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Determining the metabolic impact of dietary carbohydrate composition in the setting of low, medium and high protein diets

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The âŁ˜Geometric FrameworkâŁ™ (GF) for nutrition has revealed that âŁ˜low protein-high carbohydrateâŁ™ (LPHC) diets generate the best mid-late life cardio-metabolic health and lifespan in mice. Starch (polysaccharide of glucose) and sucrose (disaccharide of glucose + fructose) are the major dietary carbohydrates. We further evaluated if the benefits of LPHC diets depend on the *type* of carbohydrate and dietary protein content.

Male mice (C57BL/6; $n = 300$) were fed ad-libitum for 18 weeks one of 15 isocaloric diets with low (10/70), medium (20/60) or high (30/50) protein:carbohydrate energy (fat fixed at 20%). These diets provided 30% of carbohydrate energy from starch and remaining 70% from five different monosaccharide glucose-fructose ratios (100/0, 75/25, 50/50, 25/75, 0/100). GF analysis showed that in contrast to their consumption in isolation, a combination of glucose and fructose intake was most detrimental for metabolic health (Â¬â†‘weight, â†‘adiposity, â†“insulin sensitivity and â†“glucose tolerance) and this was worsened by increasing protein ingestion.

Next, the metabolic effects of sucrose and starch intake were compared in the specific context of LPHC diets. Mice ($n = 300$) were fed ad-libitum one of 15 isocaloric LPHC diets (protein:carbohydrate:- 5/75, 10/70 or 15/65, and 20% fat). Dietary carbohydrate consisted of five different sucrose-starch ratios (20/80, 35/65, 50/50, 65/35, 80/20). Metabolic status (weight, energy expenditure, adiposity, insulin sensitivity, triglyceridaemia, nutrient signalling, plasma metabolites) was adversely affected by increasing protein intake mostly in combination with high starch intake. Replacement of starch with sucrose minimally affected metabolism, producing some benefits such as reduced food intake and adiposity. Decreasing the ratio of protein to carbohydrate in the diet increased energy intake and yielded peak FGF-21 and brown fat levels.

Overall, protein was the major determinant of metabolic phenotype, glucose and fructose intake in combination were more harmful than either alone, but high sucrose intake did not have adverse consequences in a LPHC dietary setting.

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Specific targeting of TGF-β family ligands demonstrates distinct roles in the regulation of muscle mass in health and disease

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The transforming growth factor-β (TGF-β) network of ligands and intracellular signalling proteins is a subject of intense interest within the field of skeletal muscle biology. To define the relative contribution of endogenous TGF-b proteins to the negative regulation of muscle mass, we used local injection of adeno-associated viral vectors (AAVs) encoding ligand-specific antagonists into the tibialis anterior (TA) muscles of C57Bl/6 mice. Eight weeks after AAV injection, inhibition of activin A and activin B signalling produced moderate (~20%), but significant, increases in TA mass, indicating that endogenous activins repress muscle growth. Inhibiting myostatin induced a more profound increase in muscle mass (~45%) demonstrating a more prominent role for this ligand as a negative regulator of adult muscle mass. Remarkably, co-delivery of activin and myostatin inhibitors induced a synergistic response, resulting in muscle mass increasing by as much as 150%. Transcription and protein analysis indicated that this substantial hypertrophy was associated with both the complete inhibition of the Smad2/3 pathway, and activation of the parallel bone morphogenetic protein (BMP)-Smad1/5 axis (recently identified as a positive regulator of muscle mass). Analyses indicated that hypertrophy was primarily driven by an increase in protein synthesis, but a reduction in ubiquitin-dependent protein degradation pathways was also observed. In models of muscular dystrophy and cancer cachexia, combined inhibition of activins and myostatin, increased mass or prevented muscle wasting, respectively, highlighting the potential therapeutic advantages of specifically targeting multiple Smad2/3-activating ligands in skeletal muscle.

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