EDITORIAL FOCUS

Sugar-sweetened beverages and vascular function: food for thought

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OBESITY IS A well-recognized major global health problem, and the World Health Organization estimates that there are more than 600 million obese adults worldwide as of 2014. Because obesity is often the result of excess caloric intake, there has been a significant effort invested into understanding how various nutrients (e.g., carbohydrates and fatty acids) consumed in surplus adversely affect organ function and metabolic homeostasis. For example, there has been a multitude of research illustrating differences between saturated (e.g., palmitate) and unsaturated (e.g., oleate) fatty acids on obesity-related insulin resistance and type 2 diabetes (T2D), with a number of studies demonstrating that saturated fatty acids may be worse for insulin sensitivity due to promoting organ ceramide accumulation (1, 14). Extensive study has also taken place comparing the effects of various carbohydrates, primarily glucose versus fructose consumption in the form of sugar-sweetened beverages (SSBs), as SSBs are the primary source of added sugars in the diet. The main sweeteners used by the food industry for SSBs are high-fructose corn syrup and sucrose, which both contain approximately equal amounts of fructose and glucose (12). As such, robust research efforts have been invested into delineating the metabolic consequences of excess glucose and fructose consumption, with a number of studies highlighting fructose as the more detrimental sugar of the two. Indeed, it has been widely suggested that excess fructose consumption in animals increases hepatic de novo lipogenesis (DNL), dyslipidemia, and promotes obesity and insulin resistance (16). Similarly, observations in human studies from Stanhope and colleagues (13) have recapitulated these findings, as obese subjects consuming 25% of their daily energy requirements from fructose SSBs exhibited increases in fasting plasma insulin and glucose, as well as increases in hepatic DNL and visceral adiposity versus subjects consuming glucose SSBs.

In this issue of the American Journal of Physiology-Heart and Circulatory Physiology, Sangüesa et al. (10) add to the growing body of evidence implicating fructose as a more detrimental sugar than glucose with regard to metabolic homeostasis, with a specific focus on vascular health. Using a number of sophisticated techniques to assess lipid metabolism, insulin signaling, and vascular reactivity in hepatic and/or aortic tissues, Sangüesa et al. observed that although total caloric consumption was higher in glucose-supplemented female rats, fructose ingestion had a more significant negative impact on metabolic homeostasis and vascular function. It has been well documented that vascular dysfunction is a key contributor to obesity-related insulin resistance (11), and both insulin resistance and vascular dysfunction have been implicated as critical factors responsible for obesity-induced cardiomyopathy (2, 21). Thus it is tempting to speculate that fructose-mediated vascular dysfunction is a precipitating event driving the increased risk for insulin resistance, T2D, and cardiovascular disease (CVD) in humans consuming fructose SSBs in surplus. Sangüesa et al. investigated the negative actions of fructose on endothelial function by assessing endothelium-dependent vasodilation to acetylcholine and bradykinin [nitric oxide (NO)-dependent vasodilators], or the NO donor sodium nitroprusside (SNP), as well as the vasoconstrictor response to phenylephrine. They observed that fructose had minimal effects on NO-dependent vasodilation but worsened NO donor-mediated vasodilation via SNP, whereas glucose augmented NO donor-mediated vasodilation. Interestingly, fructose had no negative effects on phenylephrine-induced contractions, whereas glucose actually reduced phenylephrine-induced contractions. To potentially explain the molecular mechanism behind the differential vascular responses in rats supplemented with glucose versus fructose, Sangüesa et al. evaluated a number of signaling pathways controlling vascular relaxation. Despite fructose SSB consumption impairing and glucose SSB consumption enhancing NO donor-mediated vasodilation, cyclic GMP (cGMP)-dependent protein kinase (PKG) protein expression and activity, as indicated by phosphorylation at serine 239 of the PKG downstream target vasodilator-stimulated phosphoprotein (VASP), were not different between these two groups. However, total VASP protein expression was significantly reduced only following fructose SSB supplementation. Furthermore, changes in NO-independent vasodilation appeared to be occurring following fructose SSB consumption, as cyclic AMP (cAMP)-dependent protein kinase-mediated phosphorylation of VASP at serine 157 was impaired, while mRNA expression of the cAMP phosphodiesterase 4, which specifically hydrolyzes cAMP, was increased by ~50%. Based on these findings, it would seem prudent for future studies to assess NO-independent vasodilation in thoracic aortic rings from animals consuming either fructose or glucose SSBs, though the authors did note that it has been previously reported that SNP-induced relaxation may also involve a cGMP-independent response (19).

Of particular relevance, Sangüesa et al. also suggested that part of the beneficial actions of glucose versus fructose SSB consumption on vascular function might be due to increases in circulating adiponectin. To validate this, the authors treated endothelial EA.hy926 cells with either 25 mM glucose, 25 mM fructose, or various concentrations of adiponectin and observed that only adiponectin increased NO levels in the cell culture.
supernatant. Although these findings are not definitive in proving that adiponectin is responsible for the beneficial actions on vascular function observed in vivo in mice supplemented with glucose SSBs, they are consistent with the vast body of work supporting that adiponectin improves vascular health (4). Moreover, recent findings indicate that adiponectin improves metabolic health by reducing cellular ceramide content as activation of adiponectin receptors is associated with increases in ceramidase activity (6). As reductions in intracellular ceramide content also lead to improvements in vascular function in the context of obesity-induced metabolic dysfunction (1, 20), it would be of interest to determine whether alterations in ceramide metabolism contribute to the differential vascular effects of fructose versus glucose SSB consumption.

Another notable finding of Sangüesa et al. was that although total caloric intake in glucose-supplemented rats was significantly higher than that of fructose-supplemented rats, only fructose supplementation induced dyslipidemia and increased body and liver weight. Increases in liver weight and dyslipidemia are consistent with previous findings demonstrating that surplus fructose consumption enhances hepatic DNL (13, 16). In further support that increased hepatic DNL was occurring in the female rats supplemented with fructose, Sangüesa et al. demonstrated that liver protein expression of the lipogenic enzymes stearoyl-CoA desaturase-1, fatty acid synthase, and sterol regulatory element-binding protein 1 were all increased only in female rats supplemented with fructose SSBs. Moreover, protein expression of carnitine palmitoyl transferase-1A, the rate-limiting enzyme controlling mitochondrial fatty acid uptake and subsequent oxidation (7), was decreased, whereas protein expression of microsomal triglyceride transfer protein, an essential protein for assembly and secretion of very-low density lipoprotein-triglycerides (5), was increased in livers from fructose-supplemented rats. Collectively, these molecular signaling changes are likely to account for fructose-mediated increases in hepatic DNL and subsequent steatosis, but actual hepatic steatosis was not measured in this study. With regard to the interesting observation on body weight, this study illustrates a clear dissociation between caloric intake, body weight gain, and dyslipidemia following excess glucose versus fructose consumption. Reasons for this dissociation remain enigmatic, but it is interesting to note that glucose and fructose elicit contrasting actions on the hypothalamus and peripheral control of energy expenditure that may explain the observations by Sangüesa et al. As such, fructose has been shown to increase 5’-AMP activated protein kinase (AMPK) activity in the hypothalamus, which decreases hypothalamic malonyl CoA content (3). Conversely, glucose decreases AMPK activity and increases malonyl CoA content in the hypothalamus (17). As increases or decreases in hypothalamic malonyl CoA increase and decrease

![Fig. 1. Fructose and metabolic health. Figure depicts some of the major characterized actions of excess fructose consumption that negatively impact metabolic health. Previous studies in animals and humans have demonstrated that fructose increases visceral adiposity and hepatic de novo lipogenesis, whereas the findings of Sangüesa et al. (10) also demonstrate that fructose promotes vascular dysfunction. These 3 outcomes likely contribute to the increased risk for insulin resistance and cardiovascular disease associated with excess fructose consumption.](http://ajpheart.physiology.org/)

energy expenditure, respectively (8), it is plausible that changes in energy expenditure may explain why body weight was only increased in mice consuming fructose SSBs.

It should also be noted that the potential translation of these findings to obese and insulin-resistant humans is unclear, especially in light of the fact that consumption of fructose by the female rats in this study is likely supraphysiological. Indeed, based on the values indicated in Table 2 of the manuscript by Sangüesa et al., the rats consuming fructose SSBs were obtaining ~70% of their caloric intake from fructose, which is much higher than the average amount of fructose consumed by an obese human on a daily basis. Illustrating differences between human and animal findings, Stanhope et al. (13) demonstrated increases in both total and visceral adiposity in obese humans consuming fructose versus glucose SSBs (25% of daily energy intake), whereas Sangüesa et al. observed similar total adiposity between rats consuming either fructose or glucose SSBs. Although ex vivo assessments revealed vascular dysfunction in aortic rings harvested from rats consuming fructose SSBs, it is well documented that rodents are relatively resistant to the development of atherosclerosis unless the diet is supplemented with high cholesterol/high fat and contains cholic acid and thiouracil (18). Sangüesa et al. also did not consider the vascular effects of fructose consumption in males, where previous studies have similarly demonstrated that ingestion of fructose SSBs for 2 wk in male rats induced hepatic steatosis and plasma hypertriglyceridemia (15). However, this study also demonstrated that excess fructose consumption does not induce hyperinsulinemia, while other studies have also shown that long-term ingestion of fructose in male rats increased phenylephrine-induced contractions in thoracic aortic rings (9), thereby contrasting with the findings of Sangüesa et al. in female rats. Thus future studies using more physiologically relevant increases in fructose consumption in the appropriate animal models in both males and females are necessary to provide more definitive answers on the cardiovascular consequences of excess fructose.

Taken together, the findings of Sangüesa et al. add to the growing body of evidence implicating fructose as a more detrimental sugar on whole body health when consumed in excess versus glucose. In addition to negatively impacting insulin sensitivity, overall adiposity, and hepatic DNL, excess fructose consumption also promotes vascular dysfunction (Fig. 1). Of interest, excess glucose consumption increased caloric intake without impacting overall body weight, while also improving NO-induced vasodilation and abrogating pressor-induced vasconstriction. These observations should not be directly taken to advocate that it is safe for humans to ingest excess glucose with minimal consequences on metabolic and vascular health, as glucose consumption was also supraphysiological (~80% of daily energy intake) in this particular study. Furthermore, this was a well-controlled study in young female rats fed a standard chow diet with the only dietary manipulation being the provision of glucose or fructose to the animals’ drinking water. It is entirely possible in the context of a high-fat diet, which would be a more clinically relevant model, as most obese humans are consuming both fats and sugars in excess, that surplus glucose consumption would also produce negative effects on whole body health. Nevertheless, the study of Sangüesa et al. is suggestive that excess consumption of fructose should be avoided. Although the conclusion that glucose consumption is more favorable for vascular health than fructose as a result of increases in circulating adiponectin is not definitive, the overall outcome of this study should be a positive one for the field. The study of Sangüesa et al. should pave the way for future studies to continue exploring the molecular mechanism(s) driving the negative vascular actions of excess fructose consumption. Because there is a strong link between consumption of large amount of SSBs and the risk for obesity, T2D, and CVD, increased awareness about SSBs and their potential negative metabolic actions may lead to meaningful changes in dietary guidelines and public health education.

REFERENCES


