METABOLIC SYNDROME

Fructose and metabolic health

Table sugar and high-fructose corn syrup are widely used sweeteners that promote obesity and the metabolic syndrome. Molecularly, they consist of glucose and fructose. Previous studies in model

Credit: CreativeNature_nl/Getty

organisms have shown that blocking fructose metabolism prevents metabolic syndrome induced either by fructose or by glucose. However, the tissue-specific roles of fructose metabolism in metabolic syndrome induced by a mixture of fructose and glucose has not been directly tested.

A new study investigates the contribution of fructose metabolism to the development of the metabolic syndrome in mice in response to a sugar solution resembling that which is used in the human diet. “We decided to test the response of whole-body as well as tissue-specific fructokinase-deficient mice to a fructose–glucose solution similar to high-fructose corn syrup,” explains Miguel Lanaspá, corresponding author of the study.

The researchers observed that animals that received the fructose–glucose solution consumed more test solution than animals that received a fructose solution and that this effect was dependent on functional fructose metabolism. Blocking fructose metabolism by deleting the gene that encodes fructokinase in the whole animal prevented hallmarks of sugar-induced metabolic dysfunction, such as lipid accumulation in the liver and the rise of fasting blood levels of insulin.

Next, the researchers examined the contributions of intestinal as well as liver fructose metabolism to sugar intake and its metabolic consequences. When fructose metabolism was blocked in the intestine, fructose–glucose solution intake and overall caloric intake was reduced. When fructose metabolism was blocked in the liver, fructose–glucose solution intake remained similar to that of control mice. However, unlike control mice, liver fructokinase-deficient mice did not develop the metabolic syndrome as a result of sugar intake.

This study reveals a tissue-specific role for fructose metabolism in sugar-induced metabolic syndrome.

“Deletion of fructokinase in the liver does not reduce the appetite for sugar, unlike intestinal fructokinase knockout, and is enough to prevent metabolic syndrome induced by sugar,” summarized Lanaspá.

This research could inform the development of therapeutics that target fructokinase to treat hallmarks of the metabolic syndrome. Future work is needed to determine whether liver fructokinase activity can be leveraged to improve already existing metabolic dysfunction.

Anna Kriebs, Associate Editor,
Nature Communications

ORIGINAL ARTICLE Andres-Hernando, A. et al. Deletion of fructokinase in the liver or in the intestine reveals differential effects on sugar-induced metabolic dysfunction. *Cell Metab.* <https://doi.org/10.1016/j.cmet.2020.05.012> (2020)

BONE

Gene linked to adverse effects of osteoporosis drug

Osteoporosis is commonly treated with nitrogen-containing bisphosphonates (NBP), which target osteoclast function to inhibit bone resorption. However, these drugs are associated with serious adverse effects, including osteonecrosis of the jaw and atypical femoral fractures. A study in *Science Translational Medicine* has now identified a gene that is linked with these adverse effects.

“In this study, we identified a gene, *ATRAID*, that likely affects how well patients respond to bisphosphonates,” says author Lauren Surface. “We hope our study will provide a foundation for future genetic testing of patients prescribed these drugs.” The authors performed a cell-based genetic screen to find regulators of NBP action. The screen identified a poorly characterized gene, *ATRAID*, as well as other genes previously linked with bone disease

or NBP action, such as *SLC37A3*. In vitro experiments showed that *ATRAID* is required for the molecular responses of osteoclasts to NBPs.

Next, the authors generated *Atraid* knockout (*Atraid*-KO) mice and tested the effect of the NBP alendronate in post-menopausal or age-related models of osteoporosis. Compared with wild-type animals, the beneficial effects of alendronate were attenuated in *Atraid*-KO mice in both models of osteoporosis.

Finally, whole-exome sequencing was performed on two sets of patients who experienced adverse events after taking NBPs. This analysis revealed *ATRAID* as one of three genes containing rare nonsynonymous coding variants in these patients. Furthermore, two published gene expression datasets of patients who had taken NBPs were analysed, showing that *ATRAID*

OBESITY

Three more genes linked with childhood obesity

Although many genes have been identified that are associated with body weight regulation and obesity, much of the heritability of obesity (especially severe childhood obesity) is still unexplained. A new study published in *Cell Metabolism* starts to address this knowledge gap.

“We focused on a cohort of children with severe early-onset obesity (Genetics of Obesity Study (GOOS)) and in whom the most common causes of severe childhood obesity had already been ruled out,” explain corresponding authors Inês Barroso and Sadaf Farooqi. “We analysed data from whole-exome sequencing in these children and compared the results from those of a collection of healthy blood donors.” The study included samples from 2,737 cases and 6,704 controls. The analysis identified three genes (*PHIP*, *DGKI* and *ZMYM4*) that had a high number of rare variants in the

children with severe early-onset obesity and these variants were predicted to be deleterious to gene function.

PHIP variants have been found in children with learning difficulties, some of whom had overweight, so the researchers performed additional experiments to determine the role of *PHIP* in regulation of body weight. “Through experiments in cells we demonstrated that *PHIP* regulates transcription of pro-opiomelanocortin (*POMC*), and that the genetic variants we identified repressed *POMC* levels,” explain Barroso and Farooqi. “Given that *POMC* encodes a neuropeptide that suppresses appetite, this established a plausible link between *PHIP* variants and weight regulation.”

The researchers note that further work needs to be done to determine whether these genes are relevant to obesity across different populations, and to improve understanding of the mechanisms by