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# Liquid Sucrose Consumption Promotes Liver Lipid Accumulation, Fat Mass, and Glucose Intolerance without Altering Circulating Insulin Levels

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A variety of factors contribute to the rising rates of obesity and to difficulties in weight reduction that exist in the worldwide population. One factor that contributes to weight gain is caloric intake via consumption of sugar-sweetened beverages (SSBs). Therefore, in this study, we investigated specific metabolic outcomes associated with ad libitum liquid sucrose intake over 12 weeks in male C57BL/6J mice. Mice consuming 30% sucrose in liquid form gained 39.6% more weight ($p < 0.001$) with a 51% increase in fat mass ($p< 0.01$), stored 3.5-fold more fat in liver ($p< 0.05$), and had impaired glucose tolerance relative to control mice (AUC $p < 0.01$). Intriguingly, all of these metabolic perturbations occurred without alterations in circulating insulin levels and with no detectable changes in physical activity of the mice. In addition, liver and muscle glycogen content did not increase with sucrose consumption. However, sucrose intake produced higher RQ values ($p < 0.01$), increased serum FGF21 levels (5.9 fold; $p < 0.01$), promoted browning of white adipose tissue, and enhanced whole body energy expenditure (22% increase; $p < 0.01$). A correlation analysis based on Pearson's correlation coefficient $r$ indicated that energy expenditure (EE) correlated with total body mass (TBM: $r = 0.91$, $p<0.0001$), oxygen consumption (VO2: $r=0.75$, $p<0.001$), lean mass (LBM: $r=0.94$, $p<0001$) and fat-free mass (FFM: $r=0.94$, $p<0.0001$). Oxygen consumption (VO2) also correlated with fat-free mass (Pearson $r = 0.76$; $p < 0.001$), moderately with total body mass (Pearson $r = 0.60$; $p < 0.05$), but not with fat mass (Pearson $r = 0.31$; $p = 0.25$). Analysis of covariance (ANCOVA) for treatment effects on EE with TBM, VO2, LBM, and FFM taken as potential covariates for EE revealed that VO2 was the preferred single covariate. When the treatment means for EE were covariate adjusted for VO2, the EE mean for sucrose was significantly elevated ($p<0.025$). When multiple covariates were considered, TBM and VO2 were significant, but the difference between covariate-adjusted treatment means was not significant. Congruent with the increase in RQ, there was a marked increase in the glycolytic enzyme gene expression profile in skeletal muscle, but not in epididymal white adipose tissue. We further found that sucrose consumption downregulated the expression of the *dgat1* and *dgat2* genes in inguinal white adipose tissue (iWAT). By contrast, *dgat1* and *dgat2* expression are not suppressed in iWAT from *db/db* mice, a separate model of obesity that displays hyperinsulinemia. Taken together, we conclude that sucrose-induced weight gain occurs without an increase in circulating insulin and is associated with enhanced lipid accumulation in liver, but not skeletal muscle. This study shows that obesity driven by enhanced consumption of carbohydrate calories in liquid form is distinct from the hyperinsulinemia promoted by high-fat diet or by obesity driven secondary to deficiencies in leptin receptor signaling. Thus, molecular mechanisms responsible for the obese state are likely to be dependent on the macronutrient source of calories and route of delivery.