ISN Symposia: New Therapeutic Approaches in Neurological Diseases

Chair: Alvaro Estevez, Biochemistry & Biophysics, Oregon State University

Wednesday August 15, 8:25AM – 12:10PM
Modified Flavonoids for the Promotion of Nervous System Repair in Neurodegenerative Disease

Larry S. Sherman, PhD

Division of Neuroscience, Oregon National Primate Research Center, Oregon Health & Science University, Beaverton, OR, USA

BIOGRAPHY

Dr. Larry S. Sherman is a Professor in the Division of Neuroscience at the Oregon National Primate Research Center and in the Department of Cell, Developmental and Cancer Biology and in the Neuroscience Graduate Program at the Oregon Health & Science University (OHSU). He is also the President of the Oregon and Southwest Washington Chapter of the Society for Neuroscience. He has over 90 publications related to brain development and neurodegenerative diseases including Alzheimer’s disease and multiple sclerosis. He has made numerous television appearances, discussing various topics related to neuroscience.

Dr. Sherman has also given hugely popular talks and performances (including playing the piano) around the globe on topics that include music and the brain, the neuroscience of pleasure and love, the neuroscience of racism, and other topics. He was invited by John Frohnmayer, former head of the National Endowment for the Arts, to serve on a panel discussing the origins of creativity that was filmed for PBS. The Oregon Museum of Science and Industry and Portland Monthly Magazine recognized Dr. Sherman as one of the most innovative people in the State of Oregon.

In 2012, he was recognized by the OHSU School of Medicine Faculty Senate and the OHSU foundation for Outstanding Teaching, and was awarded the Mary Omberg Award for outstanding support of science education in Oregon and Southwest Washington.

ABSTRACT

Multiple sclerosis (MS) is an autoimmune disease characterized by the destruction of myelin, a substance required for the fast conduction of electrical impulses in the nervous system. Oligodendrocyte progenitor cells (OPCs) recruited to demyelinating lesions often fail to mature into oligodendrocytes (OLs) that can remyelinate spared axons. We found that the
glycosaminoglycan hyaluronan (HA) accumulates in demyelinating lesions and that specific sizes of HA digestion products are generated by hyaluronidases that are transcriptionally upregulated in demyelinating lesions. These products block OPC maturation and remyelination through toll like receptor 4 (TLR4) via a non-canonical AKT-dependent signaling pathway. Activation of this pathway results in elevated expression of the FoxO3 transcription factor in OPCs both in vitro and in MS lesions. We have characterized a group of modified flavonoids that act as hyaluronidase inhibitors. These compounds are specific for the hyaluronidase activity in demyelinating lesions.

One of these inhibitors prevents the accumulation of bioactive HA digestion products, prevents TLR4 activation, and reverses the inhibition of myelin gene transcription. This inhibitor also accelerates OPC maturation and remyelination in lysolecithin-induced demyelinating lesions following both intracranial and intravenous injection. Furthermore, we demonstrate that this inhibitor promotes up to 60% increases in conduction velocities in demyelinating lesions, demonstrating that inhibiting hyaluronidase activity promotes functional remyelination. This novel hyaluronidase inhibitor is now being tested for its ability to promote remyelination in a pre-clinical trial utilizing a unique non-human primate model of MS at the Oregon National Primate Research Center. Our findings definitively show that TLR4 activation by HA digestion products regulates OPC maturation by regulating myelin gene expression, that specific hyaluronidases are potent therapeutic targets for treating demyelination, and that small molecule hyaluronidase inhibitors can accelerate functional remyelination.
Modeling Human Neurodegeneration and Neuronal Cell Death

Lee J. Martin, PhD
Department of Pathology,
Division of Neuropathology,
Johns Hopkins University School of Medicine
Baltimore, MD, USA

BIOGRAPHY

Lee Martin, PhD, is a Professor in the Departments of Pathology, Division of Neuropathology, and Neuroscience at Johns Hopkins University School of Medicine, where he also serves as curriculum committee chair in Graduate Program in Pathobiology and as a co-investigator in the Neuropathology Core in the Alzheimer’s Disease Research Center. An experimental neuropathologist-neurobiologist with expertise in animal and cell physiology, rodent, pig, monkey and human neuroanatomy, he is skilled in cell biology, cortical neuron, glial and motoneuron biology, biochemistry, epigenetics, and numerous animal and cell model systems of neurodegeneration, including human induced pluripotent stem cell (iPSC)-derived cortical and motor neurons and oligodendrocytes.

For >25 years, Dr. Martin’s research has focused on forebrain neuroanatomy and mechanisms of neurodegeneration in human CNS disease and injury and in animal (small and large) and cell culture models, including neuronal death caused by chemical warfare agents, excitotoxicity, DNA damage, cerebral ischemia, axotomy/target deprivation, mitochondrial perturbations, and human gene mutations (including SOD1, α-synuclein, TDP-43, and dynactin p150glued). He was the first to describe the bed nucleus-amygdala continuum (extended amygdala) in the human forebrain, and he has identified the postnatal-experience instructed maturation on the striatal mosaic in monkey. The human neurodegenerative diseases he has expertise in include Parkinson’s disease, ALS, and Alzheimer’s disease.

Dr. Martin was a recipient of a NIA Leadership & Excellence in Alzheimer's Disease (LEAD) award for his work on glutamate receptors, excitotoxicity & neuronal cell death. Dr. Martin’s work on neurodegeneration and neuronal cell death caused by excitotoxicity, human gene mutations in SOD1 and α-synuclein, and hypoxia-ischemia in neonatal and adult small and large animal CNS has led to the concept of the apoptosis-necrosis cell death continuum/matrix. He currently has an h-index of 82 and 28,112 citations.
ABSTRACT

Neurological disorders affecting individuals in infancy to old age elude interventions for meaningful protection against neurodegeneration because preclinical work has not translated effectively to humans. Though clinical trial design has many limitations and caveats, preclinical animal and cell models are predicated on the major unvalidated assumption that mechanisms of neuronal injury and death are the same in experimental animal systems and in humans. Human embryonic and induced-pluripotent stem cell-derived neurons now allow direct interrogation of human-relevant mechanisms of real-time ongoing neuronal cell injury and degeneration. We have examined the assumption that human neurons and experimental animal neurons behave similarly to injury and degenerate similarly in cell culture.

Neural stem cell derived differentiated cortical neurons from human and mouse have widely different cell death signaling mechanisms in response to excitotoxicity, oxidative stress, and DNA damage. DNA damage response and repair are also different in human, mouse, and pig cortical neurons, though pig cortical neurons can approximate human neurons in their DNA damage responses. CRISPR/Cas9 genome edited human induced pluripotent stem cells (iPSCs) harboring a G93A superoxide dismutase-1 (SOD1) point mutation, as a cell model of amyotrophic lateral sclerosis (ALS), showed directed differentiation to functional, morphology- and immunophenotype-validated motor neurons similar to isogenic control motor neurons. However, DNA damage response, mitochondrial, and morphological phenotypes of disease in human motor neurons were very distinct from mouse motor neurons harboring G93A SOD1. Thus, human neurons and rodent neurons can degenerate and die differently. Our findings are important because they highlight that human chronic and acute neurodegenerative diseases and encephalopathies, such as ALS, Alzheimer’s disease and stroke, need to be modeled in human neurons and studied diligently in the human diseased and injured CNS because animal models might not faithfully represent humans in mechanisms of disease.
Therapeutic Intervention to Induce Immunomodulation, Remyelination and Neuroprotection – the Magic Bullet

Tiwari-Woodruff, MS, PhD

Professor in the Division of Biomedical Sciences, School of Medicine, University of California, Riverside, CA, USA

BIOGRAPHY

Dr. Tiwari-Woodruff has a MS in Chemistry and a PhD in Physiology from Southern Illinois University at Carbondale, Ill. After completing a post-doctoral fellowship in the Neurology Department at UCLA, Dr. Tiwari-Woodruff was made a member of the faculty where she served until 2014. She is presently a Professor in the Division of Biomedical Sciences in the School of Medicine at UCR at Riverside, CA. The Tiwari-Woodruff lab investigates mechanisms of demyelination-induced neurodegeneration, seizures, myelination, sex differences and therapeutic neuroprotection using immune-mediated experimental autoimmune encephalomyelitis (EAE) and non-immune-mediated toxic cuprizone diet mouse models of multiple sclerosis and postmortem human brain tissue.

Additionally, through continued collaborations with researchers at UIUC, UCI, UCLA, and pharmaceutical companies, the lab interrogates therapeutic efficacies and mechanisms of action of various approved and potential MS drugs. She currently holds a patent for the use of a novel class of estrogen receptor agonists as remyelinating drug. Dr. Tiwari-Woodruff has has been actively engaged in American Society of Neuroschemistry-ASN/International Scociety of Neurochemistry-ISN programming and governance at several levels.

ABSTRACT

Seema Tiwari-Woodruff¹, Hawra Karim¹, Sung Hoon Kim², John Katzenellenbogen²

¹Division of Biomedical Sciences, School of Medicine, University of California, Riverside, CA, USA
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Given the prominence of inflammation in MS, therapy of the disease has primarily been focused...
on immune suppressing/modifying strategies. While these aforementioned therapies may reduce/inhibit inflammation and delay disease progression, but do not directly repair ongoing axonal loss and restore myelination. At present, there are no direct neuroprotective or remyelinating agents available for use. Recently, estrogens have emerged as an attractive candidate for MS therapy that fulfill this need. Treatment with highly selective ERβ ligands modulates autoimmunity, improves neurological deficits, and increases myelination in mice with EAE, despite the ongoing infiltration of autoreactive leukocytes. CXCL1 is a major neutrophil chemoattractant that binds to the chemokine receptor CXCR2, on neutrophils and oligodendrocytes. ERβ-ligand treatment in a mouse model of MS, induces an increase in peripheral and brain CXCL1 levels. OPC recruitment and differentiation by CXCL1, in combination with attenuated IFNγ and CXCL10 production attenuated OL apoptosis, may account for at least one avenue whereby ERβ ligands exert their clinical benefits. The possibility that ERβ ligands modulate the cytokine and chemokine milieu to potentially promote repair/remyelination opens up exciting therapeutic options. To optimize these benefits, we developed and screened seven novel IndCl analogues for their efficacy in promoting primary oligodendrocyte (OL) progenitor cell survival, proliferation, and differentiation in vitro by immunohistochemistry. Two analogues, IndCl-o-chloro and IndCl-o-methyl, induced proliferation and differentiation equivalent to IndCl and were selected for subsequent in vivo evaluation for their impact on the clinical disease course, white matter pathology, and inflammation. Through our examination of the functional, histopathological, and immunological basis of the pro-myelinating effects of IndCl-based ERβ ligands, we show that two of the IndCl analogues tested exhibit therapeutic benefits by an intricate interplay between the peripheral and central immune system to enhance independent axon remyelination and neuroprotection.
Modulation of the Autophagic Flux Rate by Bioactive Plant Compounds in Postmitotic Cells

Tilman Grune, PhD

German Institute of Human Nutrition
University of Potsdam
Potsdam-Rehbruecke, Germany

BIOCHEMISTRY

Tilman Grune studied ‘Medical Biochemistry’ in Moscow. After research positions at the Humboldt University Berlin, he was Professor and Head of the Free Radical Laboratory, Research Institute of Environmental Health, Duesseldorf; Head of the Department of Biofunctionality and Safety of Food in the Institute of Biological Chemistry and Nutrition, University of Hohenheim/Stuttgart; and Head of the Department of Nutritional Toxicology in the Institute of Nutrition, Friedrich Schiller University Jena. Since 2014, he is Scientific Director of the German Institute of Human Nutrition Potsdam-Rehbruecke and Full Professor at the University of Potsdam.

His general research interests are oxidative damage and modification of macromolecules in (aging) cells and the effects of nutritional components on these processes. In particular Dr. Grune is exploring the functional consequences of the formed age-related protein aggregates. This includes how cells cope with oxidatively damaged and modified proteins or lipids and how nutrition can positively influence the systems involved in repair and detoxification.

Also, Dr. Grune is interested in the biochemical processes and biological implications of protein nitration and studies of non-enzymatic protein modification.

ABSTRACT

Tilman Grune, Christiane Ott

German Institute of Human Nutrition, Potsdam-Rehbruecke, Germany

Aging is accompanied by a decline of the Ubiquitin-Proteasome System (UPS) and the Autophagy-Lysosome Pathway (ALP) in postmitotic cells. Therefore, in postmitotic cell types, as neurons or cardiomyocytes, aging goes along with a non-physiological protein accumulation. In a set of
studies we could clearly demonstrate that the activity of the core 20S proteasome as well as the autophagosomal flux is declining during aging in various postmitotic cell types. Ferritin H, as a substrate of the ALP, accumulates in aged fibroblasts in vitro and in brain in vivo. Interestingly, using rapamycin, a well-known mTOR inhibitor, the ferritin H accumulation can be reversed, indicating a leading role of the ALP in the ferritin degradation. Therefore, we hypothesized that the use of autophagy inducers via inhibition of mTOR might be a useful tool to prevent age-associated accumulation of proteins and, perhaps, organ malfunction associated with such an accumulation. First we tested this approach in a model of cardiac hypertrophy in vivo and in vitro, where rapamycin was not only able to reduce cardiomyocyte hypertrophy, but was also improving the functional parameters, as cardiac output. These finding encouraged us to search for other –nutritional- inducers of the autophagic flux. Punicalagin, a polyphenol in pomegranate juice, caffeic acid and lycopene are promising candidates. Investigating the molecular mechanism revealed so far that the action of these compounds is not only mediated by redox mechanisms, but rather by interaction with AMPK/mTOR or the change of the LC3-II/LC3-I ratio.

Therefore, the protection from aging-associated accumulation of dysfunctional and oxidized proteins by bioactive plant compounds cannot be solemnly attributed to redox related mechanisms.
Emerging Roles for Vitamin K in the Nervous System

Doug Feinstein, PhD
University of Illinois
Jesse Brown VA Medical Center
Chicago, IL, USA

BIOGRAPHY

Doug Feinstein received his BS from MIT, his PhD from the Johns Hopkins University, and then did post-doctoral training at the Scripps Clinic in San Diego, the University of Uppsala in Sweden, and the University of Lausanne in Switzerland. He was a faculty member at Cornell University Medical College in New York for several years then moved to Chicago in 1998. He is currently Research Professor at the University of Illinois at Chicago and a Research Career Scientist at the Jesse Brown VA Medical Center.

Dr. Feinstein’s work centers around understanding the contributions of, and developing treatments for the neuroinflammation induced neuropathology in MS and AD. He also runs a program project to examine neuropathology due to poisoning with long acting anticoagulant rodenticides, and developing treatments to counteract their acute and delayed neurotoxic consequences. He has been continuously funded throughout his career by federal agencies (NIH, VA, DoD), private foundations (NMSS, Alzheimer’s Association), and pharmaceutical companies (Glaxo, Takeda, Boehringer Ingelheim, Biogen). He has published over 185 peer reviewed papers, and served on review boards for NIH, the VA, and AD and MS societies. He is an active member of the American Society for Neurochemistry where he served as President. He has been an Associate Editor for several journals including J. Neuroinflammation and J. Neuroscience Research, and recently took over as Editor in Chief of ASN NEURO.

ABSTRACT

Douglas L. Feinstein¹, Israel Rubinstein¹, Guy Weinberg¹, Richard van Breemen²

¹University of Illinois, Chicago, IL, USA
²Linus Pauling Institute, Oregon State University, Corvallis, OR, USA
The importance of Vitamin K (VK1) in human physiology is most often associated with its role in activating thrombin factors necessary for clotting, an activity mediated by carboxylation of proteins by the enzyme γ-glutamyl carboxylase (GGC). In addition to clotting proteins, there are other protein targets of GGC present throughout the body, including several in the CNS including Gas6, a ligand for tyrosine kinase receptors which regulates neuronal activity and glial inflammation; and galactosyl ceramide sulfate transferase required for sulfatide synthesis used to produce myelin. VK can also reduce oxidative stress, and thereby prevent neuronal and glial cell death.

A recent outbreak in poison cases due to ingestion of rodenticides which reduce VK1 recycling has increased attention on this vitamin. Poisoning by long acting anti-coagulant rodenticides such as brodifacoum (BDF) leads to long term (up to months to years) suppression of VK1 recycling. Current treatment for requires long term (months to over a year) daily ingestion of up to 100 mg of VK1 (available only in 5 mg tablets) at a cost of over $1,000 per day. This has led to concerns of patience adherence, and potential delayed neuropathological consequences of VK1 deficiency. A better knowledge of the roles that VK1 has in the CNS will help guide development of new treatment options for poisoned patients.
Overview of Flavonoids on Cardiovascular Health: A Review of Human Intervention Trials and Implications for Cerebrovascular Function

Professor Jeremy P E Spencer

School of Chemistry, Food and Pharmacy,
University of Reading, Reading, UK

BIOGRAPHY

Professor Jeremy P E Spencer received his PhD from King’s College London in 1997 and is currently Professor of Nutritional Biochemistry and Medicine at the University of Reading. His initial work focused on the cellular and molecular mechanisms underlying neuronal death in Parkinson’s and Alzheimer’s disease. His current interests relate to how flavonoids and other polyphenols, found in a number of fruits, vegetables and beverages, promote brain and cardiovascular health. In particular, the focus is on their ability to modulate specific intracellular signaling pathways pivotal in promoting blood flow, protecting against neurotoxins, preventing neuroinflammation and in controlling memory, learning and neuro-cognitive performance.

Dr. Spencer is a member of the BBSRCs Basic Bioscience Underpinning Health Strategy Advisory Panel, is Editor-In-Chief of Nutrition and Aging and has published over 170 research manuscripts.

ABSTRACT

Evidence suggests that dietary phytochemicals, in particular flavonoids, may exert beneficial effects on the central nervous system by protecting neurons against stress-induced injury, by suppressing neuroinflammation and by improving cognitive function. Historically, they were believed to do this via an ability to express classical antioxidant activity in the brain. However, their poor brain bioavailability and extensive metabolism means that this is unlikely. Instead, their actions on the brain appear to be mediated by effects on both the peripheral and cerebrovascular system that lead to improved blood flow to the brain capable of inducing enhanced activity within specific domains of cognitive function. Such vascular effects may also lead to the
activation of critical protein and lipid kinase signalling cascades in the brain, leading to a suppression of neuroinflammation and the promotion of synaptic plasticity. This paper will focus on the acute and chronic effects of flavonoid and flavonoid-rich food intake on human executive function (attention, sustained attentiveness and task responsiveness) and episodic memory and how such effects may be mediated by changes in peripheral and cerebrovascular blood flow, measured using flow-mediated dilatation and fMRI. Through such a mechanism, the consumption of flavonoid-rich foods throughout life holds the potential to limit neurodegeneration and to prevent or reverse age-dependent loses in cognitive performance. In addition, flavonoids may represent important precursor molecules in the quest to develop a new generation of brain enhancing drugs.
An Update on Vitamins

Chair: Adrian Gombart, PhD, and Emily Ho, PhD, Linus Pauling Institute, Oregon State University

Thursday August 15, 1:30PM - 3:50PM
Vitamin C – A Wolf in Sheep’s Clothing: from Simple Carbohydrate to Epigenetic Master Regulator

Jens Lykkesfeldt, PhD

University of Copenhagen, Copenhagen, Denmark

BIOGRAPHY

Dr. Lykkesfeldt received his MSc degree in organic chemistry (1989), a PhD degree in biochemistry (1992) and a DSc degree in medicine in 2005 for a thesis on the effect of smoking on vitamin C status. He spent two 3-yr postdocs at University of Copenhagen and UC Berkeley, respectively, the later with Professor Bruce N. Ames.

In 1998, he became a PI and associate professor University of Copenhagen, Denmark. In 2008, he was appointed professor and chair in pharmacology and toxicology at the Faculty of Health and Medical Sciences, University of Copenhagen, which is his current position. Dr. Lykkesfeldt’s research interests include the roles of oxidative stress and antioxidants in early development, chronic diseases and aging, in particular that of vitamin C, and has resulted in >100 articles on vitamin C alone.

In 2008, he received the Catherine Pasquiere award from the Society for Free Radical Research, Europe, for his work on vitamin C.

ABSTRACT

Vitamin C is a simple low-molecular weight carbohydrate, yet its ene-diol structure provide it with a complex redox chemistry. Many specific and unspecific roles of vitamin C in maintaining healthy cell metabolism have been identified. In its simplest unspecific action, ascorbate – the reduced form of vitamin C – is capable of quenching any physiologically relevant radical by donating an electron.

More specific antioxidant actions of ascorbate include providing reducing equivalents for at several monooxygenase and dioxygenase enzymes involved in pro-collagen hydroxylation, carnitine and norepinephrine biosynthesis, amidation of peptide hormones, tyrosine metabolism, hydroxylation of hypoxia inducible factor-1α and epigenetic regulation. The remarkable redox
chemistry of ascorbate has earned vitamin C its reputation as the universal antioxidant with a plethora of potential health benefits. However, while epidemiological evidence has consistently shown that vitamin C deficiency is strongly and independently associated with increased morbidity and mortality, intervention studies supplementing individuals already ingesting a healthy diet with further vitamin C have not revealed significant benefits.

Although frequently overlooked, this apparent discrepancy is easily explained by pharmacological studies showing a tight homeostatic control of vitamin C status with non-linear saturation kinetics with a plateau of about 70 µM in plasma. Most recently, efforts have gone into elucidating the role of vitamin C in epigenetic regulation. TET and JMJC dioxygenases are important components on the demethylation of DNA and histones, respectively, and ascorbate has been shown to be necessary for their optimal function. This talk presents an overview of the roles of vitamin C in biological processes with emphasis on recent discoveries.
Supporting Postpartum Homeorhesis with Nicotinamide Riboside: A Boost to Mom’s Metabolism that Produces More Capable Offspring from Eye-Opening to Adulthood

Charles Brenner, PhD

Biochemistry Department Head
University of Iowa, Iowa City, IA, USA
Chief Scientific Advisor to ChromaDex, Inc.

BIOGRAPHY

Charles Brenner is one of the world’s leading experts in NAD metabolism. In 2004, he described the existence of the eukaryotic nicotinamide riboside (NR) kinase pathway. Since then, he discovered multiple genes, enzymes, transporters and metabolites to complete the NAD metabolome. His research group developed the field of targeted quantitative NAD metabolomics using LC-MS and used it to discover that the NAD metabolome is disturbed by multiple conditions of metabolic stress including heart failure, neurodegeneration, obesity and the postpartum. In 2016, he reported the safe oral availability of NR, which has been commercialized as a GRAS-recognized new dietary ingredient.

Beyond the safe availability of NR as a supplement in multiple countries, Dr. Brenner has participated in multiple clinical trials to test its activity against diseases and conditions of metabolic stress. He has received multiple national and international awards for his research as well as his educational leadership. Since 2009, he has served as the Roy J. Carver Chair and Head of Biochemistry at the University of Iowa. He is also the chief scientific adviser of ChromaDex, Inc, which commercialized NR.

ABSTRACT

Conditions of metabolic stress dysregulate the NAD metabolome. By restoring NAD, nicotinamide riboside (NR) provides resistance to such conditions. We tested the hypotheses that postpartum might dysregulate maternal NAD and that increasing systemic NAD with NR might benefit
mothers and offspring. In postpartum mothers, the liver NAD metabolome is depressed while blood increases circulation of NAD metabolites to enable a >20-fold increase in mammary NAD+ and NADP+. Lactation and NR synergize in stimulating prolactin synthesis and mammary biosynthetic programs. NR supplementation of new mothers increases lactation and nursing behaviors and stimulates maternal transmission of macronutrients, micronutrients, and BDNF into milk. Pups of NR-supplemented mothers are advantaged in glycemic control, size at weaning, and synaptic pruning. Adult offspring of mothers supplemented during nursing retain advantages in physical performance, anti-anxiety, spatial memory, delayed onset of behavioral immobility, and promotion of adult hippocampal neurogenesis. Thus, postgestational maternal micronutrition confers lasting advantages to offspring.
The Impact of a Multivitamin and Mineral Supplement on the Immune Function of Healthy Older Adults: A Randomized Controlled Trial

Adrian F Gombart, PhD

Department of Biochemistry and Biophysics, Linus Pauling Institute, Oregon State University, Corvallis, OR, USA

BIOGRAPHY

Adrian F. Gombart received his PhD in Microbiology from the University of Washington in Seattle. He completed postdoctoral work at Cedars-Sinai Medical Center with a focus on myeloid cell differentiation and leukemia. He became an Assistant and then Associate Professor at Cedars-Sinai Medical Center in Los Angeles and the David Geffen School of Medicine at UCLA in the Department of Biomedical Sciences and Division of Hematology and Oncology.

In 2008, Dr. Gombart moved to Corvallis, Oregon where he is currently a Principal Investigator in the Linus Pauling Institute and Professor in the Department of Biochemistry and Biophysics at Oregon State University. His research interests focus on the role of vitamin D and other dietary compounds in gut barrier function, the innate immune response against infection and composition of the gut microbiota. Grants from the National Institutes of Health support the studies in his laboratory.

In 2005, the organizers of the 14th Vitamin D Workshop in Brugge, Belgium recognized Dr. Gombart for his contributions to the field of vitamin D and immunity with a Young Investigator Award.

ABSTRACT

The elderly are frequently deficient in zinc, vitamin C and vitamin D, and this may contribute to the observed age-related decline of the immune system. We hypothesized that supplementation with vitamins C, D and zinc could change immune function in the elderly. To test this hypothesis, we treated healthy adults 55 and older with either Redoxon VI (n=21) or an identical, inactive placebo control (n=21) supplement for 12 weeks. Prior to and after treatment, we collected heparinized blood to i) test for whole blood bacterial killing activity against Staphylococcus aureus and ii) measure neutrophil
phagocytic activity and production of reactive oxygen species (ROS). We expected that Redoxon VI would increase the bactericidal activity of neutrophils through changes in levels of phagocytosis and ROS production as compared to the placebo.

We measured plasma levels of vitamin C and serum levels of zinc and vitamin D prior to and after 12 weeks of supplementation. A comparison between the placebo group and the Redoxon VI group after 12 weeks supplementation showed that treatment significantly increased the levels of zinc and vitamin C, but not vitamin D in the Redoxon VI group. We did not observe an increase in whole blood killing in the Redoxon VI treated participants, but we did observe increased ROS production. Interestingly, we also observed a statistically significant decrease in severity and length of self-reported illness in the Redoxon VI participants versus placebo. Further refinement of assays for measuring functional outcomes and larger study populations should improve detection of changes in immune function after supplementation. Taken together, our findings suggest that the overall effect of multivitamin and mineral supplementation improves some aspects of immune function and possibly decreases the rate of illness and its severity in an older adult population.
Acute Vitamin C Depletion During Sepsis Leads to Prolonged Behavioral Change

Fiona E Harrison, PhD

Department of Medicine,
Division of Diabetes, Endocrinology and Metabolism
Vanderbilt University Medical Center

BIOGRAPHY

Dr. Harrison’s primary research interest is the investigation of nutritional factors that can directly impact the development of Alzheimer’s disease and age-related cognitive decline. Recent work has focused on elucidating the many roles of vitamin C in the brain in neuroprotection and neuromodulation, including prevention of oxidative stress and protecting against glutamatergic excitotoxicity and hyperexcitability. In addition to aging and Alzheimer’s disease, Dr. Harrison has ongoing projects studying the potential role of vitamin C deficiency in a number of other diseases and conditions which include cognitive or behavioral deficits including Huntington’s disease, traumatic brain injury, sepsis, and exposure to environmental toxins.

Additional work from the lab has also identified important pathways that may underlie the effects of chronic high fat diet on cognitive ability. Dr. Harrison utilizes a multidisciplinary approach including in vitro studies, ex vivo molecular biology, electrophysiology and behavioral approaches to address research questions in the lab with the ultimate goal of identifying specific pathways underlying cognitive ability that can be impacted by diet. Dr. Harrison also serves as the Director of the Vanderbilt Neurobehavioral Core facility and actively collaborates with multiple groups, locally and Nationwide, to phenotype new mouse models of a wide range of diseases, to understand responses to novel therapeutics, and to adapt and refine behavioral protocols for more detailed phenotyping to extend research findings.

ABSTRACT

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Sepsis affects more than a million Americans every year, with 30% of cases resulting in death. It is now well-acknowledged that the acute inflammatory response can also have dramatic effects in brain. Following recovery many patients experience prolonged behavioral, cognitive and emotional disturbances. The concentration of vitamin C is higher in the brain compared to other organs because of a two-step active transport system and efficient recycling by astrocytes. Nevertheless, brain levels are depleted under dietary deficiency or physiological stress. Vitamin C is now being considered as a powerful treatment for sepsis. However, its role in neural function following sepsis has not been considered. Sepsis was induced in mice by intraperitoneal injection of cecal slurry (CS) leading to acute peritonitis that peaks by 12 hours and resolves by 48 hours. In wild-type mice CS-induced sepsis led to significantly decreased brain vitamin C by 4 hours post-treatment and persisted for 24 hours.

Upregulated synthesis of vitamin C in the liver was observed from 4 hours post-treatment and beyond 24 hours, suggesting continuing oxidative stress. Unlike mice, humans are dependent on dietary vitamin C, so gulo−/− mice that are unable to synthesize vitamin C were used to further explore these effects. 48 hours following CS-induced sepsis oxidative stress in the brain was significantly increased, and the magnitude of change was greater in low vitamin C-supplemented animals. Two-weeks post CS-induced sepsis gulo−/− mice exhibited hypoactivity, decreased motor strength and deficits in two tasks of hippocampal function, despite apparent full recovery from illness. The data suggest that acute vitamin C depletion during sepsis may contribute to long-term behavioral deficits even when levels are adequate at the onset of sepsis. Future experiments will establish how long the behavioral deficits may persist, and determine the role of neuroinflammatory processes underlying the cognitive and behavioral changes.
Novel Insights into Mechanisms of Vitamin E Absorption in Humans

Maret G. Traber, PhD

Linus Pauling Institute,
Oregon State University, Corvallis, OR, USA

BIOGRAPHY

Maret G. Traber received undergraduate and graduate degrees in Nutrition from the University of California, Berkeley, CA. Currently, she is the Ava Helen Pauling Professor in the Linus Pauling Institute and the College of Public Health and Human Sciences at Oregon State University, Corvallis, USA. She has pioneered methodologies for evaluating vitamin E status in humans using stable isotopes and identified key mechanisms for the regulation of vitamin E bioavailability in humans. She has identified key pathways that are dysregulated by vitamin E deficiency using a zebrafish embryo model. In 2013, she received the DSM Nutritional Science Award on Fundamental Research in Human Nutrition.

ABSTRACT

Human vitamin E absorption has not been measured previously using stable isotopes. α-Tocopherol (α-T) absorption was quantitated using two α-T with deuterium-labels (intravenous emulsion (IV) d6- and oral d3-) and three dietary approaches (40% or 0% fat, or 0% fat with a 12 h fast) in women (age 18 to 40 y). Fractional absorption was calculated 1) from d3- to d6-α-T ratios of the areas under the plasma concentration curves, 2) using a novel mathematical model and 3) from the balance method (oral d3-α-T minus fecal d3-α-T excreted). α-T absorption during the 40% fat intervention was 55% ± 3% (mean ± SEM, n=10), during the 0% fat intervention was 64% ± 3% (n=10, P<0.02), but fasting did not change α-T fractional absorption (56% ± 3%, n=7). Both the model outcomes and balance data confirmed that fat did not potentiate d3-α-T absorption.

The IV emulsion d6-α-T clearance half-life averaged 3.0 minutes, while HDL linearly acquired d6-α-T (21± 2 nmol/L plasma per minute) over the first ~15 minutes. By contrast, oral d3-α-T absorption took several hours. On reaching the liver, the d6-α-T from the IV dose was secreted
immediately in VLDL and swiftly equilibrated in plasma lipoproteins. During the initial 8 h, the oral d3-α-T continuously enriched triglyceride-rich lipoproteins (TRL) in preference to LDL or HDL, thus showing the TRL precursor role.

Vitamin E apparently accumulates during eating in lipid droplets in intestinal enterocytes. Following the next meal, these droplets coalesce with nascent chylomicrons enriching them with vitamin E for secretion. Once these chylomicrons reach the liver, then the α-T transfer protein (α-TTP) facilitates preferential secretion into plasma. Quantitatively, α-T absorption is not limited by fat absence or by fasting. However, α-T leaves the intestine by a process that is prolonged during fasting and potentiated by eating, suggesting that α-T depends on a chylomicron assembly processes that delay its absorption. These studies suggest a mechanism why the liver, but not the intestine, requires α-TTP to facilitate α-T secretion into plasma.