PLENARY SPEAKER ABSTRACTS

The following abstracts are for the Plenary Presenters and in their order on the Program Schedule as indicated.

PLENARY 1:
Endocannabinoids in the regulation of energy homeostasis in health and disease

SUNDAY, 29 JUNE – 13:30

Professor Georg Kunos

Obesity and its metabolic complications are associated with increased activity of the endocannabinoid/CB1 receptor (CB1R) system, as indicated by the beneficial effects of CB1R antagonists. However, neuropsychiatric side effects halted the therapeutic development of this class of compounds. As these side effects are due to blockade of CB1R in the CNS, whereas blockade of CB1R in peripheral tissues contribute to metabolic improvements, limiting the brain penetrance of CB1R antagonists may be a way out of this conundrum. We have tested a novel, peripherally restricted CB1R inverse agonist, JD5037, in mice with diet-induced obesity/insulin resistance (DIO mice). Chronic treatment of DIO mice with JD5037 or its brain-penetrant parent compound SLV-319 was equieffective in reducing food intake and adiposity and reversing hepatic steatosis and insulin resistance. The JD5037-induced appetite and weight reduction, but not the improvements in steatosis or glycemic control, are due to resensitizing DIO mice to endogenous leptin. This is secondary to the rapid reversal of hyperleptinemia via inhibition of leptin production in adipocytes and facilitation of leptin clearance by the kidney. We next tested the effects of JD5037 in a rat model of overt T2DM. Young ZDF rats have compensated insulin resistance, which progresses to

uncompensated hyperglycemia due to beta-cell failure. β-Cell failure in ZDF rats is associated with CB1R-activation of the Nlrp3-ASC inflammasome in M1 macrophages infiltrating pancreatic islets. These effects are replicated in vitro by incubating human or rodent macrophages but not macrophages from CB1R-/- or Nlrp3-/- mice with the endocannabinoid anandamide (AEA). Peripheral CB1R blockade, in vivo depletion of macrophages or macrophage-specific knockdown of CB1R prevents these changes, and restores normoglycemia and glucose-induced insulin secretion. We conclude that in diet-induced obesity peripheral CB1R blockade not only improves cardiometabolic risk, but also has antiobesity effects by reversing leptin resistance. Peripheral CB1R blockade also has weight-independent beneficial effects in overt T2DM by preventing β-cell loss due CB1R-mediated inflammasome activation in macrophages that infiltrate the pancreatic islets. These findings highlight the therapeutic potential of peripheral CB1R blockade in both the metabolic syndrome and in overt T2DM.

Supported by intramural NIH funds.

PLENARY 2:
Lipids and mitochondrial function

MONDAY, 30 JUNE – 08:30

Professor Guenther Daum

Mitochondria are only partially autonomous organelles. The vast majority of their components, among them proteins and lipids need to be imported from other organelles. However, a small set of proteins and phospholipids, i.e. cardiolipin and phosphatidylethanolamine, are synthesized within mitochondria. In our laboratory the assembly of phospholipids into mitochondrial membranes has been studied in long term projects. As an experimental system for these investigations we employ the yeast Saccharomyces cerevisiae as a model system. Making use of molecular biological, cell biological and biochemical methods we were able to obtain a view of lipid traffic between organelles. Mitochondria play an important role in this process especially through their contribution to the pathway of aminoglycerophospholipid synthesis. The first lipid component of this pathway, phosphatidylserine, is formed in the endoplasmic reticulum; decarboxylation of phosphatidylserine by Psd1p, the major phosphatidylserine decarboxylase of the yeast, occurs in mitochondria; and further conversion of phosphatidylethanolamine to phosphatidylcholine by methyltransferases is localized to the endoplasmic reticulum. Thus, intense crosstalk of organelles is required for this pathway. Recently, we focussed on the molecular role and properties of the mitochondrial phosphatidylserine decarboxylase Psd1p. Biogenesis of this enzyme as well as defects in mitochondrial membranes caused by deletion of PSD1 and depletion of

phosphatidylethanolamine were studied. These investigations demonstrated the important role of phosphatidylethanolamine as a mitochondrial lipid and revealed interesting counteracting effects of phosphatidylethanolamine with the mitochondria specific cardiolipin.

Supported by the Austrian Science Fund (FWF).

PLENARY 3:
Ceramides, new actors in cell signaling

MONDAY, 30 JUNE – 13:45

Professor Erich Gulbins, MD

Although ceramides belong to the most hydrophobic molecules in a cell and are water insoluble, they are critically involved in many signalling pathways, in particular upon application of stress stimuli. Thus, activation of acid sphingomyelinase, which converts sphingomyelin to ceramide, is triggered by diverse receptors including those for CD95, TNF, IL-1, and PAF, and by cellular stress such as oxidative stress, chemotherapeutic agents or infection with bacterial and viral pathogens. We have introduced the concept that these stimuli trigger fusion of specialized secretory lysosomes with the plasma membrane, resulting in surface exposure of acid sphingomyelinase and generation of ceramide in the anti-cytoplasmic leaflet of cell membranes. Therein ceramide molecules spontaneously self associate to form small ceramide-enriched membrane domains that fuse to become large ceramide-enriched membrane platforms. These platforms serve to cluster cognate receptors and other signaling molecules to greatly amplify initial signal density, thereby mediating transmembrane effects of receptor activation or stress. Clustering of receptors seems to be mediated by the length and the aminoacid composition of the transmembrane domain. We applied these insights to cystic fibrosis and pulmonary infections with Pseudomonas aeruginosa. We have demonstrated that ceramide accumulates in tracheal and bronchial epithelial cells of cystic fibrosis mice and humans. In contrast, sphingosine is almost absent in these cells of cystic fibrosis mice and patients, while present in control mice and healthy individuals. Sphingosine very efficiently kills P. aeruginosa and prevents infection. Thus, cystic fibrosis mice and patients suffer from two defects of the sphingolipid metabolism, i.e. an increase of ceramide and a decrease of sphingosine that results in the marked sensitivity of cystic fibrosis animals and patients to develop P. aeruginosa infections. These insights may serve to develop novel strategies to prevent and treat pulmonary infections with Pseudomonas aeruginosa.

PLENARY 4:
Dietary modulation of nociceptive mediators and physical pain

TUESDAY, 1 JULY – 13:45

Professor Chris Ramsden

Many patients with chronic pain continue to experience substantial pain and impaired quality of life despite taking numerous pain-related medications. It is therefore essential to investigate novel mechanisms and alternative approaches to manage pain. As major components of immune, myelin, glial, and neuronal cell membranes, n-3 and n-6 fatty acids can be endogenously converted to several families of bioactive lipid autacoids with pro- or antinociceptive properties (eg, endovanilloids, eicosanoids, endocannabinoids, resolvins).

With a few notable exceptions, mediators derived from n-6 linoleic (LA) and arachidonic (AA) promote nociception, while mediators derived from n-3 eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) promote anti-nociception. Thus, an imbalance of mediators derived from n-3 and n-6 fatty acids is a plausible mechanism underlying initiation and perpetuation of chronic pain disorders including headaches. In a small randomized trial in 67 patients with chronic headaches, we found that increasing dietary n-3 with concurrent reduction in n-6 fatty acids (the H3-L6 diet) produced statistically significant reductions in headache frequency and severity. These clinical improvements were accompanied by increases in pathway precursors for n-3 derived lipid mediators of anti-nociception, and reductions in n-6 derived mediators of nociception in circulation. Therefore, targeted alterations in dietary n-6 and n-3 fatty acids may be able to modulate nociceptive lipid mediators to reduce physical pain. However, current understanding of the molecular pathways and specific lipid autacoids linking diet to physical pain is limited. In this presentation I will review emerging preclinical and clinical evidence and highlight key evidence gaps along the proposed causal chain linking dietary n-3 and n-6 fatty acids to the etiology of chronic pain.

PLENARY 5:
Aquatic ecosystems as the main source of essential lipids for humans

TUESDAY, 1 JULY – 16:30

Professor Michail Gladyshev

Humans and most other animals need food sources of physiologically important highly unsaturated fatty acids (HUFA), such as eicosapentaenoic acid, (EPA) and docosahexaenoic acid (DHA), because their own synthesis of these HUFA can cover only around 5% of their physiological requirements. Among all organisms only some microalgae, diatoms, cryptophytes and dinophytes can synthesize de novo high amounts of EPA and DHA. HUFA, synthesized by microalgae, are transferred through trophic chains to organisms of higher levels, invertebrates and fish. Thus, aquatic ecosystems play the unique role in the Biosphere as the principal source of EPA and DHA for most animals, including inhabitants of terrestrial ecosystems and humans. HUFA are transferred from aquatic to terrestrial ecosystems through riparian predators, shore drift, emergence of amphibiotic insects and water birds. These essential nutrients are transferred through trophic chains with about twice higher efficiency than bulk carbon. Thereby, HUFA are accumulated, rather than diluted in biomass of organisms of higher trophic levels, e.g., in fish. Humans withdraw from aquatic ecosystems through fish catch ~180 106 kg y-1 of EPA+DHA. However, global average personal daily consumption of EPA+DHA is only about 0.1 g, while healthy personal intake is 0.5 – 1.0 g day-1. Thus, humankind face with a deficiency of the physiologically important HUFA in diet. Potential ways to increase HUFA consumption are discussed. Aquaculture is based on forage, obtained from wild catch and thereby cannot substitute fishery. Microbial biotechnology – single cell oil production is cost-prohibitive. Thereby, natural fish production of aquatic ecosystems will remain the main sources of the essential PUFA for humans. Aquatic ecosystems differ significantly in HUFA production of microalgae and thereby various fish species, getting PUFA from microalgae through trophic chains, differ in EPA and DHA contents in their biomass in two orders of magnitude. Ways to increase HUFA production in natural aquatic ecosystems are discussed. Data on quantity of various fish products to be consumed for obtaining the recommended appropriate intake of EPA+DHA for humans are given.