Measurement of postprandial glucose fluxes in response to 5 and 28 days of overfeeding in healthy humans

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Background: A key factor in the drastic rise of type 2 diabetes in the past few decades is the Westernized diet, characterized by an overconsumption of energy leading to reduced glucose tolerance and whole-body insulin sensitivity. However, previous human studies utilize experimental diets that alter the proportion of macronutrients to increase fat intake, and that many people are unlikely to consume under free living conditions. Additionally, many of these studies utilize techniques such as the euglycemic hyperinsulinemic clamp that are not representative of normal, physiological living conditions. Therefore, this study aimed to determine the effect of 5 days and 4 weeks of mixed nutrient overfeeding on glucose fluxes (rates of meal glucose appearance (Ra), disposal (Rd) and endogenous glucose production (EGP)) during a mixed meal, in order to understand the physiological adaptations to an overfeeding diet.

Methods: Eight healthy young men underwent mixed meal tolerance testing combined with the triple-stable isotope glucose tracer approach to simultaneously determine glucose fluxes at baseline, and after acute (5d) and chronic (28d) mixed nutrient overfeeding (45.6% excess energy; 32% Fat, 45% CHO, 18% protein). Data are in mean ± SEM. Significance $P<0.05$.

Results: Both total body (1.64 ± 0.40 kg) and fat (1.32 ± 0.18 kg) mass were significantly increased by chronic, but not acute overfeeding, although visceral adipose volume was significantly increased by both conditions. Normal glucose tolerance was maintained after 5 days of overfeeding, whereas postprandial glycaemia was significantly impaired after 28 days. This occurred despite a slight increase in the total postprandial suppression of EGP following both acute and chronic overfeeding. Interestingly, meal glucose Ra was also elevated following both acute and chronic overfeeding, and was matched by an increase in glucose Rd. However, glucose clearance (*i.e.* the efficiency at which glucose is disposed of relative to the prevailing glucose levels) was significantly improved following acute, but impaired following chronic overfeeding.

Conclusion: Our findings suggest that the glucoregulatory system is able to compensate for transient periods of mixed nutrient overfeeding, maintaining normal postprandial glycaemic control. However, chronic exposure to this overfeeding impairs the glucoregulatory system, resulting in decreased glucose tolerance and regulatory system efficiency; where glucose clearance is reduced, despite a slight increase to the postprandial suppression of EGP.