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PLENARY LECTURES

T1:PL

The role of nutrition partitioning in the development of obesity and insulin resistance

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Body weight is regulated by a complex interplay between energy intake and energy expenditure. Energy partitioning reflects the distribution of macronutrients to pathways of energy deposition vs oxidative metabolism. We have been examining how energy partitioning reflects body weight maintenance in humans and mice. We assessed the impact of physical inactivity for just 24 h on macronutrient balance in a whole room calorimeter after 2 wk of isocaloric high fat vs. high carbohydrate feeding in human subjects, and then examined the predictability of changes in body weight/composition over 4 y. On the high carbohydrate diet, carbohydrate balance, e.g. more glycogen storage, protected subjects from body weight/fat gain. This related to insulin sensitivity, but not to usual levels of physical activity (as reflected by energy balance in the calorimeter). In mice, nutrient partitioning has been modified by skeletal muscle over-expression or deletion of lipoprotein lipase (LPL). Mice with over-expression of LPL are insulin resistant and gain less weight/fat on a high fat diet. They also expend more energy, but only when exposed to cold temperatures. In mice with skeletal muscle-specific deletions in LPL, insulin-mediated glucose uptake into muscle is typical of young mice, however, compensation by other organs, i.e. liver, adipose tissue and heart occurs. Despite insulin sensitivity in skeletal muscle, high fat feeding results in extreme obesity in young mice. Overall, nutrient partitioning does not modify caloric value, but appears to regulate energy balance and defend body fat.
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T2:PL

What can we expect from metabolomics and system biology?

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Traditional human nutrition research has used a defined hypothesis to test, usually with a limited number of relevant metabolites. Moreover, standard statistical approaches are used to compare quantitative differences. In metabolomics, the technologies concerned (^{1}H NMR and LC-MS) measure the presence of the maximum number of metabolites for which the technology is capable. It is important to note that generally the presence and relative presence are measured but not quantified. The statistical analysis uses megavariate data analysis in the form of pattern recognition technologies. When compared with pharmaceutical research, nutritional metabolomics has a number of unique challenges. Nutrition signals are more ubiquitous and softer than pharma signals and thus the effect of noise may be a bigger problem. This is exacerbated by the 'noise' of human diets in the sense that nutrients are associated with a myriad of plant phytochemicals and man-made chemicals all of which are detected using these technologies. They are particularly important in urine which is the biofluid of choice in metabolomics. The plasma metabolome is highly governed by endogenous metabolism in many instances and this leads to the possibility of exploiting new technologies for imaging in a systems biology to metabolomics. In effect if the composition of the body is known, cannot the endogenous metabolome be predicted?
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T3:PL

Visceral Obesity and Cardiometabolic Risk

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The idea that it is not the amount of fat, but its location that determines the effect of excess fat on cardiometabolic risk factors like hypertension, dysglycemia or dyslipidemia is not new. However, we now know that the presence of visceral fat is an important determinant of these risk factors in every ethnic group and at every level of body-mass index (BMI). This observation has three important implications: 1) the impact of visceral obesity, independently of BMI on the worldwide prevalence of cardiometabolic risk needs to be assessed; 2) clinicians, researchers and regulators need to re-evaluate their current weight-based definition of obesity; 3) individuals with visceral obesity within the 'normal' limits of BMI may need to reduce their body weight. The factors underlying differential fat deposition remain unclear. Factors that have been implicated include physical activity, high-protein intake, sex hormones, glucocorticoid metabolism, the hypothalamic pituitary axis, poor differentiation of subcutaneous fat and growth hormone deficiency. The previously favoured rather simplistic notion that the metabolic consequences are explained largely by the draining of free fatty acids from the visceral fat to the liver, has recently given way to more sophisticated ideas regarding the role of adipokines secreted from this highly active endocrine organ. Clearly a better understanding of what determines fat deposition in different fat depots as well as a clearer picture of why fat in different locations can promote or deter cardiometabolic problems requires further study – in order to best target those, who are at the highest risk from their excess fat.

T4:PL

Overview of social disparity in obesity

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Obese individuals are not only medically compromised, they are socially disadvantaged. Research with children and adults shows this disadvantage to be apparent in key parts of their lives. Obese people are more likely than comparable normal weight individuals to be rejected socially and romantically, and victimized because of their weight. They are more likely to receive negative comments from doctors and for their overweight to influence health care decisions. They have impaired employment prospects, clearest in the greater risk of unemployment but apparent in lower wages. Educational attainment is also affected. Unsurprisingly, obesity also threatens psychological well-being, increasing the risk of mood disorders, low self-esteem and binge eating. In turn, poor well-being reduces the uptake of and adherence to weight-reducing treatments. The process is insidious, the multiple small adverse circumstances associated with obesity accumulating from adolescence through adulthood. Vulnerability to social disparity therefore starts in childhood, is greatest in those with persistent obesity, and apparent in women more than men. Anti-fat attitudes are pervasive in Western society and the associated biases are shared by the general public, medical staff and the obese themselves. Central to this negativity is blame, directed at obese people for their failure to show the will-power to address an allegedly controllable lifestyle disorder. Actions to reduce social disparity and its maintaining role in obesity are required. They include improving the public understanding of obesity and weight loss, reviewing the coping strategies available to those affected, and learning from the circumstance of others with stigmatized conditions.

PL:5

NASH in obesity: physiopathology, outcomes and management

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Non-alcoholic steatohepatitis (NASH) is one complication of obesity. Hepatic histology in NASH includes steatosis (i.e. triglyceride accumulation), inflammation, cytolysis and fibrosis. In general, NASH occurs in patients with fatty liver (i.e. liver with steatotic hepatocytes). Fatty liver is mainly the consequence of insulin resistance (IR) in adipose tissue and liver. IR and the subsequent hyperinsulinemia increase the delivery of non-esterified fatty acids to the liver and hepatic de novo lipogenesis (DNL). DNL is due to enhanced expression of SREBP-1c, a transcription factor primarily regulated by insulin. In order to restrain steatosis, compensatory mechanisms can be set up such as increased fatty acid oxidation. Some inherited or acquired factors can favour fatty liver such as partial leptin deficiency. The progression of steatosis towards NASH requires a 'second hit' which is essentially the production of reactive oxygen species (ROS) by increased cytochrome P450 2E1 and the damaged mitochondrial respiratory chain. ROS in turn lead to the production of cytokines and lipid peroxidation products that are harmful for the liver. NASH is potentially a serious liver disease since it can progress towards cirrhosis and hepatocellular carcinoma. Importantly, livers with steatosis or NASH are prone to ethanol-induced injury. The management of NASH is still an object of investigations and currently there is no definite treatment. The ideal treatment of NASH should reduce IR and oxidative stress, and improve mitochondrial function. Besides drugs such as metformin, thiazolidinediones and some antioxidants, it seems that exercise and reduced calorie intake could be valuable ways to alleviate NASH.

PL:6

The chemoreception of fat: a role in obesity?

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Fatty acids (FA) have been implicated as chemosensory cues that convey the taste and texture of fat, and one transduction mechanism involves an interaction with delayed rectifying K (DRK) channels. Using heterologous expression and patch clamp recording to determine the FA sensitivity of DRK subtypes and quantitative real-time PCR (qPCR) to measure DRK expression, we have shown that obesity-resistant rats (S5B) express a much higher ratio of FA-sensitive (FA-s) to FA-insensitive (FA-i) DRK channels (5.2:1) than those from obesity-prone rats (O-M; 1.7:1). We hypothesize that the FA-s:FA-i ratio may be important in peripheral fat chemosensitivity and ultimately contribute to dietary fat intake. To test this idea directly, we induced obesity in a normally obesity-resistant S5B rats by placing them on a diet containing 70% fat for two months. S5B rats exhibit pronounced hyperphagia and developed obesity similar to that seen in obesity-prone rats on this diet. After 63 days on the high-fat diet, we analyzed expression of DRK channels in taste cells and found that the FA-s:FA-i DRK ratio dropped from 5.2:1 to 0.65:1. Patch clamp recording was used to verify the functional change in DRK FA responsiveness as a consequence of these changes in gene expression. On normal diets, FAs (10 μM) inhibit about 90–95% of the DRK current in taste cells from S5B rats, however, after developing obesity it was inhibited only ~30%. Thus, the FA-s:FA-i DRK ratio is sensitive to dietary fat intake and is correlated with higher dietary fat intake and may contribute to fat-induced obesity.

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