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Authors
Hofmann, Susanna M
Havel, Peter J

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Commentary

MOLECULAR METABOLISM

The good, the bad, and the unknown: Fructose and FGF21*

Susanna M. Hofmann [1,2,*], Peter J. Havel [3,4]

In this issue of Molecular Metabolism, Dushay et al. report new results demonstrating fructose ingestion in humans acutely and robustly raises circulating levels of fibroblast growth factor 21 (FGF21) [1], a recently discovered hormone that has been proposed to have beneficial effects on metabolic health, including reduction of body weight and improvements of glucose and lipid metabolism [2]. People suffering from the metabolic syndrome have higher baseline circulating FGF21 levels and exhibit a larger increase of plasma FGF21 concentrations following an oral fructose load. In contrast, the increase of FGF21 after ingestion of the same amount of glucose was delayed and much more modest. These results are paradoxical in that the metabolic effects of FGF-21 appear to be mainly beneficial while those of dietary fructose are generally deleterious [3]. The authors suggest the possibility that obese subjects with metabolic syndrome are resistant to the actions of FGF21 (akin to augmentation of circulating insulin and leptin concentrations and responses in insulin and leptin resistance) and that the exaggerated response to fructose ingestion may be a compensatory response [1]. The increases of FGF-21 in response to fructose ingestion across normal weight and overweight/obese subjects was significantly correlated with circulating insulin and glucose levels in response to oral glucose loads suggesting a relationship between FGF21 and insulin senstivity/glucose tolerance. Together, these novel results shed light on a potential mechanism related to the adverse metabolic effects of dietary fructose and raise new questions about the nutritional regulation of metabolic responses to dietary macronutrients, specifically sugars.

Fructose is a major component of Western diets, and mounting evidence points to an obesogenic role for fructose via generation of substrates for *de novo* lipogenesis through rapid hepatic metabolism [3]. To understand how fructose may mediate its deleterious effects on various tissues, the authors proposed an intriguing novel hypothesis; fructose may acutely increase the production and secretion of FGF21 by potently activating the transcription factor carbohydrate response element-binding protein (ChREBP). In their study, Dushay et al. monitored circulating FGF21 levels after ingestion of a large (75 g) fructose bolus in 21 patients, half of them lean and healthy and half of them overweight to obese and insulin resistant [1]. Although FGF21 increased rapidly and sharply within 2 h and returned to baseline levels within 5 h in all patients, the response to fructose varied widely between the subjects. These findings point to individual differences in fructose absorption, metabolism and/or sensing. If that is the case, it would be important to understand whether an individual's susceptibility to develop diabetes may be predicted by a fructose tolerance test. If so, availability of such a test would help prevent onset of metabolic disease in subjects at risk by early personalized life style intervention and treatment.

The findings of this study are in line with previous work indicating that consumption of fructose- or glucose-sweetened beverages with meals produces very different, acute effects on circulating levels of endocrine signals, including insulin, leptin, ghrelin, and glucagon-like peptide-1 (GLP-1), and triglycerides [4]. Specifically, circulating FGF21 and GLP-1 are both increased to a greater extent and ghrelin is less suppressed by fructose than glucose [4,5]. Now FGF21 can be added to the growing list of endocrine and metabolic responses known to be differentially influenced by fructose ingestion. In studies comparing prolonged ingestion of fructose with glucose, consuming fructose-sweetened beverages for 10 weeks increases visceral adiposity, lipid/lipoprotein risk factors for cardiovascular disease, decreases insulin senstitivity, and increases uric acid and markers of inflammation to a greater extent than glucose [6–8] and increases hepatic lipid deposition [9]. The effects of prolonged chronic ingestion of dietary sugars on circulating FGF21 and FGF21 responses to nutrient ingestion, however, are not known.

In the present study, a large dose of pure fructose (75 g) was ingested by the study subjects. Dietary fructose is typically consumed as a mixture of glucose and fructose in the form of high-fructose corn syrup (HFCS) or sucrose. The authors addressed this by examining the effects of a mixed glucose/fructose load on FGF-21 responses, and the mixture increased plasma FGF-21 similarly to pure fructose, by itself. Similarly, the mixture of fructose and glucose in HFCS increases lipid and lipoprotein risk factors for CVD extent as pure fructose [10]. A recent study in mice fed HFCS for 14 weeks reporting increases of

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[1]Helmholtz Zentrum München, German Research Center for Environmental Health (GmbH), Institute for Diabetes and Regeneration Research, Ingolstaedter Landstr. 1, 85764 Neuherberg, Germany [2]Medizinische Klinik Innenstadt, Ludwig Maximilian University, Munich, Germany [3]Department of Molecular Biosciences, School of Veterinary Medicine University of California, Davis, CA 95616, USA [4]Department of Nutrition, University of California, Davis, CA 95616, USA

*Corresponding author. Helmholtz Zentrum München, German Research Center for Environmental Health (GmbH), Institute for Diabetes and Regeneration Research, Ingolstaedter Landstr. 1, 85764 Neuherberg, Germany. E-mail: susanna.hofmann@helmholtz-muenchen.de (S.M. Hofmann).

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FGF21 expression in muscle [11] may confirm a potential role for FGF21 in fructose-mediated effects on metabolism. Thus, the current study warrants further research to understand how FGF21 may be related to clinical disease outcomes attributable to the consumption of large quantities of fructose-containing sugars contained in typical Western diets. This is of particular importance since FGF21 has been shown to protect against diet-induced obesity, lower circulating glucose and triglyceride levels, and increase energy expenditure, fat utilization and lipid excretion when administered to diabetic and diet-induced obese rodents (for a review, see 2).

In search of underlying mechanisms, the hypothesis raised by the authors that fructose increases FGF21 production by activating the transcription factor ChREBP points to an emerging role for ChREBP as a control lever for certain metabolic effects of dietary fructose. A recent report by Erion et al. suggests just that, demonstrating that targeting ChREBP prevents fructose-induced hypertriglyceridemia but does not improve hepatic steatosis or hepatic insulin resistance in rats [12]. In summary, Dushay and colleagues have successfully highlighted a complex new area of interplay between a potentially beneficial hormone, FGF-21, and the dietary nutrient fructose with adverse metabolic effects. The details of this interaction will need to be sorted out prior to the development of novel drugs targeting metabolic pathways regulated by fructose. Accordingly, if FGF-21 is "the good" and fructose is "the bad", the nutrient-endocrine interface between the two remains "the unknown".

CONFLICT OF INTEREST

None declared.

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