



SCIENCE FOR THE BENEFIT OF HUMANITY

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GUT BACTERIA, ARTIFICIAL SWEETENERS, AND GLUCOSE INTOLERANCE

A new study reveals that certain gut bacteria may induce metabolic changes following exposure to artificial sweeteners

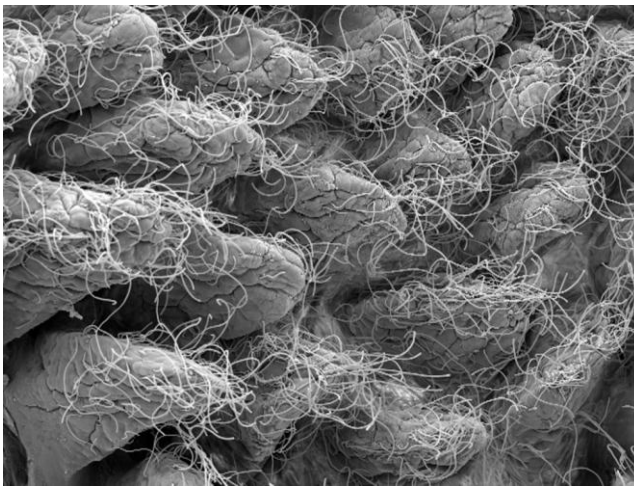
REHOVOT, ISRAEL—September 17, 2014—Artificial sweeteners – promoted as aids to weight loss and diabetes prevention – could actually hasten the development of glucose intolerance and metabolic disease, and they do so in a surprising way: by changing the composition and function of the gut microbiota – the substantial population of bacteria residing in our intestines. These findings, the results of experiments in mice and humans, were published September 17 in *Nature*. Dr. Eran Elinav of the Weizmann Institute of Science’s Department of Immunology, who led this research together with Prof. Eran Segal of the Department of Computer Science and Applied Mathematics, says that the widespread use of artificial sweeteners in drinks and food, among other things, may be contributing to the obesity and diabetes epidemic that is sweeping much of the world.

For years, researchers have been puzzling over the fact that non-caloric artificial sweeteners do not seem to assist in weight loss, with some studies suggesting that they may even have an opposite effect. Graduate student Jotham Suez in Dr. Elinav’s lab, who led the study, collaborated with lab member Gili Zilberman-Shapira and graduate students Tal Korem and David Zeevi in Prof. Segal’s lab to discover that artificial sweeteners, even though they do not contain sugar, nonetheless have a direct effect on the body’s ability to utilize glucose. Glucose intolerance – generally thought to occur when the body cannot cope with large amounts of sugar in the diet – is the first step on the path to metabolic syndrome and adult-onset diabetes.

The scientists gave mice water laced with the three most commonly used artificial sweeteners, in amounts equivalent to those permitted by the U.S. Food and Drug Administration (FDA). These mice developed glucose intolerance, as compared

to mice that drank water, or even sugar water. Repeating the experiment with different types of mice and different doses of the artificial sweeteners produced the same results – these substances were somehow inducing glucose intolerance.

Next, the researchers investigated a hypothesis that the gut microbiota are involved in this phenomenon. They thought the bacteria might do this by reacting to new substances like artificial sweeteners, which the body itself may not recognize as



Electron microscope image of a healthy mouse small intestine showing bacteria (strings) surrounding the gut villi (protrusions). A human small intestine looks very similar.

“food.” Indeed, artificial sweeteners are not absorbed in the gastrointestinal tract, but in passing through they encounter trillions of the bacteria in the gut microbiota.

The researchers treated mice with antibiotics to eradicate many of their gut bacteria; this resulted in a full reversal of the artificial sweeteners’ effects on glucose metabolism. Next, they

transferred the microbiota from mice that consumed artificial sweeteners to “germ-free,” or sterile, mice – resulting in a complete transmission of the glucose intolerance into the recipient mice. This, in itself, was conclusive proof that changes to the gut bacteria are directly responsible for the harmful effects to their host’s metabolism. The group even found that incubating the microbiota outside the body, together with artificial sweeteners, was sufficient to induce glucose intolerance in the sterile mice. A detailed characterization of the microbiota in these mice revealed profound changes to their bacterial populations, including new microbial functions that are known to infer a propensity to obesity, diabetes, and complications of these problems in both mice and humans.

Does the human microbiome function in the same way? Dr. Elinav and Prof. Segal had a means to test this as well. As a first step, they looked at data collected from their Personalized Nutrition Project (www.personalnutrition.org), the largest human trial to date to look at the connection between nutrition and microbiota. Here, they uncovered a significant association between self-reported consumption of artificial sweeteners, personal configurations of gut bacteria, and the propensity for glucose intolerance. They next conducted a controlled experiment, asking a group of volunteers who did not generally eat or drink artificially sweetened foods to consume them for a week, and then undergo tests of their glucose levels and gut microbiota compositions.

The findings showed that many – but not all – of the volunteers had begun to develop glucose intolerance after just one week of artificial sweetener consumption. The composition of their gut microbiota explained the difference: the researchers discovered two different populations of human gut bacteria – one that induced glucose intolerance when exposed to the sweeteners, and one that had no effect either way. Dr. Elinav believes that certain bacteria in the guts of those who developed glucose intolerance reacted to the chemical sweeteners by secreting substances that then provoked an inflammatory response similar to sugar overdose, promoting changes in the body's ability to utilize sugar.

Prof. Segal states, “The results of our experiments highlight the importance of personalized medicine and nutrition to our overall health. We believe that an integrated analysis of individualized ‘big data’ from our genome, microbiome, and dietary habits could transform our ability to understand how foods and nutritional supplements affect a person’s health and risk of disease.”

According to Dr. Elinav, “Our relationship with our own individual mix of gut bacteria is a huge factor in determining how the food we eat affects us. Especially intriguing is the link between use of artificial sweeteners – through the bacteria in our guts – to a tendency to develop the very disorders they were designed to prevent; this calls for reassessment of today’s massive, unsupervised consumption of these substances.”

Also participating in this research were Christoph A. Thaiss, Ori Maza, and Dr. Hagit Shapiro of Dr. Elinav's group; Dr. Adina Weinberger of Prof. Segal's group; Dr. Ilana Kolodkin-Gal of the Department of Molecular Genetics; Prof. Alon Harmelin and Dr. Yael Kuperman of the Department of Veterinary Resources; Dr. Shlomit Gilad of the Nancy and Stephen Grand Israel National Center for Personalized Medicine; Prof. Zamir Halperin and Dr. Niv Zmora of Tel Aviv Sourasky Medical Center and Tel Aviv University; and Dr. David Israeli of Kfar Shaul Hospital Jerusalem Center for Mental Health.

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