparous); loss to follow-up (11%); and compliance (89%) based on pill count did not differ between the two groups (all p>0.05). There were 968 live births and 5 still births. Blinded intent to treat analysis showed no significant differences by treatment group (all p>0.05) in mean GA (39.1 +1.8 wks), weight (3.20 + 0.46 kg), length (50.3 + 2.5 cm) and head circumference (43.3 +1.7 cm) at birth. Similarly, the prevalence of preterm (GA < 37 weeks; 8.7%), low birth weight (< 2500 g; 4.6%) and small for gestational age (3.7%) among 963 singleton live births did not differ between groups (all p > 0.05).

Conclusion: Our study provides no evidence of improved birth outcomes in a population where DHA intakes are very low (mean < 100 mg/d). The benefits of the intervention on infant health and neurodevelopment remain to be determined. The infants are currently being followed up to 18 months of age. (Supported by NIH (HD-04399) and the March of Dimes Foundation).

3:00 RANDOMIZED CONTROLLED TRIAL OF OMEGA-3 FATTY ACID SUPPLEMENTATION FOR RECURRENT PRETERM BIRTH PREVENTION

Harper MA for the NICHD Maternal Fetal Medicine Units Network
Bethesda, Maryland

Background: Omega-3 fatty acid supplementation and dietary intake have been reported to prolong gestation and decrease preterm birth (PTB).

Objective: This trial was undertaken to evaluate whether omega-3 supplementation reduces recurrent PTB in women with prior PTB when given along with 17 alpha-hydroxyprogesterone caproate (17-OHPC). Dietary intake of fish was also evaluated.

Procedures: In this randomized, double-masked, placebo controlled, multicenter trial, women with prior spontaneous PTB and a singleton gestation were assigned to take either an omega-3 supplement (1200 mg eicosapentaenoic acid and 800 mg docosahexaenoic acid) or matching placebo daily from 16–22 through 37 weeks' gestation. All participants received weekly intramuscular 17 OHPC (250mg). To detect a reduction in rate of PTB from 30% to 21% with > 80% power, 800 subjects were needed. A validated food frequency questionnaire was used to assess dietary intake of fish at baseline.

Results: Of the 852 women randomized, none were lost to follow up and all completed the food frequency questionnaire. (Table) The relative risk of PTB for omega-3 vs placebo: 0.91 (0.77–1.07), and 0.92 (0.78–1.08) when stratified by fish consumption. However, women reporting > 1 fish meal per month had significantly decreased PTB, odds ratio adjusted for baseline risk factors and treatment group: 0.62 (0.45– 0.86).

Conclusions: Among high risk women receiving 17-OHPC, omega-3 supplementation did not reduce the rate of PTB. We observed an association between dietary intake of fish and reduced PTB.

	Omega-3 Supplement	Placebo	P value for Omega-3 vs Placebo	Fish Intake ≥1 meal/month	Fish Intake < 1 meal/month	P value for fish intake
N	434	418		599	253	
PTB < 37 weeks	37.8%	41.6%	0.252	35.9%	48.6%	0.0005
Spontaneous PTB < 37 weeks	29.0%	31.8%	0.377	27.2%	37.9%	0.002
PTB < 35 weeks	18.9%	19.9%	0.722	17.2%	24.5%	0.014

1:30 THE EFFECT OF MODERATE DOSE OF EPA PLUS DHA ON LIPID PROFILE AND INFLAMMATORY MARKERS IN CAROTID ENDARTERECTOMY PATIENTS

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Background: Long-chain n-3 PUFAs are believed to be anti-inflammatory. However, there are few studies of the anti-inflammatory efficacy in patients with cardiovascular disease. **Objective:** The aim of the present study was to investigate the effects of a moderate dose of long-chain n-3 PUFAs (1.8 g/d eicosapentanoic acid, EPA + docosahexaenoic acid, DHA) in the form of ethyl esters (Omacor) on cardiovascular risk factors, particularly blood lipids and inflammatory markers. **Methods:** In a double-blind and placebo-controlled study, patients awaiting carotid endarterectomy were randomised to 2 g/d Omacor (n = 47) or olive oil (n = 53) as placebo for between 7 and 102 days until surgery. Most patients were taking statins and aspirin. Plasma phospholipid fatty acid composition and blood lipid concentrations were determined by standard procedures; plasma inflammatory markers were determined by ELISA using commercial kits. **Results:** The ratios of arachidonic acid (ARA) to EPA and of ARA to DHA in plasma phospholipids were significantly reduced, from 8.4 to 2.6 and 2.7 to 1.6, respectively, in patients taking Omacor. Total plasma cholesterol and triacylglycerol (TAG) concentrations were decreased significantly (P < 0.001) by 13% (Omacor) vs 9% (placebo) and 14% (Omacor) vs 7% (placebo), respectively. HDL-cholesterol was decreased significantly in both groups, but significant reduction in LDL-cholesterol was only observed in the Omacor group (5%). The TAG lowering effect seen suggests that Omacor may be a useful adjunct to lipid-lowering therapy with statins because the TAG lowering effect was greater in Omacor compared with the placebo group. In terms of inflammatory markers, supplementation with Omacor significantly decreased sE-selectin (P = 0.006), sVCAM-1 (P < 0.0001), MMP-2 (P < 0.001) and TGF- 1 (P < 0.046) by 23%, 25%, 17% and 22%, respectively. Supplementation with Omacor had no significant effects on some other plasma inflammatory markers including sICAM-1, IL-6, MMP-9, sCD40L, IP-10 and Mig even though trends toward decreases in these were observed. When the data were analysed by gender, sE-selection, sVCAM-1 and IL-6 were significantly decreased in male, but not female patients apart from sVCAM-1 which was decreased with Omacor supplementation. **Conclusion:** Moderate dose Omacor has anti-inflammatory effects in carotid endarterectomy patients, whereby a significant impact upon inflammatory markers known to be CVD risk factors was revealed especially in male patients.

1:45 EFFECT OF FISH OIL ON LIFE-THREATENING ARRHYTHMIAS IN PATIENTS WITH IMPLANTABLE CARDIOVERTER DEFIBRILLATORS – A COMBINED ANALYSIS OF 3 TRIALS

Brouwer IA^{1,2}, Raitt MH³, Dullemeijer C^{1,4}, Kraemer DF^{5,6}, Zock PL⁷, Morris C⁵, Katan MB², Connor WE⁸, Camm AJ⁹, Schouten EG^{1,4}, McNulty J¹⁰.

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Background: Evidence from randomized controlled trials on fish oil and life-threatening ventricular arrhythmia in patients with implantable cardioverter defibrillators (ICDs) is inconsistent. **Objective:** To determine effects of very-long-chain polyunsaturated omega-3 fatty acids from fish on the incidence of recurrent ventricular arrhythmia in ICD patients by combining results from three available published trials. **Procedure:** We pooled individual data from two randomized, double-blind, placebo-controlled trials (Portland and SOFA), and performed a meta-analysis on these two trials plus one other published ICD trial (FAAT). Patients at risk of arrhythmia with an ICD and prior malignant ventricular tachycardia (VT) or ventricular fibrillation (VF) randomly received either placebo or fish oil capsules in all three trials. The dose of omega-3 fatty acids from fish oil was 1.3 g/d in the Portland study (n=200), 0.9 g/d in the SOFA study (n=546) and 2.6 g/d in the FAAT study. Main outcome was spontaneous confirmed VF or VT for the pooled analysis, and confirmed VF or VT combined with death for the meta-analysis of all three studies. Treatment effects were analyzed on an intention-to-treat basis of all patients as randomized. **Results:** The pooled analysis of the Portland and SOFA trials (n=722) showed similar survival times free from appropriate ICD intervention for fish oil and placebo treatments (log-rank, p=0.79). The meta-analysis including results from the FAAT trial (n=1148) also showed no significant effect (HR=0.90; 95% CI 0.63–1.29). In subgroup analyses, patients with coronary artery disease at baseline tended to have lower risk on fish oil treatment (HR=0.79; 0.60–1.06). **Discussion:** This combined analysis does not support a protective effect of fish oil supplementation on ventricular arrhythmia in all patients with an ICD. The effects of omega-3 fish fatty acids may depend on specific underlying pathologies and electrocardiophysiological conditions, but this remains to be established.

2:00 LONG-TERM TREATMENT WITH EICOSAPENTAENOIC ACID SUPPRESSES ISCHEMIA-INDUCED VENTRICULAR FIBRILLATION IN PIGS – EVALUATION WITH MONOPHASIC ACTION POTENTIAL

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Background: Epidemiologic studies demonstrated that eicosapentaenoic acid (EPA) reduces sudden cardiac death (SCD). Previous in vitro studies demonstrated anti-thrombotic, anti-inflammatory, and endothelial effects of EPA. However, the mechanisms of its inhibitory effects on SCD in vivo remain to be fully elucidated.

Objective: We hypothesized that long-term treatment with EPA suppresses ischemia-induced ventricular fibrillation by altering electrophysiological properties.

Procedure: Male domestic pigs were treated with either a control chow or EPA (600 mg/kg/day, PO) for 3 weeks (n=8 each). After blood sampling, the animals were subjected to ischemia (90 min) of the left circumflex coronary artery with monophasic action potential (MAP) measurements.

Results: In the EPA group, the EPA/arachidonic acid ratio in red blood cell membrane and cardiac tissue was 2.32 ± 1.78 and 2.25 ± 0.44 mol%, respectively, which was well comparable with the EPA/arachidonic acid ratio measured in clinical studies. The EPA treatment decreased prevalence of VF (EPA: 1.6 ± 2.3 vs. control: 5.1 ± 4.8 [SD] times/animal, $P < 0.05$) and delivery of direct current cardioversion (EPA: 626 ± 438 vs. control: 1667 ± 1652 J/animal, $P = 0.05$), which resulted in the improvement in the mortality during ischemia (EPA: 0 vs. control: 50%, $P < 0.05$). Shortening of MAP duration (measured at 90% repolarization) was induced during ischemia in the control group ($-27.6 \pm 8.1\%$), whereas it was significantly improved in the EPA group ($-19.5 \pm 3.0\%$, $P < 0.05$).

Conclusions: The long-term treatment with EPA suppresses ventricular fibrillation and improves survival during ischemia in pigs in vivo. Attenuated heterogeneity of MAP between ischemic and non-ischemic regions induces ventricular electrical stability and may account, at least in part, for the beneficial effects of EPA noted in previous clinical study.

2:15 EPA/DHA SUPPLEMENTATION IMPROVES POSTPRANDIAL TRIGLYCERIDE RESPONSES IN HYPERCHOLESTEROLEMIC PATIENTS ON STATIN THERAPY

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Objective: The present clinical trial examined the potential for EPA/DHA to influence both fasting and postprandial triglyceride (TG) levels in patients receiving statin therapy.

Procedures: Sixteen patients (mean age, 52 ± 2 yrs; total cholesterol (TC), 4.76 ± 0.21 mmol/L) participated in a randomized, double-blinded, placebo-controlled, crossover trial. Subjects were initially assigned to either an encapsulated placebo (mixed vegetable oil) while the others received fish oil capsules (3000 mg of EPA+DHA/day) for a 21-day period. Following a 28-day washout period, each group was transferred for an additional 21 days to the alternate supplement. At days 0, 21, 49, and 70, fasting serum lipid profiles (TC, LDL-C, HDL-C, TG, TG/HDL-C ratio) and glucose were determined as well as fatty acid compositions of serum phospholipid (omega-3 biomarker). At days 21 and 70, postprandial lipid profiling was performed following the morning consumption of a standard test breakfast (high carbohydrate, high fat) of fixed nutritional composition via hourly venipuncture blood sampling for 7 hours.

Results: The fasting triglyceride levels (initially 2.74 ± 0.44 mmol/L) dropped considerably with fish oil supplementation (by 30%) and were significantly lower in the fish oil group (by 21%) after 21 days of supplementation relative to control. The corresponding TG:HDL(C) ratio significantly decreased by 31% (initially 2.90 ± 0.65) relative to baseline and by 25% relative to control. The results of the total area under the curve (AUC) for TG from the 7-hr postprandial testing after 21 days of fish-oil supplementation were significantly lower (by 18%) than the corresponding controls. Combined EPA+DHA levels were markedly higher (by 138%) in the phospholipid biomarker amongst patients receiving EPA/DHA supplementation.

Conclusion: These results indicate that chronic EPA/DHA supplementation from fish oil in conjunction with statin therapy produces a marked improvement in both fasting as well as postprandial triglyceride levels and the TG:HDL(C) ratio relative to statin use alone.

2:30 THE EFFECTS OF OMEGA-3 FATTY ACIDS AND COENZYME Q10 ON CARDIOVASCULAR RISK FACTORS IN PATIENTS WITH MILD RENAL IMPAIRMENT

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¹School of Medicine and Pharmacology, University of Western Australia and the Cardiovascular Research Centre, and ²Nephrology Unit, Royal Perth Hospital, Perth, Western Australia, Australia.

Background: Patients with mild renal impairment are at increased risk of cardiovascular disease (CVD). Potentially modifiable risk factors that contribute to the increased risk of CVD include hypertension, endothelial dysfunction, an atherogenic lipid profile, insulin resistance and a pro-inflammatory state. Irrespective of aetiology, hypertension is a major determinant of progression of renal disease and risk of end-stage renal failure. Omega-3 fatty acids protect against CVD via multiple mechanisms. There is also evidence that CoQ₁₀ (CoQ) may also improve BP, vascular function and insulin resistance.

Objective: To determine whether supplementation with omega-3 fatty acids and CoQ has independent or additive effects in improving the CV profile in patients with renal impairment.

Procedure: Patients were randomised to one of four groups supplemented daily with either Omega-3 fatty acids (4g), CoQ (200mg), both supplements, or placebo (4g olive oil), for 8 weeks.

Results: Eighty five patients aged 56.5 yrs; BMI 27.3 kg/m²; supine BP (systolic/diastolic) 125.0/72.3 mmHg; and GFR 35.8 ml/min/1.73m², were randomised. 74 completed the intervention. There were no changes in indices of renal function, total cholesterol, HDL-C, LDL-C, glucose, insulin, or hsCRP, following any of the treatments. Omega-3 fatty acids reduced triglycerides by 24% ($P < 0.001$). Omega-3 fatty acids, but not CoQ, significantly reduced 24 hr ambulatory SBP and DBP (group effect for both $P < 0.0001$) and HR (group effect $P < 0.0001$) with the greatest effects on reducing asleep BP. Main effects for omega-3 fatty acids were: 24hr BP $-3.3 / -2.9$, Awake BP $-2.5 / -2.4$, Asleep BP $-4.3 / -4.3$; 24hr HR -4.0 , Awake HR -4.4 , Asleep HR -3.5 . BP and HR at post-intervention showed significant interactions between treatments.

Conclusions: Omega-3 fatty acids have significant effects to reduce BP and HR in patients with mild renal impairment. These results confirm the previously documented antihypertensive and cardioprotective effects of omega-3 fatty acids.

2:45 DOSE-DEPENDENT EFFECTS OF DOCOSAHEXAENOIC ACID-RICH FISH OIL ON CARDIOVASCULAR AND INFLAMMATORY BIOMARKERS

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Background: Consumption of long-chain n-3 PUFAs (LC n-3 PUFAs) have cardioprotective and anti-inflammatory effects although the dose required for different treatments has not been well established. We have recently demonstrated a dose response relationship between consumption of DHA rich tuna oil (Hi-DHA) and reductions in plasma triglycerides (Milte et al, Br J Nutr. 2007 Oct 31;1-6).

Objective: To see whether similar relationships exist for other cardiovascular and inflammatory biomarkers.

Procedures: A total of 67 subjects (36 male, 31 female, mean age 53 years) with BMI > 25 kg/m² completed a randomized, double-blind, placebo-controlled intervention trial. Subjects took 2, 4 or 6 g/d of Hi-DHA (26% DHA, 6% EPA) or a placebo (Sunola oil). Assessments were made at baseline and after 6 and 12 weeks for blood pressure (BP), arterial compliance (AC), flow mediated dilatation (FMD), heart rate variability (HRV), high sensitivity C-reactive protein (hs-CRP) in plasma and the production of tumor necrosis factor alpha (TNF- α), interleukin 1 (IL-1) and 6 (IL-6) from stimulated mononuclear leukocytes.

Results: Erythrocyte DHA content increased in proportion to the dose of DHA consumed ($r = 0.72$, $P < 0.001$). There was a reduction in resting heart rate with increased consumption of Hi-DHA at both 6 weeks ($r = -0.38$, $P < 0.05$) and 12 weeks ($r = -0.37$, $P < 0.05$). Moreover, the high/low frequency HRV ratio increased in proportion to Hi-DHA intake at both 6 weeks ($r = -0.58$, $P < 0.001$) and 12 weeks ($r = -0.40$, $P < 0.01$). There were no significant changes in BP, AC, FMD, hs-CRP or production of TNF- α , IL-1 β or IL-6.

Conclusion: The dose-response relationships between fish oil consumption and improvements in HR and HRV support a role for LC n-3 PUFA in reducing the risk of sudden cardiac death.

1:30 FUNCTION OF THE HOMODIMERIC STRUCTURES OF CYCLOOXYGENASES

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Prostaglandin endoperoxide H synthases-1 and -2 (PGHS-1 and -2), also known as cyclooxygenases-1 and -2 (COX-1 and -2) catalyze the committed step in the synthesis of prostaglandins (PGs) and thromboxanes (TXs) from arachidonic acid (AA) and eicosapentaenoic acid (EPA). Both enzymes are homodimers. PGHS-1 and -2 have similar kinetic constants (V_{MAX} , K_M) when tested with AA. When tested under optimal conditions with saturating levels of an hydroperoxide, PGHS-1 oxygenates EPA with a V_{MAX} that is about 10% that of AA and a K_M that is similar to that of AA. Predictably, EPA is an efficient inhibitor of AA oxygenation by PGHS-1. PGHS-2 oxygenates EPA with a K_M that is similar to that of AA and a V_{MAX} that is about 30% that of AA. However, when PGHS-2 is tested with AA and EPA together, there is little inhibition of AA oxygenation and very little oxygenation of EPA. Thus, PGHS-2 exhibits an unexpected preference for AA in the presence of EPA. Both PGHSs are homodimers that exhibit half of sites COX activity with AA. There is only one high affinity binding site per dimer for COX inhibitors such as ibuprofen. However, the oxygenation of AA by PGHS-2 appears to involve the binding of AA to both COX sites of a dimer. One site acts allosterically to alter activity in the partner, catalytic site. Oxygenation of AA by PGHS-2 is stimulated 20–30% in a saturable manner by certain fatty acids that are not substrates including palmitic acid and 11*cis*-eicosaenoic acid (20:1 ω 9). Evidence that 11–20:1 ω 9 functions allosterically at one COX site to augment AA oxygenation at the second site comes from examining a cysteine-less C313S/C540S PGHS-2 (DC-PGHS-2) mutant into which cysteines were introduced at Pro127 and Ser541 at the dimer interface. Cross-linking between Cys127 and Cys541 of partner monomers of P127C/S541C DC-PGHS-2 occurs when the protein is treated with an oxidant. Cross-linking is prevented by AA but not by 20:1 ω 9; however, 20:1 ω 9 interferes with the ability of AA to prevent cross-linking. The simplest explanation for these findings is that AA is oxygenated at the COX site of one PGHS-2 monomer while 20:1 ω 9 is bound to the COX site of the partner monomer. In the case of PGHS-2 and AA plus EPA, we suggest that the binding of either fatty acid to the allosteric site promotes the use of AA in the catalytic site. In general with PGHS-2, common fatty acids either stimulate or slightly inhibit AA oxygenation at concentrations up to 10 fold that of AA. In contrast, PGHS-1 mediated oxygenation of AA is more susceptible to inhibition by common fatty acids. These different behaviors of PGHS-1 vs. PGHS-2 may contribute to the inability of PGHS-1 to oxygenate AA when it represents a relatively small fraction of the available fatty acid pool during so-called “late phase” prostaglandin synthesis in cells stimulated with mitogens or tumor promoters. Supported by NIH GM68848.

1:45 INHIBITORY EFFECTS OF Ω -3 FATTY-ACID EPOXIDES ON CARDIOMYOCYTE HYPERTROPHY

Chen J, Shearer GC, Harris WS

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Background: Despite the many beneficial effects of omega-3 fatty-acids (ω -3 FAs), little is known of the underlying biochemical mechanisms. Human cytochrome p450s produce epoxides *in vitro* from arachidonic acid (AA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), and if these have different bioactivities then these epoxide isomers could play a role explaining the ω -3 FA effects *in vivo*. AA-epoxides, epoxyeicosatrienoic acids (EETs), reduce myocardial hypertrophy *in vitro* and *in vivo*; however, the effects of the ω -3 epoxides are unknown.

Objective: This study sought to compare the effects of ω -3 epoxide analogs to EETs on an established biological model, cardiomyocyte hypertrophy.

Procedure: Cardiac myocytes were isolated from Sprague-Dawley neonatal rat hearts. Hypertrophy was initiated with 100 μ M phenylephrine (PE) and measured by 3H-leucine incorporation. The effects of the AA-derived 14(15)-EET was compared with EPA derivatives 14(15)- and 17(18)-epoxyeicosatetraenoic acids [EEQ] and with DHA derivatives 16(17)- and 19(20)-epoxydocosapentaenoic acid [EDP] at 1 μ M.

Results: PE induced almost 2-fold rate of ³H-leucine incorporation relative to vehicle-treated (control) cardiomyocytes (100 \pm 15 vs 181 \pm 18% control incorporation, P< 0.001). At 1 μ M, there was no effect of the 14(15)-EET on cardiomyocyte hypertrophy (186 \pm 28%). PE induced incorporation was lower in the presence of the EPA analog 14(15)-EEQ (152 \pm 27%, P<0.005) compared with EET, but there was no effect of the 16(17)-EDP (173 \pm 38%). In the case of ω -3 terminal epoxides, both inhibited hypertrophy: 17(18)-EEQ (120 \pm 15%, P<0.001) and 19(20)-EDP (136 \pm 33%, P<0.002).

Conclusion: These results demonstrate that certain p450-derived epoxide regioisomers from EPA and from DHA, are more potent inhibitors of cardiomyocyte hypertrophy than the AA-derived epoxides. Therefore, ω -3-derived epoxides may explain part of the cardiovascular benefits of fish oil

2:00 LIPIDOMIC ANALYSIS REVEALS CANDIDATE MEDIATORS OF THE UVR-INDUCED INFLAMMATION IN HUMAN SKINNicolaou A¹, Masoodi M¹, Haylett A³, Brownrigg M³, Gledhill K², Tobin DJ², Thody AJ⁴, & Rhodes LE³

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Objective: Sunburn is an acute inflammatory process, with vasodilatation and leucocytic infiltration occurring as central features. Polyunsaturated fatty acid (PUFA)-derived mediators may play pivotal roles in this process, following UV-induced hydrolysis of membrane lipids. We investigate the profile of pro- and anti-inflammatory eicosanoids produced during the progress of UV-induced erythema, aiming to assess their contribution and identify biomarkers characteristic of the underlying biochemical mechanisms.

Procedure: 22 healthy humans (mean age 40 yrs, skin type I-IV) were irradiated with 4 minimal erythmal doses (MED) of UVR (UV6 lamps, 290–400 nm) on buttock skin and the erythema quantified over 72h. Suction blisters were raised at 4, 18, 24, 48 and 72h post-UVR, and from unirradiated skin. Suction blister fluid was analysed by LC/ESI-MS/MS.

Results: Erythema peaked at 24 h post-UV and was maintained to 72 h. Vasoactive prostaglandins PGE₂ and PGF_{2 α} were significantly raised in the first 24 and 18 h, respectively, while PGE₃ was significantly raised to 48 h. The potent neutrophil chemotactin 12-hydroxy-eicosatetraenoic acid (12-HETE) showed significant elevation at all time points from 18–72 h. Similarly, neutrophil chemotactin 8-HETE was elevated at 24–72 h post UVR, while the neutrophil chemotactin 11-HETE was significantly raised from 4 h onwards. In contrast, neutrophil chemotactin leukotriene B₄ (LTB₄) was not detected. The potent anti-inflammatory mediator 15-HETE, reported to inhibit synthesis of 12-HETE and LTB₄, was increased at 24–72h, peaking at 72h.

Conclusion: Our results suggest that the combined influence of a series of UVR-induced prostaglandins may contribute to vasodilatation during the sunburn response. Furthermore, temporal profiles of eicosanoids with pro- and/or anti-inflammatory activities indicate a differential regulation of the early and late stages of the inflammatory response supporting 12-HETE, 11-HETE and 8-HETE, rather than LTB₄, as candidate mediators of UVR-induced neutrophil chemotaxis, while the anti-inflammatory metabolite 15-HETE may provide regulation of the inflammation.

(Project supported by the Wellcome Trust).

2:15 DIETARY CONJUGATED LINOLEIC ACID (CLA) REDUCES RENAL PROSTANOID PRODUCTION VIA SELECTIVE CHANGES IN CYCLOOXYGENASE (COX) ISOFORMS IN CHRONIC KIDNEY DISEASE

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Background: Conjugated linoleic acid (CLA) has been shown to have a plethora of physiologic effects, including effects on inflammation, obesity, carcinogenesis, hyperinsulinemia, hyperglycemia, hepatic steatosis, dyslipidemia and blood pressure. However, the effects across species are variable and the mechanism by which CLA mediates these effects remains elusive.

Objective: The objective of this study was to determine the effects of dietary CLA on prostanoids and cyclooxygenase (COX) enzymes in the kidney.

Procedures: A model of chronic kidney disease in which dietary CLA retards the progression of renal disease was used. Normal and diseased rats were given diets supplemented without and with CLA for 8 weeks, after which kidneys were analyzed.

Results: Dietary CLA reduced the endogenous and steady state renal prostanoid levels by 32–53% in both normal kidneys and in diseased kidneys (in which prostanoid levels were elevated compared to normal kidneys). COX-1 level and activity was induced by renal disease, resulting in increased production of thromboxane B₂ (TXB₂) and 6-keto-prostaglandin F_{1 α} (6-keto-PGF_{1 α} , stable metabolite of PGI₂), but not prostaglandin E₂ (PGE₂). Dietary CLA had no significant effect on either the level or activity of the COX-1 isoform. On the other hand, COX-2 activity increased the levels of all three prostanoids and dietary CLA resulted in ~27–57% lower COX-2 activities in normal and diseased kidneys. The elevated COX-2 activity in disease was accompanied by ~90% lower protein level of this isoform, consistent with previous findings. Dietary CLA partially attenuated this disease lowering effect on COX-2 protein level.

Conclusions: The beneficial effect of dietary CLA in renal disease may be mediated by a reduction in prostanoid production via selective effects on COX isoforms. The fact that dietary CLA affected both normal and diseased kidneys indicates that the CLA effect on prostanoids is a direct effect of CLA on kidney prostanoids.

2:30 DOCOSAHEXAENOIC ACID PREVENTS HIPPOCAMPAL NEURONAL APOPTOSIS: IMPLICATION OF SPECIFIC LOCALIZATION OF PHOSPHATIDYLSERINE

Frances Calderon and Hee-Yong Kim

Laboratory of Molecular Signaling, National Institute of Alcohol Abuse and Alcoholism, NIH, Bethesda, MD

Background: Docosahexaenoic acid (DHA) has been shown to prevent neuronal apoptosis through facilitating Akt translocation to plasma membrane. Although phosphatidylserine (PS) accumulation by DHA is a key event in this protection, effects of DHA on the apoptotic progression or intracellular distribution of PS remain largely unknown. As Akt activation is triggered by PIP3 generated at the plasma membrane, specific localization of PS at the plasma membrane may assist Akt activation and influence the apoptotic progression, exerting protective effect.

Objective: To investigate the effect of DHA on hippocampal neuronal apoptosis and to characterize PS intracellular localization.

Procedures: Cultures of embryonic neurons were prepared from E18 rat hippocampus and grown in chemically defined medium supplemented with or without 2 μ M DHA, oleic (OA) or arachidonic acid (AA) for 4 days. After overnight trophic factor deprivation, apoptosis was evaluated by TUNEL assay. The progression of apoptotic cell death was evaluated by immunocytochemistry. For PS localization, hippocampal neurons and Neuro-2A cells were transfected with GFP-AnnexinV, a specific PS-binding protein, using lipofectamine 2000. The intracellular distribution of GFP-Annexin was recorded after treatment with 2 μ M ionomycin by an Olympus IX81 inverted microscope. Acquisition, image processing and analyses were performed with Metamorph software.

Results: Basal apoptosis evaluated by immunostaining and TUNEL assay indicated that DHA decreased apoptosis most significantly (by 50%) in comparison to other fatty acids. Caspase-3 activation preceded PS externalization which was followed by nuclear condensation regardless of DHA supplementation. Upon stimulation of Neuro 2A and hippocampal neurons expressing GFP-AnnexinV with calcium ionophore, GFP-AnnexinV translocated to plasma membrane, nuclear envelope and recycling endosomes, indicating specific intracellular localization of PS in these structures.

Conclusion: We demonstrate that DHA has a protective role in hippocampal apoptosis without affecting progression of apoptosis, by accumulating PS specifically in the inner leaflet of the plasma membrane and in the nuclear envelope.

2:45 COMMON VARIANTS IN GENES ENCODING ELEMENTS OF THE PHOSPHATIDYLINOSITOL SIGNALING SYSTEM ARE JOINTLY ASSOCIATED WITH ADVANCED AMD

SanGiovanni JP, Agrón E, Chew EY. National Eye Institute, Bethesda, MD.

Background: Sequence variants in pleckstrin homology (PH) domains are associated with age-related macular degeneration (AMD), the leading cause of blindness in elderly people. Docosahexaenoic acid (DHA) alters actions of phosphatidylinositol signaling system partially via influence on PH binding domains in the Akt/PI3K pathway.

Purpose: To determine if variants in genes encoding elements of inositol-based pathways are jointly associated with risk of developing advanced AMD.

Methods: We used the Lipid Metabolites and Pathways Strategy (LIPIDMAPS) proteomic database to extract positional coordinates of 2,232 genes encoding 2,919 structures impacted by or impacting lipid-associated enzymatic activity, metabolic processes, and signaling pathways. We applied these coordinates to filter 11,140 LIPIDMAPS-related sequence variants from a 100K microarray tested in our 12-year longitudinal natural history study on AMD. Professional graders ascertained AMD from annual stereoscopic fundus photographs with a validated method. Gene variants with at least 95% complete data, in Hardy-Weinberg equilibrium, and associated with advanced AMD at P -values < 0.005 in age-, sex-, and smoking-adjusted logistic regression models were entered into joint action models and reduced to parsimony through a stepwise selection procedure.

Results: 2,274 inositol-related variants exist on our microarray. Of these, 28 with P -values < 0.005 met criteria for entry into joint action models. Eleven variants persisted in the final model as independent predictors – many of these are associated with PH domain binding substrates. Our predictive model identified 7-in-10 people with advanced AMD, solely on the basis of these 11 SNPs. Relative to people with a predicted probability of advanced AMD < 0.25 , the likelihood of having AMD among people with probabilities of > 0.75 was increased 99-fold (OR=99.2, 95%CI=22.3--440.9; $P=1.0 \times 10^{-17}$). Comparison of our findings to P -value distributions of 1500 analyses on randomly selected sets of SNPs indicated results were not likely due to random sampling error; the lowest P -value of the simulations was $> 1.2 \times 10^{-9}$.

Conclusion: These novel findings support further examination on joint action of inositol-related gene products as they relate to DHA-influenced mechanisms implicated in AMD pathogenesis.

1:30 CRITICAL FLUCTUATIONS IN PLASMA MEMBRANE VESICLES

Veatch SL, Holowka D, Baird B

Cornell University Department of Chemistry and Chemical Biology, Ithaca, NY 14853

Critical behavior is observed in giant plasma membrane vesicles (GPMVs) that are isolated directly from living cells. GPMVs contain two liquid phases at low temperatures, one liquid phase at high temperatures, and exhibit transition temperatures in the range of 15 to 25°C. In the two-phase region, line tensions linearly approach zero as temperature is increased to the transition. In the one-phase region, micron-scale composition fluctuations occur and become increasingly large and long-lived as temperature is decreased to the transition. These results indicate proximity to a critical point and are quantitatively consistent with established theory. Our observations of robust critical fluctuations suggest that the compositions of mammalian plasma membranes are tuned to reside near a miscibility critical point, and that heterogeneity corresponding to < 50 nm-sized compositional fluctuations are present in GPMV membranes at physiological temperatures. Our results provide new insights for plasma membrane heterogeneity that may be related to functional lipid raft domains in live cells.

2:00 PUFA DOMAINS: AN EXTREME EXAMPLE OF A NON-RAFT MEMBRANE DOMAIN

Wassall, SR

Department of Physics, Indiana University Purdue University Indianapolis, Indianapolis, USA

Polyunsaturated fatty acids (PUFA) are structurally distinguished from less unsaturated fatty acids by the presence of a recurring =CH-CH₂-CH= motif that produces an extremely flexible chain rapidly isomerizing through conformational states. The most highly unsaturated case in point is docosahexaenoic acid (DHA) with 6 double bonds. This talk will focus on the profound impact that the high disorder of DHA has on the interaction of cholesterol with the membrane phospholipids into which the PUFA incorporates. Results obtained with model membranes using an array of biophysical techniques that include solid state ²H NMR, detergent extraction, calorimetry and neutron diffraction will be presented. They demonstrate DHA and the sterol possess a mutual aversion that promotes the lateral segregation of DHA-containing phospholipids into liquid disordered (l_d) domains away from cholesterol. These domains are compositionally and organizationally the opposite of lipid rafts that are liquid ordered (l_o) domains enriched in predominantly saturated sphingolipids “glued” together by cholesterol. Rafts have recently attracted a great deal of attention because they are believed to serve as the platform for signaling proteins. We hypothesize that the coexistence of DHA-rich domains and lipid rafts in the plasma membrane is responsible, in part, for the diverse range of health benefits associated with consuming DHA in fish oils. According to our model changes in the conformation of signaling proteins when they move between these domains of greatly differing order modulate cellular activity. A novel paradigm that we now introduce into this model is that α -tocopherol, the major component of vitamin E, co-localizes in PUFA-rich domains to both confer structural stability upon the domain and prevent peroxidation. Preliminary studies will be described that demonstrate α -tocopherol, unlike cholesterol, preferentially interacts with PUFA-containing phospholipids.

2:15 OF DOMAINS AND BOUNDARIES: PHASE BEHAVIOR OF AMPHIPHILE BILAYER MEMBRANES

Tobias Baumgart, University of Pennsylvania, Chemistry Department, Philadelphia, PA, USA.

Lipid bilayer membranes of biological cells are likely to be non-random mixtures of membrane components. Lateral membrane domain formation is thought to be involved in essential functions of the membrane, including signaling, sorting, and trafficking. In order to elucidate the physical, mechanical, and physico-chemical basis and consequences of membrane heterogeneity, model systems have been developed. These typically consist of ternary lipid mixtures that under suitable conditions segregate into two fluid phases, a liquid ordered, and a liquid disordered phase. Of particular interest to us are the boundaries of domains in membranes with phase coexistence due to interfacial tension (line tension) at fluid phase boundaries. We find that this line tension couples to three dimensional membrane shape, modulating biologically relevant phenomena, including vesicle budding and fission. Line tension is also a control parameter regulating domain size and growth kinetics. We are therefore developing methods to precisely measure line tension as a function of membrane composition, using micropipette aspiration of giant vesicles, as well as capillary wave spectroscopy of thermal boundary fluctuations. We demonstrate that these two complementary techniques probe different line tension regimes. Furthermore, we are developing experimental methods to investigate the partitioning of both lipids and proteins among curvature gradients. We find that lipids are not detectably sorted among membrane with steep curvature difference, whereas peripherally membrane binding proteins are efficiently sorted. We discuss the biological relevance of our findings.

2:30 ORDERED DOMAINS IN CELLULAR AND VIRAL MEMBRANES

Polozov IV¹, Gawrisch K², and Zimmerberg J¹.

¹LCMB, NICHD and ²LMBB, NIAAA, National Institutes of Health, Bethesda, MD, USA.

Detergent resistant lipid rafts previously found in biological membranes lead to the hypothesis of ordered membrane domain as a functional biological unit. However there was a lack of direct, detergent and probe independent spectroscopic determination of ordered domains in intact biomembranes. We have recently shown that proton magic angle spinning (MAS) NMR is capable of characterizing disordered and ordered domains both in model and biological membranes. We used this novel spectroscopic approach to characterize domain organization in such diverse membranes as bovine photoreceptor rod outer segment (ROS) discs membranes, red blood cell membranes, allantoic membranes from embryonated chicken eggs and egg-grown influenza virus envelopes. With the exception of ROS discs at 40C the studied membranes are almost completely in the ordered state. At room temperature significant fractions of ordered domains exist in allantoic membranes and viral membranes where minor fractions of ordered lipids persist up to the physiological temperatures. Comparison of intact membranes and extracted lipids liposomes suggests that fraction of ordered domains is largely determined by membrane lipid composition and is only weakly modulated by membrane proteins. Cholesterol loading and depletion experiments reveal that cholesterol does change the nature of ordered domains but does not eliminate them. In the absence of cholesterol only solid ordered gel domains are observed. However, gel domains in viral membranes were observed despite the high cholesterol content. Diffusion measurements and fluorescence microscopy of viral lipid liposomes independently confirmed the existence of gel phase domains. Thus the existence of ordered regions of lipids in biological membranes is now demonstrated. Lipid ordering may contribute to viral stability at lower temperatures, recently found to be critical for airborne transmission

2:45 CONTROLLING MEMBRANE ORGANIZATION AND SHAPE: EFFECTS OF IONS, PH AND COMPOSITION

Hovis, JS

Purdue University, West Lafayette, IN, USA

Lipid bilayers are both passive and active participants in cellular function. In cells assessing the role of lipids in function is complicated, and often impossible to clearly elucidate. Over several decades there has been a significant amount of research using model systems to investigate membrane properties. These studies have the advantage that properties measured can be clearly identified as lipid properties but have the disadvantage in taking lipids out of a complex, fluctuating environment. Lipids in model systems are almost without exception studied in a passive fashion – What are their properties? In this talk we will show results from experiments examining lipids in an active fashion – What can we make them do? It will be shown that we can make them: (i) reorganize (clustering important molecules); (ii) bend (crucial for fusion/budding and organelle function); (iii) expand/contract (turning on/off integral membrane proteins).

8:15 INVIVO BRAIN ARACHIDONIC ACID METABOLISM AS A TARGET OF DRUGS, DIET AND DISEASE

Stanley I. Rapoport

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Arachidonic acid (AA, 20:4n-6) plays multiple roles in the central nervous system. It acts as a second messenger during neurotransmission and thus influences cognition and behavior, and it contributes to cell death and dysfunction when released from membrane phospholipids at high concentrations. Its participation in neurotransmission arises because AA-selective Ca^{2+} -dependent cytosolic phospholipase A_2 (cPLA₂) is coupled to a number of post-synaptic neuroreceptor subtypes. Thus, administration to unanesthetized rats of agonists to cholinergic, dopaminergic, serotonergic or NMDA receptors gives robust AA signals in brain that can be prevented by appropriate antagonists. This signaling can be imaged by injecting radiolabeled AA intravenously, then using quantitative autoradiography to determine regional AA incorporation coefficients k^* (brain radioactivity/integrated plasma radioactivity). k^* represents the AA signal because the AA that is released from synaptic membrane phospholipid by cPLA₂ activation and that then is lost by metabolism is rapidly and *completely* replaced by unesterified AA from plasma. With our neuroimaging method, we reported that mood stabilizers that are approved for treating mania in bipolar disorder – lithium, valproic acid and carbamazepine – when given chronically to rats modify neuroreceptor-mediated AA signaling in a way that would correct the neurotransmission imbalance hypothesized to account for bipolar disorder symptoms. Their effects are consistent with their ability to reduce AA turnover in rat brain phospholipids, as well as brain activities of cPLA₂, acyl-CoA synthetase and/or cyclooxygenase (COX) enzymes. Because cPLA₂, secretory sPLA₂ and COX-2 are over-expressed in post-mortem bipolar disorder brain, the mood stabilizers may be therapeutic by tempering an upregulated brain AA cascade in the disease. AA turnover in brain membrane phospholipid and cPLA₂ and COX activities are increased in animal models of neuroinflammation and excitotoxicity, as are incorporation coefficients k^* for AA. k^* , measured with positron emission tomography (PET) and [¹¹C]AA, also is elevated in patients with Alzheimer disease, where neuroinflammation and excitotoxicity play a role. Our studies (see above) predict that k^* also would be upregulated in bipolar mania. Additionally, studies in rats indicate that dietary n-3 PUFA supplementation could be therapeutic in bipolar disorder and/or Alzheimer disease by decreasing brain expression of cPLA₂, sPLA₂ and COX-2.

8:15 A NEW UNDERSTANDING OF NEURODEGENERATIVE DISEASES AND THE BIOACTIVITY OF OMEGA-3 FATTY ACIDS.

Nicolas G. Bazan

LSU Neuroscience Center of Excellence, Louisiana State University Health Sciences Center, New Orleans, Louisiana, USA.

The neuroprotective properties of omega-3 fatty acids have been demonstrated over the years by several laboratories. The identification of neuroprotectin D1 (NPD1), a biosynthetic product of docosahexaenoic acid (DHA), in brain and retina, as well as the characterization of its bioactivity, is generating a renewed interest in omega-3 fatty acid's functional role and physiopathological significance.

Hippocampal CA1 regions from Alzheimer's disease (AD) patients (rapidly sampled) show a major reduction in NPD1. Based on this finding, we developed a human brain cell aging model to further study the significance of NPD1. The aging of human neural progenitor cells (HN cells, neurons and glia) in primary culture during 8 weeks is accompanied by an 8-fold enhanced synthesis and release of Aβ40 and Aβ42 peptides, which resembles Aβ deposition during brain aging and in AD. IL-1β stimulates gamma-secretase-mediated cleavage of BAPP into Aβ peptides. Conversely, DHA suppresses both Aβ40 and Aβ42 peptide release with concomitant NPD1 synthesis. Moreover, NPD1 inhibits Aβ42-induced apoptosis in HN cells. Therefore, DHA neuroprotection in aging human brain cells involves NPD1 synthesis.

Pro- and anti-apoptotic proteins are modulators proximal to mitochondria and cell damage. Proapoptotic Bik and Bax were enhanced by Aβ42, but not by DHA or NPD1, whereas Bcl-2, Bcl-xl, and Bfl-1(A1) were increased in the presence of DHA. NPD1, on the other hand, promoted a much larger increase in antiapoptotic Bcl-2 proteins. Bfl-1(A1) increased almost 6-fold. These modulatory actions of NPD1 may play critical roles in the survival of aged and terminally differentiated cells and break the mechanistic link between inflammatory signaling and apoptosis. In fact, NPD1 also induces the antiapoptotic Bcl-2 family proteins Bcl-2 and Bcl-xl in oxidatively challenged human retinal pigment epithelial cells and promotes cytoprotection. Thus the interplay of DHA-derived neuroprotective signaling aims to counteract proinflammatory, cell-damaging events triggered by multiple, converging cytokine and amyloid peptide factors in AD.

In experimental stroke, endogenous NPD1 synthesis is upregulated, and the infusion of the lipid mediator into the brain under these conditions revealed neuroprotective bioactivity of NPD1. Furthermore, when DHA was administered i.v. after middle-cerebral artery occlusion, protection was concomitant with NPD1 synthesis on the ipsilateral brain side. In the retinal pigment epithelial (RPE) cells, NPD1 synthesis induction results in cytoprotection against oxidative stress. The bispyridinium bisretinoid, A2E (a byproduct of phototransduction that becomes toxic when it accumulates in RPE cells during aging or in age-related macular degeneration), when added to RPE cells, was found to display attenuated cytotoxicity in the presence of NPD1. Integrity of RPE cells is necessary for photoreceptor cell survival and vision.

Neurotrophins, particularly pigment epithelium-derived factor (PEDF), induce NPD1 synthesis and its polarized apical secretion, implying paracrine and autocrine bioactivity of this lipid mediator. The signaling activated by PEDF and DHA uncovered synergistic cytoprotection, with concomitant NPD1 synthesis, when cells were challenged with oxidative stress and induction of anti-apoptotic protein expression and decreased pro-apoptotic Bcl-2 protein expression and caspase 3 activation during oxidative stress. Thus, our results identify neurotrophins as regulators of NPD1 biosynthesis and of its polarized apical efflux from RPE cells.

Neural mechanisms leading toward NPD1 generation from DHA thereby appear to redirect cellular fate toward successful preservation of RPE-photoreceptor cell integrity, and brain cell aging. The Bcl-2 pro- and anti-apoptotic gene families, sAPP alpha (and/or other neurotrophins) and NPD1, lie along a cell fate-regulatory pathway whose component members are highly interactive, that function cooperatively modulating inflammation, sustaining homeostasis and promoting brain and retina cell survival. Agonists of NPD1 biosynthesis, NPD1 analogs or dietary regimens may be useful for exploring new preventive/therapeutic strategies for neuroprotection and neurorepair in neurodegenerative diseases.

3:45 FATS FOR YOUR GENESOrdovas JM,

JM-USDA Human Nutrition Research Center on Aging at Tufts University, Boston, MA USA

Objective: Over the last decade, 'omics' technologies have been heralded as 'dream toolboxes' that will make revolutionary changes in disease prevention and treatment possible. However, these expectations have yet to be fulfilled. The objective is to provide the current evidence in support to the notion of gene-environment interaction coming primarily from studies involving dietary fats, cardiovascular disease and its multiple risk factors, namely plasma lipid measures, glucose levels, body weight, blood pressure and inflammation traits.

Procedures: During the last two decades, the accumulating evidence shows that common variants at candidate genes for lipid metabolism (i.e., LIPC, APOE, APOA5), inflammation (i.e., IL1, CRP) and obesity (i.e., PLIN, ACDC) are associated with plasma levels of classical and new biomarkers of metabolic syndrome and cardiovascular disease risk. Moreover, the data support significant interactions between these genes and the responses of these biomarkers to dietary fats, but also to smoking, alcohol and physical activity. Major contributors to this effort have been a series of large population studies (i.e., the Framingham Heart Study and the Singapore National Health Survey) containing phenotype-rich databases and dietary information to which genetic data have been added using the candidate gene approach.

Results: Whereas this approach has provided strong evidence supporting the concept of gene-diet interactions modulating cardiovascular risk factors, the strength of the effects and the replication among studies is still limited. Current population studies are starting to incorporate experimental approaches (i.e., increased coverage of the genetic variation at each locus and wide genome associations) that could provide more solid and comprehensive results. However, other limitations, such as the size of the populations required to examine higher level interactions (gene-gene-diet-behavioral factors) are still major obstacles to the translation of this knowledge into practical public health applications. Moreover, when it comes to the interpretation of observational studies, the current quality of the dietary and behavioral information represents an additional and important limitation.

Conclusions: There are imperative quantitative and qualitative needs that can be fulfilled only through the collaboration of experts in the different fields involved spanning from basic scientists to computational biologists and behavioral scientists. It should be underscored that any initial finding from observational studies needs to be replicated in other populations and further verified using controlled interventional studies. Once more experience is gained from patients and/or individuals at high risk, these approaches could be applied towards primary prevention and treatment of CVD and other complex diseases.

3:45 IMPROVING HUMAN HEALTH THROUGH LIPID PROFILING: INTEGRATING THE ANALYTICS, DATABASES AND KNOWLEDGE NECESSARY TO ENABLE PERSONALIZED MEDICINE AND NUTRITION

Steven M. Watkins, Ph.D.

Background: Lipids and lipid metabolism are at the heart of some of the most devastating diseases facing Western society including diabetes, cardiovascular disease and obesity. Dysregulation of lipid metabolism is caused by factors as diverse as genotype, environment, nutrition and drug treatment. These factors all ultimately exert their influence, however, on the composition and concentration of lipid metabolite pools. Despite the critical nature of lipids, technologies for assessing metabolic health through careful measurement of lipid metabolite have lagged behind those developed for genes and other biomolecules.

Objective: To review recent progress in the analytical and statistical technologies necessary to create an integrated knowledge of lipids in cardio-metabolic disease.

Procedure and Results: Recent advances in lipid and other metabolic profiling technologies are beginning to generate biomarkers and diagnostics useful for the management of cardio-metabolic disease. This seminar will provide an overview of the analytical platforms, IT and databasing systems, biostatistics and diagnostic development programs necessary to convert lipid data into actionable diagnostics. Results from clinical trials seeking mechanistic biomarkers for metabolic disorders including fatty liver and weight gain will be presented.

Conclusion: The technology enabling the discovery and development of lipid markers for managing metabolic and cardiovascular disease exists and diagnostics developed from these technologies are moving towards clinical use. Careful measurement of lipid metabolism will enable personalized management of lipid-driven metabolic disorders.

10:30 EFFECT OF DOCOSAHEXAENOIC ACID ON AXONAL DAMAGE AFTER SPINAL CORD INJURY

Ward RE, Huang W, Priestley JV and Michael-Titus AT

Neuroscience Centre, Institute of Cell and Molecular Science, Barts and The London School of Medicine and Dentistry, London, UK

Background: We have previously demonstrated that docosahexaenoic acid (DHA) increases neuronal and oligodendrocyte survival in a rat compression model of spinal cord injury (SCI) (Huang *et al.*, 2007).

Objective: One of the major factors that contribute to the loss of neurological function following SCI is the axonal pathology (Fehlings and Tator, 1995). In the present study we have focused on the effects of DHA on axonal and dendritic damage following SCI.

Methods: Adult rats received a spinal cord compression injury at thoracic level T12. 30 minutes following compression, rats were intravenously given either saline or DHA (250 nmol/kg). After the DHA injection, one group of rats was placed on a DHA enriched diet (400 mg/kg/day) whilst one group received normal chow. 1 or 6 weeks post-injury, animals were perfused and spinal cord sections were processed for immunohistochemistry using the following primary antisera: β -amyloid precursor protein (β -APP) for axonal dysfunction, neurofilament-200 (NF-200) and SMI32 for global and non-phosphorylated neurofilament, respectively, microtubule associated protein-2 (MAP-2) for dendrites and myelin basic protein (MBP). In addition, the spinal cords of non-treated animals were processed for electron microscopy (EM) between 1 day and 6 weeks post-injury. Data was expressed as means \pm S.E.M. and analysed with one way ANOVA and post-hoc pairwise comparisons using Bonferroni's test.

Results: β -APP-positive axons were scarce in non-injured animals but prominent in the white matter tracts of saline-treated injured animals. At 1 week, in both groups of DHA treated animals, the β -APP-positive axon number in the dorsal columns was significantly reduced vs. saline-treated injured animals. By 6 weeks, a significant reduction in β -APP immunoreactivity was also observed in the corticospinal tract and ventrolateral white matter. The number of non phosphorylated neurofilament-positive axons was reduced in injured animals compared to controls. At 1 week, this reduction was significantly reversed in the DHA injection group in the ventrolateral white matter. Similar results were seen in the ventral white matter. The effect of both DHA treatments on the reduction in the number of myelin rings and myelinated neurofilament-positive axons that occurs 1 week post injury was heterogeneous and requires further evaluation. However, EM revealed a substantial loss of myelinated axons in un-treated animals by 1 week post-injury. While neither DHA treatment protected against the injury-induced loss of dendritic MAP-2, DHA injection and diet significantly prevented loss of cell body MAP 2 in the dorsal horn and ventral horn.

Conclusions: These results indicate that DHA has major neuroprotective effects against the axonal and dendritic damage caused by SCI. Fehlings M.G. and Tator C.H. (1995). *Exp. Neurol.* 132: 220–228. Huang W. *et al.*, (2007). *Brain.* 11: 3004–19.

10:45 OMEGA-3 FATTY ACID SUPPLEMENTATION REDUCES THE EXTENT OF AXON DAMAGE AFTER BRAIN TRAUMA.Bailes J¹, Mills J¹, Wilson J¹, Sedney, C¹, Hutchins H2, & Sears B2. ¹University of West Virginia Medical School, Morgantown WV, USA; ²Inflammation Research Foundation, Marblehead, MA, USA.

Background: Acute brain trauma induces axon damage that can be quantified by the increased levels of amyloid precursor protein (APP).

Objective: This study sought to explore the ability of the dose response effect of different levels of omega-3 fatty acid supplementation to diminish post-traumatic damage in the brains of rats following an acute brain injury.

Procedures: Male Sprague-Dawley rats were subjected to an impact acceleration injury in which a weight is dropped onto a “brass disc” affixed to the skull. This produces a reliable and consistent level of injured axons in the white matter of the brain. After the injury, two groups of animals subjected to the brain injury were fed either 10mg/kg/day or 40 mg/kg/day of a fish concentrate containing 60% EPA and DHA (2:1 ratio of EPA/DHA) for 30 days to be compared to non-supplemented animals and also to a sham group that had no induced injury. Fatty acid analysis of the blood and histochemical staining APP was done at the conclusion of 30-day period for all animals.

Results: The levels of omega-3 fatty acids rose in a dose response manner in the supplemented animals. There was a 25-fold reduction of the levels of APP in both groups of supplemented animals compared to the non-supplemented animals. The levels of APP in both groups of the supplemented animals were virtually identical to the animals in the sham group.

Conclusion: This experiment suggests that supplementation with omega-3 fatty acids can significantly reduce the levels of axon damage in the white matter induced by traumatic brain injury.

11:00 EFFECTS OF DIETARY OMEGA-3 FATTY ACIDS ON CORTICAL AND AMYGDALA SEIZURE THRESHOLDS IN RATSTaha AY¹, Jeffrey MA¹, Bala S¹, Bazinet RP² & Burnham WM¹Departments of Pharmacology¹ and Nutritional Sciences², Faculty of Medicine, University of Toronto, Toronto, ON, Canada.

Background: Omega-3 polyunsaturated fatty acids (n-3 PUFA) have been considered as a treatment for patients with simple and complex partial seizures. Simple partial seizures originating from the cortex are generally drug-responsive, whereas complex-partial seizures originating from the amygdala are drug-resistant.

Objective: To examine the effects of dietary omega-3 fatty acid supplementation and deprivation on cortical and amygdala seizure thresholds in rats.

Procedures: In Experiment 1, rats were surgically implanted with chronic bipolar electrodes in the cortex or amygdala, and subsequently randomized to the AIN-93G diet containing soybean oil or 40% fish oil for up to 34 weeks. In Experiment 2, rats were surgically implanted with electrodes in the cortex or amygdala, and were randomized to the AIN-93G diet containing soybean or an n-3 PUFA deficient diet. Seizure threshold in the cortex and amygdala was measured every 4-5 weeks.

Results: In contrast to soybean oil, fish oil supplementation (Experiment 1) elevated seizure threshold in the cortex and amygdala by up to 64% relative to baseline (P<0.05). Experiment 2 is currently ongoing and our preliminary observations indicate that n-3 PUFA deprivation reduced seizure threshold in the cortex and amygdala. Additional threshold measurements will be obtained over the next few months to confirm this finding.

Conclusions: At present, these observations indicate that n-3 PUFA derived from fish oil have anticonvulsant properties.

11:15 OMEGA-3 FATTY ACIDS AND EPILEPSY

Yuen AW

Department of Clinical and Experimental Epilepsy, UCL Institute of Neurology, London, UK.

Pharmacology studies have demonstrated that the omega-3 fatty acids (FA) EPA and DHA and the omega-6 FA arachidonic acid (AA) can increase seizure thresholds. In a study using ketogenic diet in the treatment of refractory epilepsy, plasma concentrations of EPA, DHA and AA were raised. This increase may contribute to the antiseizure effects of the diet. To date, 3 reports of the use of supplemental omega-3 FAs in patients with epilepsy have been published. In an open study, 5 patients took 2.3g DHA and 0.9g EPA daily for 6 months with encouraging results. In the first randomized double-blind placebo-controlled trial (n=57) where patients were given EPA 1g and DHA 0.7g daily for 3 months, there appeared to be a transient reduction in seizure frequency during the first 6 weeks of treatment only. In the second placebo-controlled trial (n=21) patients were given EPA 1.3g and DHA 0.9g. There was no effect of omega-3 supplementation during the blind phase, but 15 of 19 subjects had fewer seizures during an optional open phase than at baseline (p=0.02). Further studies are required to determine the optimal omega-3 preparation to investigate in patients with epilepsy. The effects of longterm antiepileptic drugs on FA profiles were examined in 57 patients, who were mostly on polytherapy. Patients who took carbamazepine (CBZ) had lower concentrations of omega-3 FAs whilst patients on oxcarbazepine (OXC) appeared to have higher concentrations of polyunsaturates. The Omega-3 Indices (sum of EPA and DHA), 4.0 for those on CBZ, 5.8 for those on OXC, and 5.0 for those taking neither CBZ nor OXC, were different in the 3 groups (p<0.001). The effect of CBZ on FAs may potentially explain the observations that CBZ users or high CBZ blood concentrations seem to be overrepresented in some series of sudden unexplained deaths in epilepsy.

11:30 AGGRESSIVE ALCOHOLICS AND LONG CHAIN OMEGA-3 FATTY ACIDS: A RANDOMIZED PLACEBO CONTROLLED INTERVENTION TRIAL ASSESSING BEHAVIORAL AND AFFECTIVE CSF NEUROCHEMICAL, ENDPOINTS

Hibbeln JR, Baca A, Majchrzak S, Nieminen L, Wright M, Lionetti T, Umhau JC, Salem N.
National Institutes of Health, Bethesda, MD USA

Background: Chronic alcohol consumption depletes brain docosahexaenoic acid (DHA), and may contribute to the high prevalence of aggression, anger and dysphoria.

Objective: Restoration during abstinence may potentially improve affective symptomatology, behavioral measures of aggression and CSF neurotransmitter markers associated with these pathologies.

Procedure: Alcoholics (n=97) with scores >20 on the Coccaro Lifetime History of Aggression scale who were between 21 and 40 days from last drink were randomized to receive either 2.1 g/d of EPA and DHA or soy oil placebo for 12 weeks as outpatients while on a “no seafood” diet. Assessments were conducted at base and at 12 weeks and included: CSF collection by lumbar puncture, and aggressive responses during the Point Subtraction Aggression paradigm, structural MRI for quantification of atrophy (gray+white matter /intercranial volume), NEO personality inventory, Buss Durkee Hostility index, Obsessive Compulsive Drinking scale and total plasma fatty acid composition.

Results: Plasma fatty acid composition at 12 weeks among completers (n=67) indicated that only 11 subjects could be judged treatment fully treatment compliant and 15 partially treatment compliant despite daily documentation of capsule use. Plasma and CSF essential fatty acid levels, were not correlated to the following parameters, at baseline or at 12 weeks: CSF neurotransmitter metabolites 5-HIAA, HVA and MHPG, NEO five factor scores, BDHI subscales or total or aggression measures. Lower plasma DHA upon admission was correlated with greater brain atrophy measures at baseline (greater gray+white/ ICV) (n=20).

Conclusion: Compliance was not sufficient to conclusively assess treatment efficacy. No trends were observed for reductions of anger, aggressive behaviors, abstinence or relapse measures. Assessment of treatment efficacy among aggressive addictive populations, requires close monitoring of compliance. Brain atrophy associated with alcoholism may be diminished by diets which elevate DHA and EPA status.

11:45 AN N-3 FATTY ACID DEFICIENT DIET DOES NOT WORSEN CEREBRAL ISCHEMIA OUTCOME, BUT A DIET HIGH IN DOCOSAHEXAENOIC ACID MAY INCREASE THE RISK OF CEREBRAL HEMORRHAGE IN THE RAT

Slack, Penelope J., and Innis, Sheila M.

Child and Family Research Institute, Department of Paediatrics, University of British Columbia, Vancouver, British Columbia, Canada

Background: High doses of long chain n-3 fatty acids have been reported to reduce brain damage caused by cerebral ischemia in animals. However, in humans very high intakes of long chain n-3 fatty acids have been associated with an increased risk of cerebral hemorrhage, and low rather than high intakes of n-3 fatty acids are a greater concern in many countries. Whether low brain docosahexaenoic acid (DHA) worsens cerebral ischemia outcome is unknown.

Objective: Our objectives were to determine if n-3 fatty acid deficiency alters the extent of brain damage following cerebral ischemia/reperfusion.

Procedure: Male rats were fed an n-3 fatty acid deficient, high alpha linolenic acid (ALA), or high DHA diet for 5 weeks. Brain and platelet fatty acids were analyzed by GLC. Middle cerebral artery occlusion (MCAO) was used as a model of cerebral ischemia/reperfusion, and infarct volume was measured 24 hours after the procedure. Platelet function was assessed using a PFA-100.

Results: DHA was 25% lower in brain phospholipids in the n-3 deficient compared to high ALA group, while DHA was 12% and 35% higher in brain fatty acids of the high DHA diet compared to high ALA or n-3 fatty acid deficient groups, respectively. However, we found no significant difference in infarct volume (220.5 ± 34.8 , 202.7 ± 35.5 , and 218.3 ± 38.9 mm³) among n-3 deficient, high ALA, or high DHA acid groups, respectively. Cerebral hemorrhage after MCAO was higher in rats fed the high DHA diet, although no apparent change in platelet function was found.

Conclusion: Our study provides no evidence that n-3 fatty acid deficiency worsens the extent of brain damage following cerebral ischemia. However, the increased incidence of hemorrhage in rats fed high DHA is consistent with reports an increased incidence of cerebral hemorrhage in populations with high fish intakes. Supported by CIHR.

10:30 PROPERTIES OF LIPIDS CONTAINING DOCOSAHEXAENOIC ACID AND THEIR INTERACTIONS WITH INTEGRAL THE MEMBRANE PROTEIN RHODOPSIN.

Feller SE.

Wabash College, Crawfordsville, IN, USA.

The structure and dynamics of polyunsaturated lipids, specifically those containing docosahexaenoic and docosapentanoic acid, will be described and compared with saturated and mono-unsaturated lipids. Comparison will be made between the simulation results and experimental measurements utilizing NMR and x-ray diffraction. Both simulation and experiment suggest the polyunsaturated fatty acid chains possess an extreme flexibility. The role of the torsional energy profile for rotation about single bonds between vinyl groups will be emphasized as the key factor in these observations. A mechanism by which this flexibility allows unique interactions with integral membrane proteins will be demonstrated.

10:45 THE ROLE OF MEMBRANE COMPOSITION IN THE KINETICS AND EFFICIENCY OF RECEPTOR-G PROTEIN COUPLING

Mitchell DC and Niu SL

National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health, Bethesda (USA)

Background: G protein-coupled receptors (GPCRs) are the largest group of transmembrane receptors with nearly 1000 members. These 7-helix proteins are involved in processes ranging from neurotransmitter signaling to light perception and taste, and targets for ~30% of all pharmaceuticals on the market. GPCRs function by binding and activating one or more cognate G proteins.

Objective: To determine the effects of acyl chain unsaturation and cholesterol on the kinetics and efficiency of G protein binding to the GPCR rhodopsin.

Procedures: Experiments were performed on rhodopsin retinal disk membranes and on rhodopsin purified from bovine retinas, reconstituted into membranes of 18:0,18:1 PC, 18:0,22:6n3 PC and di-22:6n3 PC with and without 30 mol% cholesterol. The cholesterol content of disk membranes was varied via treatment with methyl- β -cyclodextrin. Transducin (G_t), the G protein of the retinal rod outer segment, was purified from bovine retinas. MII is the active signaling conformation of the receptor and activates G_t . Rates of MII and MII- G_t complex formation were measured using laser flash photolysis. Measurements were performed in the absence of GTP, ensuring that all binding events between G_t and rhodopsin produced a stable complex.

Results: The rate constant for G_t binding to MII varied with acyl chain composition in the order 18:0,22:6n3 PC > di-22:6n3 PC > 18:0,18:1 PC. The addition of cholesterol slowed G_t by a factor of 200% in 18:0,18:1 PC, by ~50% in 18:0,22:6n3 PC and not at all in di-22:6n3 PC. In native disk membranes reduction of cholesterol from 12mol% to 4mol% had no effect, while increasing cholesterol to 47mol% slowed G_t binding by ~300%.

Conclusion: The lateral diffusion of activated receptor and G protein that is required for rapid G protein signaling is sensitive to 22:6n3 acyl chains and cholesterol. Increased levels of 22:6n3 acyl chains reduce the decelerating effect of cholesterol on this kinetic process.

11:00 AN IN-DEPTH IMAGE OF POLYUNSATURATED LIPID MEMBRANES REVEALED BY NEUTRON DIFFRACTIONMihailescu M¹, Soubias O², Worcester DL³, White SH¹ and Gawrisch K²¹Department of Physiology and Biophysics, University of California, Irvine, CA; ²Laboratory of Membrane Biochemistry and Biophysics, NIAAA, National Institutes of Health, Bethesda, MD; ³Division of Biological Sciences, University of Missouri, Columbia, MO

The internal structure of a fluid lipid bilayer composed of 1-stearoyl-2-docosahexaenoyl-sn-glycero-3-phosphocholine was analyzed by neutron diffraction. This technique, used in concert with specific deuteration of the molecular components permits a direct determination of the trans-bilayer distribution and position of the acyl chains or any other component of interest, with Angstrom resolution. The studies reveal an uneven disposition of the acyl chains. The polyunsaturated DHA chain has a preference to reside near the lipid water interface. That leaves voids in the bilayer center that are occupied by saturated stearoyl chain segments. Moreover, Cholesterol interacts differentially with the saturated and polyunsaturated chains, and imposes a density redistribution of the chains, compared to the neat lipid bilayer analogue. In complementarity with solid-state NMR studies, and molecular dynamics simulations, the neutron diffraction investigation give important clues on the molecular basis for function of membrane proteins, such as Rhodopsin, and their symbiosis with the lipid environment.

11:15 EXPERIMENTAL EVIDENCE FOR SPECIFICITY IN RHODOPSIN-LIPID INTERACTIONSSoubias O, Teague W.E, Gawrisch K.

Section of Nuclear Magnetic Resonance, Laboratory of Membrane Biochemistry and Biophysics, NIAAA, National Institutes of Health, Bethesda MD 20892.

It is well known that rhodopsin-dependent steps of the visual process are sensitive to membrane lipid composition, in particular to the content of polyunsaturated docosahexaenoic acid (DHA). Current theories interpreted this sensitivity exclusively as a consequence of changes in continuum elastic properties of the lipid matrix. Here we investigated if specific interactions between DHA-containing lipids and rhodopsin may contribute to the effect. By ¹H MAS NMR with saturation transfer from protein to lipids (ST-NMR) (1) we observed strongest interactions between rhodopsin with DHA-containing phosphatidylethanolamines (PE). This observation is supported by results from ²H NMR experiments which show that PEs are enriched in the first layer of lipids surrounding rhodopsin. It suggests that rhodopsin surface is heterogeneous, with sites for specific interaction with DHA-containing lipids (2). Specific interactions with particular lipid species may generate a unique microenvironment for the protein with altered membrane continuum properties and dynamics (3).

1 Soubias O., Gawrisch, K. J. Am. Chem. Soc. (2005)

2 Soubias O., Teague, W.T., Gawrisch, K. J. Biol. Chem. (2006)

3 Soubias O., Gawrisch, K. J. Am. Chem. Soc. (2007)

11:30 LITTLE THINGS MEAN A LOT: SENSITIVITY OF ELECTROSTATIC (DIPOLE) PROPERTIES OF OMEGA-3 FATTY ACID-CONTAINING AND RELATED PHOSPHOLIPID SPECIES TO SMALL STRUCTURAL ALTERATIONS.Brockman HL¹, Momsen, MM¹, King, WC² and Glomset JA²¹University of Minnesota, Austin, MN, USA; ²University of Washington, Seattle, WA, USA

Cell membranes utilize a diverse set of lipids for homeostasis. Better understanding of the need for this lipid diversity can benefit from basic knowledge of how lipid structure determines lipid physical properties. One of the least understood of these properties is the electrostatic potential within the membrane that arises from lipid dipoles and associated water. We have characterized the packing and electrostatic properties of twenty-eight physiologically-relevant phospholipid molecular species in monomolecular films. The phospholipids differed in head group, *sn*-1 chain linkage and extent/position of *sn*-2 chain unsaturation. Analysis of this data using equations of state shows that these structural motifs of the lipid molecules can contribute independently to both packing and electrostatic behavior. For example, phospholipid species containing a polyunsaturated omega-3 or an omega-6 polyunsaturated fatty acyl group at the *sn*-2 position of glycerol pack comparably in monolayers. However, the dipole moments of the omega-3 species perpendicular to the interface are approximately 80 mD lower than those of comparable omega-6 species. Comparison of data among species having different extents and positions of polyunsaturation in the *sn*-2 acyl group shows that the lower dipole moments of omega-3-containing species depend on the omega-3 double bond itself rather than double bonds proximal to the carboxyl end of the chain. Independently, substitution of an alkenyl linkage for the *sn*-1-acyl linkage lowers dipole moment by as much as 300 mD. For ethanolamine phospholipids this constitutes a 60-75% reduction in total dipole moment. Interestingly, the alkenyl linkage is commonly found in lipid species having polyunsaturation at *sn*-2, suggesting that modulation of electrostatic potential within the membrane may be one role of polyunsaturated lipid species in biological membranes. Supported by HL49180 and the Hormel Foundation.

11:45 CHARACTERIZATION OF LONG-CHAIN POLYUNSATURATED FATTY ACID BINDING TO ALBUMIN USING ISOTHERMAL TITRATION CALORIMETRYNiu SL, Culyba E, & Mitchell DC

Laboratory of Membrane Biochemistry and Biophysics, National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health, Bethesda, MD 20892, USA

Background: Docosahexaenoic acid (DHA) is highly enriched in the brain and is essential for optimal brain function. The mechanism of how DHA is concentrated in the brain remains an enigma. One hypothesis is a preferential supply or retention of DHA in the brain.

Objective: To characterize and compare the binding of n-3 and n-6 long-chain polyunsaturated fatty acids (PUFA) to albumin as an initial step towards the understanding of the enrichment of DHA in the brain. Though the binding of fatty acid to albumin has been extensively studied previously, there is limited information on the number of PUFA binding sites on albumin and their binding affinities. Methods: Isothermal titration calorimetry is used for the first time to study the binding of PUFA to albumin.

Procedure: The titration was conducted by injecting a series of small aliquots of PUFA into albumin or albumin into PUFA solution, until no further heat signal was evolved. The binding isotherm was analyzed using the Scatchard and Sequential Binding models to determine the binding parameters.

Results & Conclusion: The binding of PUFA to albumin produced a series of well-resolved exothermic peaks. Albumin has much higher binding capacity, both in terms of the number of binding sites and binding affinities, to PUFA than to the monosaturated or saturated counterparts. Such difference is likely due to the structural flexibility of PUFA, which allow them to adopt the correct conformation with minimal energy barrier to accommodate the binding site in albumin. No significant difference was observed between the binding of n-3 and n-6 PUFA to albumin. Our finding could provide insights into the physiology of transport and utilization of PUFA, which is an important step toward the understanding of the enrichment of DHA and PUFA in the brain.

10:30 ESSENTIAL FATTYACID RECOMMENDATIONS: OLD AND NEW

Sheila M. Innis.

Child and Family Research Institute, University of British Columbia, Vancouver, B.C., V5Z 4H4, Canada.

Recommendations for essential fatty acids in North America have been set based on endpoints that can be considered broadly in three ways. Using a traditional model of essentiality, early dietary recommended intakes were established for linoleic acid (LA) in the U.S., and later for alpha linolenic acid (ALA) in Canada using data to indicate those intakes at which signs of deficiency are apparent and levels of intakes at which these signs are reversed, with an estimated safety factor to cover 97-98% of the healthy population. The 2002 Dietary Reference Intakes macronutrient panel rejected this approach because much of the information was derived from institutionalized individuals fed with enteral or parenteral formulas. These estimates placed the recommended intakes for linoleic acid considerably lower than current U.S. and Canadian intakes, and also indicated a need for a two fold increase in alpha linoleic acid, bringing the ratio of these two fatty acids down to about 4: 1. When an estimated adequate requirement (EAR) cannot be set, then an adequate intake (AI) is published. The AI for fatty acids is the median intake by life stage and gender observed in the U.S. As such, the AI is a descriptor of current U.S. intakes only and has no value as a benchmark against which to base judgment of those n-6 and n-3 fatty acids intakes that minimize risk of adverse health outcomes relevant to fatty acid nutrition. A second approach is to consider disease risk, rather than absence of deficiency as the correct endpoint for dietary n-6 and n-3 fatty acids. This model underlies recommendations from expert groups for long chain n-3 fatty acids, eicosapentaenoic acid and docosahexaenoic acid (EPA+DHA). Recommendations for LA were also so derived; arising from a belief among some that deriving down LDL cholesterol by increasing LA would have positive effects in reducing disease morbidity and mortality. Finally, fatty acids contribute energy, thus fatty acids must be summed and balanced with carbohydrate and protein to derive the distribution of energy from macronutrients, and from the different fatty acids. Judgments on the health risk (or benefit) of energy from fat versus carbohydrate, or saturated fatty acids thus contribute to the upper and lower boundaries for total fat and polyunsaturated fat. Current DRI for n-6 and n-3 fatty acids, both the AI and AMDR, were not established using models to minimize adverse effects of high intakes and disease risk due to low intake, and as such cannot be used as a basis on which to consider food policy.

11:00 ESTABLISHING DIETARY REFERENCE INTAKES FOR NUTRIENTS: CURRENT METHODOLOGY AND DATA NEEDS

Yates AA, Beltsville Human Nutrition Research Ctr, USDA/ARS, Beltsville, MD, USA

Background: Since 1941, reference values for nutrients have been based on observations of amounts needed to prevent deficiencies in apparently healthy individuals, termed recommended dietary allowances (RDAs) in the U.S. These nutrient intake values were related to specific outcomes equated to health, such as maintaining normal blood levels, enzyme function, or tissue growth and repair. With growing evidence that nutrient deficiencies are only one part of the role nutrients and other food components play in maintaining health, an expanded set of reference values, Dietary Reference Intakes (DRIs), was established by the Food and Nutrition Board of the Institute of Medicine of the National Academies in the U.S. from 1997 to 2004. Designed to serve as the basis for all federal food and nutrition programs and policy, from food stamps to school lunch to MyPyramid, they also serve as assessment tools to determine when inadequacy exists in vulnerable subgroups.

Procedure: The process of establishing DRIs for energy-yielding nutrients is quite complex: frank deficiencies are rare (although known, such as essential fatty acid deficiency) so biomarkers of adequacy are difficult to define, particularly if related to chronic disease risk reduction; and efforts to determine amounts required for a given health outcome are confounded by the need for total energy intake to remain constant, resulting in the alteration of intake of other energy-yielding nutrients to maintain energy balance.

Conclusion: Thus while increased amounts of omega-3 fatty acids may be associated with decreased risk of specific diseases such as cardiovascular disease in some populations, there must also be a concomitant decrease in the relative intake of carbohydrate, protein, and/or other fatty acids, confounding the relationship; this points to the need for a strong data set relating intakes with specific disease biomarkers or outcomes and with as few confounding variables as possible.

11:30 EPA AND DHA RECOMMENDATIONS IN THE NETHERLANDS: IMPLICATIONS FOR INCREASED INTAKE IN THE DUTCH POPULATIONS

Zock P.

Unilever Corp..etc.

ABSTRACT AVAILABLE AT SESSION

11:45 ASSESSING THE ENVIRONMENT FOR REGULATORY CHANGE FOR EPA AND DHA NUTRITION LABELING

Michael Falk, Ph.D.

Life Sciences Research Office, Inc. (LSRO), Bethesda, MD, USA, 20814

Interested participants from US federal government agencies, academia, and industry met for a one-day workshop to address the environment for change in the national nutrition policy recommendations for EPA and DHA. The US Food and Drug Administration (FDA) sets the reference daily intakes (RDI) and daily reference values (DRV) that combine to form the daily values (DV) that are listed the nutrition facts and supplement facts labels on items sold in the US. Currently, there are no DV for EPA or DHA. Changes in nutrition labeling could have a profound impact on the omega-3 industry and consumer use patterns, as well as the health and well-being of the US population. The goals of the workshop were to provide a common understanding of the path towards change, what new information would be persuasive to decision makers, and how new information might be evaluated. Participants discussed the current process for setting the DV on the nutrition and supplements facts labels, the type of information required to support change, the role of the nutrition facts label in attaining national health goals, and the role EPA and DHA may play in attaining those goals. Also discussed were the roles the FDA, US Department of Agriculture, US Department of Health and Human Services, Dietary Guidelines Advisory Committee, and Institute of Medicine play in this process. The workshop was organized by LSRO under sponsorship of the Global Organization for EPA and DHA Omega-3s (GOED).

10:30 RETROCONVERSION OF DOCOSAHEXAENOIC ACID (22:6) TO EICOSAPENTAENOIC ACID (20:5) IS NEGLIGIBLE IN SERUM OF HEALTHY YOUNG OR AGED ADULTS

Brenna JT¹, Vandal M², Zhang Y¹, Cunnane S², ¹Division of Nutritional Sciences, Cornell University, Ithaca, NY, USA, and ²Research Center on Aging, Université de Sherbrooke, Canada

Background: The polyunsaturated fatty acid (PUFA) 22:6 is widely accepted to be synthesized from 20:5 via these steps: 20:5 > 22:5 > 24:5 > 24:6 > 22:6. Many papers report apparent retroconversion of 22:6 to 20:5, presumed to be by the reverse pathway, but this pathway has not been adequately verified in human adults.

Objective: The goal was to look for evidence that [¹³C]-22:6 (22:6*) is converted to other fatty acids, specifically, shorter chain n-3 PUFA, and to determine if this process could be different in healthy young or elderly subjects.

Procedure: Six young (20s) and four healthy elderly (70s) subjects were given a single oral 50 mg dose of 22:6*, and serum was collected at baseline, and 4 h and 1, 8, and 28 d post-dose. FAME were prepared and analyzed by high precision GC-combustion isotope ratio mass spectrometry.

Results: For both groups, 22:6* peaked at 24 h and was easily detectable in plasma up to 28 d post-dose. In contrast, the other n-3 PUFA* showed an average increase in labeling of no more than a few percent of that of 22:6* at any time point. ¹³C Enrichment in 20:5* and 22:5* was greatest at 24 h but isotope ratios were very similar at all time points, which would not be expected if 20:5* or 22:5* arose by retroconversion. On average, there were no changes in 16:0*, 18:0*, 18:3n-3*, or in n-6 PUFA*. There was no evidence of metabolic differences in the young or aged subjects.

Conclusions: In humans, increases in plasma 20:5 often ascribed to increasing dietary 22:6 may not be due to retroconversion but rather to other mechanisms such as sparing of 20:5 oxidation. Alternatively, retroconversion may be driven by much higher levels of dietary 22:6. Funding: Canadian Institutes of Health Research.

10:45 ALTERED N-6 AND N-3 FATTY ACID PROFILES IN BLOOD LIPIDS OF CYSTIC FIBROSIS PATIENTS ARE RELATED TO CHANGES IN THEIR METABOLIC PATHWAYS.

Risé P¹, Colombo C.¹, Volpi S.², Padoan R.³, Melotti P.², Assael BM², Galli C.¹

¹Dept. Pharm. Sciences, Milano; ²Cystic Fibrosis Center, Verona; ³Ospitale Civile, Brescia; Italy

Objective: To compare the fatty acid (FA) profile in whole blood of cystic fibrosis patients (CF) versus control subjects (C) with the aim to elucidate possible mechanisms responsible of the altered FA status in CF.

Procedure: 90 CF and 29 C, attending to the Cystic Fibrosis Centre of Verona, and to the Ospitale Civile of Brescia, Italy were investigated. Whole blood was collected from a fingertip on a strip of paper and fatty acid methyl esters directly prepared (Marangoni et al. 2004).

Results: Saturated, monounsaturated FA are higher, whereas polyunsaturated FA (PUFA) are lower in CF versus C. In particular there is a reduction of total n-6 FA and of DPA and DHA (22:5 n-3 and 22:6 n-3). The desaturation indexes, expressed as product/precursor ratios are evaluated: $\Delta 6$ desaturase (18:3 n-6/18:2 n-6) is similar whereas $\Delta 5$ desaturation (20:4 n-6/20:3 n-6) is significantly lower in CF versus C. In CF the low index of $\Delta 5$ desaturase is related to an increase of 20:3 n-6 and to a concomitant decrease of 20:4 n-6; 20:3 n-6 positively correlates with age and weight in CF, whereas no correlation is found in C. The product LA x DHA, recently proposed as a marker for the pathology (Batal et al. 2007), is lower in CF than in C of about 30%.

Conclusion: These data, in an Italian population, show that changes in FA metabolism are present in CF. Verona and Brescia, in the North-East of Italy, have similar food habits. It appears that the low levels of FA are not due to pancreatic insufficiency, and lipid malabsorption but possibly to a basal metabolic alteration in CF. In fact desaturation steps are affected, both in vivo and in vitro, as assessed in a pilot study in CF cells, with reduced $\Delta 5$ desaturase activity in CF versus C.

11:00 STEARIDONIC ACID DOSE RESPONSE STUDY IN PIGS

Harris W¹, Hansen S¹, Christianson A,¹ Lucas D², Hartnell G², Lemke SL², Perez T², and Ellis M³.

¹Sanford Research/USD, Sioux Falls, SD; ²Monsanto Co., St. Louis, MO; ³Dept Animal Science, Univ of Illinois, Urbana, IL.

Background: The human health benefits of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are well documented. To meet the rapidly growing demands for these n-3 fatty acids (FAs), plant, instead of fish-based alternatives are needed. Alpha-linolenic acid (C18:3 n3, ALA) is poorly converted to EPA because of limited delta-6 desaturase conversion to stearidonic acid (SDA, C18:4 n3). An SDA-enriched soybean oil (SBO) has been produced from genetically engineered soybeans. The extent of conversion of SDA to EPA and DHA has not been well defined.

Objective: This study examined the effects of dietary SDA on tissue EPA and DHA in pigs.

Procedure: Diets containing 0%, 0.2%, 0.4%, 0.6% and 0.8% SDA (w/w, provided as 72% w/w SDA ethyl ester from fish oil, KD Pharma) were fed to five groups of pigs (n=4 each) for the last 35 days prior to reaching market weight (125 kg). At slaughter, multiple tissues (brain, heart, kidney, liver, muscle, plasma, red blood cell, subcutaneous fat) were harvested and analyzed for FA composition. Regression of means analysis was performed.

Results: The EPA content of tissue phospholipids (PL) rose in a dose-dependent manner in all tissues [e.g., the regression model estimated heart PL EPA increased from 0.32% to 1.91% of total PL FAs as SDA dose increased from 0 to 0.2%. p value for the slope was 0.0003]. SDA content increased slightly with dose in all tissues except brain and liver. DHA levels were related to SDA dose in the heart.

Conclusion: In pigs, SDA is converted to EPA in a dose dependent manner. DHA may be elevated at higher SDA intake levels in heart tissue. These data suggest that achievable SDA intakes may raise tissue long-chain n-3 FA levels in humans. Funding Source: The Monsanto Co.

11:15 FLAXSEED OIL PREVENTS TRANS-10, CIS-12 CONJUGATED LINOLEIC ACID (CLA) INDUCED INSULIN RESISTANCE IN MICE.

Kelley DS^a, Vemuri M^a, Adkins Y^a, Gill SHS^a, Fedor D^a, Mackey BE^b,

^aWestern Human Nutrition Research Center, ARS, USDA, and Department of Nutrition, University of California, Davis, California, ^bWestern Regional Research Center, ARS, USDA, Albany, CA.

Background: Nonalcoholic fatty liver disease (NAFLD) is the most prevalent liver disease in the Western world, and 25% of adult US population has insulin resistance (IR). T10, c12-CLA causes both these disorders in several animal models.

Objective: Test if IR and NAFLD caused by CLA result from (n-3) fatty acid deficiency; can these disorders be prevented by a concomitant supplementation with flaxseed oil (FSO).

Procedures: Eight-week-old, pathogen-free C57BL/6N female mice (10 per group) were fed either a control diet or diets containing t10, c12-CLA (0.5 %) or CLA + FSO (0.5% + 0.5 %) for 8 weeks. In the CLA supplemented group the weights of livers, concentration of circulating insulin, values of homeostatic model 1 for insulin resistance (HOMA1-IR) and HOMA1-% β cell function (HOMA1-% β) were 2.6, 7.4, 10.8, and 6.2 fold of corresponding values in the control group. CLA supplementation also reduced perirenal and ovarian adipose tissue weights by 84, and 78 %, and concentrations of circulating leptin and adiponectin by 87 and 85%. Concomitant supplementation with FSO decreased fasting glucose by 20 % (p<0.05), and restored circulating insulin, HOMA1-IR, and HOMA1-% β cell functions to those found in the control group. It partially (37%) reduced liver weights, but had no effect on the leptin and adiponectin concentrations. Our results suggest that some of the adverse effects of CLA may be corrected by concomitant increase in the intake of linolenic acid (18:3 n-3). These findings may have clinical implications in the dietary management of NAFLD and IR.

11:30 A HIGH INTAKE OF CONJUGATED LINOLEIC ACID DOES NOT AFFECT LIVER AND KIDNEY FUNCTION IN HEALTHY HUMAN SUBJECTS.⁴

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Background: Conjugated linoleic acid (CLA) is a mixture of positional and geometric conjugated isomers of linoleic acid. The knowledge of health effects of CLA supplementation in humans is limited. Up until now, amounts of 0.7g to 6.8g CLA a day are used as supplements to study safety in humans. Health effects of short-term, high-dose CLA supplementation may indicate long-term, low-dose effects of CLA supplementation.

Objective: To study the effect of a daily intake of 19.3g CLA for three weeks on liver and kidney function in healthy human volunteers.

Procedure: Twenty, apparently healthy, normal weight subjects, aged 18–60, with normal liver and kidney function were included in the study. All subjects received food products enriched with a 19.3g CLA mixture, of which 80% cis-9,trans-11 and 20% trans-10,cis-12 CLA a day for a duration of 3 weeks. At baseline and after 3, 7, 10, 16, and 21 days, we measured liver and kidney function. Treatment effects were analysed with paired t-tests.

Results: Serum levels of aspartate aminotransferase, alanine aminotransferase, bilirubin, alkaline phosphatase and amylase did not change significantly during the intervention period. Lactate dehydrogenase (mean \pm sd) increased from 290.9 ± 43.6 U/L to 322.5 ± 60.7 U/L ($p=0.04$), normal level is <450 U/L. Gamma-glutamyltranspeptidase increased from 12.1 ± 5.9 U/L to 13.5 ± 6.2 U/L ($p=0.002$), normal level is <50 U/L for men and <40 U/L for women. Creatinine clearance according to Cockcroft–Gault increased from 116.2 ± 10.6 ml/min to 119.9 ± 10.7 ml/min ($p=0.17$), normal level is ≥ 90 ml/min. All parameters stayed within the normal limits and none of the changes could be considered clinically relevant.

Conclusion: An intake of 19.3g CLA mixture per day for a period of 3 weeks did not produce clinically relevant effects on liver and kidney function in healthy human volunteers.

11:45 ROLES OF FATTY ACID BINDING PROTEINS AND POLYUNSATURATED FATTY ACIDS IN HIPPOCAMPAL NEUROGENESIS.

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Background & Objective: New neurons are explosively generated in the brain during the embryonic period, and the neurogenesis continues throughout life in certain brain regions such as the hippocampal dentate gyrus (DG) where neural stem cells persist. We have previously shown that Pax6 transcriptional factor is necessary for keeping neural stem/progenitor cells in the postnatal hippocampus (Maekawa et al., 2005), most likely by regulating expression of fatty-acid binding protein 7 (FABP7, B-FABP, BLBP) (Arai et al., 2005). Fatty acid binding proteins (FABPs) are postulated to serve as a lipid shuttle, solubilizing hydrophobic fatty acids and delivering them to the appropriate metabolic system. Among the FABP family proteins, FABP7 and FABP5 (E-FABP, DA11) are expressed in the neural stem/progenitor cells in embryonic stages. However, their specific role in the postnatal neurogenesis is not yet fully established. In this study we have examined detailed expression of FABP7 and FABP5 during hippocampal neurogenesis and effects of polyunsaturated fatty acids (PUFAs) on neurogenesis.

Methods: Detailed expression of FABP7 and FABP5 was observed in the wild type rats. Mice deficient for Fabp7 and Fabp5 were assayed for hippocampal neurogenesis. Effects of PUFA on neurogenesis were examined by dietary administration with arachidonic acid (ARA) and docosahexaenoic acid (DHA).

Results & Discussion: We found that FABP7 was mostly expressed in the neural stem/early progenitor cells, whereas FABP5 in the late progenitors. As expected, cell proliferation in the hippocampal DG was approximately 30% reduced in knockout mice deficient with FABP7 (Watanabe et al., 2007) or FABP5, indicating their importance in neurogenesis. We next challenged to increase neurogenesis by administering wild type rats with PUFAs. Interestingly, neural progenitor cells dramatically increased in rats fed with ARA, while DHA exhibited little effect. Taken together, it is concluded that FABPs and PUFAs are essential for neurogenesis in the DG. Neurogenesis is related to learning ability and to mental diseases such as depression and schizophrenia (Watanabe et al., 2007).

1:30 DOCOSAHEXAENOIC ACID (DHA) SUPPLEMENTATION DURING PREGNANCY AND LACTATION INCREASES THE RATE OF MILDLY ABNORMAL GENERAL MOVEMENTS (GMS) COMPARED TO PLACEBO OR DHA PLUS ARACHIDONIC ACID (AA)

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Background: DHA and AA are important for neurodevelopment. Evaluation of GMs is a sensitive technique for evaluating brain function in young infants. GMs are qualified as clinically normal (normal-optimal, normal-suboptimal, or mildly abnormal (MA)) or clinically abnormal (definitely abnormal (DA)). MA GMs, especially at three months, are associated with development of minor neurological dysfunction at later age in high-risk populations. Little is however known on its predictive power in the general population.

Objective: We investigated whether supplementation of DHA and AA during pregnancy and lactation improves GM-quality. Procedure. Women were randomly assigned to placebo (n=36), DHA (220 mg/day, n=42) or DHA+AA (220 mg each/day, n=41) from week 17 of pregnancy till 12 weeks postpartum. The infant's spontaneous motility was videotaped in supine position at 2 and 12 weeks. Between-group differences in GM-quality were tested using chi-square with Bonferroni-correction at $p<0.017$.

Results: One child exhibited DA GMs (DHA group) at 12 weeks. The DHA group exhibited more MA GMs compared to both the placebo and the DHA+AA groups. MA GMs: Placebo 32%; DHA 61%; DHA+AA 34% ($p=0.016$). Although not significant, a similar trend was found in GM-quality at 2 weeks.

Conclusion: The higher rate of MA GMs in the DHA group at 12 weeks is intriguing. In high-risk populations, MA GMs are associated with later minor neurological dysfunction, whereas a higher neonatal DHA status and higher DHA intakes are associated with better neurodevelopment. A possible explanation is a changing DHA/AA balance in favor of DHA in early pregnancy although other investigators, who supplemented up to 2.2 g DHA/day from 16–20 weeks of pregnancy till delivery, reported slightly positive effects at 2.5 years, employing different developmental outcome parameters. Another option is a non-linear relation between DHA status and certain aspects of neurodevelopment, for which there is some support from rat studies.

1:45 THREE RANDOMIZED CLINICAL TRIALS OF EARLY LONG-CHAIN POLYUNSATURATED FATTY ACID SUPPLEMENTATION ON MEANS-END PROBLEM SOLVING IN NINE MONTH-OLDS

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Background: Studies investigating the effects of long-chain polyunsaturated fatty acid (LCPUFA) supplementation on cognitive development have yielded mixed results perhaps due to low dietary LCPUFA concentrations and the age at which cognitive development is assessed.

Objective: We assessed whether LCPUFA supplementation with concentrations representative of that found worldwide in human milk improves cognitive function in 9 month-old infants.

Procedure: Participants included 173 infants from three double-blind, randomized clinical trials. Children were assigned to receive either formula supplemented with docosahexaenoic acid and arachidonic acid (0.36% and 0.72% of total fatty acids, respectively) or a control formula with neither docosahexaenoic acid nor arachidonic acid. Infants were fed the assigned formula beginning at 5 days (12 month feeding study), or following 6 weeks (6 week weaning study) or 4 to 6 months of breastfeeding (4 to 6 month weaning study). At 9 months of age, infants were assessed using the two-step means-end problem solving task. The number of intentional solutions and intention scores were recorded.

Results: In both the 12 month feeding study and the 6 week weaning study, the LCPUFA-supplemented group achieved more intentional solutions (12 month study, $P = 0.03$; 6 week study, $P = 0.05$), had higher intention scores (both $P = 0.04$), and were more likely to be successful on all trials compared to the control group (both $P < 0.05$). There were no significant diet group differences in the 4 to 6 month weaning study.

Conclusion: These results indicate that LCPUFA-supplementation beginning shortly after birth, or after 6 weeks of breastfeeding, is associated with superior means-end problem solving. The lack of diet group differences in the 4 to 6 month weaning study might suggest that these infants were still demonstrating beneficial effects of the extended period of breastfeeding.

2:00 ASSOCIATIONS OF PRENATAL ESSENTIAL N-3 AND N-6 POLYUNSATURATED FATTY ACID STATUS WITH CHILD 3-YEAR ADIPOSITY: RESULTS FROM A US PREGNANCY COHORT

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Background: Higher prenatal intake of elongated n-3 polyunsaturated fatty acids (PUFA) may reduce fetal growth. In infancy, formula supplemented with n-3 PUFA may slow postnatal growth, whereas addition of n-6 PUFA may result in faster growth.

Objective: Investigate associations of prenatal n-3 and n-6 PUFA status with child 3-year adiposity.

Procedure: Subjects were participants in Project Viva, a prospective cohort study. We determined maternal PUFA intake in mid-pregnancy using semi-quantitative food frequency questionnaires. Using gas-liquid chromatography, we analyzed PUFA composition of mid-pregnancy maternal erythrocyte total lipid extracts and umbilical cord plasma lipids. We used multivariable linear regression to examine associations of PUFA intake in mid-pregnancy (n = 1,064) and of PUFA concentration in mid-pregnancy erythrocytes (n = 945) and umbilical cord plasma (n = 288) with child 3-year adiposity, measured by the sum of subscapular (SS) and triceps (TR) skinfold thicknesses.

Results: Mean (SD) maternal energy-adjusted intake in mid-pregnancy of total n-3 PUFA was 1.16 (0.42)g/d and the mean 3-year SS+TR was 16.7 (4.3)mm. After adjusting for parental and child factors, including fetal growth and gestation length, higher maternal intake of total n-3 PUFA during mid-pregnancy was associated with lower SS+TR at age 3 (β = -0.76mm per g/d, 95% CI -1.35, -0.17), as was intake of docosahexaenoic and eicosapentaenoic acids (DHA+EPA) (β = -0.20mm per 100 mg/d, 95% CI -0.39, -0.01). DHA+EPA concentration in cord plasma was also inversely associated with SS+TR at age 3 (β = -0.64mm per % of total fatty acids, 95% CI -1.14, -0.13). The ratio of total n-6:n-3 PUFA in cord plasma had a positive association with SS+TR at age 3 (β = 0.54mm, 95% CI 0.05, 1.03). Maternal erythrocyte PUFA were not related to child adiposity.

Conclusion: These data suggest that higher prenatal exposure to elongated n-3 PUFA is associated with less adiposity in early childhood.

2:15 LCPUFA SUPPLEMENTED FORMULA FOR PRETERM INFANTS: A META-ANALYSIS REVEALS NO CONSISTENT EFFECT ON NEURODEVELOPMENT

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Background: Preterm formulas enriched with LCPUFA are widely used in neonatal nurseries based on improved visual outcomes in infancy. LCPUFA formula trials in preterm infants with global developmental outcomes have reported mixed results.

Objective: To systematically review and quantitate the effect of feeding LCPUFA-supplemented formula to preterm infants on global neurodevelopment in early childhood.

Procedure: We identified seven randomised controlled trials testing LCPUFA-supplemented compared with unsupplemented formulas in preterm infants (<37 weeks gestation), that measured neurodevelopment with a validated assessment between 12 and 18 months corrected age (CA). The weighted mean difference (WMD) in developmental quotient was calculated using fixed and random effects models. Sensitivity analyses were conducted to evaluate the effect of LCPUFA-supplemented formula on infant neurodevelopment in trials with high methodological quality.

Results: All included trials used the Bayley Scales of Infant Development (BSID), in which performance is assessed according to mental development index (MDI) and psychomotor development index (PDI). An analysis of all trials revealed no clear differences in MDI or PDI between infants fed LCPUFA-supplemented and control formula. When only trials that used version-I of the BSID were examined, lower PDI scores were reported in LCPUFA-treated infants compared with control (WMD -7.99, 95%CI -14.00, -1.99, p=0.009, n=87), but the finding was limited by sample size. Conversely, compared with control, infants fed LCPUFA-supplemented formula that were tested with version-II of BSID scored 3.4-point higher in MDI (WMD 3.44, 95%CI 0.56, 6.31, p=0.02, n=879), an effect that was driven by two trials with large effect sizes and wide confidence intervals. Sensitivity analyses suggested that sample size was a limiting factor in detecting an effect on neurodevelopment.

Conclusions: Further large scale trials are needed to determine the extent of benefit of LCPUFA-supplemented formula on neurodevelopment of preterm infants.

2:30 THE DINO TRIAL: GROWTH AND NEURODEVELOPMENTAL OUTCOMES FOLLOWING HIGH DOSE N-3 LCPUFA IN PRETERM INFANTS

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Background: The requirement of preterm infants for n-3 LCPUFA is unclear.

Objective: To evaluate the effect of high dose DHA (approximately 1% of dietary fatty acids) on growth and neurodevelopment of preterm infants at 18 months' corrected age compared with standard practice (0.2-0.3% DHA).

Methods: Infants born <33 weeks' gestation (n=657) were randomly allocated to high-DHA or standard practice according to a concealed schedule stratified for sex and birth weight (<1250 g and \geq 1250 g). Infants received breast milk or formula with either high (1.0%) or standard (0.3%) DHA. The dietary AA content of both diets was constant at 0.4% total fatty acids. Intervention was from day 2-5 of life until the infant's due date. Growth, Bayley Mental (MDI) and Psychomotor Developmental Indices (PDI) were assessed at 18 months' corrected age.

Results: Preliminary unadjusted analyses indicate sex and birth weight differences in the response to dietary treatments. Girls born <1250g responded to high-DHA (MDI scores of 99.9 \pm 2.4) which were greater than girls fed according to standard practice (92.1 \pm 2.7). Girls born >1250g achieved near normal MDI (96.9 \pm 2.3 vs 97.6 \pm 2.1) with current dietary levels of DHA. The MDI of boys was lower (mean values 91-92) and did not differ between groups. Although the ratio of AA to DHA was lower in the high DHA group (0.4:1), the weight and length of infants born >1250g was higher than control (AA:DHA ratio 2:1) regardless of sex.

Conclusion: The neurodevelopmental needs of female infants born >1250g are met by current DHA levels in human milk or formulas. Female infants born <1250 appear to have a higher requirement for DHA. The neurodevelopmental unresponsiveness of boys to dietary DHA is of concern and requires further investigation. There may be advantages to growth of higher dietary DHA in the neonatal period.

2:45 PRELIMINARY DATA INDICATE THAT SUPPLEMENTING INFANT FORMULA WITH 3 LEVELS OF DOCOSAHEXAENOIC ACID (DHA) PROVIDES SIMILAR RESULTS IN VISUAL ACUITY AT 12 MONTHS.

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Background: Supplementing infant formula with DHA at 0.32% fatty acids and arachidonic acid (ARA) at 0.64% improves infants' visual development. The optimal level of DHA supplementation has not been determined.

Objective: The primary objective was to evaluate effects of 3 levels of DHA supplementation on infants' visual development at 12 months (mo) of age.

Procedure: In this two-site, double-masked, controlled, parallel group, prospective study, we randomly assigned healthy term infants (Site 1 n=181; Site 2 n=158) to receive one of 4 milk-based formulas from 1-9 days to 12 mo of age: Control=no added DHA or ARA (at 12mo: n=56); DHA 1=0.32% fatty acids from DHA (n=63); DHA 2=0.64% (n=57); DHA 3=0.96% (n=65). All DHA formulas provided 0.64% ARA. Sources of DHA and ARA were algal and fungal oils, respectively. Nutrients other than fatty acids were identical among formulas. Sweep visual evoked potential (VEP) acuity was measured at 12 mo. Values were reported in log minimal angle of resolution (MAR) with higher values indicating lower acuity. Data were analyzed by ANOVA. Comparison of means used Tukey-Kramer adjustment.

Results: At 12 mo, site by formula interaction was significant as was the formula effect. Site 1 Control had significantly higher VEP values than all DHA groups and Site 2 Control (p<0.05). Site 2 Control did not differ from any Site 2 DHA group. Within sites, there were no differences among DHA groups. Site 1 results: Control=0.38 logMAR \pm 0.016 (SE), DHA 1=0.16 \pm 0.016, DHA 2=0.17 \pm 0.015, DHA 3=0.19 \pm 0.015. Site 2 results: Control=0.28 \pm 0.020, DHA 1=0.23 \pm 0.017, DHA 2=0.21 \pm 0.020, DHA 3=0.22 \pm 0.017.

Conclusions: From this preliminary analysis, infants at Site 1, but not Site 2, fed DHA formula for the first year, had better visual acuity at 12 mo than Control infants. Increasing DHA from 0.32% up to 0.96% did not provide additional improvements in visual acuity at 12 mo.

1:30 FATTY ACID TRANSCRIPTOMICS

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The applications of 'omics' (genomics, transcriptomics, proteomics and metabolomics) technologies in nutritional studies have opened new possibilities to investigate the genome-wide effects of nutrients at the molecular level. Nutrigenomics uses these techniques in combination with a range of models and molecular tools as a strategy to understand the mechanistic basis of nutrition. Microarray analysis of genes regulated by dietary fatty acids can serve as a paradigm for this strategy. Subtle changes in the structure of a fatty acid can have profound effects on target organ specificity, effects on metabolic and signaling processes and ultimately physiological effect. In this presentation we summarize and discuss the application of transcriptomics to study the effects of dietary fatty acids in multiple cell types. In addition, we will discuss some of the challenges inherent to the application of transcriptomics to nutrigenomics research.

2:00 GENETIC FACTORS MODULATING PLASMA LIPID RESPONSES TO DIETARY FATTY ACIDS

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Objective: To illustrate the significant contribution of common genetic variants at multiple candidate genes on the inter individual variability in response dietary fatty acids

Procedures: We have carried out genotyping of common single nucleotide polymorphisms (SNPs) at candidate genes in several cohorts with extensive biomarker and behavioural information including dietary records. Statistical analyses were carried out to identify associations between SNPs and disease risk biomarkers as well as their interaction with dietary fat.

Results: The current evidence shows that when it comes to cardiovascular health, n-6 and n-3 families of PUFAs interact very different with genetic variants to modulate cardiovascular risk factors. Thus, while some subgroups of individuals may be at higher risk from high consumption of PUFA n-6 [i.e., carriers of the minor allele at the APOA5-1131T>C single nucleotide polymorphism], others may greatly benefit from increased consumption of PUFA n-3 (i.e., carriers of the APOA5-1131C or the A allele at the APOA1 -75 G > A SNP).

Conclusion: The continuous progress in Nutrigenomics will allow us to identify those persons for whom diet plays no major role in their risk of CVD as well as those persons who may benefit from specific gene-based dietary advice.

2:30 LIPIDOMIC CHARACTERIZATION OF OBESITY RELATED HEPATIC STEATOSIS

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Background: The ob/ob is an obese, insulin resistant mouse model resulting from the spontaneous mutation of the *ob* gene encoding leptin protein. It is commonly studied as a model for early onset of severe obesity, insulin resistance and fatty liver. The deposition of triacylglycerols (hepatosteatosis) in the liver tissue is typical in obesity.

Objective: To apply the combined bioinformatics and UPLC/MS-based analytical approach in characterization of the fatty liver of the ob/ob mouse model and to use correlation networks combined with gene expression data to investigate and reconstruct the pathways of specific molecular lipid species.

Design: Wild Type (WT) and ob/ob genotypic mice (n=10 and 12, respectively) were studied at the age of 16 weeks. Lipid extracts of liver tissues were run by UPLC/Q-Tof MS and the data collected were analyzed using multivariate analysis to investigate the correlation structure of the lipidome.

Outcomes: The lipidomic platform data flow involving MZmine based data processing, lipid identification, quantification and multivariate analysis showed upregulation of tri- and diacylglycerols and diacylglycerol-phospholipids as well as reactive ceramide species in the ob/ob mouse liver. Ceramides associated with short-chain triacylglycerols. Sphingomyelins, ceramide precursors, appeared downregulated. The correlation network showed a decrease in the number of correlations among the lipid species under ob/ob condition compared to WT suggesting less co-regulation among lipid species in the ob/ob mouse liver. Gene expression data revealed that sphingosine-1-phosphate phosphatase and galactosylceramidase linked to ceramide *via* metabolic reactions were upregulated.

Conclusions: The ob/ob liver profiling exhibited associations between the elevated triacylglycerol levels and the ceramides, which may be involved in the development of obesity associated insulin resistance. Combining lipid pathways with gene expression data showed that two of the three known ceramide synthesis pathways were activated.

2:45 LOSS OF NCB5OR RESULTS IN IMPAIRED FATTY ACID DESATURATION, LIPOATROPHY AND DIABETES

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Background: NCB5OR is a novel flavoheme reductase with a cytochrome b5 like domain at the N-terminus and a cytochrome b5 reductase like domain at the C-terminus. *Ncb5or*^{-/-} (KO) mice, during the first 6 weeks of life, undergo progressive loss of and white adipose tissue and pancreatic β -cells, leading to severe diabetes.

Objective: We aimed to determine whether the lipoatrophy in KO mice was due to the metabolic consequences of diabetes or was an independent phenomenon. Experiments were designed to test whether the diabetes and lipoatrophy in KO mice could be explained by impairment of fatty acid desaturation.

Procedure: KO mice were transplanted with normal islets. Comprehensive lipid profiles were performed on liver from TKO and WT mice. The *Ncb5or* null gene was bred into C57BL/6 mice deficient in the pro-apoptosis gene *Chop* as well as into mice outbred for sensitivity (ALS) or resistance (ALR) to the oxidant diabetogenic agent alloxan.

Results: Lipodystrophy persisted in KO animals in which the confounding metabolic effects of diabetes were eliminated by islet transplantation (TKO). Lipid profiles in livers prepared from TKO animals were markedly deficient in triglycerides and diacylglycerides. Accumulation of palmitoleic and oleic acids ($\Delta 9$ fatty acid desaturation) was decreased relative to WT controls. Treatment of KO hepatocytes with palmitic acid reduced cell viability and increased apoptosis, a response blunted by co-incubation with oleic acid. The onset of diabetes was accelerated in an alloxan-sensitive genetic background and delayed in the absence of expression of *Chop*, suggesting that oxidant and ER stress impair the viability of *Ncb5or*^{-/-} β -cells.

Conclusion: Our results support the hypothesis that *Ncb5or* supplies electrons for fatty acid desaturation, offer new insight into the regulation of a crucial step in fatty acid biosynthesis, and provide a plausible explanation for both the diabetic and lipoatrophic phenotype in *Ncb5or*^{-/-} mice.

1:30 POTENTIAL OF GANGLIOSIDES TO IMPROVE INTESTINAL HEALTH

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Ganglioside GM₃ and GD₃ are glycosphingolipids present in milk. Both gangliosides when present in the diet exert anti-protozoan activity resulting in the rapid elimination of *Giardia* infection. In intestinal epithelial cells, GD₃ is incorporated into lipid rafts formed from the brush border surface and transported into the cell in a time and concentration dependent manner. GD₃ has potent anti-inflammatory properties in response to enterotoxic stimuli. Using an infant bowel model of necrotizing enterocolitis, gangliosides were shown to modulate the inflammatory response to infection and hypoxia to improve bowel survival. Cultured infant bowel was treated with enterotoxic LPS and hypoxia in the presence of nitric oxide (NO), endothelin-1 (ET-1), eicosanoids and pro-inflammatory cytokine balance measured. Gangliosides reduced bowel necrosis by suppressing infant bowel production of NO, ET-1, leukotriene B₄, prostaglandin E₂, IL-1 β , IL-6 and IL-8 in response to LPS and hypoxia demonstrating the bowel protective effect of gangliosides during acute inflammation through pro-inflammatory signal suppression and modulation of vasoactive mediators. These observations suggest that dietary gangliosides have a roll in preventing weaning diarrhea caused by *Giardia* and modulating intestinal inflammatory responses.

2:00 SPHINGOLIPIDS AND THE GUT

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Sphingolipids (SLs) are minor dietary lipids which are not essential for growth or energy supply, although a source choline and fatty acids. Glyco-SLs are also abundant in the microvillar membrane of intestinal epithelial cells, where they are essential for structural integrity and may act as receptors for toxins, virus and bacteria. Metabolism of dietary and membrane SLs in the intestine generates ceramide, sphingosine, sphingosine-1-phosphate (S1P), and ceramide-1-phosphate (C1P), via the action of alkaline sphingomyelinase (NPP7), neutral ceramidase, sphingosine-1-kinase, and ceramide-1-kinase. These intermediary metabolites act as bioactive lipid messengers, influencing numerous cellular functions including growth, differentiation and apoptosis of both epithelial and immunocompetent cells in the gastrointestinal tract, and also the progress of inflammation and responsiveness of the mucosal cells to pathogens. Due to their slow digestion by the action of mucosal rather than pancreatic enzymes they may also interact with sterols to inhibit cholesterol absorption and influence triacylglycerol metabolism. In rodents dietary SLs have antimour effects in the gut. In the adult human diet the most important SL sources are meat, dairy products, eggs, soy products and wheat flour. Human milk contains more SLs than the milk replacement formulations. Milk gangliosides may have anti-infectious effects and SLs may affect mucosal maturation in the neonate. Procedures for enrichment of milk SLs in dairy products without solvent extraction are now available and products are ready for human testing.

2:30 EFFECTS OF ORAL SUPPLEMENTATION WITH A COMPLEX MILK LIPID CONTAINING GANGLIOSIDES DURING THE NEONATAL AND EARLY POSTNATAL PERIOD ON COGNITION AND LEARNING IN YOUNG NORMAL RATS

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Background: Gangliosides, a family of sphingolipids abundant in the brain, have been shown to affect neuronal plasticity during development, adulthood and aging. However, the effects of dietary ganglioside supplementation on learning behavior during early development are not well established.

Objective: The present study was designed to investigate the effect of nutritional supplementation with a complex milk lipid containing gangliosides (GANG) at physiologically relevant doses on learning behavior in young normal rats.

Procedures: Male Wistar rat offspring from normal pregnancies were treated from neonatal d10 until postnatal d80 with either vehicle or GANG at a dose of 0.01% (low) or 0.05% (high) based on total food intake (n=16 per group). Neonatal dosing was via daily oral gavage while post-weaning dosing was via gel supplementation to a standard chow diet. Animals underwent a range of behavioral tests to examine effects of dietary supplementation with GANG on tasks related to spatial memory, learning and cognitive function using the Morris Water Maze, Novel Object Recognition Task and operant learning paradigms.

Results: Supplementation of the GANG composition to infant and growing rats resulted in statistically significant improvements in parameters related to novelty recognition (p<0.02) and spatial memory (p<0.05) using standard behavioral techniques. Moreover, these effects were not attributable to the contribution to total energy intake of the GANG composition. Operant testing showed no significant differences between the treatment groups.

Conclusion: GANG supplementation via a complex milk lipid formulation at physiologically relevant doses to normal young growing rats resulted in an improvement in some markers of learning ability using classical behavioral paradigms. Further investigation of the efficacy of this formulation as an infant formula supplement is warranted.

2:45 DIETARY SUPPLEMENTATION OF RATS DURING PREGNANCY WITH A DAIRY DERIVED LIPID PRODUCT SIGNIFICANTLY INCREASES BRAIN GANGLIOSIDES IN TWO DAY OLD PUPS.

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Background: Gangliosides (GA) are a significant component of brain lipids and have important roles in neuronal migration and axonal extension during brain development. GA supplementation of young, adult and aged animals by diet and injection have shown to induce cognitive changes and changes in lipid composition in the brain.

Objective: To supplement the rat dam diet during pregnancy to effect changes in the GA brain composition of their offspring.

Procedure: Wistar rats were mated at 100 days of age. Upon confirmation of mating rats were put on a control or supplemented diet. The supplemented diet contained gangliosides at 0.05% of measured food intake. The supplement was delivered in the form of gels. At two days of age the pups were sacrificed and brains removed for analysis. The brains were extracted using the Svennholm and Fredman extraction protocol. The upper phase was used for ganglioside analysis.

Results: Concentrations of GM1, GD1a, GD1b and GT1b were found to be higher (p<0.05) in the supplemented group compared to the control group. No significant difference was observed for the other GS measured (GQ1b, GD3, GM2 and GM3). The total GA in this study had also increased significantly (p=0.018).

Conclusion: Supplementation of rat dams during pregnancy with a dairy derived complex lipid product containing GA caused significant changes in the GA concentrations in the brains of rat pups at two days of age.

1:30 IMPACT OF ARACHIDONIC ACID IN HUMANS

O. Adam

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Storage of arachidonic acid (AA) in humans is fuelled by endogenous biosynthesis from linoleic acid, and by preformed AA coming from nutrients of animal origin. People from western societies store on average 30 grams of AA in body lipids, although only 3 grams in Greenland Inuits. We know little about what a normal amount should be. Biosynthesis of AA in mammals is under genetic and dietary control. Diets high in polyunsaturated fatty acids decrease AA biosynthesis. AA provided from the diet differs in many metabolic respects from other PUFA, leading to more than 90 percent incorporation of dietary AA into lipids. It is preferentially taken up from the intestine, protected against oxidation while being transported in lipoproteins or stored in body lipids. AA serves as precursor of proinflammatory eicosanoids, leukotrienes, lipoxins, hydroxyl fatty acids and other mediators or signalling substances. There is epidemiological evidence that the prevalence of atherosclerosis and allergic, autoimmune and certain neoplastic diseases increase with augmented AA intake. While causal relations are not established, vegetarian diets seem to decrease prevalence and incidence of these diseases. Additionally, AA is part of numerous lipid mediators, such as Endocannabinoids and N-acyl ethanolamines regulating a wide range of biological functions including food intake. Animal experiments reveal that dietary intake of AA can modulate the formation of these mediators. AA is a potent mitogenic factor for cells through the production of both 5-lipoxygenase (5-LOX) and cyclooxygenase-2 (COX-2) metabolites. While 5-LOX controls cell survival by regulating the Bcl-2/Bax ratio, COX-2 activity stimulates the release of transforming growth factor- α (TGF- α) and pro-inflammatory cytokines. Conversely, AA in cell culture studies show decreased cell proliferation by inducing apoptosis. These observations underline the intriguing effects of AA in pathogenesis of these diseases, which additionally are modulated by the background-diet.

2:00 DIETARY ARACHIDONIC ACID IMPROVES AGE-RELATED DECLINE OF VASCULAR RESPONSE IN RATS.Kiso Y¹, Nakano D², Ishii F², Fujii K², Ishikura Y¹, Akimoto K¹, Kontani M¹, Kawashima H¹ & Matsumura Y².¹Institute for Health Care Science, SUNTORY Ltd., Mishima-gun, Osaka, Japan; ²Department of Pharmacology, Osaka University of Pharmaceutical Sciences, Takatsuki, Osaka, Japan

Background & Objective: Arachidonic acid (ARA) is a major constituent of cell membrane and plays important roles in the maintenance of physiological function. Several studies have demonstrated that the content of ARA in membrane phospholipids in the brain is lower in aged animals than in young animals and certain neural deficiencies in aged animals are closely related to this decrease. It has recently been reported that dietary ARA supplementation to aged rats can alleviate age-related neural dysfunction. The purpose of our study was to evaluate whether the supplementation of ARA in the diet of aged animals could improve age-dependent decline vascular response.

Methods: Young (2-mo-old) and aged (22-mo-old) Fisher-344 rats were fed with non ARA-supplemented diet (young control, YC; old control, OC) or ARA-supplemented diet (young ARA, YA; old ARA, OA). After a 2-mo feeding period, vascular responses were evaluated using both endothelium-intact and -denuded aortic rings.

Results & Discussion: Phenylephrine-induced vasoconstrictor responses in endothelium-intact rings from group OC tended to be augmented compared with those of rings from groups YC and YA, although this augmentation was significantly suppressed by dietary supplementation of ARA. There were no significant differences in vascular responses to phenylephrine in endothelium-denuded rings among groups YC, YA, OC and OA. Acetylcholine (ACh)-induced, endothelium-dependent vasorelaxation was attenuated in groups OC and OA compared with that in groups YC and YA. ARA supplementation induced slight enhancement of ACh-induced vasorelaxation in aged rats. ACh-induced vasorelaxation correlated very well with aortic ARA concentration in aged rats, but not in young rats. There were no significant differences in endothelium-independent vasodilator responses to sodium nitroprusside in endothelium-denuded rings among groups YC, YA, OC and OA. These findings suggest that dietary ARA supplementation improves the age-related endothelial dysfunction that leads to various cardiovascular diseases.

2:15 NEURONAL DIFFERENTIATION OF HUMAN BONE MARROW DERIVED MESENCHYMAL STEM CELLS INDUCES CHARACTERISTIC CHANGES IN PUFA METABOLISMGreen P¹, Kan I², Melamed E², & Offen D²¹Laboratory for the Study of Fatty Acids; ²Laboratory of Neurosciences; both at the FMRC, Sackler Faculty of Medicine, Tel-Aviv University, Beilinson Campus, Petah-Tikva, Israel

Background: In a previous study we demonstrated that exogenously supplied docosahexaenoic acid (DHA) and arachidonic acid (AA) to human mesenchymal stem cells (MSCs) during induction of neuronal differentiation enhanced neurite outgrowth concomitant with the attainment of a fatty acid profile typical of neural tissue.

Objective: In the present study we investigated the effects of neuronal differentiation on polyunsaturated fatty acid (PUFA) metabolism.

Procedure: Neuronal differentiation of MSCs was induced by a previously described method from our laboratory (JLR, 48:513, 2007). Cellular fatty acid composition was determined by gas chromatography and enzyme expression was determined by RT-PCR and real time PCR.

Results: Upon induction of neuronal differentiation, AA concentration decreased from 9.0 weight% to 6.2 weight% ($p=0.0006$), resulting in an overall decrease in the n-6 PUFA. No significant differences were found in any of the other fatty acid groups or subgroups. When DHA (40 μ M) was added to MSCs before differentiation, the decrease in AA was much more profound (46%), while DHA concentration increased by 65%, accounting for most of the increase of total n-3 PUFAs. Induction of neuronal differentiation, with or without the supplementation of DHA, significantly elevated the expression of phosphatidylserine synthases (PSI and PSII).

Conclusion: Neuronal induction resulted in reduced concentration of cellular AA, enhanced incorporation of supplemented DHA and increased expression of PS synthases. Whilst the reduction in the concentration of AA may point towards a necessary participation of AA metabolites (e.g., prostanoids) in the differentiation process, the changes in DHA incorporation and PS synthases expression indicate that the differentiated cells acquired mechanisms necessary for neural tissue-characteristic PUFA metabolism.

2:30 ARACHIDONIC ACID PRESERVES HIPPOCAMPAL SYNAPTIC PLASTICITY AND CALCIUM HOMEOSTASIS IN SENESCENT RATS.Sakakibara, M.¹, Kashiyae, Y.¹, Fukaya, T.¹, Kontani, M.², Kawashima H.², Kiso, Y.²¹Graduate School of High-Technology for Human Welfare, Tokai University, Numazu 410-0321, Japan,²Institute for Health Care Science, SUNTORY Ltd., Mishima-gun, Osaka 618-8503, Japan

Background & Objective: Based on the previous studies, aged rats of long term supplementation with Arachidonic acid (ARA) (OA) showed the significant better water-maze performance than aged control animals (OC) and the magnitude of hippocampal LTP was significantly larger in OA than OC. Furthermore we observed that hippocampal neuronal membrane in OA was more fluid than those in OC whereas the fraction of diffusible protein remained smaller than in young control (YC) with FRAP observation. The aim of this study is to evaluate the calcium homeostasis at hippocampus in OC, OA and YC by the technique of electrophysiology and imaging-physiology.

Methods: Aged Fischer-344 rats (24-mo-old) fed with 50mg/D ARA containing foods or aged and young (4-mo-old) rats with control diet were used. After 3 mo feeding period, electrophysiological observation was made whether Ca^{2+} flows into hippocampal CA1 pyramidal neuron through NMDA receptor or VDCC for induction of LTP among OC, OA and YC. The Ca^{2+} level at hippocampus was estimated with calcium imaging technique using FURA-2 AM.

Results & Discussion: Blockade of NMDA channel with APV in OA relative contribution between NMDA and VDCC to induce and maintain LTP was not altered the LTP as well as YC, whereas blockade of VDCC with nifedipine blocked induction of LTP in OC. These facts suggested that age-dependent alteration of calcium entry pathway into the neuron to induce and maintain LTP took place. Application of 50 mM K^+ containing artificial cerebrospinal fluid depolarized YC-CA1 pyramidal neuron to increase intracellular Ca^{2+} twice as that of OC and OA. Calcium mobilization in aged preparations (OC and OA) was significantly smaller than that in YC. Selective activation of NMDA channel with bath-application of 200 mM NMDA, Ca^{2+} increase in CA1 area was significantly smaller in OC and OA compared to YC, whereas Ca^{2+} in dentate gyrus showed no significant difference between OA and YC keeping significant smaller increase in OC. This may reflect the active neurogenesis in OA at the dentate area.

2:45 MATERNAL DIETARY ARACHIDONIC ACID SUPPLEMENTATION AND RAPID CATCH UP GROWTH OF OFFSPRING OF DIABETIC DAMS ARE NOT ASSOCIATED WITH GLUCOSE TOLERANCE OR BODY COMPOSITION AT YOUNG ADULT AGE

Zhao J, Weiler HA

McGill University, Ste-Anne-de-Bellevue, QC, Canada

Background: Maternal AA supplementation during pregnancy improves neurodevelopment of offspring of diabetic dams in poor glycemic control (glucose > 13 mmol/L).

Objective: To explore the long term effects on offspring at 8 wk and 12 wk of age.

Procedure: Female Sprague Dawley rats (n=24) were randomized to 6 groups using a 3 x 2 design: treatments were saline injection, streptozotocin (60 mg/kg) induced-diabetes (glucose > 13 mmol/L) in good glycemic control (<13 mmol/L, STZ/GC) or poor control (13-20 mmol/L, STZ/PC) using insulin; and diets were either control or AA diet (0.5 % of fat w/w). After 1 wk adaptation to diet and treatment, rats were mated. Offspring were nourished by their biological mother and then fed a standard chow. Measurements included weight at d3, d14, d28 plus 8 and 12 wk. Whole body composition and bone mineral density (BMD) was measured at 4, 8 and 12 wk and oral glucose tolerance (OGTT) tested at 8 and 12 wk. Main and interaction effects of treatment and diet were assessed using factorial ANOVA.

Results: Only offspring from STZ/GC group weighed less than saline control at d3 (7.1 vs 6.4g, P=0.0001), d14 (30.3 vs. 27.0g, P<0.0001) and d29 (83.8 vs. 76.2g, P<0.0001), STZ/PC had lower BMD at d28 (0.080 vs. 0.078 g/cm², P=0.0023). However growth and BMD were not different by 8 and 12 wk. The AA diet only elevated weight in the saline offspring at d3 (interaction P=0.049). Total weight gain was higher in the STZ/GC compared to saline group (521% vs. 636%, P<0.01). Body composition and OGTT at 60 min were not different among groups.

Conclusion: The rapid catch-up growth in the offspring of diabetic dams was not associated with glucose intolerance. While dietary AA improved neurodevelopment neonatally, there were no implications for growth or body composition at young adult age.

7:00 IMPACT OF LINOLEIC ACID INTAKE ON ARACHIDONIC ACID FORMATION AND EICOSANOID BIOSYNTHESIS IN MAN

O. Adam

Ludwig-Maximilians-University; Munich, Germany

Epidemiological findings purportedly indicate that a diet rich in linoleic acid (LA) can favour cardio-vascular diseases by increasing pro-inflammatory eicosanoids derived from arachidonic acid (AA). Clinical trials and observations in vegetarians show a cardio-protective role of LA. If a vegan diet is followed, the percentages of LA in plasma lipids are higher, and that of AA are lower, compared to omnivores. Cell culture experiments showed an inhibition of delta-6-desaturase, the rate limiting enzyme in AA biosynthesis, by all polyunsaturated fatty acids. Employing liquid formula diets (LFD) containing no AA, we investigated the effect of LA intake on the formation of AA and prostaglandins in healthy volunteers. A LFD containing 0 energy% LA lowered the percentage of LA in plasma CE from 54+5% to 35+4 % at the end of a two weeks experimental period. Concomitantly, the percentages of AA increased from 10+2 % to 16+3 %. The intake of 20 energy% LA for 2 weeks increased LA from 54+4 % to 62+5 %, while AA decreased from 10% to 8% of total fatty acids. The calculated amount of AA present in plasma lipids decreased by 30% with a linoleic acid intake of 20 en%. Determinations of tetranor-prostanoic acid, the joint metabolite of prostaglandins D, E, F and isoprostanes in 24-h-urines of volunteers at the end of 2-weeks LFD periods with a linoleic acid intake of 0, 4, 8, 12 and 20 energy%, showed a significant increase with a linoleic intake of 12 and 20 energy%. This increase was not found for native prostaglandins, indicating stimulated metabolism of linoleic acid via cytochrome P450. Compared to lower intake rates, the increase of LA with 12 and 20 energy% was small, indicating a higher oxidation rate, in agreement with the increased formation of tetranorprostanedioic acid. The findings are discussed in context with the literature.

8:15 OMEGA-3 PUFA: GOOD OR BAD FOR PROSTATE CANCERBrouwer IA¹¹Institute of Health Sciences, Faculty of Earth and Life Sciences, Vrije Universiteit, Amsterdam, The Netherlands.

Background: The effects of intake and status of omega-3 fatty acids on prostate cancer are still unclear. There are some indications that alpha-linolenic acid and the very long-chain omega-3 fatty acids EPA and DHA may differently affect the risk of prostate cancer. Furthermore, there might be differences depending on the grade of prostate cancer.

Objective: To provide an overview of human studies on the relationship of very-long chain omega-3 fatty acids and alpha-linolenic acid with the risk of prostate cancer.

Procedure: Studies in humans on the relationship between intake of omega-3 poly-unsaturated fatty acids and prostate cancer were identified in the MEDLINE databases and by checking citations in identified publications. Meta-analyses to provide quantitative estimates of the associations between omega-3 PUFA and prostate cancer were performed by using the risk estimates of the individual studies. All individual studies had to provide a quantitative estimate of relative risk and its standard error. Separate meta-analyses were performed on the relationship between alpha-linolenic acid and the very-long chain omega-3 fatty acids and the risk of prostate cancer.

Results: Results will be presented during the Issfal 2008 conference.

8:15 PROSTAGLANDINS, CANCER AND THE CLINIC: FROM BENCH TO BEDSIDE AND BACK.

Andrew Dannenberg, M.D. Weill Cornell Medical College, New York, NYC

Cyclooxygenases (COX) catalyze the first step in the synthesis of prostaglandins (PG) from arachidonic acid. The COX-2 gene is an immediate early-response gene that is induced by a variety of mitogenic and inflammatory stimuli. Multiple lines of evidence suggest that COX-2 plays a significant role in carcinogenesis. COX-2 is overexpressed in transformed cells and in premalignant and malignant tissues. The most specific data that support a cause-and-effect relationship between COX-2 and tumorigenesis come from genetic studies. Overexpression of COX-2 has been observed to drive tumor formation whereas COX-2 deficiency protects against several tumor types. Selective COX-2 inhibitors protect against both the formation and growth of tumors in a variety of experimental models. Several potential mechanisms may explain the link between COX-2 and malignancy. Enhanced synthesis of PGE₂ has been shown to stimulate cell proliferation, induce angiogenesis, inhibit apoptosis and suppress immune surveillance. Collectively, these findings provided a strong rationale for evaluating selective COX-2 inhibitors as anticancer agents in humans. Selective COX-2 inhibitors reduced the colorectal polyp burden in familial adenomatous polyposis patients. Moreover, several large clinical trials showed that selective COX-2 inhibitors caused a significant reduction in the recurrence of sporadic colorectal adenomas. However, an increased risk of cardiovascular complications was also observed in these chemoprevention studies. The mechanism underlying this toxicity is not fully understood, but inhibition of COX-2 results in the loss of all downstream PGs. It has been suggested that selective COX-2 inhibitors block the production of cardioprotective PGI₂ by vascular endothelium, without inhibiting COX-1-dependent platelet thromboxane A₂ synthesis, supporting a pro-thrombotic mechanism. To improve the therapeutic index, alternate treatment strategies are being explored. One possibility is to selectively inhibit the formation of PGE₂ without suppressing levels of PGI₂. Microsomal prostaglandin E synthase-1 (mPGES-1), an inducible enzyme that is commonly overexpressed in neoplastic tissues, catalyzes the conversion of COX-derived PGH₂ to PGE₂. Silencing of mPGES-1 can suppress both the synthesis of PGE₂ and inhibit cell proliferation. Selective inhibitors of this enzyme are being developed. An alternate strategy is to block the actions of PGE₂ rather than to inhibit its production. PGE₂ exerts its effects by binding to G protein-coupled receptors. Four subtypes of PGE₂ receptor (EP1-4) have been cloned and defined pharmacologically. Different EP receptors have been implicated in regulating cell proliferation, immune function and angiogenesis. Evidence suggesting that both mPGES-1 and EP receptors are *bona fide* therapeutic targets will be reviewed.

1:00 THE DINO TRIAL OUTCOMES: DOES HIGH-DOSE DIETARY DOCOSAHEXAENOIC ACID (DHA) IMPROVE THE NEURODEVELOPMENTAL OUTCOME OF PRETERM INFANTS?Makrides M¹⁻⁴, Gibson RA¹⁻⁴, Collins CT¹⁻⁴, McPhee AJ³ on behalf of the DINO Study Team¹ Women's and Children's Health Research Institute, Adelaide, South Australia² University of Adelaide, South Australia³ Women's and Children's Hospital, North Adelaide, South Australia⁴ Flinders Medical Centre, Bedford Park, South Australia

Objective: To determine whether preterm infants receiving the estimated in utero supply of DHA (approximately 1% of dietary fatty acids) have improved neurodevelopment at 18 months' corrected age compared with standard practice (0.2-0.3% DHA).

Methods: Infants born <33 weeks' gestation were randomly allocated to high-DHA or standard practice according to a concealed schedule stratified for sex and birth weight (<1250 g and ≥1250 g). Mothers providing breast milk consumed 3 g of oil in capsules containing either tuna oil (900mg DHA) or soy oil (no DHA) that resulted in milk with either high (1.0%) or standard (0.3%) DHA. Infants requiring supplemental formula feeds were fed a formula with a matching fatty acid composition. Intervention was from day 2-5 of life until the infant's due date. Bayley Mental (MDI) and Psychomotor Developmental Indices (PDI) were assessed at 18 months' corrected age.

Results: 657 infants were allocated to the high-DHA (n=322) and standard practice (n=335) groups. 639 (97.3%) infants completed the treatment phase and 96.4% completed the 18 month follow-up. Preliminary analyses indicate that there were no overall differences in MDI or PDI between groups, but that there were significant interactions for MDI between diet and sub-groups. In the <1250g sub-group, infants fed high-DHA had greater MDI scores than infants fed according to standard practice. The MDI of infants born <1250g and fed high-DHA did not differ from infants born ≥1250g irrespective of diet. Girls fed high-DHA had MDI scores of 99±13 which were greater than girls fed according to standard practice. The MDI of boys was lower and did not differ between groups.

Conclusion: Infants born <1250g may have a conditional essentiality for high-DHA in the neonatal period and high-DHA may normalize the MDI scores of girls. The mechanism for the differential response in girls and boys requires further investigation.

1:00 DOCOSAHEXAENOIC ACID AND EARLY BIOBEHAVIORAL DEVELOPMENT

Colombo J

University of Kansas, Lawrence, KS, USA

Docosahexaenoic acid (DHA) is an omega-3 fatty acid found in high concentration in the brain and retina. Studies have shown DHA to be related to the development of visual function in infancy, but evidence is also mounting that DHA has effects that are relevant in the realm of biobehavioral and neurocognitive development. This plenary address will review and evaluate the available evidence on this topic, with particular emphasis on longitudinal studies of measures taken in infancy and the relevance for these studies to long-term outcome.

10:30 DECREASED BRAIN DOCOSAHEXAENOIC ACID CONTENT PRODUCES NEUROBIOLOGICAL EFFECTS ASSOCIATED WITH DEPRESSION: INTERACTIONS WITH REPRODUCTIVE STATUS IN FEMALE RATS

Levant B, Carlson SE, & McCarson KE
University of Kansas Medical Center, Kansas City, KS, USA

Background: Decreased tissue levels of docosahexaenoic acid (DHA; 22:6n-3) are implicated in the etiology of depression. We have shown that brain phospholipid DHA content of adult female rats can be decreased roughly 20%, similar to that reported in depressed humans, by feeding an alpha-linolenic acid-deficient diet for a sufficient period of time. This loss of brain DHA is accelerated by the physiological demands of pregnancy and lactation.

Objective: With the aim of determining neurobiological sequelae of decreased brain DHA content, this study examined the effects of a loss of brain DHA content and concurrent reproductive status in adult female Long-Evans rats.

Procedure: An alpha-linolenic acid-deficient diet and breeding protocols were used to produce virgin and parous female rats with cortical phospholipid DHA levels 23-26% lower than virgin and parous rats fed a diet containing adequate alpha-linolenic acid. Parous dams were tested/euthanized at weaning (postnatal day 20) of the second litter; virgin females, were tested during diestrus.

Results: Decreased brain DHA was associated with decreased hippocampal BDNF gene expression and increased relative corticosterone response to an intense stressor, regardless of reproductive status. In virgin females with decreased brain DHA, serotonin content and turnover in frontal cortex were decreased compared to virgin females with normal brain DHA. In parous dams with decreased brain DHA, the density of 5-HT1A receptors in the hippocampus was increased, corticosterone response to an intense stressor was increased, and the latency to immobility in the forced swim test was decreased compared to parous dams with normal DHA.

Conclusion: These findings demonstrate neurobiological alterations attributable to decreased brain DHA, or an interaction of parous status and brain DHA level. Furthermore, these alterations are consistent with findings in depressed humans, and thus support a causative role for reduced brain DHA in the multifactorial pathogenesis of depressive illnesses, particularly postpartum depression.

10:45 SYNERGISTIC EFFECTS OF STRESS AND N-3 POLYUNSATURATED FATTY ACID DEPRIVATION ON EMOTIONAL RESPONSE AND BRAIN LIPID COMPOSITION IN ADULT RATS

Mathieu G, Denis S, Lavalie M & Vancassel S.
Nu.Re.Li.Ce, INRA, Jouy en Josas, France

Background: Inadequate intake of n-3 polyunsaturated fatty acids (PUFA) during development strongly reduces the docosahexaenoic acid (DHA) brain levels, leading to behavioral impairment. Particularly, emotional state is altered with elevated indices of anxiety, aggression and depression. This is associated to changes in function of the meso-cortico-limbic dopaminergic pathway, largely involved in reward process and emotional behavior. Chronic early life stress induces similar modifications in neurotransmission function and leads to changes in adult reward response and hedonia expression.

Objective: Our aim was to study the consequences of n-3 PUFA dietary deficiency on the emotional response in adult rats subjected to maternal separation (MS) as chronic early life stress.

Procedure: Pups fed a control or an n-3 PUFA deficient diet were maternally separated daily for two weeks before weaning. In adult rats, reward response was quantified by chronic sucrose consumption and after acute stress. Then the brain phospholipid fatty acid composition was analyzed.

Results: Daily sucrose consumption was identical in both dietary groups in non stressed animals but it was significantly increased in stressed rats fed the n-3 PUFA deficient diet. The acute stress increased the sucrose intake in stressed rats of both dietary groups and in non-stressed deficient rats. Moreover, the MS procedure had a synergistic effect with the lack of n-3 PUFA in increasing sucrose intake by 80 % compared to control condition. N-3 PUFA deprivation dramatically depleted brain membranes of DHA whereas n-6 PUFAs, and specifically arachidonic acid (AA) levels were increased. However, the diet-induced AA increase was significantly 20 % higher in MS rats.

Conclusion: Our results showed that chronic n-3 PUFA deprivation and stress caused some common long-lasting changes related to the emotional status. This suggests that n-3 PUFA deficit could be an environmental risk to increase vulnerability to depressive-like response induced by early life chronic stress.

11:00 DOCOSAHEXAENOIC ACID MODULATES THE NORADRENALINE RELEASE IN NEUROBLASTOMA SH-SY5Y CELLS

Mathieu G, Denis S, Lavalie M & Vancassel S.
Nu.Re.Li.Ce, INRA, Jouy en Josas, France

Background: Dietary deficit in docosahexaenoic acid (DHA) induces a dramatic fall in membrane DHA levels and some abnormalities in rodent behaviour related to alteration of neurotransmission function. More particularly, monoamine and acetylcholine release, vesicular storage pool and expression of several neurotransmitter receptors are modified in different brain structures. Recent works suggest that polyunsaturated fatty acids (PUFA) can regulate the SNARE complex (Soluble NSF Attachment Receptor) assembly, which initiates the membrane fusion, leading to exocytosis of neurotransmitters.

Objective: Our aim was to study the release of neurotransmitter by the neuroblastoma cell line SH-SY5Y, in response to modifications of the PUFA phospholipid membrane contents. These cells contain functional vesicles which release noradrenaline (NA) and provide a valid model to study exocytosis pathway.

Procedure: SH-SY5Y cells were cultured with DHA, eicosapentaenoic (EPA) or arachidonic (AA) acids for 72 hours (70 µM) and further NA uptake and release (basal and K+-evoked) were measured. Fatty acid composition of membrane phospholipids was determined and quantification of mRNA encoding for synaptotagmine and SNARE complex protein genes was assessed by qPCR.

Results: The phosphatidylethanolamine contents of DHA were 4-fold increased in cells incubated with DHA compared to non-supplemented cells, whereas they were reduced by 30 % and 70 % after EPA and AA supplementation, respectively. Incorporation of DHA specifically enhanced basal but not K+-evoked NA release (25%, p < 0.05); no effect of EPA or AA was observed. The mRNA levels of synaptotagmine 1, syntaxin 1A and VAMP 1 were identical in all the cultured conditions, without effect of any PUFA.

Conclusion: We showed that incorporation of DHA in phospholipid membranes of SH-SY5Y cells potentiated the basal release of NA. This suggests that, in vivo, the lipid environment, and more particularly the levels of DHA in membranes, could influence the efficiency of exocytosis with consequences on behaviors.

11:15 EFFECTS OF ENRICHED EICOSAPENTAENOIC ACID (E-EPA) OMEGA-3 FATTY ACID SUPPLEMENTATION ON HOT FLASHES: A DOUBLE-BLIND, PLACEBO-CONTROLLED, RANDOMIZED CLINICAL TRIAL

Lucas M¹, Asselin G¹, Mérette C², Poulin M-J², Dodin S^{1,3}

¹Lucie and André Chagnon Chair for the Teaching of an Integrated Approach in Prevention, Laval University; Saint-François d'Assise Hospital (CHUQ), Québec (QC) Canada; ²Department of Psychiatry, Robert Giffard Research Centre, Laval University, Québec (QC) Canada; ³Department of Obstetrics and Gynecology, Laval University, Québec (QC) Canada

Background: Hot flashes (HF) are the most common symptoms noted during menopause. More than one-third of women seek medical advice for the management of menopausal symptoms and most of them do so because of the discomfort associated with HF.

Objective: To compare the effects of E-EPA omega-3 supplementation and placebo on HF among middle-aged women.

Procedure: A total of 120 women aged between 40 and 55 years with moderate to severe psychological distress were randomly assigned to E-EPA supplementation or placebo for 8 weeks. Only women with HF were included in this analysis (E-EPA n = 45, placebo n = 46). Outcomes were change from baseline to week 8 post-intervention regarding HF frequency (number of HF/d), intensity and score (frequency x intensity). Outcomes were tested with repeated-measures analysis of covariance (rANCOVA) with baseline score as covariate.

Results: At baseline, mean HF frequency was 2.8±2.8 (SD) per day. According to rANCOVA, main effects were observed in the treatment group regarding HF frequency (P = 0.01) and score (P = 0.04). Moreover, time x group interaction was significant for HF frequency (P = 0.005), which decreased by a mean of 1.58/d (95% CI): -2.18, -0.98), corresponding to 55% of the baseline value in the E-EPA group, and by 0.50/d (95% CI: -1.20, 0.20) (25% of baseline value) in the placebo group. After 8 weeks, HF intensity improved significantly in the E-EPA but not in the placebo group. However, there was no difference in the change of HF intensity between groups. MENQOL scores improved significantly over time in both groups but no significant differences were noted between them.

Conclusions: E-EPA omega-3 supplementation reduced HF frequency and improved the HF score relative to placebo. These results need to be confirmed by a clinical trial specifically designed to evaluate HF in more symptomatic women.

11:30 AN ENRICHED EICOSAPENTAENOIC ACID (E-EPA) SUPPLEMENT IN THE TREATMENT OF PSYCHOLOGICAL DISTRESS AND DEPRESSIVE SYMPTOMS AMONG MIDDLE-AGED WOMEN: A DOUBLE-BLIND, PLACEBO-CONTROLLED, RANDOMIZED CLINICAL TRIAL

Lucas M¹, Asselin G¹, Mérette C², Poulin M-J², Dodin S^{1,3}

¹Lucie and André Chagnon Chair for the Teaching of an Integrated Approach in Prevention, Laval University; Saint-François d'Assise Hospital (CHUQ), Québec (QC) Canada; ²Department of Psychiatry, Robert Giffard Research Centre, Laval University, Québec (QC) Canada; ³Department of Obstetrics and Gynecology, Laval University, Québec (QC) Canada

Background: Menopausal transition is known to be associated with increasing vulnerability to psychological distress (PD) and depressive symptoms. Studies suggest that omega-3 supplements could be of benefit in depressive symptoms.

Objective: To compare E-EPA to placebo for the treatment of PD and depressive symptoms among middle-aged women.

Method: 120 women aged between 40 and 55 years with moderate to severe PD were randomly assigned to 1.05 g/day of EPA plus 0.15 g/day of docosahexaenoic acid (n = 59) or placebo (n = 61) for 8 weeks. Main outcome measures were 8-week change in scores on PD (Psychological General Well-Being (PGWB) Schedule) and depressive scales (21-item Hamilton Depression Rating Scale (HAM-D-21)).

Results: At baseline, PD women were mildly to moderately depressed, and 24% met DSM-IV major depressive disorder (MDD) criteria. After 8 weeks of intervention, PD and depressive symptoms improved in both groups, but no significant differences were noted between them. However, stratification analyses for MDD diagnosis at baseline indicated that 8-week E-EPA changes were greater than placebo among PD women without MDD. Compared to placebo, E-EPA-adjusted mean differences were 6.9 (95% CI): 0.0009, 13.7, p=0.050) for PGWB and -2.2 (95% CI: -0.005, -4.5, p=0.049) for HAM-D-21. Among PD women with MDD, E-EPA changes were not significant compared to the placebo group.

Conclusions: To our knowledge, this is the first trial of omega-3 supplementation in the treatment of PD and depressive symptoms among middle-aged PD women. In all PD women, 8-week E-EPA omega-3 monotherapy failed to show benefits over placebo. However, stratification analyses for MDD diagnosis revealed that 8-week change on PD and depressive scales improved significantly in E-EPA compared to placebo among PD women without MDD.

11:45 ARE LOWER THAN NORMAL BLOOD LEVELS OF ARACHIDONIC ACID IN PEOPLE WITH LEARNING DISORDERS PHYSIOLOGICALLY AND CLINICALLY IMPORTANT?

Morse NL¹, Fahey TJ², Clough PM³, Richardson AJ⁴

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Background: Numerous small individual studies have reported that people with learning disorders have lower than normal blood levels of docosahexaenoic acid (DHA) and to a lesser extent arachidonic acid (AA). There has been much speculation pertaining to how and why the DHA levels are lower than normal and the physiological consequence on brain function. However, relatively little attention has been paid to the significance of the low AA levels.

Objective: This presentation highlights the results of a meta-analysis showing that red blood cell (RBC) and plasma/serum AA levels are lower than normal in people with learning disorders and speculates on the potential importance of this observation.

Procedure: Reports including subjects with various learning disorders or symptoms thereof and age-matched controls, that included RBC and/or plasma and/or serum fatty acid profiles prior to treatment with fatty acid supplements were identified through a literature search. Meta-analyses on RBC and plasma/serum AA and DHA as a percent of total fatty acids (subject minus control) were completed.

Results: RBC AA and DHA levels were significantly lower than normal [-3.93 and -18.92 respectively (weighted mean difference as a % of weighted mean control)] although there was significant heterogeneity among studies for AA. Plasma/serum AA and DHA were also significantly lower than normal [-4.54 and -13.70 respectively (weighted mean difference as a % of weighted mean control)] but in this case the significant heterogeneity was found for DHA. The observed heterogeneity may or may not be physiologically or clinically relevant. In addition, even though DHA is even more severely depressed than AA, the magnitude of the physiologically and clinically relevant consequences may or may not be relative to their respective subnormal concentrations.

Conclusion: Meta-analysis confirms statistically-significant reductions in blood levels of AA and DHA are associated with learning/developmental disorders. Heterogeneity between studies bears further investigation as does the consequences and relative importance of subnormal AA levels.

11:45 LOW LONG-CHAIN OMEGA-3 LEVELS CORRELATE WITH ADHD SYMPTOMS, ATTENTION AND LITERACY PROBLEMS IN CHILDREN WITH LOW OMEGA-3 STATUS.

Sinn N^{1,2}, Milte C^{1,2}, Buckley J^{1,2}, Coates AM^{1,2}, Howe PRC^{1,2}

¹Nutritional Physiology Research Centre, University of South Australia

²Australian Technology Network Centre for Metabolic Fitness

Background: Studies have reported lower long-chain omega-3 polyunsaturated fatty acid (LC n-3 PUFA) levels in children with attention deficit hyperactivity disorder (ADHD) compared with controls and clinical trial results indicate that some children with ADHD may benefit from LC n-3 PUFA supplementation.

Objective: To investigate relationships between LC n-3 PUFA levels and severity of learning and behaviour problems in children. It was hypothesised that lower LC n-3 PUFA levels would be associated with greater symptom severity.

Procedures: Thirty five 7-12 year old South Australian children with ADHD and learning difficulties (LD) provided blood samples for assessment of erythrocyte fatty acids and underwent cognitive assessments; their parents completed Conners' Parent Rating Scales.

Results: Mean erythrocyte EPA, DPA and DHA levels were 0.61, 2.19 and 3.45% of total fatty acids respectively. In 27 children with LC n-3 PUFA levels < 75th percentile (< 6.8%, equivalent to EPA+DHA < 4.3%), lower LC n-3 PUFA and lower DPA were associated with higher scores on the ADHD index subscale (r = -.39, p < .05; r = -.43, p < .01 respectively) and on the DSM-IV Inattentive subscale (r = -.38, p < .05; r = -.56, p < .01 respectively). Higher DHA levels were associated with improved vocabulary (r = .54, p < .05). When children in the upper quartile of LC n-3 PUFA were included in the analysis, these associations were not observed.

Conclusion: Suboptimal LC n-3 PUFA status may be a contributing factor to inattention and literacy in this group. However, in children who have higher levels of LC n-3 PUFA, problems with ADHD and LD may be attributable to other factors. Further analyses with a larger data set and correlations with degree of improvement following supplementation are needed to confirm this possibility and to determine optimal n-3 levels in these children.

10:30 ALTERED DIFFERENTIAL EXPRESSION OF CCAAT/ENHANCER BINDING PROTEIN (C/EBP) GENES BY USING N-3 POLYUNSATURATED FATTY ACIDS (PUFAS) IN ADIPOGENESIS OF ATLANTIC SALMON (*SALMO SALAR*) INVITROTien-sheng Huang¹, Marijana Todorovic², Bente Ruyter², and Bente E. Torstensen¹¹National Institute of Nutrition and Seafood Research (NIFES), P. O. Box 2029 Nordnes, N-5817 Bergen; ²AKVAFORSK, Institute of Aquaculture Research, NO-1432 Ås, Norway**Background:** The proliferation and differentiation of preadipocytes into adipocytes were investigated in many experimental models. However, it is not fully clear whether differentiation of preadipocytes is associated with a specific gene expression pattern in fish.**Objective:** We study the effects of n-3 polyunsaturated fatty acids (PUFAs) on adipogenesis to address how PFA signaling influences lipid metabolism *in vitro*.**Procedures:** Here, for the first time we reported orthologs of CCAAT/enhancer binding protein genes, *c/ebp*, *c/ebp*, and *c/ebp*, from salmon adipocytes by using EST sequences and RT-PCR, whose expression was distinct in a variety of tissues. The differential expression patterns of *c/ebp*, peroxisomal proliferator-activated receptor (*ppar*), and the adipogenic gene markers were observed in the development of preadipocytes *in vitro*. Furthermore, their expression and the triacylglycerol (TAG) accumulation in adipocytes were affected by the medium enriched with either the PUFAs or oleic acid compared to the cells incubated with normal differential medium.**Conclusion:** Our results suggest that the expression of *c/ebps* is important markers as well as that of *ppars* in adipogenesis, and nutritional factors, e. g., fatty acids, lead to manipulation of this process to affect the formation of adipogenic cells.**10:45** DIFFERENTIAL MODIFICATION OF THE PHOSPHOLIPID PROFILE BY TRANSIENT ISCHEMIA IN RAT HIPPOCAMPAL CA1 AND CA3 REGIONS.

Hamazaki K & Kim HY

Laboratory of Molecular Signaling, NIAAA, NIH, Bethesda, MD, USA

Background: The CA1 region of the hippocampus is most susceptible to cerebral ischemia in both rodents and humans, while CA3 region is remarkably unaffected. Docosahexaenoic acid (DHA) has been shown to exert therapeutic and preventive effects on ischemic damage. DHA has been also shown to promote neuronal survival through the accumulation of phosphatidylserine (PS). These findings suggest a role of DHA-containing membrane phospholipids in hippocampal survival under ischemic conditions.**Objective:** To investigate the involvement of phospholipids in hippocampal survival by characterizing phospholipid profile in CA1 and CA3 in relation to ischemic damage.**Procedure:** The transient ischemia was induced via bilateral occlusion of rat common carotid arteries for 20 minutes followed by 4 days of reperfusion. The phospholipid contents in CA1 and CA3 regions were evaluated by LC/MS.**Results:** The levels of total PS and phosphatidylethanolamine (PE) in CA1 were 20% (p=0.02) and 14% (p=0.02) higher than those in CA3, respectively. After ischemia, about 79% of pyramidal cell death occurred in the CA1 region with significant interneuronal atrophy. Total PS and PE contents were decreased by 24% (p=0.002) and 33% (p=0.0001) in CA1 compared to the sham group, respectively. The decrease was evenly distributed in most molecular species of PS and PE regardless of unsaturation status, suggesting that selective activation of PLA2, which prefers polyunsaturated release, may not be directly involved in cell death in CA1. Despite the high abundance of DHA and its susceptibility to oxidation, DHA containing species were not lost disproportionately but retained in PS or PE. In the CA3 region, where no cell death was detected, no significant differences were observed in total PS and PE, either.**Conclusion:** Based on our data, we suggest that maintaining high concentrations of DHA-containing aminophospholipids in the hippocampal CA1 may be important in supporting neuronal survival in this susceptible region.**11:00** OLEOYL-ETHANOLAMIDE AND ITS NON-HYDROLYSABLE ANALOG REDUCE BODY FAT MASS IN HIGH FAT FED MICE BY INCREASING POST-PRANDIAL LIPID OXIDATIONThabuis C¹, Destailats F², Tissot-Favre D², Maillot M¹, Martin JC¹¹INSERM, 476 “Nutrition Humaine et Lipides”, Marseille, F-13385 France; INRA 1260, Marseille, F-13385 France; Univ Méditerranée Aix-Marseille 2, Faculté de Médecine, IPHM-IFR 125, Marseille, F-13385 France;²Nestlé Research Centre, CH-1000 Lausanne Switzerland.**Background:** Exogenous oleoylethanolamide (OEA) regulates feeding and body weight gain through activation of the peroxisome proliferator-activated receptor- α signaling pathway in the intestine. OEA could also regulate food intake through binding to the G-protein coupled receptor GPR119.**Objectives:** Our aim was to evaluate the body fat lowering effect of OEA on diet-induced obesity (DIO) mice by comparison to its non hydrolysable analog KDS 5104 upon chronic oral administration.**Procedure:** Male C57BL6j mice were challenged with a DIO diet enriched with either 100 mg/kg bw of OEA or KDS-5104 for 5 weeks (n=10 per group). Control mice received only the DIO diet. Food intake and weight gain were monitored. Lipid and carbohydrate oxidations were evaluated using indirect calorimetry. The expression of genes involved in food intake and body fat mass regulations was measured by real-time quantitative PCR.**Results:** Orally administrated OEA and KDS significantly lowered food intake (-6%, $P < 0.05$) over the 5 weeks, decreased adipose tissue (AT) mass (-18%, $P < 0.05$) and body weight gain (-8%, $P < 0.05$). Both N-acylethanolamine derivatives increased the oxidation of lipid substrates, and decreased the oxidation of carbohydrate substrates. OEA also increased total energy expenditure, but not KDS. Both molecules increased the cumulated total activity (post-prandially and over 24h). These results were associated to an up-regulation of some genes involved in lipid oxidation (CPT 1 in intestine and liver, FIAF in intestine and AT), in lipogenesis (SREPB1c in liver), in food intake control (intestinal CCK and GPR119), and endocannabinoid signaling (adipose CB1).**Conclusion:** Our data suggest that orally administrated OEA is highly bioavailable and as biologically potent as its non-hydrolysable analog to reduce body weight gain and fat mass in high fat fed mice. This would be achieved mostly by modifying energy balance, especially during the post-prandial period (lipid oxidation).**11:15** THE EFFECT OF POLYUNSATURATED FATTY ACIDS AND 9-CIS RETINOIC ACID ON ABCA1-MEDIATED CHOLESTEROL EFFLUX IN RAW264.7 MACROPHAGESChiang AN¹, Chiu WC¹, Chen CJ², & Juan CC³¹Institute of Biochemistry and Molecular Biology, and ³Institute of Physiology, National Yang-Ming University, Taipei, Taiwan;²Department of Education and Research, Taichung Veterans General Hospital, Taichung, Taiwan**Background:** How to decrease the cholesterol accumulation in macrophages is an important issue to prevent atherosclerosis.**Objective:** This study sought to explore the effects of polyunsaturated fatty acids (PUFAs) and 9-cis retinoic acid (9-cis-RA) on the regulation of ATP-binding cassette transporter A1 (ABCA-1) expression and cholesterol efflux in macrophages.**Procedure:** RAW264.7 macrophages were cultured in DMEM with fatty acid (80 mM)-albumin mixture in the presence or absence of 9-cis-RA (5 mM). After 24 h incubation, cells were washed and harvested with lysis buffer. mRNA and protein levels of ABCA-1 were measured by RT-PCT and Western blot analyses, respectively. To investigate the effect of PUFAs and 9-cis RA on the cholesterol efflux from macrophages, RAW264.7 macrophages were incubated with [³H] cholesterol and acetylated LDL (AcLDL) containing 0.2% BSA with or without 10 μ g/ml apoAI. The percent of cholesterol efflux was calculated by counting the radioactivity in medium over that in medium and cells after subtracting the % medium radioactivity without apoAI treatment.**Results:** Arachidonic acid (AA) and *cis*-linoleic acid (LA) increased the protein levels of ABCA-1 by 22.6- and 26.6-fold, respectively. However, docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) alone had no significant effect on ABCA-1 expression. 9-cis RA markedly enhanced the expression of ABCA-1 both at mRNA and protein levels. Cholesterol efflux was not altered significantly in cells treated PUFAs alone. However, the impaired effect of PUFAs on cholesterol efflux was all restored when macrophages were treated in the presence of 5 μ M 9-cis RA. Incubation with 9-cis RA resulted in more than 2-fold increase in cholesterol efflux than which without 9-cis RA treatment.**Conclusion:** These results suggest that PUFAs in the presence of 9-cis RA may have the potential to protect macrophages from foam-cell formation through the retinoid X receptor (RXR)-mediated enhancement of ABCA-1 expression and cholesterol efflux.

11:30 THE EFFECT OF n-9 EICOSATRIENOIC ACID (MEAD ACID) ON OSTEOBLASTS

Hamazaki T¹, Suzuki N², Widyowati R¹, Miyahara T¹, Kadota S¹, Ochiai H1, Hamazaki K1
¹University of Toyama, Toyama-city, Toyama, Japan; ²Kanazawa University, Hosu-gun, Ishikawa, Japan

Background: In the case of essential fatty acid deficiency, n-9 eicosatrienoic acid (mead acid) is synthesized from oleic acid as a 20-carboned analog of arachidonic acid. Actually the ratio of 0.4 between mead acid and arachidonic acid is used as a criterion of essential fatty acid deficiency. It was reported that the mead acid levels were markedly higher in the human fetal cartilage than in the muscle, liver and spleen (Cleland KA et al, Lipids 1995). We asked why there is a considerable amount of mead acid in the fetal cartilage.

Objective: To investigate whether mead acid decreases osteoblastic activity.

Procedures: Exp 1. Goldfish scales were incubated either with mead acid or with oleic acid at 15C for 6 and 18 h (method: Suzuki N et al J Bone Miner Metab 2004). Both osteoblastic and osteoclastic activities in the scale were assessed by measuring alkaline phosphatase (ALP) and tartrate-resistant acid phosphatase, respectively. Exp 2. MC3T3-E1 cells (an osteoblast cell line derived from the mouse) were incubated with mead acid or oleic acid at 37C for 6 and 18 h. ALP activity in cell lysate was measured.

Results: Exp 1. Mead acid (10⁻⁶ to 10⁻⁴ M) significantly suppressed osteoblastic activity after 6 and 18 h of incubation, whereas oleic acid did not change this activity. Osteoclastic activity was not affected either by mead acid or by oleic acid.

Exp 2. Osteoblastic activity was again significantly decreased with mead acid (3-30 x 10⁻⁶ M) after 6 h incubation but not after 18 h incubation. Oleic acid did not influence osteoblastic activity.

Conclusion: The presence of mead acid in the fetal cartilage may be important in terms of the inhibiting of calcification in the cartilage. Mead acid could be applied to some clinical situations where bone formation should be inhibited.

11:45 DIHOMO-GAMMA-LINOLENIC ACID (DGLA) PREVENTS ATOPIC DERMATITIS AND ARTERIOSCLEOSIS IN MICE.

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Background & Objective: Dihomo-gamma-linolenic acid (DGLA, 8,11,14-eicosatrienoic acid) is one of the n-6 polyunsaturated fatty acids (PUFA). Previously, ingestion of gamma-linolenic acid (GLA), the precursor of DGLA, was expected to increase DGLA in the body and to suppress allergy, dermatitis, cardiovascular diseases *etc.*, but there were so many contradictory reports that efficacies of GLA are unclear. Recently, a new fermentation technique using a fungus *Mortierella alpina* was established to obtain triglycerides consisting of 40% DGLA. The purpose of this study was to examine whether DGLA ingestion prevents development of atopic dermatitis (AD) and arteriosclerosis in mice.

Methods: NC/Nga mice, spontaneously developing AD-like symptoms, were fed the modified AIN-76A diet either containing (0.6% in diet) or not containing DGLA for 8 weeks. Using the same diet, arteriosclerosis in apoE knock-out mice was investigated for 6 months.

Results & Discussion: Clinical skin severity scores of NC/Nga mice were markedly lower in the DGLA group. Scratching behavior and plasma total IgE level were also reduced in the DGLA group, in association with histological improvement. DGLA suppressed the severity scores in dose-dependent manner, with an increase in DGLA contents of skin, spleen, and plasma. At that time, arachidonic acid contents were also increased slightly. As for arteriosclerosis, lipid deposit in main artery was highly reduced in the DGLA group, though lipidemia was not changed. The endothelium-dependent vascular response was improved and the elevation of gene expressions of NADPH oxidase and ICAM-1 were also normalized.

Conclusion: These data indicate that oral administration of DGLA effectively prevents AD and arteriosclerosis in mice, and that DGLA must be a compound of key importance in these models. It is also suggested that DGLA should give quite different effects from GLA. These findings provide a novel potential of DGLA, and suggest that we have to reconsider the role of DGLA and n-6 PUFA.

10:00 DIETARY POLYUNSATURATED FATTY ACIDS AFFECT THE RESPONSE OF PROSTATE CANCER TO HORMONE ABLATION THERAPY AND PROGRESSION TO ANDROGEN INDEPENDENT GROWTH

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University of Tennessee, Knoxville, TN, USA

Background: Prostate cancer depends on androgen (testosterone) for initial growth. Hormone ablation therapy will result in regression but tumors often start growing again, independent of androgen, with fatal consequences.

Objective: Determine whether dietary polyunsaturated fatty acids (PUFA) affect the response of prostate cancer to androgen ablation therapy and/or subsequent progression to androgen-independence.

Procedure: Male mice with androgen-dependent human prostate cancer xenografts (CWR22) were fed diets containing 1.5% oleic acid (OA, as control), arachidonic acid (AA) or eicosapentaenoic acid (EPA) before undergoing androgen ablation therapy. Tumors were then: 1) harvested 5 days later for analysis of regression responses and biochemical or molecular analysis; or, 2) monitored for renewed androgen-independent growth, which will occur in this model months after removing testosterone stimulation.

Results: Exchanging dietary OA for n-3 or n-6 PUFA dramatically altered tumor fatty acid content. Tumors from mice fed EPA had significantly more apoptosis and less proliferation 5 days after castration in comparison to those fed AA, reflecting an enhanced response to ablation therapy. Furthermore, when animals on experimental diets were monitored for up to 6 months after ablation, relapse to androgen-independent growth (with renewed increases in tumor volume and serum PSA levels) occurred significantly sooner when they were fed AA. Tumor n-3 PUFA and linoleic acid content significantly correlated with a greater response to ablation therapy and were negatively correlated with progression to androgen-independent growth. There was no correlation between tumor responses and expression of 15-lipoxygenase isozymes or their metabolites.

Conclusion: These results suggest that dietary n-3 PUFA may enhance the response of prostate cancer to ablation therapy and retard its progression to fatal, androgen-independent growth; therapeutic adjuvant effects that could prolong the lifespan of affected patients.

10:30 A MODEL TO ASSESS DOCOSAHEXAENOIC ACID REQUIREMENTS FOR BRAIN ACCRETION DURING EARLY CHILDHOOD

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Martek Biosciences Corporation, 6840 Dobbin Road, Columbia, Maryland 21045

Background: Adequate docosahexaenoic acid (DHA, 22:6n-3) is important for normal development of the central nervous system.

Objective: To estimate the brain DHA accretion in early childhood

Procedure: Using accretion, concentration, and turnover rates estimated from human and non-human primate studies, a model for brain DHA homeostasis is described. The model is based on physiological demands of the brain rather than on estimates derived from the DHA levels of human milk or the caloric contribution of alpha-linolenic acid (ALA, 18:3n-3).

Results: It is estimated that approximately 3.75 mg of DHA per day is necessary to support total brain accretion in children 1-2 years of age.

Conclusion: Sufficient data exist to develop a model for the requirements for DHA based upon brain metabolism. Future work is needed in order to establish dietary requirements for specific age groups and those populations at risk for low DHA intake.

11:30 MODULATION OF PROSTATE CANCER GENETIC RISK BY OMEGA-3 AND OMEGA-6 FATTY ACIDS

Yong Q. Chen

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Objective: Although a causal role of genetic alterations in human cancer is well established, it is still unclear whether dietary fat can modulate cancer risk in a predisposed population. Epidemiological studies suggest that diets rich in omega-3 polyunsaturated fatty acids reduce cancer incidence. The objective of our study was to determine the influence of fatty acids on prostate cancer risk in animals with a defined genetic lesion.

Procedure: Prostate-specific Pten knockout mice, an immune-competent, orthotopic prostate cancer model, and diets with defined polyunsaturated fatty acid levels were used. In addition, omega-3 desaturase, which converts omega-6 to 3 fatty acids, was introduced into the Pten-null mice.

Results: We found that omega-3 fatty acids reduced prostate tumor growth, slowed histopathological progression and increased survival, whereas omega-6 fatty acids had opposite effects. Introducing an omega-3 desaturase into the Pten knockout mice reduced tumor growth similarly to the omega-3 diet. Tumors from mice on omega-3 diet had lower proportions of phosphorylated Bad and higher apoptotic indexes compared to those on omega-6 diet. Knockdown of Bad eliminated omega-3-induced cell death, and introduction of exogenous Bad restored the sensitivity to omega-3 fatty acids in culture. Knockout of Bad abolished the tumor suppressive effect of omega-3 fatty acids in vivo.

Conclusion: Our data suggest that modulation of prostate cancer development by polyunsaturated fatty acids is mediated in part through Bad-dependent apoptosis. This study highlights the importance of gene-diet interactions in prostate cancer.

10:30 THE EFFECTS OF STEARIDONIC ACID-ENRICHED SOYBEAN OIL ON THE OMEGA-3 INDEX

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Background: An alternate plant-based source of omega-3 fatty acids (FAs) is needed to meet growing demand for these FAs as fish supplies dwindle and because plant-derived alpha-linolenic acid (ALA) is poorly converted to EPA and DHA. Stearidonic acid (SDA), the delta-6 desaturase product of ALA, is converted into EPA more readily than is ALA. To address these needs, soybeans genetically modified to produce oil (SBO) with 15-20% SDA are under development.

Objective: To compare the effects of SDA-SBO to EPA and to regular SBO on erythrocyte EPA+DHA levels (the omega-3 index).

Procedures: Non-fish eating healthy volunteers (n=45) were randomized to active treatment with SDA-SBO (24 mL/day providing 3.7 g SDA; SDA group) or to regular SBO (control group) without or with EPA ethyl esters (1 g/d; EPA group). Serum lipids, blood pressure, heart rate, platelet function and safety labs were measured along with the omega-3 index at baseline and after 16 weeks.

Results: A per-protocol analysis was conducted on 33 subjects (11 per group). The overall mean (\pm SD) omega-3 index at baseline was $4.11 \pm 0.89\%$ (n=33). The omega-3 index was unchanged at 16 weeks in the control group but increased vs. the control by 19.7% in the SDA group and by 25.0% in the EPA group. These changes were statistically significant (ANCOVA, p= 0.042, 0.026, respectively). RBC DHA levels did not change in any group. Relative to EPA, SDA increased RBC EPA with about 17% efficiency. None of the other endpoints were affected by SDA or EPA treatment (vs. control), and no SDA-related adverse effects were reported.

Conclusions: SDA-enriched SBO significantly raised the omega-3 index. Since EPA supplementation has been shown to raise the omega-3 index and lower risk for cardiac events, SDA-SBO may be a viable plant-based approach to providing meaningful intakes of cardioprotective omega-3 FAs.

Sponsorship: Monsanto Company.

11:00 METABOLIC ENGINEERING OF TRANSGENIC PLANTS FOR BIOSYNTHESIS OF OMEGA-3 POLYUNSATURATES

Graham IA

CNAP, Department of Biology (Area 7), University of York, PO Box 373, York YO10 5YW, UK. iag1@york.ac.uk

The health-beneficial effects of long-chain polyunsaturated fatty acids (LC-PUFAs), derived mainly from fish oil, together with the growing requirement for an alternative and sustainable source of these compounds, has led to efforts to engineer oilseed crops for their production. LC-PUFA synthesis has been achieved using combinations of heterologous endomembrane desaturases and elongases expressed in a number of oilseed plants. Two general approaches have been employed that both use endogenous 18 carbon fatty acids as the starting substrates: the Delta6- and Delta8-pathways, which perform desaturation followed by elongation or elongation followed by desaturation, respectively. However, yields above 20% have not yet been realized owing to bottlenecks that become apparent in the endogenous biosynthetic pathways when heterologous genes are expressed. These bottlenecks might be caused partly by inefficient non-native enzymes in the host system or also by suboptimal acyl-exchange mechanisms between the acyl-CoA and lipid class pools. The fine-tuning of the fatty acid flux between the acyl-CoA, phospholipid, and triacylglycerol pools will be essential to maximise polyunsaturated fatty acid yields in seed oils. Recent advances and hurdles encountered will be discussed along with strategies to overcome these hurdles.

11:30 BIOTECHNOLOGY APPROACH TO PROVIDING A SUSTAINABLE SOURCE OF OMEGA-3 PRODUCTS FOR FOOD AND FEED

Sanders EE Fuchs RL, Wilkes R, Valentin H, Klopff G, and George C. The Monsanto Co., St. Louis, MO.

Background: Health benefits of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are well documented. To meet future demands for these omega-3 fatty acids (FAs), plant-based instead of fish-based alternatives are needed. Biotechnology, molecular breeding and genomics have given us new tools to provide these omega-3 essential FAs from a land based sustainable resource of a farmed crop. New omega-3 rich products will be able to be produced without having to over-harvest fish from the oceans.

Objective: Review and update the current state of technology for omega-3 production and provide an overview of technology in the pipeline for the future.

Procedure: Soybean plants are optimal vehicles for oil and protein production. The modification of oil composition in canola and soybean plants has been actively pursued for over 15 years. A soybean that has been genetically modified to produce Stearidonic acid (SDA) has been developed by the addition of two genes from plant and microbial sources. SDA is the delta-6 desaturase product of alpha-linolenic acid (ALA) and is more readily converted in vivo to EPA than is ALA.

Results: SDA levels in the soybean plant average 20% of the oil composition. The SDA-rich oil has been extracted using conventional refining methods and utilized to make potential food products containing a nutritionally relevant dose of SDA.

Conclusion: Soybeans have been genetically modified to provide an essentially endless supply of SDA. The oil can be extracted, stabilized and formulated into food-based products which would allow the consumer to increase their intake of heart healthy omega-3 FAs from a wide variety of conventional foods other than oily fish.

Funding Source: The Monsanto Co.

8:15 BASIC MECHANISMS BEHIND THE EFFECTS N-3 FATTY ACIDS ON CARDIOVASCULAR DISEASE

Raffaele De Caterina, M.D., Ph.D. and Marika Massaro, Ph.D.
“G. d’Annunzio” University – Chieti – Italy

The epidemiological association between high intakes of n-3 fatty acids (FA) and decreased cardiovascular morbidity and mortality from cardiovascular disease (CVD) can be explained by two main basic mechanisms: (a) an effect on atherothrombosis; (b) an effect on cardiac arrhythmias. These mechanisms are probably the expression of different effects of n-3 FA on cardiovascular biology. Effects on atherothrombosis include effects on the expression of pro-atherogenic genes (e.g., effects on endothelial leukocyte adhesion molecules, inflammatory cytokines and cyclo-oxygenase(COX)-2) and the hepatic modulation of the synthesis of very low density lipoproteins (VLDL), slow in onset, requiring incorporation into cell membrane phospholipids, and usually doses in humans in the order of 3 g/day or higher. Effects on cardiac arrhythmias include complex interactions with ion channels (sodium, potassium and calcium channels), typically requiring the presence of free fatty acids in extracellular fluids and usually occurring with lower doses (around 1 g/day) of nutritional or pharmacological intake. We have focused most of our research effort in unraveling the pathophysiological background of protection by n-3 FA from atherothrombosis. As the result of incorporation of n-3 fatty acids in the sn-2 position predominantly of phosphatidyl ethanolamine pool in the inner leaflet of the plasma membrane, n-3 FA appear on the one hand to increase the production of bioactive lipid mediators (protectins and resolvins) affecting cytokine-induced signal transduction; and on the other hand to directly interfere with the generation of reactive oxygen species (mostly hydrogen peroxide) directly responsible for the activation of the transcription factor nuclear factor (NF)- κ B, controlling the expression of a variety of pro-inflammatory, pro-atherogenic genes, including those encoding for interleukin(IL)-1, IL-6, IL-8, tumor necrosis factor- α , vascular cell adhesion molecule-1 (VCAM-1), E-selectin, and COX-2. The upstream – direct or indirect – interference with cytokine- and other atherogenic trigger-induced signal transduction may involve interference with protein kinase C isoforms and the activation of NAD(P)H oxidase. Such interference may also explain the blunt anti-inflammatory effect of n-3 FA in many models and clinical conditions of inflammation. All together, these mechanisms may provide an integrated view of how n-3 FA may affect cardiovascular disease.

8:15 DIETARY FATTY ACIDS AND RISK OF SUDDEN CARDIAC DEATH:

Christine M. Albert. Brigham and Women’s Hospital, Boston, MA

Dietary intake of long-chain n-3 fatty acids from fish has been inversely associated with SCD risk in four observational studies among primarily healthy populations. In two of these populations, those individuals in the highest quartile of omega -3 fatty acid blood level had 81-90% lower risks of SCD as compared to those in the lowest quartile. In addition, a supplement of long-chain n-3 fatty acids lowered SCD risk in a randomized trial among post-MI patients. The reduction in SCD risk reported in observational studies and clinical trials, along with supportive basic science data, led to the hypothesis that these long chain n-3 fatty acids may be anti-arrhythmic in humans. However, the evidence base is not entirely consistent, and a number of randomized trials have failed to show a protective effect of n-3 PUFAs against ventricular arrhythmias in high-risk populations, and some of these studies have even suggested possible pro-arrhythmic effects. In addition to the long chain n-3 fatty acids, alpha-linolenic acid (ALA), an intermediate chain n-3 fatty acid found in select foods of plant origin, has also been demonstrated to have direct anti-arrhythmic properties in animal models. ALA intake has been inversely associated with risk of SCD in one cohort of healthy women, but has not yet been adequately tested in randomized trials. Finally, an interesting relationship between trans-fatty acids and SCD has been reported in two separate studies. Both studies found significantly increased risks associated with the *trans* isomer of linoleic acid (*trans*-18:2), and decreased risks associated with the *trans* isomer of oleic acid (*trans*-18:1). The current state of the evidence, along with existing controversies, regarding the influences these fatty acids may or may not have on sudden death risk will be reviewed in this lecture.

3:45 TRANS FATTY ACIDS AND NUTRITION POLICY:THE NEW YORK CITY STORY

Plenary Speaker: Angell SY, Goldstein GP, Johnson CJ, Silver LD, Bassett, MT
New York City Department of Health and Mental Hygiene, New York City, NY

Heart disease remains the leading cause of death in the US, despite advances in the medical management of coronary heart disease (CHD) and its risk factors. Population level interventions which moderate diet associated risk offer great opportunity to reduce disease burden and related health disparities. Dietary trans fat is associated with increased CHD risk. The replacement of just 2% of energy intake from trans fat with heart healthy alternatives will decrease coronary heart events by 6%-22%. Such evidence has prompted governmental regulation of trans fat; Denmark severely restricts synthetic sources of trans fat and Canada is considering regulation. In January 2006, the US Federal Government requirement that food labels disclose trans fat content went into effect. This policy, however, does not apply to restaurants, leaving diners with no practical way to avoid trans fat. Restaurants are an important source of intake as an estimated one third of daily calories come from foods prepared away from the home. In 2005, the NYC Department of Health responded with an education campaign aimed at voluntary restaurant trans fat use reduction. Pre and post evaluation showed no significant change. Like lead in paint, trans fat is dangerous and replaceable. Given the absence of evidence that voluntary efforts would significantly reduce exposure, the NYC Board of Health pursued regulatory measures. In December 2006, New York City became the first in the US to restrict restaurant use of industrially produced trans fat. To support restaurant compliance and replacement with heart healthy alternatives, the Department established the Trans Fat Help Center. Since the passage of NYC’s regulation, 7 jurisdictions have passed similar restrictions, and others are considering action. The regulation’s first phase went into effect July 1, 2007, restricting artificial trans fat use in fry oils and spreads. By December, 97% of restaurants inspected were in compliance.

3:45 TRANS FATTY ACIDS AND CARDIOVASCULAR DISEASE, DIABETES, AND OBESITY

Mozaffarian D.
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Trans-fatty acids (TFAs), unsaturated fats with at least one double bond in the trans configuration, are formed during the industrial hydrogenation of vegetable oils for food manufacturing. Average consumption in industrialized countries is 4 to 7% of total dietary fat, with major sources being fast foods, bakery products, packaged snacks, and margarines. Several physiologic effects of TFAs may increase cardiovascular and metabolic risk. Adverse effects on serum lipids are well established, including lowering of HDL cholesterol and raising of LDL cholesterol, triglycerides, and lipoprotein(a). TFA intake also increases systemic inflammation, a potent risk factor for atherosclerosis, sudden death, and diabetes. In experimental studies, TFAs also impair endothelial cell function, have other adverse lipid effects, and possibly increase visceral adiposity and insulin resistance. The molecular mechanisms underlying the physiologic effects of TFAs are not yet well understood. TFAs may directly influence macrophage membrane phospholipids and signaling pathways and also bind to tissue-specific intranuclear receptors such as PPAR- γ . TFAs are also incorporated into endothelial cell membranes, which have numerous tissue-specific pathways relating to inflammatory activation, insulin sensitivity, atherogenesis, and plaque stability. Consumption of TFAs independently predicts poor cardiovascular health, including higher incidence of coronary heart disease, sudden death, and possibly diabetes. Further research is needed to continue to characterize the relations between TFAs and cardiovascular health, but the evidence from experimental and observational studies indicates that a significant proportion of coronary heart disease deaths and possibly new cases of diabetes would be prevented by replacing partially hydrogenated fats in the food supply with unhydrogenated polyunsaturated fats.

10:30 OMEGA-6 FATTY ACIDS ARE ASSOCIATED WITH BONE MINERAL DENSITY IN HEALTHY 8-YR-OLD CHILDREN.Eriksson S¹, Mellström D², Strandvik B¹.¹Dept of Pediatrics and ²Center for Bone Research, Sahlgrenska Academy, Göteborg University, Göteborg, Sweden.

Background: Animal studies have shown that essential fatty acids influence bone mineralization and that prostaglandins, important products of omega-6 fatty acids, influence bone resorption and modelling in a dose dependent way. In different diseases, associations between fatty acids and bone mineral density (BMD) have also been shown in the humans.

Objective: The aim of this study was to investigate if serum phospholipid fatty acid concentration was associated with BMD in healthy children.

Methods: Ninety-two healthy 8-yr-old children were investigated with DXA (Lunar DPX-IQ, GE Lunar Corp, Madison, WI, USA) and fasting serum phospholipid fatty acids were analysed with gas-liquid chromatography.

Results: Serum phospholipid concentration of linoleic acid (18:2w6) showed significant negative association to BMD in total body ($r=-0.25$, $p<0.05$), lumbar spine ($r=-0.27$, $p<0.01$) and the hip ($r=-0.21$, $p<0.05$) as did the total amount of w6 fatty acids to lumbar spine ($r=-0.28$, $p<0.01$). The concentration of arachidonic acid (20:4w6) was positively associated with BMD in total body ($r=0.35$, $p<0.001$) and in the hip ($r=0.22$, $p<0.05$). No association was found to w3 fatty acids or the ratio between these series of fatty acids.

Conclusion: Since osteoporosis is a serious problem in the elderly and a high peak bone mass achieved during childhood and adolescence is one protective factor, this study implies that the quality of dietary fatty acids might be important during childhood for the mineralization of the bone.

10:45 FETAL ARACHIDONIC ACID AVAILABILITY AND PERINATAL ARACHIDONIC ACID STATUS ARE NOT RELATED TO IMMUNE STATUS PARAMETERS IN CHILDHOODDirix CE¹, Hogervorst JG², Rump P¹, Hendriks JJ⁴, Bruins MJ⁵, Hornstra G^{1,6}¹Department of Human Biology, Maastricht University, The Netherlands²Department of Epidemiology, Maastricht University, The Netherlands⁴Department of Pediatrics, University Hospital Maastricht, The Netherlands⁵DSM Food Specialties, DSM Food Specialties, Delft, The Netherlands⁶Nutrition and Toxicology Research Institute, Maastricht University, Maastricht and NUTRI-SEARCH, Gronsveld, The Netherlands

Background: Arachidonic acid (AA; 20:4n-6) is considered essential in fetal development and some of its metabolites are thought important mediators of the immune responses.

Objective: To investigate whether early-life AA availability may modulate immune system development.

Procedure: In 280 mother-child pairs of the Maastricht-Essential-Fatty-Acid-Birth (MEFAB) cohort, relationships were investigated between early-life AA availability and immune status parameters of children at age 7. Relative AA concentrations (wt%) were measured in plasma phospholipids of pregnant women (gestational weeks 16, 22, 32, and just after delivery) and in cord phospholipids of their neonates (plasma, arterial and venous wall, and vein-artery wall differences). Immune-related parameters of primary interest comprised childhood atopy (parent-completed questionnaire) and pulmonary function (Peak Expiratory Flow decline after exercise: $PEF_{exercise}$; two-week average PEF at rest: PEF_{rest} ; and two-week average daily PEF amplitude at rest: $PEF_{amplitude}$). Exploratory parameters comprised plasma concentrations of fibrinogen, C-reactive protein, leptin, von Willebrand factor, leukocytes, lymphocytes, granulocytes, and monocytes. Associations were investigated by univariable and multivariable linear and logistic regression analyses adjusted for covariates. $P \leq .05$ and $P \leq .01$ were considered significant for primary and exploratory analyses, respectively.

Results: $PEF_{exercise}$ of the children at 7 years of age was positively associated ($P=.03$) with maternal plasma AA concentrations at gestational week 16 and $PEF_{amplitude}$ was negatively related ($P=.02$) to cord plasma AA concentrations. These relationships were no longer significant after adjusting for relevant covariates ($P=.06$ and $P=.17$, respectively). Plasma fibrinogen concentration at age 7 was positively associated with maternal AA concentration in late pregnancy before ($P=.006$) and after ($P=.014$; trend) adjustment for covariates. Other association between maternal or neonatal AA concentrations and any of the immune-related variables of the children were not significant after adjusting for relevant covariates.

Conclusion: Early-life AA availability seems not related to immune status of children at 7 years of age.

11:00 THE MINOR ALLELE OF THE FADS1 GENE POLYMORPHISM IS ASSOCIATED WITH LOWER ERYTHROCYTE ARACHIDONIC ACID (AA) IN PREGNANT WOMEN AND PROVES SENSITIVE TO AA STATUS LOWERING BY DOCOSAHEXAENOIC ACID (DHA) SUPPLEMENTATION.Dijck-Brouwer DAJ¹, Sanjabi B¹, van Goor SA², Terpstra P³, Kema IP¹, Hadders-Algra M⁴, Muskiet FAJ¹¹Department of Laboratory Medicine, ²Pathology and Laboratory Medicine, ³Department of Epidemiology,⁴Department of Pediatrics, UMCG, University Medical Center Groningen, The Netherlands

Background: AA and DHA are important for neurodevelopment. DHA is considered conditionally essential. Maternal DHA status may become compromised by pregnancy. Minor alleles of genetic variants of the delta-5 desaturase (FADS1) are associated with lower serum phospholipid AA contents. DHA and AA compete for incorporation in at least some compartments.

Objective: Determine the association between a tag single nucleotide polymorphism (SNP) of the FADS1 gene and erythrocyte fatty acids (FA) during pregnancy, prior to and following supplementation with DHA.

Procedure: Pregnant women were randomly assigned to placebo, DHA (220 mg/day) or DHA+AA (220 mg each/day) from week 17 of pregnancy till 3 months postpartum. Blood samples were collected at 16 and 36 weeks for erythrocyte FA analyses and DNA isolation. Linkage Disequilibrium analysis of the FADS1 gene resulted in a tagging SNP in the 3' untranslated region of the messenger RNA (rs174545, C major allele; G minor allele) that was determined with real-time PCR.

Results: We analyzed 86 genotype-erythrocyte FA pairs before (week 16) and 101 genotype-erythrocyte FA pairs after supplementation (week 36; 38 DHA, 33 DHA+AA, 30 placebo). Before supplementation, subjects with GG showed lower erythrocyte AA, 22:4w6, 22:5w6 and LCPw6 and higher 18:2w6, 20:3w6 and DHA/AA compared with the CC genotype. CG subjects showed higher 20:3w6 compared with CC subjects, and higher AA, 22:4w6, LCPw6 and lower DHA/AA compared with GG subjects. In CC subjects, DHA supplementation increased erythrocyte DHA and DHA/AA, while DHA+AA increased their DHA, as compared to placebo. In CG subjects, DHA supplementation increased erythrocyte DHA, but decreased AA, 22:4w6 and LCPw6, whereas DHA+AA decreased their erythrocyte LCPw6 as compared with placebo.

Conclusion: The minor allele of the FADS1 gene polymorphism is associated with lower AA status in pregnant women. Carriers of this G-allele are sensitive to further AA status lowering following supplementation with DHA-only.

11:15 LIMITED EFFECT OF FISH OIL SUPPLEMENTATION DURING LACTATION ON DIETARY INTAKE, PHYSICAL ACTIVITY, BLOOD PRESSURE AND BODY COMPOSITION OF 7 YEAR-OLD CHILDREN.Lauritzen L¹, Asserhoj M¹, Nehammer S¹, Matthiessen J², and Michaelsen KF¹.¹Department of Human Nutrition, University of Copenhagen, Frederiksberg, Denmark and ²National Food Institute, Technical University of Denmark, Søborg, Denmark.

Background: Early nutrition may programme obesity and cardiovascular risk later in life and one of the potential programming agents are n-3 polyunsaturated fatty acid (PUFA).

Objective: To see if fish oil (FO)-supplementation during lactation affects later blood pressure and body composition in the children.

Procedure: In a randomized blinded trial, 122 Danish mothers were supplemented with FO (1.5 g/day n-3 long-chain (LC)PUFA) or olive oil (OO) during the first 4 month of lactation. The trial also included a high-fish-intake reference group (n=53). Ninetyeight (66%) of the children were followed-up with blood pressure and body composition measurements at 7 years of age. Diet and physical activity was assessed by 4 day-weighted dietary records and a validated position and motion instrument (ActiReg).

Results: The physical activity level (PAL) was found to be 4% lower in the FO-group ($p=0.048$) and the energy intake of the boys in this group was 1.13 ± 0.4 MJ higher ($p=0.014$) relative to the OO-group. There were no differences in overall diet composition. No clear difference between the randomized groups was observed in body composition before or after adjustment for energy intake and PAL. Boys in the FO-group had a 5 mmHg higher blood pressure than those in the OO-group ($p<0.01$), but no difference was observed among the girls. No significant correlation was found between body composition or blood pressure and the relative content of n-3 LCPUFA in maternal erythrocytes immediately after the intervention.

Conclusion: We have previously found this FO-supplementation to give higher BMI at 2.5 years of age, but this difference appears to be diminished at 7 years. Differences in energy intake, PAL and blood pressure among the 7 year-old boys in the randomized groups suggest that early n-3 LCPUFA intake may have some adverse effects, but these need to be confirmed in future studies.

11:30 EFFECT OF LCPUFA MATERNAL SUPPLEMENTATION DURING LACTATION ON COGNITIVE ABILITIES OF 7-YEAR-OLDS: A FOLLOW-UP STUDY AND FURTHER EXPLORATORY ANALYSES

Cheatham, C.L.¹, Nerhammer, S.², Asserhoj, M.², Michaelsen, K.F.², Lauritzen, L.²

¹Dept. Of Dietetics & Nutrition, University of Kansas Medical Center, Kansas City, KS USA; ²Department of Human Nutrition, of Life Science, University of Copenhagen, Fredriksberg, Denmark

Background: Long-chain n-3 polyunsaturated fatty acids (n-3 LCPUFA) accumulating in the brain early on are thought to be integral to brain development and function. Work by Helland et al. suggests maternal supplementation with fish oil during pregnancy and lactation has long-lasting effects. The ubiquitous presence of LCPUFA in the frontal lobes implicates it in the development of the later-emerging, higher-order cognitive functions known as executive functions.

Objective: To assess working memory, inhibitory control, and speed of processing in 7-year-olds whose mothers were supplemented with fish oil or olive oil during lactation or were habitual fish eaters.

Procedures: Children from an RCT in which mothers were supplemented with fish oil (n=36) or olive oil (n=28) during the first 4 months of lactation or were high habitual fish eaters (n=32) were invited into a 7-year follow-up. Participants' cognitive abilities were tested with a speed of processing task (SoP) and a working memory/inhibitory control task (WMIC).

Results: Analyses of variance revealed no main effects. Thus, data were collapsed across groups to take advantage of this rich data set by determining the best early predictors of later cognition. Exploratory multivariate model-building to predict SoP and WMIC proceeded using backward elimination of conceptually relevant measures (maternal intake of LCPUFA during intervention, DHA content of breastmilk at 4 months, infant RBC DHA at 4 months, maternal education, and total weeks breastfed). No variables met the .05 criterion for inclusion when predicting the SoP measure. When predicting the WMIC score, infant RBC DHA at 4 months was the only variable to meet criterion (p=0.02).

Conclusion: Group membership in this randomized intervention of early n-3 LCPUFA intake was of no significance to long-term cognitive function, but exploratory model-building suggests WMIC at 7 years of age is related to levels of DHA in infants' blood at 4 months of age.

11:45 GENETIC VARIANTS OF THE FADS1 FADS2 GENE CLUSTER MAY BE ASSOCIATED WITH REDUCED ARACHIDONIC ACID IN BOTH ETHANOLAMINE PHOSPHOGLYCERIDE OF RED BLOOD CELL IN PREGNANT WOMEN AND BREAST MILK IN LACTATING WOMEN.

Xie L.^{1,2}, and Innis SM¹.

¹Child and Family Research Institute, Department of Paediatrics, University of British Columbia, Vancouver, British Columbia, Canada; ²Department of Nutrition and Food Hygiene, The School of Public Health, Jilin University, Changchun, Jilin, China.

Background: The enzymes encoded by FADS1 and FADS2 are the rate-limiting enzymes in the synthesis of long chain PUFAs. Arachidonic acid (ARA) is one of the important PUFAs which plays a central role in inflammatory process and infant development. The variation of ARA during pregnancy and lactation can not be only explained by diet.

Objective: To determine if SNPs in FADS1 and FADS2 are associated with differences in n-6 and n-3 fatty acids in blood during pregnancy and in breast milk during lactation.

Procedure: rs174553, rs99780, rs174575, and rs174583 in FADS1 and FADS2 gene cluster of 69 pregnant women were genotyped. Fatty acid composition of red blood cell ethanolamine phosphoglyceride and breast milk was also measured.

Results: The 4 SNPs are in one linkage disequilibrium block. There were no significant differences in the intake of n-6 and n-3 fatty acids. The content of ARA was the lowest in minor allele homozygotes of rs174553(GG), rs99780(TT), rs174583(TT) (P=0.003, P=0.002 and P=0.002 respectively), whereas linoleic acid was the highest in minor allele homozygotes of rs174553(GG), rs99780(TT), rs174583(TT) (P=0.007, P=0.005 and P=0.005 respectively). The content of ARA in breast milk of the women was also the lowest in the subgroup of the minor allele homozygotes of rs174553(GG), rs99780(TT) and rs174583(TT) (P=0.003).

Conclusion: Our study provides evidence that genetic variants of FADS1 and FADS2 may play an important role in moderation of the fatty acid composition both in pregnancy and lactation. Supported by CIHR.

10:30 FAT-1 TRANSGENIC MICE: A NEW MODEL FOR OMEGA-3 RESEARCH

Kang JX

Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts 02114, USA

An appropriate animal model that can eliminate confounding factors of diet would be very helpful for evaluation of the health effects of nutrients such as n-3 fatty acids. We recently generated a *fat-1* transgenic mouse expressing the *C. elegans fat-1* gene encoding an n-3 fatty acid desaturase that converts n-6 to n-3 fatty acids (which is lacked in mammals). The *fat-1* transgenic mice are capable of producing n-3 fatty acids from the n-6 type, leading to abundance of n-3 fatty acids with reduced levels of n-6 fatty acids in their organs and tissues, without the need of dietary n-3 supply. Feeding an identical diet (high in n-6) to the transgenic and wild type littermates can produce different fatty acid profiles in these animals. Thus, this model allows well-controlled studies to be performed, without the interference of the potential confounding factors of diet. The transgenic mice are now being used widely as a new tool for studying the benefits of n-3 fatty acids and the molecular mechanisms of their action.

11:00 HEPATIC PROTEOMICS OF FAT-1 MICE

de Roos B¹, Ross K¹, Rucklidge G¹, Reid M¹, Duncan G¹, Horgan G², Wang J³, Kang JX³

¹Rowett Research Institute, Aberdeen, United Kingdom, ²Biomathematics and Statistics Scotland, Aberdeen, United Kingdom,

³Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts, USA

Background: Long chain n-3 polyunsaturated fatty acids (LC n-3 PUFA), present in fish and fish oil, lower the risk of coronary heart disease by mechanisms that are not well understood. We have taken a genetic approach to modify essential fatty acid composition by engineering mice that express the humanized *fat-1* gene from *C. elegans*. *Fat-1* mice can produce n-3 fatty acids from the n-6 type and have a balanced ratio of n-6 to n-3 fatty acids. These animals serve as a novel and useful model for studying the roles of LC n-3 PUFA in the human body.

Objective: In this study we assessed differential protein expression in the liver of transgenic *fat-1* mice, as compared with wild type littermates.

Procedure: Male *fat-1* mice and male C57Bl/6j control mice were offered a omega-6 rich safflower-based diet for 12 weeks (n=5 per group), or breast fed by mothers on the omega-6 rich diet for 4 wks followed by this diet containing 0.5% uridine-5'-monophosphate (UMP) for 8 weeks (n=5 per group). Livers were collected and frozen on the last day of dietary intervention. Analysis of the hepatic proteome was done by 2D gel electrophoresis and differentially regulated proteins were identified by LC-MS/MS.

Results: Proteomic analysis revealed thirty hepatic proteins that were differentially regulated in *fat-1* mice compared with control mice, independent of the diet consumed. The changes included significant (P<0.05) down-regulation of apolipoprotein A4, annexin A6, superoxide dismutase, α -glucosidase, α -1-antitrypsin and adenosine kinase protein levels, and significant up-regulation (P<0.05) of sorbitol dehydrogenase and glycerol-3-phosphate dehydrogenase protein levels.

Conclusion: Differential regulation of hepatic proteins in *fat-1* transgenic mice provided novel insights into the effects of endogenous LC n-3 PUFA production on pathways involved in the inflammatory response, lipoprotein metabolism, blood glucose control, and oxidative stress.

This study was funded by the Scottish Government Rural and Environment Research and Analysis Directorate (RERAD).

11:15 REGULATION OF INTRACELLULAR LIPID DROPLET SIZE IN CAENORHABDITIS ELEGANS

Mak HY

Stowers Institute for Medical Research, MO, USA

Background: Genes that govern lipid droplet size and formation can ultimately impact systemic lipid metabolism. Lipid droplet size varies widely in different tissues and the mechanisms that underlie giant lipid droplet formation in fat storage cells are not well-understood.

Objective: We use *C. elegans* as a model to identify genes that regulate lipid droplet size in the intestine, the major fat depot of the organism.

Procedure: Using fluorescently labeled fatty acids to monitor lipid droplets in live animals, we performed a forward genetic screen for mutants that accumulate grossly enlarged intracellular lipid droplets.

Results: We identified mutant alleles in at least 3 genes that promote giant intracellular lipid droplet formation. Cloning of two genes from this screen implicates a link between peroxisomal fatty-acid beta-oxidation and giant lipid droplet formation.

Conclusion: Lipid droplet size may be determined by the relative abundance of different fatty acid species that are normally metabolized in the peroxisomes.

11:30 DESIGNING HUMAN EQUIVALENT DIETS FOR RODENTS WHEN FEEDING

N-3 POLYUNSATURATED FATS.

Whelan J

Department of Nutrition, University of Tennessee, Knoxville, TN 37996-1920 USA.

Background: Experimental animal models are the primary tool to test intervention strategies for human chronic diseases. These models generate data important for pre-clinical screening purposes; however, their ability to predict human responses has been disappointing, particularly when it comes to dietary n-3 and n-6 polyunsaturated fatty acids (PUFA), where there is a real disconnect between experimental results and those of clinical trials. It has been suggested that rodent diets are designed only to generate positive results with little thought on predictability. As such, the levels of n-3 PUFA used in rodent diets are typically on the extreme and rarely justified. A search of the literature reveals no guidelines establishing appropriate levels for the use of n-3 PUFA in rodent diets although extrapolation to human conditions is quite common despite being inappropriate.

Objective: To establish human equivalent doses (HED) of n-3 PUFA in rodent diets to improve pre-clinical screening using experimental models.

Procedures: A mathematical model was generated based on metabolic efficiency that predicted human equivalent responses. To test this model, mice were fed diets designed to approximate the Western diet (equivalent distribution of macronutrients and fatty acid composition, i.e., saturated, monounsaturated and polyunsaturated fatty acids). These background diets were supplemented with alpha-linolenic acid (ALA) or eicosapentaenoic acid (EPA) at three HED (0.3, 0.8 and 1.4% energy).

Results: Changes in plasma and erythrocyte phospholipid compositions were compared with archival human data from over 100 clinical trials. With the appropriate levels of ALA in the background diet, supplementation of ALA and EPA to the diet changed tissue phospholipid levels of arachidonic acid, EPA and docosahexaenoic acid in mice to the same extent as observed in humans whose diets were supplemented with n-3 PUFA.

Conclusions: These results are the first to create a mathematical model establishing HED for dietary n-3 PUFA in rodent diets. (Supported by the Tennessee Agricultural Experiment Station and in conjunction with the USDA Multistate Research Group NC1039)

11:45 WHY MICE MAY BE A POOR MODEL FOR HUMANS RELATIVE TO N-3 PUFA AND INFLAMMATORY/IMMUNE RESPONSES.

Fritsche, K.L.

University of Missouri, Columbia, MO – USA

Omega-3 polyunsaturated fatty acids (n-3 PUFA) are noted for their ability to diminish inflammatory and immune responses in vitro and in a variety of animal-based models of autoimmunity and inflammation. Yet, recent systematic reviews suggest that the evidence for these fatty acids having beneficial effects on inflammation or autoimmunity in humans is equivocal. In this presentation, a few possible explanations for these disappointing and somewhat paradoxical findings will be offered. Central to this presentation will be the dose-response curves, recently generated from a cross-study regression analyses, showing the relationship between immune cell fatty acid profiles and dietary LC-PUFA intake for mice, rats, and humans. These dose-response curves suggest that a clear difference exists between how mice respond to n-3 PUFA intake compared to humans. Additionally, possible reasons for the poor predictive value of many in vitro as well as animal trials will be presented for your consideration. Recommendations for improving the preclinical value of future in vitro and animal-based studies with n-3 PUFA will be provided.

10:30 ROLE OF OMEGA-3 FATTY ACIDS AND TRANS FATTY ACIDS IN SUDDEN CARDIAC DEATH AND VASCULAR REMODELING.

Siddiqui RA^{1,2}, Harvey KA¹, Ruzmetov N¹, Arnold T¹ & Zaloga GP³.

¹Methodist Research Institute, Clarian Health Partners Inc. and ²Department of Medicine, Indiana University School of Medicine, Indianapolis, IN 46202, USA and ³Clintec Nutrition, Baxter Healthcare, Deerfield, IL 60015, USA

Background: Omega-3 polyunsaturated fatty acids (n-3 PUFAs) have well-recognized cardio-beneficial effects. In contrast, premature coronary deaths are associated with consumption of high levels of trans polyunsaturated fatty acids (TFAs).

Objectives: This study explored the effects of n-3 PUFAs and TFAs on sudden cardiac death and vascular remodeling using *in vivo* and *in vitro* systems.

Procedures: A rat coronary ligation model was used to study the effect of fatty acids on sudden cardiac death, whereas a mice femoral artery ligation model was used to study compensatory vascular remodeling. Human arterial endothelial cells were utilized for the *in vitro* studies to demonstrate expression of inflammatory molecules.

Results: Feeding animals an n-3 PUFA-enriched diet caused a 7-fold increase in plasma n-3 PUFAs compared to that of the TFA-fed group, whereas a TFA-enriched diet caused a 2.5-fold increase in plasma TFAs compared to the n-3 PUFA group. A diet high in TFAs was associated with a lower survival rate (6 months post-myocardial infarction) due to sudden cardiac death. Animals on a TFA diet also exhibited variable degrees of aortic atherosclerotic lesions. Animals on a TFA diet had diminished collateral vascular growth, whereas animals on the n-3 PUFA diet exhibited extensive compensatory vascular growth around ligated regions. Human arterial endothelial cells treated with docosahexaenoic acid (n-3 PUFA, 22:6) inhibited expression of intracellular adhesion molecule-1 (ICAM-1; CD54), whereas those treated with TFAs (*trans*18:2) showed significantly increased expression of adhesion molecules.

Conclusion: The *in vivo* study demonstrates that, in contrast to TFAs, n-3 PUFAs improve animal survival after myocardial infarction, prevent development of atherosclerotic lesions, and stimulate compensatory vascular remodeling. The *in vitro* study demonstrates that TFAs induce, while n-3 PUFAs prevent, endothelial dysfunction.

10:45 THE RELATIONSHIP BETWEEN PLASMA FATTY ACID COMPOSITION AND CORONARY ARTERY DISEASE IN HYPERCHOLESTEROLEMIC PATIENTS: FINDINGS FROM JELIS.

Itakura H¹, Yokoyama M², Matsuzaki M³, Saito Y⁴, Origasa H⁵, Ishikawa Y⁶, Oikawa S⁷, Sasaki J⁸, Hishida H⁹, Kita T¹⁰, Kitabatake A¹¹, Nakaya N¹², Sakata T¹³, Shimada K¹⁴, Shirato K¹⁵, Matsuzawa Y¹⁶, for the JELIS Investigators, Japan ¹Ibaraki Christian University, College of Life Science, Hitachi, Japan, ²Kobe University Graduate School of Medicine, Kobe, Japan, ³Yamaguchi University Graduate School of Medicine, Ube, Japan, ⁴Graduate School of Medicine, Chiba University, Chiba, Japan, ⁵University of Toyama, Toyama, Japan, ⁶Kobe University School of Medicine, Kobe, Japan, ⁷Nippon Medical School, Tokyo, Japan, ⁸International University of Health and Welfare Graduate School of Public Health Medicine, Fukuoka, Japan, ⁹Fujita Health University School of Medicine, Toyoake, Japan, ¹⁰Kyoto University Graduate School of Medicine, Kyoto, Japan, ¹¹Kano General Hospital, Osaka, Japan, ¹²Nakaya Clinic, Tokyo, Japan, ¹³Nakamura Gakuen University, Fukuoka, Japan, ¹⁴Jichi Medical School, Tochigi, Japan, ¹⁵Saito Hospital, Ishinomaki, Japan, ¹⁶Sumitomo Hospital, Osaka, Japan.

Background: N-3 polyunsaturated fatty acid (PUFA) improves lipid metabolism in hyperlipidemia, and thus helps to prevent coronary artery disease. The preventive effect of eicosapentaenoic acid (EPA) on coronary artery disease was already demonstrated in a large-scale clinical trial, the Japan EPA Lipid Intervention Study (JELIS).

Objective: We performed an additional analysis to determine the relationships between effects of various plasma fatty acid levels including n-3 PUFA and the risk of coronary artery disease.

Procedures: Among JELIS participants, we divided 15535 patients who gave informed consent for annual blood sampling into 3 groups composed of approximately 5000 each by average level of plasma fatty acids on-treatment, and calculated the adjusted hazard ratio of major coronary events in the middle and the highest tertiles relative to the lowest tertile as a standard.

Results: Higher plasma stearic acid level was associated with decrease in risk of major coronary events (hazard ratio=0.77, p=0.023). In addition, oleic acid (C18:1 n-9)/stearic acid (C18:0) ratio was, as an index of stearoyl-CoA desaturase (SCD) activity, positively associated with risk of major coronary events (hazard ratio=1.30, p=0.026). EPA (hazard ratio=0.77, p=0.018) and docosapentaenoic acid (DPA, hazard ratio=0.72, p=0.002) levels were negatively associated with risk of major coronary events, while docosahexaenoic acid (DHA) level was not. In the EPA-treated group, plasma oleic acid and linoleic acid levels and C18:1 n-9/C18:0 ratio were decreased. EPA and DPA levels were increased to compare with control group.

Conclusion: Stearic acid level and C18:1 n-9/C18:0 ratio appeared to be related to risk of cardiac events, and also the higher plasma level of n-3 PUFA showed the preventive effects for the risk of coronary artery diseases. Furthermore, increase in EPA and DPA levels with EPA intervention was important for prevention of coronary artery disease in Japanese hypercholesterolemic patients.

11:00 INTAKE OF VERY LONG CHAIN N-3 FATTY ACIDS FROM FISH AND INCIDENCE OF HEART FAILURE. THE ROTTERDAM STUDY.

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¹Division of Human Nutrition, Wageningen University, The Netherlands; ²Department of Epidemiology and Biostatistics, Erasmus MC, Rotterdam, The Netherlands; ³Institute for Health Science, VU University Amsterdam, The Netherlands.

Background: The public health burden of heart failure is rising, particular in elderly. Observational and experimental studies suggest that fish and its long chain n-3 fatty acids favorably affect mechanisms, which could reduce risk of heart failure.

Objective: To investigate the association between intake of fish and its long chain n-3 fatty acids eicosapentaenoic acid (EPA) plus docosahexaenoic acid (DHA) and risk of incident heart failure.

Procedure: The Rotterdam Study is a prospective, population based cohort study among 7983 elderly. At baseline, dietary data were available for 5299 subjects free of heart failure. Dietary intake was assessed using a semiquantitative food-frequency questionnaire. Heart failure was defined according to criteria of the European Society of Cardiology. Incidence of heart failure was continuously monitored during follow-up. The association between fish intake and EPA plus DHA and incident heart failure was examined by Cox proportional hazard models with adjustment for lifestyle, dietary and disease factors.

Results: During a mean follow-up of 11.4 (± 4.3) years, 669 subjects developed heart failure. Multivariate-adjusted analyses showed no association between intake of fish or EPA plus DHA and risk of heart failure. The relative risk for the highest compared with the lowest tertile of EPA plus DHA was 0.93 (95% CI 0.76-1.13). The relative risk for intake >20 g fish per day compared with no fish intake was 0.99 (95% CI 0.81-1.21).

Conclusion: This study suggests that neither the consumption of fish nor intakes of EPA plus DHA are associated with the risk of incident heart failure.

11:15 BLOOD CELL FATTY ACID PROFILES DISCRIMINATE ACUTE CORONARY SYNDROME CASE STATUS BETTER THAN STANDARD CARDIOVASCULAR RISK FACTORS

Shearer GC, Pottala JV, Harris WS

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Background: The Framingham risk score is currently the gold standard for predicting risk for coronary heart disease (CHD) events. None of the emerging risk markers have been shown to add to the predictive power of the standard. Low tissue levels of omega-3 fatty acids (FAs) have been proposed as an independent risk factor for CHD.

Objective: We sought to determine the extent to which blood cell FA profiles could discriminate acute coronary syndrome (ACS) cases from healthy controls, and whether this marker could improve upon a Framingham-like risk score (FRS).

Procedure: Using FA and demographic data from 668 ACS cases and 680 controls, we constructed Receiver Operating Characteristic (ROC) curves to assess the discriminatory power (c-statistic; area under the ROC curve) of FAs alone (in various multivariable models) and in combination with the FRS. A separate analysis was done for the omega-3 index (EPA+DHA; O3I).

Results: The FRS resulted in a c-statistic of 0.75. However, a FA profile-based prediction method (that included 10 FAs in a multiple logistic regression model) gave a c-statistic of 0.88, significantly greater than the ROC area of the FRS alone (P<0.0001). When FA profiles and the FRS were combined, the resulting c-statistic was 0.90, a significant increase over the FRS alone and the FA profile alone (P<0.01 both). For the O3I, the c-statistic was 0.64. However, the combination of the O3I and the FRS significantly improved case detection over the FRS alone ($\Delta_c = 0.02$; P<0.01). All models had good calibration as tested by the Hosmer-Lemeshow statistic.

Conclusion: FA profiles were found to be substantially better than the FRS in discriminating ACS cases from controls, but the FRS added little discriminatory power to FA profiles. Although cross sectional, these findings suggest that FA profiles alone may have substantial CHD risk prediction potential.

11:30 DIETARY N-3 PUFA AND DIRECT RENIN INHIBITION IMPROVE ELECTRICAL REMODELING IN A MODEL OF HIGH HUMAN RENIN HYPERTENSION

Fischer R¹, Dechend R¹, Qadri F², Markovic M², Feldt S¹, Herse F¹, Park JK³, Gapelyuk A¹, Schwarz I¹, Zacharzowsky UB¹, Plehm R², Safak E¹, Heuser A², Schirdewan A¹, Luft FC^{1,2}, Schunck WH² and Muller DN^{1,2}

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Objectives: Hypertensive heart disease causes heart failure and arrhythmias. We compared the effect n-3 polyunsaturated fatty acids (PUFA) with direct renin inhibition (DRI) on electrophysiological remodeling in a sudden cardiac death model of high human renin hypertension.

Procedure: We treated double transgenic rats expressing the human renin and angiotensinogen genes (dTGR) from week 4 to 7 with n-3 PUFA ethyl-esters (Omacor 25 g/kg diet) or a direct renin inhibitor (aliskiren, 3 mg/kg/d). Sprague-Dawley (SD) rats were controls. We performed Electrocardiography, Magnetocardiography and programmed electrical stimulation.

Results: Dietary n-3 PUFA increased the cardiac content of eicosapentaenoic and docosahexaenoic acid. At week 7, mortality in dTGR was 31%, whereas none of the n-3 PUFA- or aliskiren-treated dTGR died. Systolic blood pressure was modestly reduced in n-3 PUFA-treated (180±3 mmHg) compared to dTGR (208±5 mmHg). Aliskiren-treated dTGR and SD were normotensive (110±3 and 119±6 mmHg, respectively). Both n-3 PUFA treated and untreated dTGR showed cardiac hypertrophy and increased ANP levels. Prolonged QRS and QTc intervals and increased T-wave dispersion in dTGR were reduced by n-3 PUFA or aliskiren. Both treatments reduced arrhythmia induction from 75% in dTGR to 17%, vs. 0% in SD. Macrophage infiltration and fibrosis were reduced by n-3 PUFA and aliskiren. Connexin 43, a mediator of intermyocyte conduction, was redistributed to the lateral cell membranes in dTGR. N-3 PUFA and aliskiren restored normal localization to the intercalated disks.

Conclusion: Omega-3 PUFA and aliskiren improved electrical remodeling, arrhythmia induction, and connexin 43 expression, despite a 70 mm Hg difference in blood pressure and the development of cardiac hypertrophy. DRI and n-3 PUFA may be future potent therapeutic agents providing cardioprotection and reduction in risk of arrhythmias, in particular. The discovery of the n-3 PUFA signaling pathway may present new candidates for antiarrhythmic drugs.

11:45 DOES DAIRY FAT CONSUMPTION INCREASE THE RISK OF CARDIOMETABOLIC DISEASE?

Murphy KJ¹, Boyd KA¹, Coates AM¹, Pettman TL^{1,2}, Milte C¹, Misan GM^{1,2}, Noakes M³, Buckley JD¹ & Howe PRC¹

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Background: Saturated fat from dairy has been implicated in hypercholesterolemia and risk of cardiovascular disease (CVD), which has impacted negatively on consumer perception of dairy as a healthy food. However, a number of epidemiological studies, observational studies and intervention studies have independently shown that dairy intake can improve CVD risk factors such as obesity, blood pressure and dyslipidemia.

Objective: To explore relationships between consumption of dairy fat and cardiometabolic risk factors.

Design: A cross-sectional analysis was undertaken with data from food frequency questionnaires (FFQ) and assessments of cardiometabolic risk factors including blood pressure and body composition (waist circumference; WC, BMI, % body fat) obtained at baseline from 565 individuals enrolled in clinical trials. Linear regression analyses were controlled for age, gender and total energy intake. Statistical significance was set at P<0.015 to allow for multiple comparisons.

Outcomes: There were positive relationships between total fat intake and BMI, WC (P<0.0001) and % body fat (P=0.001) and between total saturated fat intake and BMI and WC (P<0.0001) but there was no relationship between total or saturated fat from dairy (as a proportion of total fat intake) and any cardiometabolic risk factor. Interestingly, dairy protein as a proportion of total protein intake was negatively related to BMI ($\beta = -0.203$, P<0.0001, n=565), WC ($\beta = -0.231$ P<0.0001, n=329), % body fat ($\beta = -0.253$, P=0.006, n=342, systolic blood pressure ($\beta = -0.118$, P=0.004, n=564) and plasma glucose ($\beta = -0.159$, P=0.001, n=418).

Conclusion: These data provide further evidence that dairy fat does not increase the risk of cardiometabolic disease; moreover, increased consumption of dairy protein may improve cardiometabolic health.

Supported by a grant from the Geoffrey Gardiner Dairy Foundation

1:30 OVERVIEW OF MAJOR CARDIOVASCULAR TRIALS WITH OMEGA-3 FATTY ACIDS: PAST, PRESENT AND FUTURE

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Several large-scale randomized intervention trials have been and are being performed in the cardiovascular field with omega-3 fatty acids. The seminal trial, DART, was a dietary intervention trial in 2033 persons after a first myocardial infarction, and demonstrated a 29 % reduction in total mortality in participants advised to consume fatty fish twice weekly. DART's sequel, another dietary intervention trial in persons with angina, while properly designed, could not be performed adequately, which precludes drawing conclusions from this trial. Smaller trials, e.g. in carriers of implanted cardioverter-defibrillators, in persons with coronary artery disease, and in persons with carotid stenoses jointly indicate that eicosapentaenoic (EPA) and docosahexaenoic (DHA) acids have stabilizing effects on cardiac rhythm and on unstable plaques. These stabilizing effects may very well be responsible for the reductions in sudden cardiac death and in non-fatal cardiac events. A protective effect of alpha-linolenic acid has yet to be convincingly demonstrated. In addition to two ongoing trials from the GISSI group, there are several randomized, placebo controlled trials with >500 participants currently being conducted. These are listed below with disease: n, endpoint, daily dose of EPA+DHA, acronym (if any), and clinicaltrials.gov number.

- Atrial fibrillation: n=660, 6 month recurrence, 4g, NCT00402363; n=1600, 12 mo recurrence, 1 g, FORWARD, NCT00597220.
- Diabetes mellitus type 2: n=12612, cardiovascular events, 1 g, ORIGIN, NCT00069784; n=10,000, cardiovascular events, 1 g, ASCEND, NCT00135226.
- Post myocardial infarction: n=4800, coronary mortality, 400 mg + 12 g ALA, Alpha Omega Trial, NCT00139464; n=3800, sudden cardiac death, 1 g, OMEGA, NCT00251134.

The trials are sponsored by Reliant, Fundacion GESICA, McMaster University, Sanofi-Aventis, University of Oxford, British Heart Foundation, Bayer, Solvay, Netherlands Heart Foundation, Trommsdorff, or Pronova respectively. Thus, the interest in the field is growing enormously.

2:00 GISSI PREVENZIONE STUDY: LANDMARK STUDY OF OMEGA-3 FATTY ACIDS FOR REDUCING RISK FOR CARDIOVASCULAR DISEASE

Marchioli R. Consorzio Mario Negri Sud, S. Maria Imbaro, Chieti, Italy

The purpose of this paper is twofold: on the one hand, to confirm the positive results on n-3 PUFA from the overall results Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI)-Prevenzione trial; on the other, to summarize and describe how the results of an important trial can help generate hypotheses either on mechanisms of action or on differential results in particular subgroups of patients, as well as test the pathophysiological hypotheses that have accompanied in the years the story of the hypothesized mechanisms of action of a drug. GISSI-Prevenzione was conceived as a pragmatic population trial on patients with recent myocardial infarction and it was conducted in the framework of the Italian public health system. In GISSI-Prevenzione, 11,323 patients were enrolled in a clinical trial aimed at testing the effectiveness of n-3 polyunsaturated fatty acids (PUFA) and vitamin E. Patients were invited to follow Mediterranean dietary habits, and were treated with up-to-date preventive pharmacological interventions. Long-term n-3 PUFA at 1 g daily, but not vitamin E at 300 mg daily, was beneficial for death and for combined death, nonfatal myocardial infarction, and stroke. All the benefit, however, was attributable to the decrease in risk for overall (-20%), cardiovascular (-30%), and sudden death (-45%). At variance from the orientation of a scientific scenario largely dominated by the "cholesterol-heart hypothesis", GISSI-Prevenzione results indicate n-3 PUFA (virtually devoid of any cholesterol-lowering effect) as a relevant pharmacological treatment for secondary prevention after myocardial infarction.

2:30 REDUCING THE RISK OF CARDIOVASCULAR EVENTS : EVIDENCE FROM THE JAPAN EPA LIPID INTERVENTION STUDY (JELIS)

Mitsuhiro Yokoyama for the JELIS Investigators.
Hyogo Prefectural Awaji Hospital, Japan

The Japan EPA lipid intervention study (JELIS) is the first randomized controlled trial to examine the efficacy of eicosapentaenoic acid (EPA) on preventing cardiovascular events in hypercholesterolemic patients (n=18,645) with or without coronary artery disease. Patients were randomly assigned to receive either 1800mg of EPA daily with statin (EPA group) or statin only (controls). The primary endpoint was any major coronary events (MCE) including sudden cardiac death, fatal and non-fatal MI and other non-fatal events including unstable angina pectoris, angioplasty, stenting, or CABG. At mean follow-up of 4.6 years, the cumulative event rate was significantly lower in the EPA group than in the control group (2.8% vs 3.5%). Unstable angina and non-fatal coronary events were also significantly reduced in the EPA group. Sudden cardiac death and coronary death did not differ between groups. We performed several sub-analyses to determine who benefits most by EPA treatment in primary and secondary prevention strata. In the primary prevention cases (n=14,981), incidence of MCE was lower for the EPA group than for the control group regardless of the number of risk factors, including the high triglyceride-low HDL-C phenotype which was the most adverse risk profile. In the secondary prevention cases (n=3,664), the incidence of MCE was significantly lower in the EPA group than in the control group (8.7% vs 10.7%), particularly in those patients with prior MI. In the primary prevention arm, EPA had no effect on stroke (1.3% control, 1.5% EPA). In contrast, the secondary prevention subgroup showed a significant 20% reduction in the recurrence of stroke with EPA treatment (6.8% vs 10.5%). Accumulating data suggest that EPA is a promising treatment for prevention of cardiovascular events, particularly high risk primary prevention as well as secondary prevention subgroups.

1:30 COMBINATION CHEMOTHERAPY IN THE COLON: CAN THE EFFICACY OF FISH OIL BE ENHANCED?

Chapkin, RS^{1,5,6}, Davidson, LA^{1,5,6}, Wang, N^{2,5}, Ivanov, I^{3,5}, McMurray, DN^{4,5,6} & Lupton, JR^{1,5,6}. Departments of ¹Nutrition and Food Science, ²Statistics, ³Veterinary Pharmacology and Physiology, ⁴Microbial and Molecular Pathogenesis, ⁵Center for Environmental and Rural Health, and ⁶Intercollegiate Faculty of Nutrition, Texas A&M Health Science Center and Texas A&M University, College Station, Texas, USA.

There are cogent data indicating a protective effect of n-3 polyunsaturated fatty acids (PUFA) e.g., eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), on colon cancer. In contrast, dietary lipids rich in n-6 PUFA, e.g., linoleic acid (LA) and arachidonic acid (AA), enhance the development of colon tumors. This is significant because the typical Western diet contains 10 to 20 times more n-6 than n-3 PUFA. Unfortunately, to date, a unifying mechanistic hypothesis addressing why n-3 PUFA selectively suppress colon cancer compared to n-6 PUFA (the major dietary form of PUFA in the U.S. diet) is lacking. We have demonstrated that (i) dietary n-3 PUFA induce perturbations in colonocyte membrane microdomain (caveolae) lipid composition, suppressing oncogenic signaling and Ras protein trafficking; (ii) n-3 PUFA supplant arachidonic acid (AA) in colonocyte membrane phospholipids, with EPA in particular being metabolized into a novel 3-series E-prostaglandin (PGE3), a putative antitumorigenic-cyclooxygenase (COX) metabolite; and (iii) the proapoptotic-chemoprotective effect of n-3 PUFA is enhanced when a highly fermentable fiber, pectin (or its fermentation product, butyrate) is added to the diet. We postulate that the failure to address an interaction between dietary fat and fiber may explain why the chemoprotective effects of fiber are obscured in prospective cohort studies. An array of experimental approaches (post-transcriptional regulation of mRNA targets) and models (in vivo, azoxymethane-injected and dextran sodium sulphate chronic inflammation stressed fat-1 transgenic mouse, and in vitro, normal and malignant transformed mouse and human colonocyte cell lines) have been used to determine precisely how n-3 PUFA modulate cell signaling networks and reduce colon cancer risk. Findings from our studies demonstrate that the consumption of EPA and DHA may prove to be an effective adjuvant therapy in colon cancer. Supported by NIH grants CA59034, CA129444, DK071707, P30ES09106 and USDA CSREES 2006-34402-17121 “Designing Foods for Health”.

2:00 DHA-INDUCED MKP-1 OVER-EXPRESSION AND APOPTOSIS IN LUNG CANCER CELLS

Calviello G¹, Serini S¹, Trombino S², Oliva F², Piccioni E¹, Monego G¹, Resci F¹, Boninsegna A¹, Picci N², & Ranelletti FO¹. ¹Catholic University, School of Medicine, Rome, Italy; ²Calabria University, Cosenza, Italy g.calviello@rm.unicatt.it

Background: The dual phosphatase MAP-kinase-phosphatase-1 (MKP-1) is involved in the effect of different apoptotic modulating agents. It has been shown that, depending on the tissues, its over-expression may inhibit or induce apoptosis. Its expression has been considered a potential positive prognostic factor in lung cancer, and smoke has shown to lower its level in ferret lung.

Objective: Our aim was to examine whether docosahexaenoic acid (DHA), whose apoptotic-inducing activity has been observed by us and others in different kinds of cancer cells, was able to induce apoptosis also in lung cancer cells through the modification of MKP-1 expression.

Procedures: Mv1Lu mink, A549 and BEN human lung carcinoma cells were used. Apoptosis was detected by annexin V-FITC cytofluorimetry and by morphological fluorescence microscopy analysis of acridine orange-ethidium bromide stained cells. The protein expression of MKP-1, and of phosphorylated-ERK1/2 (p-ERK1/2) and -p38 (p-p38) was evaluated by Western blotting analysis. siRNA transfection for knockdown of MKP-1 was performed using siRNA duplex oligonucleotides from Qiagen (Milan, Italy). MKP-1 RNA was analyzed by real-time polymerase chain reaction (RT-PCR).

Results: DHA showed a pro-apoptotic effect in all the cells tested. As an early response, before the development of apoptosis, DHA treatment increased MKP-1 mRNA and protein expression in all the lung cancer cell lines, later decreasing the expression of p-ERK1/2 and p-p38. The transcriptional silencing of MKP-1 inhibited the pro-apoptotic effect of DHA and reverted the decreasing effect of DHA on the levels of p-ERK1/2 and p-p38. Conclusion: The data herein presented demonstrate that DHA induces apoptosis in lung cancer cells, and suggest that one possible mechanism may be the induction of MKP-1 expression and the decrease of ERK1/2 and p38 phosphorylation and activity. Moreover, they support the hypothesis that DHA may exert chemopreventive and chemotherapeutic action also in lung cancer.

2:15 LONG CHAIN POLYUNSATURATED FATTY ACIDS INCREASE THE CYTOTOXICITY OF CHEMOTHERAPY AGENTS IN THREE BREAST CANCER CELL LINES,

Catherine J. Field¹, Marnie Newell¹, Michael B. Sawyer², David N. Brindley³.

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Background: Long chain n-3 polyunsaturated fatty acids (PUFA) have cytotoxic effects against mammary tumors when fed to rodents and when cultured with tumor cells. Our previous research suggests that the cytotoxic effect may be mediated via the same membrane-mediated mechanism as many of the current chemotherapy drugs used to treat breast cancer. This suggests a potential adjuvant role for n-3 PUFA.

Objective: To determine the effects of docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) alone and in combination with doxorubicin (DOX) or Trastuzumab (TRA) on the growth of cell lines (MCF-7, MDA-MB-231, SK-BR-3) that model various forms of breast cancer.

Procedures: Cells were incubated with a mixture of fatty acids with or without varying concentrations of DHA or EPA for 48 h. The fatty acids were removed, the media replaced and the change in cytotoxicity (using the WST-1 assay) associated with incubating for 24 h with a previously established IC₅₀ for DOX (MCF-7, MDA-MB-231) or TRA (SK-BR-3) determined.

Results: Prior incubation with either DHA or EPA (in the presence of oleic and linoleic acid), compared to an equal concentration of a mixture of oleic acid and linoleic acid, significantly increased both the incorporation of DHA and EPA into the cell phospholipids and the cytotoxic activity of DOX by MCF-7 and MDA-MB-231 cells and TRA by SK-BR-3 cells (P<0.05). Isobologram analysis (using the Calcsyn program) confirmed a synergistic relationship for these two long chain n-3 polyunsaturated fatty acids with the drugs in all cell lines studied. For each of the human breast cancer cell lines, at similar concentrations, pretreatment with DHA had a greater effect on drug cytotoxicity than EPA (P<0.05).

Conclusions: Prior exposure of three established cancer cell lines to long chain n-3 PUFA improved the cytotoxic action of two chemotherapy drugs used in the treatment of breast cancer.

2:30 MINERVAL FOR TREATMENT OF HUMAN GLIOMA

Lladó V, Terés S, Barceló-Coblijn G, Barceló J, Martín L, Higuera M, Busquets X, & Escribá PV
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Background: Gliomas are brain cancers of glial cells, with diverse nature and poor prognosis. Temozolomede, the drug of choice for treatment of human gliomas, extends a few months the survival rate of patients.

Objective: The aim of this study was to determine the molecular bases and potential effectiveness of Minerval (2-hydroxy-9-cis-octadecenoic acid) for treatment of glioma.

Procedures: We used human glioma cancer cells (SF767, U118) and animal models of human glioma (Nu/Nu mice). Immunoblotting, RT-PCR, microscopy and flow cytometry techniques were used to study the anti-cancer effect of this compound. In animals, we determined the tumor volume and their molecular and cytological features.

Results: Minerval induced changes in the lipid composition of human glioma cell membranes. In addition, these cells underwent morphological changes that suggested induction of differentiation. Glutamine synthase and GFAP are not expressed in undifferentiated glioma cells but abundant in mature glial cells, from which they are derived. The high expression of these proteins in Minerval-treated glioma cells was high indicated the induction of cell differentiation. On the other hand, ERK and MEK appeared to be hypophosphorylated, suggesting that the MAP kinase pathway is repressed. Additionally, the activity of Elk1, a pivotal transcription factor activated by ERK, was reduced in glioma cells treated with Minerval. In nude mice developing human gliomas, Minerval induced tumor regression along with cytological and molecular changes associated with its anti-cancer action. By contrast with temozolomide, tumors cured using Minerval (>90%) did not relapse.

Conclusion: Minerval induces differentiation of glioma to glial cells and causes tumor regression. These effects appeared to be related to regulation of membrane lipid composition and repression of the MAP kinase pathway. The oral administration of this drug, its lack of side-effects and greater therapeutic efficacy suggest that Minerval could be used successfully for treatment of gliomas.

2:45 MECHANISMS OF ACTION OF GAMMA-LINOLENIC ACID AS A MODULATOR OF TUMOUR GROWTH AND ANGIOGENESIS IN THE C6 GLIOMA MODEL

Benadiba M, Miyake JA, Colquhoun A

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Background: Gamma-linolenic acid (GLA) is an inhibitor of glioma cell proliferation both in vitro and in vivo, although its mechanisms of action are not yet fully understood.

Objective: identify specific targets of GLA in the C6 glioma model.

Procedures: mRNA and protein expression profiles were determined for proteins of importance in glioma proliferation and spread in C6 cells, after 24 hours exposure to 150µM GLA in vitro. Similar studies were also performed in the C6 glioma model in vivo after 14 days treatment with 5mM GLA by osmotic pump infusion.

Results: GLA increased mRNA expression of cyclin D1, p53, p65, bax, nm23β, prostaglandin receptors EP1 and EP4, and decreased expression of E2F1 and tenascin C. No changes were found for c-myc, pRb, p21, p27, bcl2, Ku70, Ku80, ERK1, ERK2, nm23α, prostaglandin receptor EP2, GPI-brevican, matrix metalloprotease 2 (MMP2), vascular endothelial growth factor A (VEGFA) or VEGF receptor flt1. Protein expression at 24 hours was altered for bax, E2F1 and Ku80. In vivo, GLA decreased the mRNA expression of E2F1, p16, p53, p65, ERK1, PPARγ, Ku70, Ku80, Bax, nm23β, MMP2, vascular endothelial growth factor A (VEGFA), VEGF receptor Flt1, cyclooxygenase 2 (COX2) and prostaglandin receptors EP1, EP2 and EP3, and increased the expression of VEGF receptor Flk1, tenascin R, and secreted brevican. No changes were found for cyclin D1, c-myc, pRb, p21, p27, bcl2, nm23α, prostaglandin receptor EP4, GPI-brevican. The infusion of 5mM GLA in CSF caused a significant decrease in C6 tumour growth in comparison with CSF alone. The average tumour area and volume was reduced by 75% and 85%, respectively. The microvessel density of the GLA treated tumour was approximately 44% of the control tumour.

Conclusion: GLA alters glioma growth in vitro and in vivo through proteins involved in cell cycle/apoptosis and angiogenesis.

1:30 FISH OIL USE IN RHEUMATOID ARTHRITIS

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Meta-analysis and mega-analysis of randomised controlled trials (RCT) provides high-level evidence for a modest symptomatic benefit of fish oil in patients with established rheumatoid arthritis (RA). RA is a condition with increased cardiovascular mortality. Thus, an additional expected benefit of fish oil in RA is reduced cardiovascular risk via direct mechanisms and via decreased non-steroidal anti-inflammatory drug use. Potential mechanisms for anti-inflammatory effects of fish oil include inhibition of both lipid and peptide mediators of inflammation (eicosanoids and cytokines), as well as providing substrates for formation of lipid suppressors of inflammation (resolvins). Given the high-level evidence along with plausible biological mechanisms, the poor uptake of clinical use of fish oil indicates that there are barriers to its use. Some of these reflect the commerce-driven dominance of RA therapies in medical practice. Another impediment to wider uptake of clinical fish oil use may be the incomplete understanding of mechanisms of action that is manifest in variability in the reports of suppression of inflammatory mediators such as cytokines. Progress will require better understanding of the reasons for variable suppression of cytokines and this will include studies of the large variability in tissue levels of omega-3 fats when dietary intake is constant, and studies of the genetic component of the variability in cytokine responses to dietary fish oil. There needs also to be progress in clinical trial design for studies of fish oil use in RA. We are conducting a double-blind RCT of fish oil use in recent-onset RA. Unlike previous studies, this aims to intervene before joint damage has occurred and it uses drug regimens determined by an algorithm designed to be responsive to disease activity and intolerance. This systematisation allows drug use to be an outcome measure whereas previously the clinical need to alter drug use was seen as a 'problem'.

2:00 EFFECT OF FISH OIL OR DOCOSAHEXAENOIC ACID ON HEPATIC LEVELS OF SOLUBLE EPOXIDE HYDROLASE, THE HEPATIC PROTEOME, AND AORTIC PLAQUE SIZE IN APOLIPOPROTEIN E KNOCKOUT MICEMavrommatis Y¹, Ross K¹, Gordon MJ¹, Rucklidge G¹, Reid M¹, Duncan G¹, Horgan G², Sneddon A¹, Thies F^{1,3}, de Roos B¹.¹Division of Vascular Health, Rowett Research Institute, Aberdeen, UK²Biomathematics and Statistics Scotland at the Rowett Research Institute, Aberdeen, UK³Department of Medicine and Therapeutics, University of Aberdeen, Aberdeen, UK

Background: Long chain n-3 polyunsaturated fatty acids from fish oil protect against cardiovascular disease but mechanisms are not well understood. Preliminary results indicate that fish oil may affect soluble epoxide hydrolase (sEH) and thereby inflammatory pathways in a time-dependent manner.

Objectives: To determine the effects of dietary DHA or fish oil on hepatic sEH protein levels and gene expression, hepatic proteome, and atherosclerotic plaque size in the aortic root.

Procedures: Male apolipoprotein E knockout (*ApoE*^{-/-}) mice (n=75) were randomized to three dietary groups receiving a high fat-high cholesterol diet supplemented with 2% (w/w) of either high oleic acid sunflower oil (HOSF) or DHA or fish oil. Livers and proximal aortas were collected from 5 mice/group on day 2 and after 1, 2, 4, and 10 weeks of intervention. Hepatic sEH protein levels were assessed by Western blots, gene expression by semi-quantitative RT-PCR, analysis of the hepatic proteome by 2D gel electrophoresis, and atherosclerotic plaque size by staining with Sudan IV counterstained by H&E.

Results: DHA and fish oil did not affect hepatic sEH protein levels or gene expression. However, proteomics analysis revealed decreased sEH protein levels in time only in the fish oil group (P<0.05). In time, both fish oil and DHA intervention caused a down-regulation of hepatic apolipoprotein A1 (P<0.05), suggestive of a shift towards the larger, more cholesterol-rich HDL₂ particles, and a down-regulation of hepatic peroxiredoxin 3 (P<0.05), indicating decreased hepatic oxidative stress upon intervention with fish oil and DHA, compared with HOSF oil. All groups developed atherosclerosis but plaque size did not differ between the three intervention groups in time.

Conclusion: Dietary EPA may be responsible for the down-regulation of sEH in the long term, potentially leading to an anti-inflammatory response. Down-regulation of sEH is unlikely to affect plaque development.

This study was funded by the Scottish Government Rural and Environment Research and Analysis Directorate (RERAD).

2:15 LIPID EMULSION WITH FISH OIL (EPA AND DHA) DECREASES INFLAMMATORY MARKERS AFTER OPEN HEART SURGERY IN INFANTSLarsen BM^{1,4}, Goonewardene L², Joffe AR³, Van Aerde J³, Field CJ^{2,4} and Clandinin MT^{2,4}.

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Background: Tumor necrosis factor α (TNF- α) released by monocytes can be suppressed by 20:5n-3(EPA) and 22:6n-3(DHA) fatty acids. Infusing intravenous emulsions containing predominantly n-6 fatty acid (53% n-6, 8 % n-3) increases inflammation. Surgery and infection lead to excessive inflammation resulting in systemic inflammatory response syndrome and multi-organ dysfunction.

Objective: This study compares the inflammatory response of infants undergoing cardiopulmonary bypass for open-heart surgery who are given emulsions with or without fatty acids EPA and DHA.

Procedure: Critically ill infants (n=32) (40 \pm 2.7 weeks) were randomized prospectively to an emulsion treatment with (test) or without (control) added EPA and DHA fatty acids. Emulsion was initiated preoperatively. Cytokines were determined in blood at baseline, before surgery and day 1, 7 and 10 after surgery. Data was analyzed using the mixed model of SAS with a repeated measures structure.

Results: TNF- α overall was significantly (p=0.003) lower in the test group (5.9 pg/ml) vs. control group (14.8 pg/ml). The interaction of time and treatment was significant (p=0.02). When sepsis was absent the TNF- α for the control group and the test group was 8.6 pg/ml and 10.4 pg/ml respectively, where as when sepsis was present TNF- α was 21.1 pg/ml and 1.5 pg/ml (p=0.0007). TNF- α had a positive relationship with total length of stay (TLOS) (p < 0.01) in the control group. The pro and anti inflammatory ratios of TNF- α /IL-4 (p=0.056) and IL-6/IL-10 (p=0.18) did not differ between treatments.

Conclusions: Providing a lipid emulsion containing n-3 fatty acids reduces a key inflammatory cytokine in infants undergoing heart surgery. It is concluded that EPA and DHA fatty acid may provide a useful therapy for the hyper inflammatory state of these infants and may improve clinical outcomes. The increase in TLOS associated with the increase in TNF- α in the control may warrant change in critical care feeding practice.

2:30 MARINE-DERIVED N-3 POLYUNSATURATED FATTY ACIDS SELECTIVELY AFFECT PLASMA CYTOKINES AND DECREASE ILLNESS IN THAI SCHOOLCHILDRENThienprasert A¹, Samuhaseneetoo S¹, Popplestone K², West AL², Miles EA² & Calder PC²¹Silpakorn University, Nakornpathom, Thailand; ²University of Southampton, Southampton, United Kingdom

Background: The immunologic effect of n-3 polyunsaturated fatty acids (PUFAs) in children is not clear and whether such an effect influences illness has not been investigated.

Objective: To determine the efficacy of very long-chain n-3 PUFAs with regard to illness and selected plasma cytokines in schoolchildren.

Procedure: Thai schoolchildren were randomly allocated to placebo (n = 86) or fish oil (n = 94) groups in a double blind fashion. On five days per week for 6 months they consumed two x 200 ml milk fortified with placebo (soybean) oil or fish oil; the latter provided 1 g docosahexaenoic acid plus 200 mg eicosapentaenoic acid each day. Episodes and duration of illness were recorded. Plasma interleukin (IL)-2 receptor, IL-6, IL-10, and transforming growth factor (TGF)- β 1 concentrations and the fatty acid profile of plasma phospholipids were determined.

Results: After intervention, very long chain n-3 PUFAs in plasma phospholipids were significantly higher in the fish oil group than in the placebo group (p < 0.001). Episodes and severity of illness (mainly upper respiratory tract) in the fish oil group were significantly less than in the placebo group (p = 0.05). Plasma IL-6 concentration tended to decrease in the fish oil group, but this did not reach significance. Plasma TGF- β 1 concentration increased in both groups, but the increase was significantly less in the fish oil group. At the end of supplementation TGF- β 1 concentration was lower in the fish oil group (p < 0.001). Plasma IL-2 receptor and IL-10 concentrations were not affected by either treatment.

Conclusions: Marine-derived n-3 PUFAs reduce episodes and severity of illness in schoolchildren. They modify the circulating concentrations of some cytokines; whether this is due to reduced disease-induced inflammation or a direct effect on cytokine production remains to be determined.

2:45 DO FISH OIL AND LINOLEIC ACID INTAKE AFFECT CYTOKINE PRODUCTION IN HEALTHY HUMANS?

Damsgaard CT¹, Frøkiær H², Calder PC³ & Lauritzen L.

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²DTU-Biosys, Technical University of Denmark, Lyngby, Denmark

³Institute of Human Nutrition, School of Medicine, University of Southampton, Southampton, England

Background: It is a widespread belief that n-3 long-chain polyunsaturated fatty acids (LCPUFA) from fish oil (FO) are anti-inflammatory and decrease *ex vivo* cytokine production in humans. A high intake of linoleic acid (LA) may impair any n-3 LCPUFA effects.

Objective: In a randomized controlled 2×2-factorial intervention, we investigated how 8-weeks FO-supplementation in combination with a high or low LA-intake affected the *ex vivo* production of interleukin (IL)-6, tumor necrosis factor- α (TNF- α), IL-10, and interferon- γ (IFN- γ) in healthy men. We also investigated how different n-3 LCPUFA-concentrations affected *in vitro* cytokine production in a human monocytic cell line (MonoMac6).

Procedure: Healthy men ($n=64$) aged 19–40 years were allocated to FO (3.1 g/d n-3 LCPUFA) or olive oil capsules. Within each group they were also randomized to oils/spreads with either a high or a low LA-content, resulting in mean LA-intakes of 7 ± 2 energy% and 4 ± 1 energy%, respectively. Before, after and 8-weeks after the intervention we measured dietary intake, n-3 LCPUFA-content in mononuclear cells (PBMC) and cytokine production from 24h cultures of whole-blood, PBMC and monocytes stimulated with lipopolysaccharide (LPS) or UV-killed *lactobacillus acidophilus*.

Results: FO-capsules effectively raised the n-3 LCPUFA-content in PBMC ($P<0.001$) with only slight effects of the oils/spreads. FO lowered LPS-stimulated whole-blood IL-6 ($P=0.02$), but neither FO nor the LA-intake affected the production of TNF- α , IFN- γ or IL-10 from any of the cultures. In contrast, the *in vitro* studies showed that n-3 LCPUFA dose-dependently increased the production of the inflammatory cytokines IL-6 and TNF- α , and decreased the anti-inflammatory cytokine IL-10, in MonoMac6 ($P<0.05$).

Conclusion: Fish oil and linoleic acid-intakes did not markedly affect *ex vivo* cytokine production in a large group of healthy men. The observed pro-inflammatory effect of n-3 LCPUFA in MonoMac6 underlines the limited applicability of *in vitro* models to *in vivo* situations.

ABSTRACT

THURSDAY MAY 22

8:15 RESOLVINS AND PROTECTINS: A NEW GENUS OF DUAL ANTI-INFLAMMATORY AND PRO-RESOLVING MEDIATORS FROM OMEGA-3 EFA

Charles N. Serhan

Center for Experimental Therapeutics and Reperfusion Injury, Department of Anesthesia, Perioperative and Pain Medicine, Brigham and Women's Hospital and Harvard Medical School

The well-integrated inflammatory response is essential in health and disease. It is important to achieve a complete understanding of the cellular and molecular events that govern resolution of acute inflammation and the return to homeostasis. Since we identified novel local chemical mediators, coined the resolvins and protectins in animal models that control the duration and magnitude of inflammation, mapping of these resolution circuits may provide new avenues for appreciating the molecular basis of many inflammatory disorders. This presentation will give an update and overview of recent advances from our studies on resolvins and protectin biosynthesis and the actions of these novel anti-inflammatory and pro-resolving lipid mediators in vivo and in vitro. These new families of lipid derived mediators were originally isolated from murine models of acute inflammation captured during the natural spontaneous resolution phase using mediator lipidomics-based LC-MS-MS and complete structural elucidation. They are biosynthesized from omega-3 fatty acids (EPA and DHA) and possess potent anti-inflammatory, pro-resolving and anti-fibrotic actions in murine and rabbit disease models. Together these results give rise to a paradigm shift suggesting that defective resolution mechanism(s) may underlie inflammatory phenotype(s) that characterize many prevalent human diseases rather than excessive over production of pro-inflammatory mediators. Moreover, these new families of endogenous pro-resolving and anti-inflammatory agonists (i.e. resolvins and protectins) constitute a new genus of anti-inflammatories.

8:15 THE RELATIONSHIP BETWEEN THE FATTY ACID COMPOSITION OF IMMUNE CELLS AND THEIR FUNCTION

Calder PC

School of Medicine, University of Southampton, Southampton, UK

Although the fatty acid composition of human immune cells varies, partly according to variation in the pattern of fatty acid consumption from the diet, arachidonic acid (AA) is typically the predominate PUFA. The ability of immune cells to produce eicosanoids capable of modulating the immune response, including its inflammatory component, is strongly related to their AA content: increasing AA in cells as a result of increased consumption of AA results in greater eicosanoid synthesis. Conversely decreasing AA in cells as a result of increased consumption of long chain (LC) n-3 PUFAs results in less eicosanoid synthesis. LC n-3 PUFAs also affect production of cytokines. This effect is again linked to changes in the fatty acid composition of the cell membrane perhaps because an alteration in eicosanoid milieu is the mechanism involved. Alternatively intracellular signaling mechanisms generated at the membrane level and leading to altered rates of cytokine gene expression may be influenced by membrane fatty acid composition independent of eicosanoid profiles. Phagocytosis is a membrane-mediated event that is reliant upon a fluid and flexible plasma membrane. Studies have linked differences in fatty acid composition of phagocyte phospholipids with differences in phagocytic capacity. Signaling mechanisms in T cells are affected by LC n-3 PUFAs and early data suggested that fatty acids act upstream in the signaling cascade. Recent data has indicate that EPA incorporation into T cell membranes modifies lipid raft function in a way that interferes with signaling pathways. Early data on MHC II expression and antigen presentation cell (APC) function suggested that alterations at the membrane level are involved. Recent data has shown that AA and DHA decrease MHC I expression and APC function and that this is related to trafficking of MHC I from the endoplasmic reticulum to the Golgi. Thus the fatty acid composition of intracellular membranes may play a role in protein targeting to different cellular compartments, indicating a highly novel mechanism by which fatty acids can affect cell function.

10:30 AN N-3 PUFA DEFICIENT DIET GENERATES ALTERATIONS IN VITAMIN A NUCLEAR RECEPTOR EXPRESSION: CONSEQUENCES ON COGNITIVE PROCESSESBuaud B¹, Vaysse C¹, Combe N¹, Higuieret P², & Pallet V²¹ITERG – Département Nutrition & Santé, Université Bordeaux¹, Talence, France; ²Unité de Nutrition et Neurosciences, Universités Bordeaux¹ et Victor Segalen Bordeaux², Talence, France

Background: N-3 polyunsaturated fatty acids (PUFAs), particularly 22:6n-3 (DHA), are major components of the brain. Rats fed an n-3 PUFA deficient diet exhibit altered memory and learning capacities. Vitamin A via its nuclear receptors (RAR and RXR) plays a central role in the maintenance of such processes. Among its target genes, vitamin A controls the expression of neurogranin RC3 and neuromodulin GAP-43, two proteins considered as good markers of the dendrite spine density. Vitamin A and n-3 PUFA signaling pathways can interact via RAR, RXR and PPAR.

Objective: The present work deals with the hypothesis that an n-3 PUFA deficient diet could modify the expression of RC3 and GAP-43 by altering the expression pattern of RAR and RXR.

Procedures: Male Wistar rats at weaning were divided into two groups: the first one received a control diet (18:2n-6/18:3n-3=5.5), and the second one an n-3 PUFA deficient diet (18:2n-6/18:3n-3=232) for 3, 9, 18 and 25 weeks.

At the end of each period, RAR β , RXR $\beta\gamma$ and PPAR δ mRNAs were quantified in the striatum. The expression of RC3 and GAP-43 was estimated at mRNA and protein levels. Blood and brain fatty acid compositions were also investigated.

Results: From 18 weeks, RAR β , RXR $\beta\gamma$ and PPAR δ mRNAs were simultaneously decreased in n-3 PUFA deficient rats (-19.8, -13.8, and -27.6% respectively (P<0.05)). The expression of RC3 and GAP-43 was also diminished (-18% and -24% respectively (P<0.001) at protein level). In blood and brain phosphatidylethanolamine (PE), the 22:5n-6 percentage was strongly increased (twelve-fold (P<0.001) in PE) concomitantly to a decrease of the DHA percentage (-31% (P<0.001) in PE).

Conclusion: These results show that an n-3 PUFA deficient diet may induce changes in the expression pattern of vitamin A nuclear receptors, and by this way, lead to neurobiological alterations, similar to those described during normal brain aging.

10:45 PLASMA PHOSPHOLIPID FATTY ACID STATUS AND COGNITIVE PERFORMANCE IN NORMAL HEALTHY AGING ADULTS RESULTS FROM THE 12-YEARS FOLLOW-UP OF THE MAASTRICHT AGING STUDYde Groot RHM¹, van Boxtel MPJ¹, Hornstra G², & Jolles J¹.¹School for Metal Health and Neuroscience; Division of Cognitive Disorders, and Department of Psychiatry & Neuropsychology, Maastricht University, The Netherlands; ²Nutrition and Toxicology Research Institute Maastricht (NUTRIM), Maastricht University, The Netherlands

Background: Regular consumption of fatty fish or of n-3 long-chain polyunsaturated fatty acids is thought to protect against different neurodegenerative disorders. However previous research has its limitations and only one previous study used sensitive longitudinal data on objective cognitive functioning in normal healthy aging individuals.

Objective: In this study we investigated: 1. Whether current plasma phospholipids fatty acid status is associated with objective cognitive functioning in a normal aging population with a broad age range, and 2. Whether fatty acid status was associated with changes in cognitive functioning over the past 12 years.

Design: Cognitive functioning of 241 participants (aged 24-81) of the Maastricht Aging Study was determined at baseline and after 12 years using a comprehensive cognitive test battery covering different functional domains (memory, attention, speed of information processing). Plasma phospholipids fatty acid status was determined at 12 years follow-up.

Results: Hierarchical linear regression analyses corrected for age, education, and sex showed that higher concentrations of DHA and of adrenic acid (22:4n-6) were associated with lower performance on simple speed, whereas no associations were found with changes in cognitive performance over the last 12 years. Relationships with other fatty acids were not significant. Interestingly, high fish consumption was associated better performance on a memory tasks and with slower decrease in memory performance over the last 12 years. No associations were found in other cognitive domains.

Conclusions: Results regarding the association between fatty acid status and cognitive performance are not convincing, but they indicate a negative relationship. The positive association between fish consumption and memory performance suggests that another constituent than the fatty acids may be responsible for the observed positive association between fish consumption and cognitive functioning.

11:00 HIGHLY UNSATURATED OMEGA-3 FATTY ACIDS AND ASPIRIN ACT SYNERGISTICALLY TO MODIFY RISK OF ADVANCED AGE RELATED MACULAR DEGENERATION.

SanGiovanni JP¹, Agrón EA¹, & Chew EY¹. ¹National Institutes of Health: NEI-CTB, Bethesda, MD, USA

Background. Pathogenesis of age-related macular degeneration (AMD) is driven partially by an inflammatory component. Inflammation activates cleavage-biosynthetic enzymes of diet-based highly unsaturated fatty acids (HUFAs) that serve as precursors to molecules exerting potent autocrine effects on retinal inflammation, neovascularization, and cell survival (i.e. eicosanoids, docosanoids, resolvins, and neuroprotectins). These autocoids may be synthesized through aspirin (ASA)-driven pathways.

Objective. To investigate the relationship of n-3 HUFA intake and ASA use with advanced AMD.

Procedures. We analyzed dietary and genomic data from people at moderate risk of AMD as part of a 12-year multi-center study on age-related eye disease. 1033 people contributed to diet-ASA-AMD analyses; 561 of these were analyzed with 100K microarray platforms. We collected exposure data collected with validated questionnaires. Masked graders at a centralized fundus reading center applied a standardized protocol to ascertain outcomes from annual stereoscopic photographs taken across the course of the study. We applied multivariable logistic regression to estimate relationships of ASA interactions on calorie-adjusted nutrients. Genomic data were analyzed with a pathway-centered approach.

Results. People reporting highest intake of docosahexanoic acid (DHA) were half as likely to have advanced AMD as their peers (odds ratio [OR] = 0.48; 95%CI, 0.30—0.77, $P < 0.002$). ASA-HUFA relationships modified this effect: people reporting regular ASA use (> 5 times/week) and highest levels DHA intake were less likely to have advanced AMD than their peers consuming similar levels of DHA but not using ASA regularly. The OR was 0.51 (0.27—0.97, $P < 0.05$) in ASA users and 0.63 (0.29—1.38, n.s.) in non-users. Genomic analyses elucidated relationships of AMD with inflammation-associated genes in the PI3K/AKT pathway.

Conclusions: The relationship of n-3 HUFA intake with NV AMD is modified by regular ASA use. The PI3K/AKT signaling pathway may be associated with an inflammatory basis of AMD pathogenesis.

11:15 UNRESOLVED ISSUES IN THE LINK BETWEEN DOCOSAHEXAENOIC ACID AND ALZHEIMER'S DISEASE

Plourde M, Fortier M, Vandal, M, Tremblay-Mercier J, Freemantle E, Bégin M, Pifferi F, Cunnane SC
Research Center on Aging, Université de Sherbrooke, Sherbrooke, QC, Canada,

Background: Lower consumption of docosahexanoic acid (DHA) is commonly but not always associated with higher risk of cognitive decline and diagnosis of Alzheimer's disease (AD).

Objective: To review the available data relating DHA to AD, with emphasis on DHA content of plasma and brain.

Results: Our assessment of this literature is that low DHA is not consistently observed in AD plasma or brain. However, in dietary and population studies, low DHA intake is usually associated with low plasma DHA. Therefore, at present, there is no clear explanation of why the usual low DHA intake – low plasma DHA relationship appears not to exist in AD. Adding to the confusion, preliminary and inconclusive reports tentatively suggest that dietary DHA could potentially reduce cognitive deterioration in AD. These inconsistencies between dietary DHA, plasma/tissue DHA and possible DHA efficacy in AD may be more methodological than biological, and may arise in part because only one study to date has reported both DHA intake and plasma DHA values in the same AD patients.

Conclusion: Studies reporting DHA intake and plasma levels while also undertaking a DHA intervention in AD would presumably help resolve these issues.

11:30 APOLIPOPROTEIN E AND PPAR- L162V POLYMORPHISMS INFLUENCE PLASMA OMEGA-3 RESPONSE

Plourde M^{ac}, Vohl MC^{bc}, Caron-Dorval D^{bc}, Couture P^{bc}, Lemieux, S^c, Cunnane SC^{ac}

^aResearch Center on Aging, Université de Sherbrooke, Sherbrooke, ^bCRML, ^cINAF, Université Laval, Québec, Canada.

Background: Apolipoprotein E and peroxisome proliferator-activated receptor alpha (PPAR-alpha) gene polymorphisms are associated with plasma lipid perturbations such as increase cholesterol and dyslipidemia, but it is unknown whether plasma fatty acids such as omega-3 fatty acids are also varying according to genetic polymorphisms. Low plasma omega-3 is sometimes associated to increase risk to develop diseases such as cognitive decline.

Objective: To determine the plasmatic content of omega-3 in response to an omega-3 supplementation in subjects having either ApoE4 or PPAR-alpha L162V or both polymorphisms.

Methods: 28 healthy men were recruited according to their PPAR-alpha polymorphism (14 subjects with normal PPAR-alpha and 14 subjects with PPAR-alpha L162V). ApoE polymorphism was determined in each subject, allowing their separation into four groups based on their genotypes (Normal (N) n = 11, ApoE4 n = 3, PPAR-alpha L162V (L162V) n = 9, ApoE4 and PPAR-alpha L162V (E4 + L162V) n = 5). Omega-3 supplementation of 5g/d of fish oil (4g/d of omega-3) last for 6 weeks. Blood samples were collected before and after omega-3 supplementation.

Results: Before supplementation, plasma of subjects with ApoE4 and E4 +L162 had respectively 59% and 46% higher omega-3 compared to the N and L162V groups ($p = 0.07$). There was two times more omega-3 in plasma of N and L162V after supplementation while plasma omega-3 was not significantly increased in the ApoE4 and E4 +L162 groups.

Conclusion: These results suggest that genetic polymorphisms, and more specifically those of ApoE and PPAR-alpha, may explain in part the interindividual variability observed in the incorporation of fatty acids before and after an omega-3 supplementation.

11:45 DHA METABOLISM IN THE HEALTHY ELDERLY

Vandal M¹, Pifferi F¹, Plourde M¹, Freemantle E¹, Zhang Y², Tremblay-Mercier J¹, Fortier M¹, Bégin M¹, Brenna JT², and Cunnane SC¹

¹Research Center on Aging, Université de Sherbrooke, Canada, ²Division of Nutritional Sciences, Cornell University, Ithaca, NY, USA

Background: Little is known about whether docosahexanoic acid (DHA) metabolism changes during healthy human aging.

Objective: To use tracer and supplementation approaches to evaluate DHA metabolism in the healthy elderly.

Procedure: We first studied plasma DHA in healthy young (Y) and elderly (E) before and after DHA-rich fish oil supplementation providing 680 mg/d of DHA and 320 mg/d of eicosapentaenoic acid for 3 weeks. In that part of the study, compliance was monitored by a new method in which the capsules were spiked with carbon-13 (¹³C)-glucose, the excretion of which was measured in breath CO₂. In a separate study, we then assessed the plasma incorporation and beta-oxidation of an oral 50 mg dose of ¹³C-DHA in Y vs. E over 1 wk.

Results: At baseline, both the Y and E groups had similar plasma DHA content. Despite raising DHA intake by 5-10 fold and plasma total DHA, the supplement did not raise DHA in plasma free fatty acids in either group. Our ¹³C-glucose method of testing compliance was simple, efficient and led to two non-compliant subjects being excluded. Four h post-dose, beta-oxidation of ¹³C-DHA was significantly higher in E compared to Y ($P = 0.05$) and averaged 4-5% over 1 wk.

Conclusion: The plasma response of DHA to short-term fish oil supplementation in the healthy elderly is broadly similar that in young adults. The form of DHA presumably available for brain incorporation (DHA in plasma free fatty acids), was not affected by healthy aging nor by the supplement, leading us to ask what pool is responsible for transferring DHA to the brain.

10:30 FISH OIL FEEDING MODULATES INFLAMMATION IN A RAT MODEL OF HEMORRHAGIC SHOCK

Van Way CW¹, Yang R¹, Harris WS², Xu D¹, Almenoff M¹, Thomas AM³, Vernon K¹, Qureshi N¹, & Morrison DC¹.
¹Univ of Missouri, Kansas City, Kansas City, MO, USA, ²Univ of South Dakota, Sioux Falls, SD, USA, ³Univ of Texas, Austin, TX, USA.

Background: In the rat model of hemorrhagic shock, the inflammatory reaction plays a critical role.
Objective: We hypothesized that pre-feeding rats with fish oil rich in omega-3 fatty acids (EPA+DHA) would modulate the inflammatory response following experimental shock.
Procedures: Male rats (350±30g; n=48) were randomized to either control or fish oil diets. The latter contained 600 mg fish oil/kg diet/day; 150 mg EPA+DHA /kg/day, about 1% energy needs) whereas the former contained corn oil. Under fluothane anesthesia, shock was initiated by bleeding, and resuscitation carried out by reinfusing the shed blood and lactated Ringer's solution (21 ml/kg). Half of each group (n=12) was sacrificed at 30 minutes and half at 4 hours post-resuscitation. The effect on inflammation was determined in two ways. First, liver samples were assayed for mRNA for iNOS and IL-1-beta mRNA as indicators of inflammation, and for heat shock protein 25 (Hsp25). Second, at 4 hours, the lung tissue edema index was evaluated by measuring the ratio between the wet weight and dry weight of the whole lungs.

	Corn Oil	Fish Oil
iNOS mRNA (30 minutes) delta-delta-C _t	6.16±2.2	1.57±0.73*
IL-1beta mRNA (4 hours) delta-delta-C _t	3.39±1.56	1.83±0.75
Hsp25 mRNA (4 hours) delta-delta-C _t	1.14±0.22	2.11±0.74*
Lung edema index (4 hours)	5.28±0.28	4.69±0.14*
Mean±SEM; *p<.05		

Results: In the fish oil group, iNOS mRNA was reduced at 30 minutes. At 4 hours, IL-1-beta mRNA was reduced (p=0.08), while Hsp25 mRNA was increased. The lung edema index was reduced at 4 hours.

Conclusion: Fish oil pre-feeding reduced several markers of inflammation in a rat model of hemorrhagic shock. Whether higher tissue omega-3 levels would improve outcomes in humans with severe blood loss should be explored. (This work was supported by grants or contracts from the St. Luke's Foundation for Education and Research, the US Army Medical Research and Materials Command (USAMRIC, W81XSH-06-1-530), the Coffey Foundation, and the Sosland Foundation.)

10:45 ORALLY ADMINISTERED EVENING PRIMROSE OIL IMPROVES SKIN BARRIER FUNCTION AND BIOPHYSICAL PARAMETERS OF EXPERIMENTALLY IRRITATED HUMAN SKIN

Muggli R.
AdviServ Consulting, Hofstetten, Switzerland.

Background: Evening primrose oil (EPO) contains about 10% gamma-linolenic acid (GLA) and has been shown to improve and repair skin barrier function and to provide relief in atopic dermatitis after topical application.
Objective: To test the effect of orally administered EPO in a human model of skin irritation on various skin parameters.
Procedures: The study was designed as a randomised, double blind, placebo controlled intervention trial. 22 healthy adult females and 18 males consented to take either 3 x 500 mg Efamol EPO b.i.d. or placebo (medium-chain triglycerides) in soft gel capsules for 12 weeks. The oral treatment provided 345 mg GLA per day. Experimental skin irritation was induced with a cotton pad soaked with a solution of 2% SDS applied to the inner sides of both forearms for 24 hours. Outcome variables were: skin moisture, transepidermal water loss (TEWL), skin firmness, elasticity, fatigue resistance and roughness. Measurements were taken before application and 4 hr after removal of the SDS test patch, and after EPO or placebo treatment for 28 and 84 days.
Results: The two treatment groups did not differ at baseline and at day 28. At day 84, however, all measured variables, were different in favour of the EPO group. Skin moisture, TEWL, firmness, fatigue resistance, and roughness had significantly improved by 13.9, 10.2, 19.2, 22.2 and 13.0%, respectively. These results confirm earlier findings in non-irritated skin (Muggli R. Int J Cosmet Sci 2005;27:243-249).

Conclusions: Biophysical skin parameters are indicators of age-related structural and functional changes in skin tissues. EPO has a long history of safe use as an ingredient in foods, dietary supplements and topical cosmetics. These findings support its oral use as a nutritional supplement to help fight visible signs of skin aging.

This work was supported by Efamol Ltd.

11:00 EFFECTS OF INCREASING DOSES OF DOCOSAHEXAENOIC ACID ON LOW-DENSITY LIPOPROTEIN REDOX STATUS AND OXIDIZABILITY IN HUMAN VOLUNTEERS.

Calzada C¹, Colas R¹, Guillot N¹, Laville M^{1,2}, Véricel E¹, & Lagarde M¹.
¹UMR 870 Inserm/Insa-Lyon, Villeurbanne, France; ²Centre de Recherche en Nutrition Humaine Rhône-Alpes, Lyon, France

Background: There is strong evidence for beneficial effects of n-3 polyunsaturated fatty acids (PUFA) on cardiovascular diseases. However, enrichment of low-density lipoprotein (LDL) with n-3 PUFA may increase oxidative modification of LDL which plays a significant role in atherosclerosis.

Objective: To determine the effects of a range of oral doses of docosahexaenoic acid (DHA) on the redox status of LDL and on its susceptibility to oxidation *ex vivo*.

Procedures: Twelve healthy men aged 50 to 65 years ingested consecutive doses of DHA (200, 400, 800 and 1600 mg DHA/day, as triglycerides containing 35% DHA as the only PUFA), each dose for two weeks. Fatty acid compositions, vitamin E and lipid peroxide concentrations were determined in LDL at baseline and after each supplementation period. Oxidizability of LDL in response to copper sulfate was also investigated.

Results: There was a dose-dependent increase in the proportions of DHA in LDL phospholipids and cholesteryl esters, at even the lowest tested dose of DHA. A significant increase of α -tocopherol concentration was observed after two weeks of 200 mg DHA, which was partly maintained at higher doses of DHA. Malondialdehyde levels, assessing overall lipid peroxidation, decreased after 200 and 400 mg DHA but were not different at 800 and 1600 mg DHA compared to baseline levels. Intake of 200 to 800 mg DHA resulted in an increased lag phase, indicating a protective effect of DHA on LDL oxidizability.

Conclusion: Supplementation of healthy middle-aged volunteers with 200-400 mg DHA improves the redox status of LDL and increases their resistance to oxidation.

11:15 EICOSAPENTAENOIC ACID DECREASES EXPRESSION OF SURFACE MOLECULES INVOLVED IN ANTIGEN PRESENTATION ON DENDRITIC CELLS INVITRO.

Stefansdottir A^{1,2}, Hardardottir I², Freysdottir J^{1,3}.
¹Centre for Rheumatology Research, ³Department of Immunology, Landspítali University Hospital, Reykjavik, Iceland; ²Faculty of Medicine, University of Iceland, Reykjavik, Iceland.

Background: Dendritic cells play a central role in polarization of T cell-derived immune responses. Omega-3 polyunsaturated fatty acids affect activation of macrophages and T cells, but less is known about their effects on dendritic cells.

Objective: In this study the effects of the omega-3 fatty acid eicosapentaenoic acid (EPA) on the maturation of dendritic cells was investigated.

Procedures: Human CD14⁺ monocytes were matured into immature dendritic cells for a week with EPA at 50 μ M being present during the last 24 hours. For comparison, some cells were cultured with the omega-6 fatty acid arachidonic acid (AA) or without any fatty acids. After a thorough wash, the immature dendritic cells were cultured with the maturation factors IL-1 β and TNF- α for 2 days. The expression of various molecules linked to maturation of the dendritic cells was measured by flow cytometry and secretion of cytokines (IL-10 and IL-12p40) measured by ELISA.

Results: When immature dendritic cells were cultured for 24h with EPA prior to activation with IL-1 β and TNF- α , fewer cells expressed the activation-linked molecules CD40 (interacts with CD40L on T cells), CD80 and CD86 (interact with the co-stimulatory molecule CD28 on T cells), CD197 (CCR7, directs mature dendritic cells to lymph nodes), CD209 (DC-SIGN, mediates adhesion to naïve T cells in lymph nodes), and HLA-DR (participates in antigen presentation to T cells). Changes in cytokine secretion were not significantly different between the EPA-treated and untreated cells.

Conclusion: Treatment of immature dendritic cells with EPA affects expression of molecules that direct DCs into lymph nodes, mediate adhesion between the dendritic cells and naïve T cells, and participate in antigen presentation and activation of the naïve T cells. Treatment with EPA may thus lead to reduced potential of the dendritic cells for T cell activation and affect polarization of the immune response.

11:30 DIETARY FISH OIL DECREASES SECRETION OF THE CHEMOKINES KC AND MCP-1 BY MURINE RESIDENT PERITONEAL MACROPHAGES

Arnardottir HH, Petursdottir DH, & Hardardottir IH
University of Iceland, Faculty of Medicine, Reykjavik, Iceland

Background: Dietary fish oil, rich in omega-3 polyunsaturated fatty acids, increases secretion of the pro-inflammatory cytokine, TNF- α , but decreases secretion of the anti-inflammatory cytokine, IL-10, by murine resident peritoneal macrophages. The effects of dietary fish oil on chemokine secretion by these cells have been less studied. The chemokines KC and monocyte chemoattractant protein (MCP)-1 play important roles in recruitment of neutrophils and monocytes to a site of infection.

Objective: The aim of this study was to determine the effects of dietary fish oil on the secretion of KC, MCP-1, MIP-1 α , and RANTES by murine peritoneal macrophages.

Procedure: Mice were fed diets supplemented with 18% fish oil + 2% corn oil or 20% corn oil for six weeks. Resident peritoneal macrophages were stimulated with LPS with or without indomethacin (a cyclooxygenase inhibitor) or antibodies against TNF- α or IL-10. Concentration of the chemokines was measured by ELISA.

Results: Dietary fish oil decreased LPS induced KC and MCP-1 secretion by resident peritoneal macrophages. Incubation with indomethacin or antibodies against TNF- α or IL-10 did not prevent the effects of dietary fish oil on KC or MCP-1 secretion. The effects of dietary fish oil on KC secretion were evident 3 hours after administration of LPS whereas its effects on MCP-1 secretion were demonstrated only 12 hours after LPS administration. Dietary fish oil did not affect LPS induced secretion of MIP-1 α or RANTES.

Conclusion: Dietary fish oil decreased KC and MCP-1 secretion by resident peritoneal macrophages independent of prostaglandin production. Neither were the effects of dietary fish oil on KC and MCP-1 secretion dependent on its effects on TNF- α or IL-10 secretion. That dietary fish oil decreases KC and MCP-1 secretion by resident peritoneal macrophages may indicate that fish oil has the potential to decrease neutrophil and monocyte recruitment to the peritoneum following infection or inflammation.

11:45 IMPACT OF SOYBEAN OIL- AND OLIVE OIL-BASED LIPID EMULSIONS IN MURINE ACUTE LUNG INJURY.

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Background: Alveolar generation of MIP-2 initiates acute lung injury (ALI) with subsequent leukocyte invasion. Arachidonic acid (AA) gives rise to eicosanoids and through these controls inflammation. Soybean oil(SO)-based lipid emulsions used may also provide precursors for lipid mediators. We compared impact of an olive oil-based (OO) vs. a SO-based lipid emulsion in a murine model of ALI.

Procedures: After infusion of mice for three days with SO, OO, or NaCl using a changeable osmotic pump and a central venous line ALI was induced by endotoxin (LPS) instillation intra-tracheally.

Results: Infusion of OO significantly reduced free AA in plasma as compared to SO. After LPS challenge, MIP-2 markedly increased at 4h, and decreased at 24 h in all groups. However, it was augmented at 8h in the SO group in contrast to OO and NaCl. LPS induced a marked recruitment of leukocytes into the lung peaking at 8h in NaCl group. Leukocytes continued to rise after SO infusion after 24 h in contrast to OO and NaCl. Mortality assessed at 24 h was 0 % and 20% after infusion of NaCl or OO groups, respectively, but increased to 80 % in animals receiving SO.

Conclusion: In a murine ALI, infusion of SO increased free AA, amplified rise in MIP-2, induced a prolonged recruitment of leukocytes into the lung, and increased mortality. OO in contrast did only slightly rise mortality compared to NaCl.

10:30 OMEGA-3 / OMEGA-6 FATTY ACIDS IN NEURODEVELOPMENTAL AND PSYCHIATRIC DISORDERS – AN OVERVIEW OF EVIDENCE FROM CLINICAL TRIALS

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Background: Substantial epidemiological and experimental evidence shows that deficiencies or imbalances of omega-3 and omega-6 fatty acids (as assessed via dietary or biochemical measures) are associated with many neurodevelopmental and psychiatric disorders in both children and adults. Clinical trials of fatty acid supplementation have therefore investigated whether simple dietary treatments might ameliorate symptoms of these conditions.

Objective & Procedure: A summary review and interpretation of current findings from clinical trials of fatty acid treatment for neurodevelopmental and psychiatric disorders, highlighting key issues for research and implications for clinical practice.

Results: Three recent meta-analyses of randomised controlled trials of omega-3 for mood disorders (using differing methodologies and inclusion criteria) have concluded that adjunctive treatment with omega-3 (particularly EPA) is beneficial in major depression, and may also alleviate depressive symptoms in bipolar disorder, although no benefits have yet been demonstrated for manic symptoms, nor schizophrenia. Current evidence also suggests that fatty acid supplementation may improve behaviour and/or learning in at least some children with developmental disorders including ADHD, dyslexia, dyspraxia and possibly autism, although such trials have been few and small, with populations, treatments and outcome measures too varied to allow meaningful meta-analyses. Successful trials with such children have used the omega-3 EPA and DHA in varying ratios, along with some omega-6 fatty acids and Vitamin E. Improved attention and impulse control are the most consistently reported benefits, although literacy skills also improved in one trial.

Conclusion: Large-scale clinical trials in these areas are clearly warranted, ideally involving systematic comparisons of treatment formulations and dosages. Given the high comorbidity between neurodevelopmental and psychiatric disorders, a trait- or symptom-based approach may prove more fruitful than focusing exclusively on standard categorical diagnoses. Dietary and biochemical assessments (including genetic markers) could also help to identify those individuals most likely to benefit from fatty acid supplementation.

11:00 OMEGA-3/OMEGA-6 FATTY ACIDS FOR ATTENTION –DEFICIT/HYPERACTIVITY DISORDER. A RANDOMIZED PLACEBO-CONTROLLED TRIAL IN CHILDREN AND ADOLESCENTS

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Objective: To assess whether supplementation with Omega 3/6 fatty acids (Equazen eye q[®]) was effective in the treatment of ADHD and its diagnostic subtypes and comorbid conditions, in children and adolescents.

Procedure: Randomized double-blind placebo-controlled one-way crossover trial with 75 children and adolescents aged 8-18 years receiving Omega 3/6 or placebo for three months followed by open phase of 3 months with Omega 3/6 for all. ADHD symptoms were measured with the investigator-rated ADHD Rating Scale-IV-Parent Version and the Clinical Global Impression (CGI) scale of symptom severity and impairment.

Results: After 3 months a subgroup of 26% of the active group (vs. 7% on placebo) responded with a clinically meaningful improvement of more than 25% reduction of ADHD symptoms and a drop of CGI scores into the near normal range. After 6 months 47% of all showed such improvement. Responders tended to be more frequent in those with ADHD inattentive subtype and neurodevelopmental disorders (reading/writing difficulties, learning disorders, developmental coordination disorder and autism spectrum conditions).

Conclusion: This trial suggests that a clinically meaningful reduction of ADHD symptoms occurs in a large subgroup. This subgroup appears to be characterized by inattention and possibly by associated developmental/ or learning disorders.

11:15 THE RELATIONSHIP BETWEEN TOTAL RED BLOOD CELL CONCENTRATIONS OF OMEGA-3 FATTY ACIDS AND EMOTIONAL PROCESSING IN ATTENTION DEFICIT HYPERACTIVITY DISORDER

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Background: Abnormalities in the way emotional stimuli are perceived have been reported in ADHD, depression, anxiety, and conduct disorders. Event-related potential (ERP) and behavioural studies suggest there is an exaggerated bias in the automatic processing towards fear-related stimuli in anxiety, while depressed patients display a distinct bias towards negative stimuli involving more controlled processing. Essential fatty acids (EFAs) are involved in the neurodevelopment of cognitive and emotional function. Low levels of long-chain polyunsaturated fatty acids (LC-PUFA), specifically omega-3 (ω -3) fatty acids and higher levels of ω -6 in blood measures have been linked to a range of behavioural and mood disorders including ADHD. However, no studies to date have directly investigated the relationship between EFAs and brain function in ADHD adolescents.

Objective: In light of previous research suggesting a cognitive bias in the processing of facial expressions in ADHD, it was hypothesised that Eicosapentaenoic acid (EPA) would be positively associated with a bias in the overt ERP response measured by P300 amplitude towards happy faces relative to fear or sadness. Associations were also explored between other fatty acid indices and ERP measures.

Procedures: In the context of baseline assessments during a clinical trial, 20 adolescent ADHD boys were assessed for total lipid fractions in red blood cells and their ERP responses to the presentation of facial expressions of happiness, sadness and fearfulness.

Results: As predicted, EPA significantly correlated with frontal P300 responses to happy stimuli relative to the response to fear or sadness. There were significant relationships between both levels of ω -6 fatty acids, docosahexaenoic acid (DHA) and the right temporal N170 and P300 responses to fear.

Conclusion: These findings indicate relationships between specific essential fatty acids and distinct aspects of emotional processing in ADHD participants. Results are also discussed in relation to disorders comorbid with ADHD, such as offending behaviour, anxiety and depression.

11:30 RANDOMIZED PLACEBO CONTROLLED TRIAL OF PLUSEPA (OMEGA-3) AS TREATMENT FOR ADHD IN CHILDREN AGES 7-12

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Objective: RCT of EPA treatment for ADHD.

Procedure: The study comprised 82 children, 66 boys (mean age 9.8 yr) and 16 girls (10.2 yr) with ADHD (DSM-IV).

The experiment group received 0.5 g EPA/day for 15 weeks. Efficacy evaluation was done with Conners' Teacher Rating Scale (CTRS). Fatty acid analysis was done in serum.

Results: We found significant effects of EPA treatment in two subgroups. Children with oppositional behaviour indicating problems at a clinical level (n=43) had a significant reduction of ADHD symptoms in the treatment group (p=0.015, effect size 0.80). Among the 37 boys in this subgroup; 52% receiving PlusEPA had \geq 25 % improvement on CTRS scores, compared to 6 % in the Placebo group (p=0.003). For children with little hyperactive/impulsive behaviour, 54 % of the 27 boys improved \geq 25 % on CTRS compared to 21 % in the Placebo group (p=0.102). In a small group of boys (n=14) with both oppositional behaviour and little hyperactivity/impulsivity; 7/8 boys in the PlusEPA group improved \geq 25 % compared 1/6 in the Placebo group (p=0.026). In the group with oppositional symptoms regression analyses were run with age, gender, socio-economic status, baseline symptoms scores on CTRS and cognitive ability. Only cognitive ability had an influence (positive) on symptomatic improvement. Children that responded to EPA treatment had significantly lower EPA levels (p=0.040), as well as lower quotient EPA/AA (p=0.038) in serum at baseline. There were also significant correlations between measures of EPA relative improvement and symptomatic improvement. Thus these fatty acids findings support the overall findings.

Conclusion: We found improvement in subgroups with special characteristics, but not in the whole, unselected group of children with ADHD seeking medical help. That is in line with the notion that EPA supplementation only could be beneficial for children who have some form of PUFA deficiency at baseline.

11:45 VALIDATION OF A BIMODAL DISTRIBUTION OF POLYUNSATURATED FATTY ACIDS IN SCHIZOPHRENIA

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Background: There has been conflicting evidence of a bimodal distribution of erythrocyte (RBC) polyunsaturated fatty acids (PUFA) in schizophrenia.

Objective: In a clinical trial, we tested the bimodality hypothesis of schizophrenia and schizoaffective disorder.

Procedure: Acutely psychotic patients were recruited. All were prescribed antipsychotic drugs, and were randomly assigned to active or placebo Ethyl-EPA 2 g/d and active or placebo Vitamin E 364 mg/d + Vitamin C 1000 mg/d. Patients were followed up for 16 weeks. The main clinical variable was the Positive and Negative Syndrome Scale (PANSS). RBC fatty acids, S- α -tocopherol and other biochemical variables were measured. We used Linear Mixed Model for longitudinal analyses.

Results: 99 patients aged 18-39 years were included. At baseline, PUFA levels were bimodally distributed, one of three patients having very low levels compared to healthy controls. The only robust predictor of low PUFA was low α -tocopherol. In the low PUFA group, negative symptoms were stronger, hypertriglyceridemia five times as prevalent, and antipsychotic medication dosage was lower. The risk of drop-out during the trial was four times higher in the low PUFA group. In the whole sample, adding EPA or vitamins to antipsychotic drugs had no significant effect on symptoms. However, PUFA group was a strong effect modifier. In the low PUFA group only, EPA and vitamins given separately had a harmful effect on positive symptoms. Combining agents prevented these effects. PUFA group was also an effect modifier regarding blood pressure and sustained and selective attention.

Conclusion: We have validated a bimodal distribution of PUFA levels among patients with schizophrenia and schizoaffective disorder, suggesting two genetically different populations. The two differed with respect to several clinical and biochemical variables. S- α -tocopherol was a robust predictor of the bimodality. A deficient endogenous redox regulatory system in a subgroup of patients may best explain our findings.