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Preview

Fructose: Not sweet enough for brown fat?

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In a randomized crossover study in humans, high fructose feeding reduced glucose uptake in brown fat without affecting the tissue's oxidative capacity. These effects were independent of alterations in the gut microbiome.

Obesity and type 2 diabetes (T2DM) are closely intertwined diseases that pose a major threat to global public health. Worldwide, over 2 billion people are overweight or obese and more than 450 million individuals have diabetes mellitus, the majority being T2DM linked with insulin resistance. Processed foods enriched in added sugars, particularly fructose, are thought to be a significant contributor to the rising prevalence of metabolic diseases, and growing evidence suggests that increased fructose consumption adversely affects human health beyond excess calories alone. However, relatively little is known about specifically how fructose affects the pathogenesis of metabolic disorders, particularly in humans.

In this issue, Richard et al. test the effects of high-glucose or -fructose diets on brown adipose tissue (BAT) function in humans.[1] Our ancestors consumed fructose only a few months a year at the time of harvest, amounting to about 20 g per day. However, with modern diets and the use of artificial sweeteners, such as high fructose corn syrup, consumption has more than quadrupled. The well-described negative impact of fructose on the liver is driven by enhanced *de novo* lipogenesis, elevated triglyceride (TG) levels, and increased risk of hepatic steatosis.[2] These metabolic perturbations appear to play a key role in the pathogenesis of insulin resistance associated with high dietary fructose consumption in humans and animal models. However, it has been less clear how fructose affects other key organs that modulate cardiometabolic health, such as brown fat.

BAT is the main site of adaptive thermogenesis, an energy dissipating process induced by environmental cold that relies on the large number of mitochondria in this tissue that perform uncoupled respiration.[3] Targeting functional BAT, present in several depots in adult humans, has the potential to be a promising new approach to treating obesity and diabetes due to its ability to increase energy expenditure; sequester toxic metabolites, such as glucose, lipids, and branched-chain amino acids; and possibly secrete endocrine mediators with favorable metabolic effects.[4] Indeed, the presence of BAT is associated with significantly decreased odds of T2DM, dyslipidemia, hypertension, and coronary artery disease, as well as a healthier white-fat distribution and reduced hepatic steatosis.[5,6] BAT activation has been shown to result in improved insulin sensitivity and lower circulating TG, whereas decreased BAT activity has been associated with aging and T2DM.[7] The primary energetic substrate for BAT appears to be fatty acids released from intracellular TG stores, but during thermogenesis, brown fat also demonstrates substantially increased glucose uptake.[8] Understanding the interconnections between diet, organismal metabolism, and brown fat may reveal novel mechanisms underlying obesity and its sequelae.

In their new study, Richard et al. test the hypothesis that a high-fructose (HF) diet impairs BAT function, which may be an important contributor to fructose-induced metabolic dysfunction in humans.[1] They further postulate that HF feeding changes the composition of the microbiome, increasing short-chain fatty acid levels, and thereby suppressing oxidative metabolism and blunting intracellular TG depletion during BAT activation. To test this hypothesis, they conducted a randomized crossover study of ten young (ages 20–40 years), non-obese men exposed to 2 weeks of fructose or glucose overfeeding separated by a 4-week isocaloric washout period. Neither dietary regimen led to a change in total body weight or adiposity. Notably, 2 weeks of HF, but not high-glucose diet, led to significantly impaired BAT glucose uptake, but unexpectedly, this was uncoupled from effects on oxidative metabolism in BAT.

Following each diet period, subjects were exposed to an acute cold challenge (3 h at 18°C), and BAT activity was evaluated. ^{11}C-acetate positron emission tomography (PET) imaging was performed to estimate blood flow by tracer uptake and oxidative activity by tracer washout. Cold exposure led to increased blood flow and oxidative metabolism in BAT in all subjects, and these parameters were not affected by HF. Magnetic resonance imaging (MRI) and magnetic resonance spectroscopy (MRS) were used to evaluate changes in BAT intracellular TG content, which decreased following cold exposure but was unchanged by HF diet. Following cold exposure, they extensively evaluated levels of circulating substrates and hormones and found a significant increase in markers of adipose tissue lipolysis and fatty-acid oxidation with cold, which were also unaffected by HF. The HF diet did however result in significantly reduced glucose uptake and metabolic rate in BAT, as measured by ^{18}F-fluorodeoxyglucose (FDG) PET imaging. These effects were independent of changes in insulin, glucagon, cortisol, or glucagon-like peptide-1 (GLP-1). Moreover, neither diet led to changes in gut microbiome composition or microbial metabolites.

This study represents an important contribution toward unraveling the links

between HF diets and metabolic dysregulation. The significant effect of HF on BAT glucose uptake also highlights a significant issue for the field that has been overlooked until now. Since most studies of BAT in humans rely on ^{18}F-FDG PET imaging, decreased BAT glucose uptake may actually be due to dietary factors, which could be an important confounding factor leading to an erroneous assumption of decreased BAT activity. Future studies investigating BAT in human subjects will need to consider diet as a potentially important covariate. While the uncoupling of BAT glucose uptake and oxidative metabolism noted here were unanticipated, the effect sizes for all of the outcomes, with the exception of glucose uptake, were somewhat heterogeneous and smaller than expected. It is therefore possible that a larger study may identify other unique effects of HF diet on BAT metabolism. Finally, the lack of an association between diet and the microbiome here leaves open the question of the mechanism linking HF to decreased BAT glucose uptake. Further studies in animal models and human subjects will be necessary to further elucidate how HF diet contributes to BAT dysfunction, altered whole-body metabolism, and downstream pathology.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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