Artificial sweeteners linked to glucose intolerance

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Aspartame, saccharin and sucralose made mice glucose intolerant – a risk for diabetes – probably by altering their gut flora. Is it happening in humans too?

ARTIFICIAL sweeteners can cause glucose intolerance in mice, and perhaps in humans, by altering gut bacteria, a series of experiments suggests. Although artificial sweeteners – among the world's most widely used food additives – are approved by most food regulation agencies as safe for humans, the researchers who led the work suggest that their use should be reassessed.

"The most shocking result is that the use of sweeteners aimed at preventing diabetes might actually be contributing to and possibly driving the epidemic that it aims to prevent," says Eran Elinav at the Weizmann Institute of Science in Rehovot, Israel, who co-supervised the work with his colleague Eran Segal.

Industry bodies are adamant that this is not the case. "Decades of clinical research shows that low-calorie sweeteners have been found to aid weight-control when part of an overall healthy diet, and assist with diabetes management," says Gavin Partington of the British Soft Drinks Association.

Non-caloric artificial sweeteners are synthetic alternatives to sugar that can taste up to 20,000 times sweeter. They provide no calories because we cannot digest them. They are found in many common foods such as diet sodas, cereals and sugar-free desserts, and often form part of recommended diets for people with type 2 diabetes.

For decades, sweeteners have been subject to intense scrutiny, after some studies suggested they may be bad for our health. This has led to several reassessments of safety by regulatory agencies. However, the US Food and Drug Administration says that, currently, "all approved high-intensity sweeteners have been thoroughly studied and have a reasonable certainty of no harm to consumers under their approved conditions of use".

Nevertheless, Segal and Elinav were concerned that some studies have shown a link between the use of sweeteners and a tendency towards weight gain and diabetes. To probe for a causal link, their teams carried out a series of experiments. They began by adding one of three commonly used sweeteners – saccharin, sucralose or aspartame – to the drinking water of healthy young mice. The dose of sweetener was the equivalent to the maximum acceptable daily intake in humans, as set by the FDA. The mice drinking sweeteners – which are made up of 5 per cent active ingredient and the rest glucose – were compared with mice drinking plain water or water supplemented only with glucose.

After 11 weeks, the researchers tested all the rodents' glucose tolerance by giving them a high-glucose drink and taking regular blood samples. Under normal conditions, the blood tests should show an initial spike in glucose, followed by a decline as the body secretes the insulin in response. Insulin instructs cells to use the extra glucose for energy or turn it into fat. Glucose intolerance occurs when this process becomes inefficient, and is strongly associated with type 2 diabetes.

The blood-glucose levels of the mice consuming the sweeteners spiked at a higher level than all the control groups and also took longer to drop back down to normal. "They showed significant glucose intolerance," says Segal, "at levels comparable to a metabolic disease."

Segal says most artificial sweeteners pass through the gastrointestinal tract without being digested. This means that when they get to our intestine, they directly encounter our gut bacteria. Because what we eat can shift this bacterial make-up, the researchers wondered whether the glucose intolerance might be caused by a change in the bacterial composition.

A second test, with saccharin, confirmed this. Wiping out the rodents' gut bacteria using antibiotics abolished all the effects of glucose intolerance in the mice. In other words, no bacteria, no problem regulating glucose levels.

Further experiments supported this conclusion. For example, when the researchers transferred the gut bacteria of mice who had consumed saccharin into mice whose guts were bacteria-free, it caused these previously healthy mice to become glucose intolerant. Similar transplants from mice drinking glucose-enriched water had no negative effects on health.

So what was going on? When the team analysed the gut bacteria present before and after the experiments, they saw an increase in several different types of bacteria in the mice that consumed sweeteners. Segal says these bacteria have already been linked with obesity in humans in previous studies.

Human effect

But can the results in mice be extrapolated to humans? To find out, the team examined data from 381 people. They found an association between glucose intolerance and general sweetener use. "But you could argue that maybe these people first gained weight and started getting aspects of metabolic disease, such as glucose intolerance, and then started consuming the artificial sweeteners to counteract that," says Elinav.

To explore this, the team asked seven healthy people who don't normally consume sweeteners to eat the FDA's maximum daily allowance of saccharin. For a person weighing 68 kilograms, this would equate to three to four sachets of sweetener taken three times per day.

By day five, four of the seven people had a significant decrease in their glucose tolerance, while three saw no change. Sequencing showed that those who responded to the sweetener started out with different gut bacteria to those who didn't respond. What's more, the gut bacteria of the four responders changed significantly after consuming sweeteners, while the non-responders' barely changed.

To further show that bacterial changes were playing a role, the team took stools from two responders and two non-responders and transplanted them into sterile mice. Only the mice that received gut bacteria from responders became glucose intolerant (Nature, DOI: 10.1038/nature13793).

Segal says that the global rise in sweetener consumption – along with other major shifts in human nutrition – coincided with the dramatic increase in obesity and diabetes epidemics around the world. He also suggests that sweeteners may have directly contributed to the exact epidemic that they were created to fight.

Ailbhe Fallon, a representative for Ajinomoto Sweeteners Europe, one of the world's largest manufacturers of aspartame, rejects this conclusion. The body of science does not support the opinion of the authors, Fallon says.

The International Sweeteners Association (ISA) says it strongly refutes the claims made in the study: "There is a broad body of scientific evidence which clearly demonstrates that low-calorie sweeteners are not associated with an increased risk of obesity and diabetes as they do not have an effect on appetite, blood glucose levels or weight gain. As shown by numerous peer-reviewed studies, by providing sweetness without the calories, low-calorie sweeteners can help with weight management and can be enjoyed by people with diabetes."

"We are by no means thinking that based on this study we could deduce direct recommendations for artificial-sweetener consumption," says Elinav. "We want to be very cautious about that. But the fact that we could induce glucose intolerance at a level that corresponds to a metabolic disease in five days should at the very least be a call for government agencies to reassess the unsupervised use of artificial sweeteners."

Food for thought

A spokesperson for the European Food Safety Authority says that the agency will consider in due course whether the paper should be brought to the attention of its review panel of experts, as with all newly published studies related to its work. They point out that a panel of experts considered the issue of whether aspartame modulates blood sugar levels in humans in 2013 and concluded that the hypothesis would merit further investigation.

"This is a really important paper," says Susan Swithers at Purdue University, West Lafayette, Indiana. "It's always a concern to make a direct extrapolation to humans, but they provide a small amount of evidence that the same effect happens in humans, and then put the results back into animals – that was clever."

Naveed Sattar at the University of Glasgow, UK, is more cautious, saying that animal data does not always reflect what's going on in people. "Current epidemiological data in humans do not support a meaningful link between diet drinks and risk for diabetes, whereas sugar-rich beverages do appear to be associated with higher diabetes risk. These findings wouldn't make me choose sugary drinks over diet drinks."