proving opportunity for preclinical diagnosis. This is dependent, to some extent, on the long term stability of these marks, which is in most cases unknown. This makes their predictive value unclear. I will discuss how the meaning of the word epigenetics has changed over the last ten years and why this has caused confusion. Empirical evidence has altered our view of the importance of DNA methylation in the determination of phenotype.

Over the last fifty years, obesity levels have increased dramatically and changes to adipose tissue and epigenetic marks in adipose tissue have been detected. Whether these marks are drivers of obesity or consequences of obesity is yet to be determined. Moreover, there is some evidence that obesity can be inherited across generations, not just via DNA sequence (genotype) but also via epigenetic marks in the gametes. The idea is that mothers or fathers who have become obese transmit this to their offspring independent of any genetic susceptibility to obesity. The current evidence for this is weak.

I will discuss these ideas using data collected from studies in mice and humans.

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4

Invited talk: Hot and sweet: Brown fat beyond thermo-regulation in humans

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There are three kinds of fat tissue. White adipose tissue (WAT) stores energy and in excess leads to obesity. Brown adipose tissue (BAT) consumes energy and produces heat for thermoregulation. Beige adipose tissue (BeAT) emerges within WAT during cold exposure and manifests thermogenic function comparable to BAT. Animals with high BAT/BeAT status are protected against diabetes and obesity. Recent re-discovery of thermogenic BAT in humans has brought the relation between ambient temperature, thermogenesis and systemic energy and substrate metabolism to the forefront [1].

Humans maintain core temperature through a complex neuroendocrine circuitry, coupling environmental thermal and nutritional cues to heat-producing and dissipating mechanisms. Up to 40% of resting energy expenditure contributes to thermal homeostasis maintenance. The dynamic interplay between BAT, BeAT and WAT modulates systemic energy homeostasis and highlights the presence of a previously under-appreciated thermogenic adipose axis in humans.

In addition to well-known pituitary-thyroid-adrenal axis, recently identified endocrine signals, such as FGF21 and irisin [2], orchestrate crosstalk between WAT, BAT and muscle, tuning non-shivering and shivering thermogenesis responses. Cold-activated BAT modulates systemic metabolic and endocrine milieu, and cold-induced hormones cause bioenergetics transformation sufficient to impact whole body energy and substrate balance [3], suggesting BAT may serve important physiologic functions beyond thermoregulation in humans.

References

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5

Short-term exposure to energy-matched diets enriched in fat or sugar differentially affects memory, gut microbiota and markers of brain inflammation and plasticity

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Short-term exposure to high-energy diets impairs memory but there are limited data regarding the relative contributions of fat and sugar to these deficits or the mechanisms responsible. Here, we investigated how these different macronutrients affect memory, neuroinflammation and neuroplasticity markers and the gut microbiota in the short-term. Rats were fed matched purified diets for 2 weeks; Control, Sugar, Saturated Fatty Acid (SFA) or Polyunsaturated Fatty Acid (PUFA), which varied only in the percentage of energy available from sugar and the amount and type of fat. Memory was assessed after 8—9 days and rats were culled after 12—13 days exposure. The expression

of genes related to inflammation and plasticity was determined via reverse transcription polymerase chain reaction (RT-PCR) and the fecal microbiota was quantified via high-throughput sequencing of the 16S ribosomal RNA. Weight gain and energy intake were comparable across the diets. Rats consuming the SFA and Sugar diets were impaired on hippocampal-dependent place recognition memory compared to Controls and PUFA rats. All rats performed comparably on the perirhinal-dependent object recognition task. Hippocampal and hypothalamic inflammatory and neuroplasticity genes were not substantially affected, but each of the diets significantly altered the microbial composition in distinct ways. Specifically, the relative abundance of 89 taxa differed between groups with the majority of changes accounted for by the Clostridiales order and within that, *Lachnospiraceae* and *Ruminococcaceae*. These taxa showed a range of macronutrient specific correlations with place memory. In addition, Distance based Linear Models found relationships between memory, a cluster of hippocampal inflammation-related genes and gut microbiota composition. In conclusion, our study shows that even in the short-term the macronutrient profile of the diet is crucial for diet-induced memory deficits and suggests a possible link between diet, gut microbiota and hippocampal inflammatory genes. Longer term studies are warranted.

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6

AMPK-ACC signalling is required for increasing appetite under conditions of metabolic stress

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Activation of AMP-activated protein kinase (AMPK) during increased energy demand promotes food intake and reduces brown fat thermogenesis to shift the organism to neutral energy balance. The underlying molecular interactions are not entirely understood.

The acute effects of AMPK on lipid metabolism are mediated by phosphorylation of acetyl-CoA carboxylase (ACC) 1 at Ser79 and ACC2 at Ser212, thereby inhibiting fatty acid synthesis and promoting fatty acid oxidation. To investigate the physiological impact of this regulation on whole body energy balance, we generated mice with Ser79Ala/Ser212Ala knock-in mutations (ACC double knock-in, ACC DKI). ACC DKI mice have increased ACC1/2 activity in peripheral tissues and a propensity for increased lipid synthesis. Despite deregulated lipid metabolism, ACC DKI mice do not gain more weight when compared to wild type control mice and, in contrast, show a tendency for reduced body weight from 15 weeks of age.

Food intake measurements showed that ACC DKI mice have reduced appetite in response to metabolic stress, such as overnight fasting or cold exposure. Furthermore, while ACC DKI mice are able to maintain normal body temperature under cold stress, they compensate for reduced energy intake by utilising lipids as preferred energy source. Cold exposure and overnight fasting are accompanied by increased plasma levels of the orexigenic hormone ghrelin in ACC DKI mice. Importantly, we demonstrate that feeding in response to ghrelin is attenuated and ghrelin-induced expression of the orexigenic neuropeptides NPY and AgRP is inhibited, indicating that the anorexic phenotype of ACC DKI mice may be due to ghrelin insensitivity.

These results show that AMPK regulation of ACC is an important physiological mechanism in the control of body weight regulation, whereby the lipid accumulating effects in the periphery are outweighed by anorexic effects in the hypothalamus.

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7

Invited talk: Executive dysfunction in obese individuals

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Research has indicated that individuals with obesity have neurocognitive deficits, especially in executive function, which may in turn impact on weight loss and maintenance. In this talk I will review the evidence of this relationship, highlighting some of the mechanisms, and limitations of the literature. I will then present data on our latest randomised controlled trial which examined efficacy of a manualised cognitive remediation therapy for obesity (CRT-O) in terms of improving executive function, reducing binge eating behaviour and helping with weight loss. 80 adults with obesity (body