Sunday, July 15, 2012

SYMPOSIA AND ORAL SESSIONS
ASN-ADSA®-ASAS Preconference: Regulation of Nutritional Intake and Metabolism

1   Role of the central melanocortin system in appetite regulation and nutrient homeostasis. B. L. Panaro and R. D. Cone,* *Department of Molecular Physiology and Biophysics, Vanderbilt University School of Medicine, Nashville, TN.*

The central melanocortin system has long been implicated as a key regulator of energy homeostasis. The melanocortin-4 receptor (MC4R) integrates various homeostatic signals to control body weight through altering food intake and energy expenditure. Inhibition of MC4R signaling causes obesity in all vertebrate species tested, from fish to humans. The most notable differences caused by MC4R deficiency are hyperphagia and decreased energy expenditure, both of which contribute to the obesity observed in humans and mice. There is substantial evidence that MC4R deficient mice overconsume high-fat diets compared with obese controls, in a single food choice model. Previous rodent studies have investigated this feeding behavior in single-diet paradigms without offering another diet choice. Surprisingly, under 2-choice diet paradigms featuring a high-fat or high-sucrose diet paired with standard chow, MC4R deficient mice invariably have a lower preference for palatable high-fat and high-sucrose diets compared with wild-type littermates. Furthermore, while dietary preference for high fat or high sucrose seems to be attenuated in the MC4R deficient mice, the drive for hyperphagia is consistently enhanced by dietary variety, as a result of increased consumption of standard chow. Together, these food preference observations suggest a role for MC4R in the processing of food-directed behaviors, with reduced MC4R signaling leading to hyperphagia in an environment presenting a variety of foods. The mechanisms that guide these behaviors are largely uncharacterized, though we hypothesize that MC4R regulates dietary behaviors through both central and peripheral contributions to gut-brain communication. For example, in additional to hypothalamic sites of action, MC4R may also affect food intake indirectly through effects on gut motility, and even effects on enteroendocrine cell function.

2   The regulation of hepatic glucose uptake in vivo. A. Cherrington,* *Vanderbilt University School of Medicine, Nashville, TN.*

In the postprandial state, the liver takes up and stores glucose to minimize the fluctuation of glycemia. Elevated insulin concentrations, an increase in the load of glucose reaching the liver, and the oral/enteral/portal vein route of glucose delivery (compared with the peripheral intravenous route) are factors that increase the rate of net hepatic glucose uptake (NHGU). The entry of glucose into the portal vein stimulates a "portal glucose signal" that not only enhances NHGU but concomitantly reduces muscle glucose uptake to ensure appropriate partitioning of a glucose load. This coordinated regulation of glucose uptake is likely neurally mediated, at least in part, since it is not observed following total hepatic denervation. Moreover, there is evidence that both the sympathetic and the nitrergic innervation of the liver exert a tonic repression of NHGU that is relieved under feeding conditions. Further, the energy sensor AMPK appears to be involved in regulation of NHGU and glycogen storage. Consumption of a high fat and fructose diet impairs NHGU and glycogen storage, in association with a reduction in glucokinase protein

and activity. An understanding of the impact of nutrients themselves and the route of nutrient delivery upon liver carbohydrate metabolism is fundamental to the development of therapies for impaired postprandial glucoregulation.

3   Active and reactive amino acid homeostasis during feeding, lactation, and disease. G. E. Lobley,* *Obesity and Metabolic Health Division, Rowett Institute of Nutrition and Health, University of Aberdeen, Aberdeen, UK.*

Amino acids (AA) are critical responders and regulators during both anabolism and catabolism. In response to either acute or chronic intake AA are partitioned between oxidation and protein gain. Trans-hepatic studies suggest the utilization of ingested AA is driven primarily by the anabolic process while AA oxidation of any excess restores homeostasis. This mechanism provides a simple (and universal) means to regulate inter-tissue metabolism. Feeding exerts 2 aspects on AA metabolism. First, pattern of supply (e.g., meal or continuous) can influence net protein anabolism. In the neonate, intermittent supply gives greater efficiency whereas in the elderly single large meals may be preferred. Second, protein (AA) is the most satiating macronutrient and is used in many weight loss strategies. Satiety may be regulated through release of gut hormones that provide state of "hunger" (e.g., ghrelin) or "fullness" (e.g., PYY) signals. These may be released in response to either protein per se or to free AA. Uptake of AA by specific organs is linked to both direct (e.g., muscle growth, milk protein output) and indirect (e.g., precursors for other AA, gluconeogenesis, energy) needs. Infection increases the demands for specific AA to produce key proteins or peptides. Therefore, AA supply needed during disease differs from requirements for normal physiological processes and the deleterious effects of inflammation may be offset by extra provision of specific AA, such as glutamine, threonine and cysteine. AA or their metabolites can also indicate health status. For example, a key role played by methionine (Met) is to supply C-1 groups that methylate macromolecules involved in metabolic regulation. When either Met or other factors of the methionine cycle are limited, this results in hyperhomocysteinemia, an independent risk factor for several diseases. Kinetic studies in rodents have shown that less than 20% of tissue homocysteine flows through plasma and that uptake by key tissues, including heart, may link to disease progression. AA, both separately and as part of protein, play key roles in maintaining mammalian health and well-being.

4   Adipose and endocrine integration of metabolism. P. E. Scherer,* *UT Southwestern Medical Center, Dallas, TX.*

During the progression from the lean to the obese state, adipose tissue undergoes hyperplasia as well as hypertrophy in an attempt to cope with the increased demand for triglyceride storage. This requires a high degree of plasticity at both the cellular and at the tissue level. Even though adipose tissue as a whole seems to be a relatively static tissue containing many adipocytes that turn over slowly, these cells are embedded in

an environment that can rapidly adapt to the needs of expanding and newly differentiating adipocytes. The extracellular matrix of adipose tissue faces unique challenges with respect to adjusting to the need for remodeling and expansion. In parallel, the vasculature has to adapt to altered requirements for nutrient and oxygen exchange. A decrease in the plasticity of these processes leads to metabolic dysfunction. Furthermore, to maintain a healthy, non-inflamed phenotype, complex regulatory mechanisms are in place to ensure adipocytes and stromal vascular cells efficiently crosstalk to allow adipose tissue to expand upon increased demand for storage of triglycerides. Therefore, we propose a model of stepwise adipose tissue dysfunction that is initiated by rapid expansion of existing adipocytes to accommodate triglycerides during excess caloric intake. This leads very quickly to an acute, and eventually chronic, state of hypoxia in adipose tissue. Changes during the expansion process also affect adipocyte-derived secretory factors (adipokines), such as adiponectin. Adiponectin promotes insulin sensitivity, decreases inflammation, and promotes cell survival. Its levels are frequently downregulated in the obese state. We have recently demonstrated that adiponectin potently stimulates a ceramidase activity associated with its 2 receptors, adipoR1 and adipoR2, and enhances ceramide catabolism and formation of its anti-apoptotic metabolite, sphingosine-1-phosphate (S1P). Our observations suggest a novel role of adipocyte-derived factors that have beneficial systemic effects, with sphingolipid metabolism as its core upstream component.

5 Heat stress and post-absorptive metabolic perturbations. L. H. Baumgard*[1] and R. P. Rhoads[2], *[1]Iowa State University, Ames, [2]Virginia Polytechnic Institute and State University, Blacksburg.*

Environmental-induced hyperthermia compromises efficient animal production by marginalizing efforts to reduce food production inputs while negating the contribution of animal genetics toward performance endpoints. Modification of farm infrastructure has yielded modest success in mitigating heat stress-related losses yet heat stress remains arguably the costliest issue facing progressive livestock producers. Reduced output (e.g., milk yield, muscle growth, egg production) during heat stress was traditionally thought to result from decreased nutrient intake (a classic biological response shared by all animals during environmental-induced hyperthermia). Recent observations by our group challenges this belief, indicating heat-stressed animals employ novel homeorhetic strategies to direct metabolic and fuel selection priorities independently of nutrient intake or energy balance. Alterations in systemic physiology support a shift in carbohydrate metabolism, evident by changes such as basal and stimulated circulating insulin levels. Cellular metabolism of the hepatocyte and myocyte also show clear differences in glucose production and use, respectively due to heat stress. The apparent dichotomy in intermediary metabolism between the 2 tissue types may stem from factors such as mitochondrial function and antioxidant capacity. Perhaps most intriguing given the energetic shortfall of the heat stressed animal is the apparent lack of basal adipose tissue mobilization coupled with a reduced responsiveness to lipolytic stimuli. Thus, the heat stress response markedly alters post-absorptive carbohydrate, lipid, and protein metabolism independently of reduced feed intake through coordinated changes in fuel supply and utilization by multiple tissues. Interestingly, the systemic, cellular, and molecular changes appear conserved among different species and physiological states as our work has characterized similar events between growing and lactating ruminants, growing pigs and adult rodents. Ultimately, these changes result in the reprioritization of fuel selection during heat stress, which appears to be primarily responsible for reduced animal productivity during the warm summer months.

6 Linoleic acid and inflammation: Evidence-based research from human clinical studies. K. L. Fritsche*[1] and G. H. Johnson[2], *[1]University of Missouri, Columbia, [2]Johnson Nutrition Solutions, Kalamazoo, MI.*

The authors conducted a systematic review of randomized controlled trials that permitted the assessment of dietary linoleic acid (LA) on biological markers of chronic inflammation among the healthy non-infant population was conducted. A search of the English and non-English literature using MEDLINE, the Cochrane Controlled Trials Register, and EMBASE was conducted to identify relevant articles. Fifteen studies (8 parallel and 7 crossover) met inclusion criteria. None of the studies reported significant findings for a wide variety of inflammatory markers including C-reactive protein, fibrinogen, plasminogen activator inhibitor type 1, cytokines, soluble vascular adhesion molecules or tissue necrosis factor-α. The only significant outcome measures reported for higher LA intakes were greater excretion of prostaglandin E2 and lower excretion of 2,3-dinor-thromboxane B2 in one study 1 and higher excretion of tetranorprostanedioic acid in another. However, both authors observed that these effects were not an indication of increased inflammation. It is concluded that virtually no evidence is available from randomized, controlled intervention studies among healthy, non-infant humans to show that variations in the level of LA in the diet affects in vivo inflammation in healthy humans.

7 Microbial hydrogen metabolism in colonic health and disease. H. R. Gaskins,* *University of Illinois, Urbana-Champaign.*

In mammals, dietary fiber (polysaccharides, oligosaccharides, lignin and associated plant substances) and other nutritional components not absorbed in the upper digestive tract reach the colon where they are fermented by the cooperative metabolism of a complex microbiota. Fermentation products include short chain fatty acids (SCFAs; acetate, propionate and butyrate) and gases including molecular hydrogen (H_2). Colonic SCFAs, which are present at high concentrations (>100 mM), serve as the primary energy source for epithelial cells and modulate cell fate through influences on differentiation, growth arrest, and apoptosis. The H2 produced during fermentation is either excreted or used as a source of electrons by 3 groups of H_2-consuming microorganisms (hydrogenotrophs); the acetogens (generating acetate), methanogens (methane) and sulfate reducing bacteria (SRB; hydrogen sulfide, H_2S). Hydrogenotrophic organisms are present at much lower densities than are fermentative bacteria. However, in the absence of microbial H_2 consumption, the H_2 partial pressure rapidly reaches a level that thermodynamically inhibits further fermentation. Methane and sulfide production have been recognized as major pathways for H_2 disposal in the colon, but various factors such as colonic pH, sulfate availability, transit time, and microbial composition may influence which of these mechanisms predominates. Our research seeks to better understand the nature of the hydrogenotrophic microbiota and the extent to which end products of their metabolism vary among individuals and contribute to chronic inflammation and colorectal cancer. Of particular interest are SRBs and host epithelial responses to their toxic end product H_2S. Host and microbial aspects of our related working hypothesis will be described and data presented from recent studies that demonstrate the prevalence of hydrogenotrophs in the human colonic mucosa and their responsiveness to diet.

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8   Characterizing the cellular mechanisms of postprandial thermogenesis in skeletal muscle. B. A. Henry* and I. J. Clarke, *Department of Physiology, Monash University, Victoria, Australia.*

Thermogenesis is the dissipation of energy through specialized heat production. This process contributes to 10–15% of total energy expenditure in lean individuals. Thermogenesis is well characterized in brown adipose tissue, but whether other tissues are thermogenic is contentious. To characterize this in sheep we developed a model of postprandial thermogenesis, whereby sheep were entrained to a meal-feeding regimen with food restricted to a set meal time. We demonstrate increased skeletal muscle heat production at the onset of feeding and that central infusion of leptin upregulates this. Furthermore, central administration of leptin increases the expression of uncoupling protein (UCP) 2 and 3, but not UCP1 in skeletal muscle. The increase in UCP3 is associated with a switch to uncoupled respiration in isolated mitochondria. Thus, leptin-induced heat production in skeletal muscle is concomitant with the induction of thermogenesis. In addition to mitochondrial function, we examined changes in calcium cycling. Meal-feeding increased heat production as well as the expression of ryanodine receptor 1 (RyR1) mRNA and sarcoplasmic Ca^{2+}-dependent ATPase (SERCA) 2 protein in skeletal muscle. Thermogenesis in muscle, therefore, is facilitated via both mitochondrial uncoupling as well as calcium cycling pathways. Finally, we characterized differences in thermogenesis in animals predisposed to obesity. To do this we utilized two unique models, the genetically lean and obese sheep as well as a model of cortisol responsiveness. We show that animals characterized as high cortisol responders (HR) have greater propensity to obesity when fed a high energy diet compared to low cortisol responders (LR). Resistance to obesity in the LRs is preceded by a higher thermogenic response in muscle. This contrasts the genetically lean and obese animals, where lean animals have increased thermogenesis in adipose tissue, but not muscle. In conclusion, we show that skeletal muscle heat production is associated with altered mitochondrial function and enhanced calcium cycling. Furthermore, innate differences in thermogenesis (either muscle or fat) predispose animals to weight gain and obesity.