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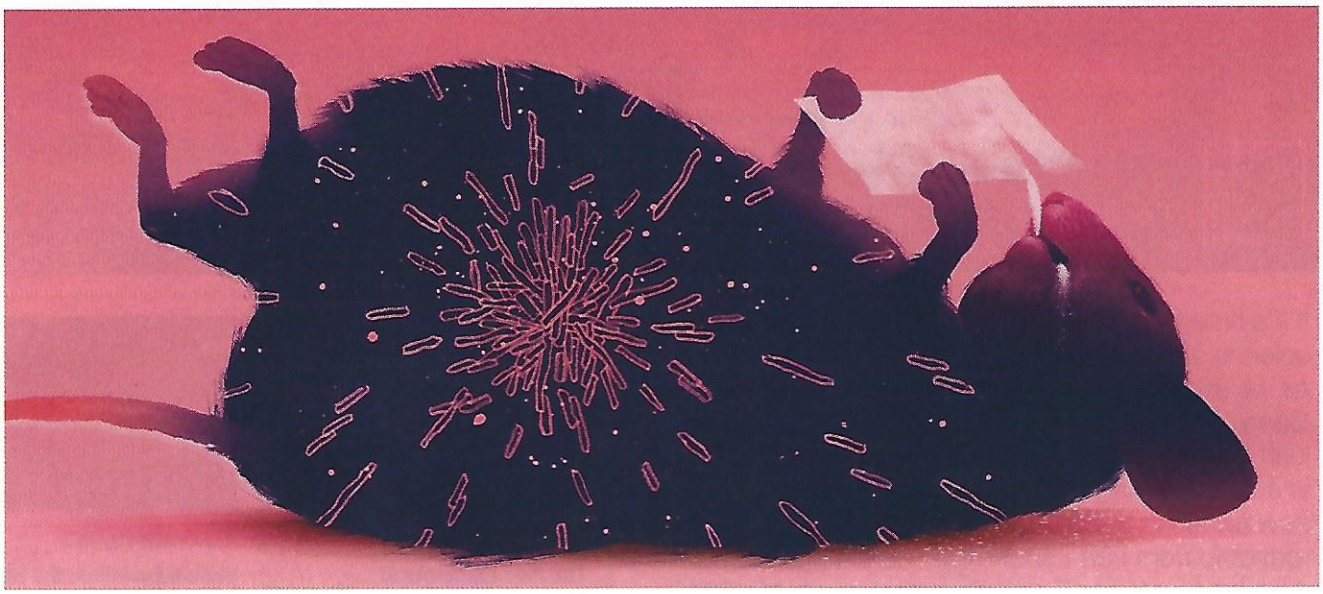

Artificial Sweeteners Get a Gut Check

The substances may change bacteria in our digestive systems in ways that lead to obesity

Many of us, particularly those who prefer to eat our cake and look like we have not done so, have a love-hate relationship with artificial sweeteners. These seemingly magical molecules deliver a dulcet taste without its customary caloric punch. We guzzle enormous quantities of these chemicals, mostly in the form of aspartame, sucralose and saccharin, which are used to enliven the flavor of everything from Diet Coke to toothpaste. Yet there are worries. Many suspect that all this sweetness comes at some hidden cost to our health, although science has only pointed at vague links to problems.

Last year, though, a team of Israeli scientists put together a stronger case. The researchers concluded from studies of mice that ingesting artificial sweeteners might lead to—of all things—obesity and related ailments such as diabetes. This study was not the first to note this link in animals, but it was the first to find evidence of a plausible cause: the sweeteners appear to change the population of intestinal bacteria that direct metabolism, the conversion of food to energy or stored fuel. And this result suggests the connection might also exist in humans.

In humans, as well as mice, the ability to digest and extract energy from our food is determined not only by our genes but also by the activity of the trillions of microbes that dwell within our digestive tract; collectively, these bacteria are known as the gut microbiome. The Israeli study suggests that artificial sweeteners enhance the populations of gut bacteria that are more efficient at pulling energy from our food and turning that energy into fat. In other words, artificial sweeteners may favor the growth of bacteria that make more calories available to us, calories that can then find their way to our hips, thighs and midriffs, says Peter Turnbaugh of the University of California, San Francisco, an expert on the interplay of bacteria and metabolism.

BACTERIAL GLUTTONS

IN THE ISRAELI EXPERIMENT, 10-week-old mice were fed a daily dose of aspartame, sucralose or saccharin. Another cluster of mice were given water laced with one of two natural sugars, glucose or sucrose. After 11 weeks, the mice receiving sugar were doing fine, whereas the mice fed artificial sweeteners had abnormally high blood sugar (glucose) levels, an indication that their tissues were having difficulty absorbing glucose from the blood. Left unchecked, this "glucose intolerance" can lead to a host of health problems, including diabetes and a heightened risk of liver and heart disease. But it is reversible: after the mice were treated with broad-spectrum antibiotics to kill all their gut bacteria, the microbial population eventually returned to its original makeup and balance, as did blood glucose control.

Illustration by Skip Sterling

"These bacteria are not agnostic to artificial sweeteners," says computational biologist Eran Segal of the Weizmann Institute of Science in Rehovot, Israel, one of the two scientists leading the study. The investigators also found that the microbial populations that thrived on artificial sweeteners were the very same ones shown—by other researchers—to be particularly abundant in the guts of genetically obese mice.

Jeffrey Gordon, a physician and biologist at Washington University in St. Louis, has done research showing that this relation between bacteria and obesity is more than a coincidence. Gordon notes that more than 90 percent of the bacterial species in the gut come from just two subgroups—Bacteroidetes and Firmicutes. Gordon and his team found several years ago that genetically obese mice (the animals lacked the ability to make leptin, a hormone that limits appetite) had 50 percent fewer Bacteroidetes bacteria and 50 percent more Firmicutes bacteria than normal mice did. When they transferred a sample of the Firmicutes bacterial population from the obese mice into normal-weight ones, the normal mice became fatter. The reason for this response, Gordon says, was twofold: Firmicutes bacteria transplanted from the fat mice produced more of the enzymes that helped the animals extract more energy from their food, and the bacteria also manipulated the genes of the normal mice in ways that triggered the storage of fat rather than its breakdown for energy.

Gordon believes something similar occurs in obese humans. He found that the proportion of Bacteroidetes to Firmicutes bacteria increases as fat people lose weight through either a low-fat or low-carbohydrate diet. Stanford University microbiologist David Relman says this finding suggests that the bacteria in the human gut may not only influence our ability to extract calories and store energy from our diet but also have an impact on the balance of hormones, such as leptin, that shape our very eating behavior, leading some of us to eat more than others in any given situation.

The burning question, of course, is whether artificial sweeteners can truly make humans sick and fat. Segal thinks they probably do, at least in some cases. He and his team analyzed a database of 381 men and women and found that those who used artificial sweeteners were more likely than others to be overweight. They were also more likely to have impaired glucose tolerance. Obesity is, in fact, well known as a risk factor for the development of glucose intolerance as well as more severe glucose-related ailments, such as diabetes.

These patterns do not prove that the sweeteners caused the problems. Indeed, it is quite possible that overweight people are simply more likely than others to consume artificial sweeteners. But Segal's team went further, testing the association directly in a small group of lean and healthy human volunteers who normally eschewed artificial sweeteners. After consuming the U.S. Food and Drug Administration's maximum dose of saccharin over a period of five days, four of the seven subjects showed a reduced glucose response in addition to an abrupt change in their gut microbes. The three volunteers whose glucose tolerance did not dip showed no change in their gut microbes.

Although not everyone seems susceptible to this effect, the findings do warrant more research, the scientists say. The Israeli group concluded in its paper that artificial sweeteners "may have directly contributed to enhancing the exact epidemic that they themselves were intended to fight"—that is, the sweeteners may be making at least some of us heavier and more ill.

A cause-and-effect chain from sweeteners to microbes to obesity could explain some puzzles about obese people, says New York University gastroenterologist Ilseung Cho, who researches the role of gut bacteria in human disorders. He points out that in studies, most people who switch from sugar to low-calorie sweeteners in an effort to lose weight fail to do so at the expected rate. "We've suspected for years that changes in gut bacteria may play some role in obesity," he says, although it has been hard to pinpoint this effect. But Cho adds that it is clear that "whatever your normal diet is can have a huge impact on the bacterial population of your gut, an impact that is hard to overestimate. We know that we don't see the weight-loss benefit one would expect from these nonnutritive sweeteners, and a shift in the balance of gut bacteria may well be the reason, especially a shift that results in a change in hormonal balances. A hormone is like a force multiplier—and if a change in our gut microbes has an impact on hormones that control eating, well, that would explain a lot."

MICROBES VS. GENES

NATURALLY THERE ARE MANY QUESTIONS left to answer. Cathryn Nagler, a pathologist at the University of Chicago and an expert on gut bacteria and food allergies, says that the enormous genetic variations in humans make extrapolations from mice suspect. "Still, I found the data very compelling," she says of the Israeli artificial sweetener study. Relman agrees that rodent studies are not always reflective of what happens in humans. "Animal studies can point to a general phenomenon, but animals in these studies tend to be genetically identical, while in humans, lifestyle histories and genetic differences can play a very powerful role," he says. The constellation of microbes in a human body is a reflection of that body's particular history—both genetic and environmental.

"The microbiome is a component intertwined in a complex puzzle," Relman continues. "And sometimes the genetics is so strong that it will override and drive back the microbiota." Genetic variations might explain why only four of the seven saccharin-fed humans had a change in their gut bacteria, for instance, although genetics is only one of a number of possible factors. And if someone is genetically predisposed to obesity and consumes a diet that promotes that obesity, the microbes might change to take advantage of that diet, thereby amplifying the effect.

The Israeli researchers agree that it is far too soon to conclude that artificial sweeteners cause metabolic disorders, but they and other scientists are convinced that at least one—saccharin—has a significant effect on the balance of microbes in the human gut. "The evidence is very compelling," Turnbaugh says. "Something is definitely going on." Segal, for one, is taking no chances: he says that he has switched from using artificial to natural sweetener in his morning coffee. SA

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