the potential of HCC to have wide-spread impact by changing the expectations around healthy food provision.

Conclusion: This study shows engagement methods and potential challenges of the HCC, and provides lessons for other local governments in the UK and abroad considering similar actions to address the healthiness of food businesses in their community.

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Cellular energy sensing and metabolism: implications for treating obesity

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The survival of all cells is dependent on the constant challenge to match energetic demands with nutrient availability, a task which is mediated through a highly conserved network of metabolic fuel sensors that orchestrate both cellular and whole organism energy balance. A mismatch between cellular energy demand and nutrient availability is a key factor contributing to the development of obesity, thus understanding the fundamental mechanisms by which cells sense nutrient availability and demand may lead to the development of new treatments. Glucose lowering therapies such as caloric restriction, exercise, metformin and cold all induce an energetic challenge that results in the activation of the cellular energy sensor AMP-activated protein kinase (AMPK). Activation of AMPK in turn suppresses lipid synthesis and inflammation while increasing glucose uptake, fatty acid oxidation and mitochondrial function. In contrast, high levels of nutrient availability, suppress AMPK activity while also increasing the production of peripheral serotonin, a gut-derived endocrine factor which suppresses beta-adrenergic-induced activation of brown adipose tissue. Identifying new ways to manipulate these two ancient fuel gauges, by activating AMPK and inhibiting peripheral serotonin, may lead to the development of new therapies for treating obesity.

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What should we over-eat?

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The diverse obesity phenotypes – Implication for treatment

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Over the past 30 years researchers described varied metabolic phenotypes in overweight and obesity with diverse disease outcomes. Well-conducted randomized large cohort clinical trials in individuals with overweight and prediabetes or type 2 diabetes suggest mixed response to caloric restriction or metformin, the first-line medication in type 2 diabetes [1]. In the Diabetes Prevention Program, 21% of individuals with prediabetes treated with metformin progressed to diabetes at 3 years [2]. Similarly, 55% of individuals with prediabetes in the Tubingen Lifestyle Intervention Program did not revert to normal glucose tolerance in response to energy restriction and moderate exercise intervention [3]. Using gold-standard phenotyping tools of hepatic and peripheral glucose regulation, we find different levels of insulin resistance in liver and muscle in individuals with obesity. Using latest-generation plasma metabolomic and lipidomic analyses combined with machine learning, random forest-based feature selection and classification we identified three plasma lipids that can classify subcohorts of liver versus muscle insulin resistance in obesity with remarkable accuracy. We propose that therapy guided by plasma biomarkers will be more therapeutically effective, have less side-effects, and be more cost-effective.

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Disruption of AMPK-glycogen binding in vivo reveals novel roles in whole-body and tissue metabolism

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The AMP-activated protein kinase (AMPK) and glycogen are essential for maintaining metabolic homeostasis. The energy-sensing AMPK heterotrimer contains a regulatory β subunit with a carbohydrate-binding module (CBM) known to bind glycogen. However, the physiological roles of AMPK-glycogen binding in metabolism *in vivo* are unknown. To determine the effects of disrupting AMPK-glycogen binding, two whole-body knock-in (KI) mouse lines were generated targeting tryptophan residues known to mediate glycogen binding in either the AMPK β1 (W100A KI) or β2 (W98A KI) subunit, predominantly expressed in liver and skeletal muscle, respectively. Whole-body, serum and tissue analyses were performed in male KI and wild type (WT) litter mate mice maintained on an *ad libitum* chow diet. Intraperitoneal glucose tolerance testing revealed normal glucose tolerance in W100A mice but impaired glucose handling in W98A mice (56% increase in AUC; $P < 0.05$) compared to WT, with no differences observed in fasting serum insulin. Body composition (determined from EchoMRI) showed normal whole-body fat and lean mass in W100A mice. Strikingly, W98A mice displayed a 42% increase in fat mass ($P < 0.05$) and 5% decrease in lean mass ($P < 0.05$) relative to WT. Metabolic caging demonstrated no changes in cumulative food intake, O_2

consumption, indirect calorimetry or infrared-based activity levels. No differences were observed in resting tissue glycogen content, epididymal fat pad mass, hindlimb muscle mass or liver and muscle mitochondrial content between KI and respective WT mice. Fat deposition was increased by 61% in W100A liver ($P < 0.05$) and 54% in W98A quadricep muscle ($P < 0.05$) versus WT, concomitant with reductions in total protein content of AMPK α and β subunits. These data suggest that glycogen-bound AMPK is central to whole-body and tissue metabolism. We reveal new insights into the physiological roles of AMPK and suggest that loss of glycogen binding negatively impacts metabolism via reductions in the cellular AMPK pool.

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Muscle membrane permeability to glucose and blood flow explain increased insulin sensitivity in muscle after exercise

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The relationship between skeletal muscle perfusion, interstitial glucose concentration and sarcolemmal permeability to glucose in exercise-induced increases in muscle insulin sensitivity is not well established. In 10 young men, a euglycemic hyperinsulinemic clamp was initiated 4 h after 1-legged exercise, and leg blood flow (LBF), leg glucose uptake (LGU) and muscle interstitial glucose concentration were measured. During the clamp LGU and LBF were higher ($P < 0.05$) in the previously exercised than the control leg whereas the interstitial glucose concentration decreased to lower ($P < 0.05$) values in the exercised (~3.1 mM) than the control (~4.8 mM) leg. Apparent sarcolemmal glucose permeability was twice as high ($P < 0.05$) in the exercised compared with the rested leg. The NOS inhibitor L-NMMA decreased LBF in both legs and interstitial glucose concentration dropped to ~2.3 mM in the exercised but only to ~3.7 mM in non-exercised muscle. This abrogated the augmented effect of insulin on LGU in the exercised leg while apparent sarcolemmal permeability to glucose remained unchanged with L-NMMA in both legs. Doubling LBF by local infusion of ATP increased LGU in both legs without any major change in interstitial glucose concentration or sarcolemmal permeability to glucose. These findings suggest that during flow restriction due to L-NMMA, the interstitial glucose concentration becomes limiting for insulin-stimulated glucose uptake in previously exercised but not in non-exercised muscle. Therefore, the vasodilatory effect of insulin is an important component of the increased insulin sensitivity to stimulate glucose uptake following exercise by limiting the drop in the interstitial glucose concentration that occurs due to the increased sarcolemmal permeability to glucose.

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Time restricted feeding

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Light/dark cycle aligned (circadian) rhythms regulate the processes associated with the acquisition and metabolism of food. In mice, limiting food intake to the non-resting phase induces circadian desynchrony, and results in obesity and impaired glucose tolerance (1). A feature of modern human lifestyles is an extended period of eating, and a curtailed period of fasting, that likely induces circadian desynchrony. Time restricted feeding (TRF) is a novel dietary approach that limits when, rather than what, food is eaten. Time restricted feeding is emerging as a powerful regulator of health and longevity in mouse models, and TRF restores peripheral circadian rhythmicity in liver of mice that are fed a high fat diet. The evidence as to whether TRF will be beneficial for metabolic health in humans is currently limited. Short-term studies are beginning to emerge that suggest that the health effects observed in mice will translate to people who are at risk of type 2 diabetes. Particularly, TRF improves glucose tolerance independently of food intake. Our data similarly shows that TRF improves glycaemic control in men who are at risk of type 2 diabetes. Further, we show that there may be at least some flexibility in the clock time that the fasting time is initiated. We are currently conducting metabolic studies in humans to examine whether TRF can improve 24-hour glucose metabolism, and reset peripheral clocks in adipose tissue. We have also tested the metabolic impacts of TRF during simulated shift work and show that TRF may be a tool to rescue the metabolic consequences of shift work in people.

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Alternating periods of energy restriction and energy balance

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Circadian rhythms, diet and exercise

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