Sugar Substitutes, Gut Bacteria, and Glucose Intolerance

The consumption of artificial sweeteners results in glucose intolerance mediated by changes in the gut microbiota in both mice and humans, researchers report.

By Anna Azvolinsky | September 17, 2014

WIKIMEDIA, STEVE SNODGRASS

Non-caloric sweeteners can spur glucose intolerance in mice and some people, according to a study published today (September 17) in *Nature*. Researchers from the Weizmann Institute of Science in Israel and their colleagues have uncovered "the unexpected effect that artificial sweeteners drive changes in the [gut] microbiota, which promote glucose intolerance," said University of Chicago pathologist Cathryn Nagler, who studies how the microbiota regulate allergic responses to food and penned an editorial accompanying the study.

Immunologist Eran Elinav and computational biologist Eran Segal, both of the Weizmann Institute, identified changes in the composition and function of the mouse gut microbiome after the animals consumed artificial sweeteners—changes similar to those previously linked to obesity and diabetes in humans, the authors noted.

A previous study showed that sucralose can alter the rat gut microbiome—specifically, by decreasing beneficial bacteria—but this latest work pinpoints a microbe-mediated mechanism by which artificial sweeteners might influence glucose metabolism, said Yanina Pepino, who studies how non-caloric sweeteners influence glucose metabolism at the Washington University in St. Louis School of Medicine.

Elinav and Segal's team observed that mice given a 10 percent solution of one of three types of commonly consumed commercial artificial sweeteners—saccharin, sucralose, or aspartame—in place of regular drinking water had elevated blood-glucose levels after 11 weeks compared to mice given either a 10 percent glucose solution or water alone. The researchers used saccharin for subsequent experiments as this artificial sweetener showed the most pronounced effect on glucose levels in preliminary trials. Mice fed a high-fat diet plus the 10 percent saccharin solution showed the same effect on glucose metabolism as animals given an even higher saccharin dose—comparable to the US Food and Drug Administration's (FDA's) upper limit for safe human consumption.

Four weeks of treatment with gut bacteria-depleting antibiotics reversed the glucose intolerance in mice that continued to receive saccharin. This led the team to examine whether the microbiomes of the mice were somehow altering glucose metabolism. Transplantation of feces from non-antibiotic-treated mice

that consumed saccharin- or glucose-containing water into germ-free mice within six days induced the same blood-sugar elevations in animals that were never themselves exposed to the sweeteners.

"This is the elegant and home run experiment that shows causality in mice," said Nagler.

Using shotgun metagenomic sequencing on the fecal samples, the researchers showed that mice given saccharin or those that received a fecal transplant from saccharin-fed mice had a different microbiome composition compared to mice given sugar or no sweeteners.

The team also found similar glucose metabolism and gut microbiota changes in humans.

In a cohort of 381 non-diabetic volunteers who answered diet questionnaires, those who regularly consumed artificial sweeteners—particularly those who consumed the highest amounts—showed higher fasting glucose levels, poorer glucose tolerance, and different gut microbe profiles compared to those who did not consume such sweeteners. The difference between the two populations remained even after correcting for body mass index.

Further, the team exposed seven young, healthy volunteers who did not have a history of artificial sweetener consumption to one week of the FDA's maximum acceptable daily saccharin intake, and continuously monitored their glucose levels. Four of the seven volunteers showed a poorer glycemic response at the end of the week compared to their baseline responses. Those who showed no metabolic response to the sweetener had no change in their gut microbiomes, while those who exhibited the worst glycemic responses at the end of the week showed a different gut microbiota profile after sweetener exposure. Fecal transplants from two artificial sweetener-responder volunteers into germ-free mice resulted in a similar gut microbe profile and glucose intolerance as did transplants from saccharin-consuming mice. But the same transplants from two non-responder volunteers had no such effect in germ-free mice.

"The extensive work done with the microbiome [in this study] continues to point to the potential importance of our dietary habits on this previously underappreciated variable in our metabolism," Christopher Gardner, a professor of medicine at Stanford University who was not involved in the study wrote in an e-mail to *The Scientist*. Gardner was the former chair of the working group of the American Heart Association that generated a position statement on artificial sweeteners in 2012. He added that while the dose of artificial sweeteners used in this study is acceptable according to the FDA, this high dose—equivalent to 340 milligrams of saccharin (8.5 packets of Sweet N' Low) per day—is an unlikely dose for the typical artificial sweetener user.

Although the human data provide some evidence that artificial sweeteners may have a detrimental effect on glucose metabolism in a subset of people, the authors cautioned that additional studies are needed to understand who is susceptible to the potential negative effects of artificial sweeteners and to further elucidate the mechanism by which gut microbes may drive metabolic changes.

"I am very excited about these results because they demonstrate the need for more research," said Pepino. "There are many aspects of these sweeteners that we don't understand. Artificial sweeteners may have no calories but mounting evidence indicates that they do have metabolic consequences and may not be the solution for having a sweet taste without the calories."

J. Suez et al., "Artificial sweeteners induce glucose intolerance by altering the gut microbiota," *Nature*, doi:10.1038/nature13793, 2014.

Tags

sugar, microbiome, human research, gut microbiota, Glucose metabolism, blood glucose and artificial sweeteners

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SweetenerFacts
Posts: 1

September 17, 2014

In contrast to the assertions made by the researchers of this study, the overall evidence from studies on low-calorie sweeteners, including numerous human studies, show that these sweeteners are safe and do not have adverse effects on blood glucose control.

Investigators of more than 40 studies in people, including a recent meta-analysis of clinical trials and other available evidence, have concluded that the use of low-calorie sweeteners does not lead to either an increased risk of obesity or diabetes.

Leading health organizations, including the Academy of Nutrition and Dietetics (AND), the American Diabetes Association (ADA) and the American Heart Association (AHA), as well as numerous scientific studies agree that low-calorie sweeteners can be used as a safe tool to help manage calorie intake, which, in turn can be helpful for both weight management and diabetes management.

-Calorie Control Council

Sign in to Report

skrymsli
Posts: 1

September 17, 2014

@SweetenerFacts The fact that an organization funded by the low calorie food industry is out posting refutations to the findings (not assertions) of the researchers in this study is disturbing and does not strengthen your position.

If your product is causing harm to consumers, I'm sure what you meant to say is: "The Low Calorie food industry wants to commit 10 million dollars to studying the effects of our products on gut microbiota to ensure that we are not causing inadvertent harm to our customers."

Yes, I'm joking. I know you would never say something like that. But you should.

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John Salerno
Posts: 3

September 18, 2014

A 10% solution of sacharin? Or a 10% solution of sucralose? I'll start to believe this is a 'home run' finding when a significant effect shows up at any reasonable dose. A liter of diet soda might contain 100 mg of

sucralose or 150 mg of saccharin, equivalent to a .01% or .015% solution. To get to the FDA cutoff, 5 mg/kg body weight, the researchers gave their animals the equivalent dose for a typical human drinking liters of soft drinks a day. I'd avoid doing that just because of the expense. The study won't make me think twice about having a Coke Zero with a burger once in a while.

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Seth Crosby
Posts: 4

September 18, 2014

A 10% solution in lieu of drinking water. Rats consume ~10 ml H2O/100 gm body weight/day (http://vetmed.duhs.duke.edu/GuidelinesforRodentAnalgesia.html). That translates to 100mg/kg sweetner/day.

The FDA has set the ADI for saccharin, sucralose and aspartame at 15, 5, 50mg/kg, respectively. (http://www.fda.gov/Food/IngredientsPackagingLabeling/FoodAdditivesIngredients

I'm just saying is all.

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Elizabeth V H
Posts: 3

Replied to a comment from skrymsli made on September 17, 2014

September 18, 2014

I wonder if the Sugar Association watches these types of study?

Also, I'm pretty sure that the Sugar Association funded research over the decades to slam the low-calories sweeters.

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NutrFitPro
Posts: 1

September 18, 2014

What a joke!

First of all, you can't lump all artificial sweteners together. They're completely different chemicals.

So sad to see money and time devoted to looking at insignificant and questionable findings. Not a fan of saccharin or sucrolose, but aspartame is just a dipeptide that's a godsend for diabetics or anyone who wants to enjoy a sweet taste WITHOUT elevating blood sugar or insulin. Of course, any food/drink can be abused, including water! That's where all these ridiculous anecdotes come from...wackos who drink gallons of diet pop!

Focus on sugar..sugar..sugar..and refined carbs...the real culprit causing metabolic syndrome. I recall an encounter with someone eating a sugary pastry and drinking a coke, while I was drinking a dit 7-UP. That person said to me, " That's stuff's gonna kill you!" Really????????

Persepective people!!!!!!!

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