EASTBIO DTP Research Training Strand 1

2014-2015

Basic Bioscience Underpinning Health (Ageing) priority area

Session 3: Mitochondria metabolism and Ageing

Speakers Abstracts

Professor Lora Heisler (Rowett Institute of Nutrition and Health, University of Aberdeen)

How energy balance is controlled within the brain

Adiposity commonly accumulates with age from early adulthood (human 20 years old) through late middle-age (human 65 years old). This increase in adiposity has significant health implications; age-related obesity represents the primary cause of metabolic syndromes. Distilling the mechanisms underlying age-associated adiposity has clinical implications both for obesity treatment and the prevention of chronic obesity-related comorbidities in the aging population. Like adult humans, adult mice accumulate adiposity with age, in the face of constant environmental conditions (i.e. *ad libitum* access to the same diet and existing at a constant temperature). Underpinning the middle-aged spread is a reduction in energy expenditure in mouse and man alike. While the biological factors driving reduced energy expenditure and increased fat accumulation with age are not well understood, recent reports reveal age-related melanocortin system remodelling and link these functional changes with age-associated obesity.

Dr Giuseppe D'Agostino (Rowett Institute of Nutrition and Health, University of Aberdeen)

The role of adipocyte hormone leptin in energy expenditure with age

The prevalence of obesity in older people is the leading cause of metabolic syndromes. It is a clinical imperative to understand the underpinnings of age-dependent obesity, owing the rapid rise of the ageing population and the consequences of such rise for public health services. The phenomenon commonly described as the middle-age spread is the result of elevated adiposity accumulation throughout adulthood until late middle-age. As observed in humans, this phenomenon is phenocopied in mice. Middle-aged mice (12-14 months old) manifest increased adiposity when compared with young adult mice (3-4 months old). Comprehensive metabolic characterizations of mice revealed that the increased adiposity in middle-aged mice is due to a sharp decrease thermogenic capacity, rather than increased energy intake or substantially reduced physical activity. In line with increasing adiposity, middle-aged mice and humans show increased circulating level of leptin – an adipostatic hormone that regulates energy homeostasis, including thermogenesis. Our current working hypothesis is that increased circulating leptin levels promote leptin resistance within discrete brain regions that coordinate energy dissipation via thermogenesis and that this phenomenon plays a causative role in the metabolic decline observed with age. We observed a specific age-related reduction in leptin sensitivity in the dorsomedial nucleus of the hypothalamus (DMH), while leptin responses in other hypothalamic nuclei were unaffected. *In vivo* manipulation of leptin-responsive DMH neuronal circuits in young-adult mice recapitulates the metabolic phenotype observed in middle-aged mice and also suggests that leptin's action on energy expenditure and food consumption is via parallel and functionally independent neuronal circuits. We propose that this discrete anatomical and functional leptin-resistance phenomenon constitutes an adaptive mechanism to promote a slow increase in fat storage as individuals age and become less adept at acquiring food. However, in individuals living under conditions of plentiful food availability this mechanism become maladaptive contributing to the development of age-related adiposity and metabolic syndrome.

Dr Pablo Martinez de Morentin (Rowett Institute of Nutrition and Health, University of Aberdeen)

CNS signals to brown adipose tissue to stimulate energy expenditure

Central nervous system (CNS) control of energy intake is crucial for life span, but management of energy usage is also vital. In environmental conditions where food is not always available, individuals tend to eat more than necessary for future needs, and the body stores this food as energy in fat depots. However, in conditions where food is readily available, overeating results in a chronic positive energy balance which leads to obesity. Brown adipose tissue (BAT) is a specialized type of fat which dissipates energy to produce heat in a process called nonshivering thermogenesis. This process plays an important role in the regulation of energy balance, and understanding how the CNS regulates BAT thermogenesis is essential for finding treatments for obesity.

Dr Justin Rochford (Rowett Institute of Nutrition and Health, University of Aberdeen)

What does fat do?

In obesity adipocytes can become hypertrophied and no longer act as a hormonally responsive, safe store for nutrients after a meal. In the absence of this storage capacity lipids may instead accumulate in other tissues causing lipotoxicity and metabolic disease. Altering the function of adipocytes offers a potentially attractive means to counter this and improve metabolic health. Adipose tissue depots may be comprised of principally triglyceride filled white adipocytes, more oxidative, intermediate brite/beige adipocytes or classically thermogenic, mitochondria-rich brown adipocytes. Each can be altered by nutritional, hormonal and neuronal signals and ageing. Targeting these regulatory pathways has significant potential to ameliorate metabolic disease.

Dr Xuming Zhang (Rowett Institute of Nutrition and Health, University of Aberdeen)

UCP-1, a molecular gateway to energy balance and body weight

Reduced energy expenditure and exceeding energy accumulation are at the core of obesity development. Stored energy can be expended in the form of heat in brown fat

tissues through the action of uncoupling protein-1 (UCP-1) in the mitochondria of fat cells, a process known as thermogenesis. UCP-1 is thus the key to controlling energy expenditure and body weight. Indeed, a variety of hormones and factors influence energy balance and body weight through regulating UCP-1 expression. Here, I will discuss our current understanding of UCP-1 gene regulation. A deeper understanding of the regulation of UCP-1 will have enormous potential to be exploited for obesity treatment.