

New study shows therapeutic bacteria prevent obesity in mice

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Credit: Martha Sexton/public domain

A probiotic that prevents obesity could be on the horizon. Bacteria that produce a therapeutic compound in the gut inhibit weight gain, insulin resistance and other adverse effects of a high-fat diet in mice, Vanderbilt University investigators have discovered.

"Of course it's hard to speculate from mouse to human," said senior investigator Sean Davies, Ph.D., assistant professor of Pharmacology. "But essentially we've prevented most of the negative consequences of obesity in mice, even though they're eating a high-fat diet."

Regulatory issues must be addressed before moving to human studies, Davies said, but the findings published in the August issue of the *Journal of Clinical Investigation* suggest that it may be possible to manipulate the bacterial residents of the gut – the [gut microbiota](#) – to treat obesity and other chronic diseases.

Davies has a long-standing interest in using [probiotic bacteria](#) – "friendly" bacteria like those in yogurt – to deliver drugs to the gut in a sustained manner, in order to eliminate the daily drug regimens associated with chronic diseases.

In 2007, he received a National Institutes of Health Director's New Innovator Award to develop and test the idea.

"The NIH basically said, 'we like this idea, now make it work,'" Davies said. "The New Innovator Award was critical to our success."

Other studies have demonstrated that the natural gut microbiota plays a role in obesity, diabetes and cardiovascular disease.

"The types of bacteria you have in your gut influence your risk for [chronic diseases](#)," Davies said. "We wondered if we could manipulate the gut microbiota in a way that would promote health."

To start, the team needed a safe bacterial strain that colonizes the human gut. They selected *E. coli* Nissle 1917, which has been used as a probiotic treatment for diarrhea since its discovery nearly 100 years ago.

They genetically modified the *E. coli* Nissle strain to produce a lipid compound called NAPE, which is normally synthesized in the small intestine in response to feeding. NAPE is rapidly converted to NAE, a compound that reduces both food intake and weight gain. Some evidence suggests that NAPE production may be reduced in individuals eating a high-fat diet.

"NAPE seemed like a great compound to try – since it's something that the host normally produces," Davies said.

The investigators added the NAPE-producing bacteria to the drinking water of mice eating a high-fat diet for eight weeks. Mice that received the modified bacteria had dramatically lower food intake, body fat, [insulin resistance](#) and fatty liver compared to mice receiving control bacteria.

They found that these protective effects persisted for at least four weeks after the NAPE-producing bacteria were removed from the drinking water. And even 12 weeks after the modified bacteria were removed, the treated mice still had much lower body weight and body fat compared to the control mice. Active bacteria no longer persisted after about six weeks.

"We still haven't achieved our ultimate goal, which would be to do one treatment and then never have to administer the bacteria again," Davies said. "Six weeks is pretty long to have active bacteria, and the animals are still less obese 12 weeks out.

"This paper provides a proof of concept," he said. "Clearly, we can get enough bacteria to persist in the gut and have a sustained effect. We would like for that effect to last longer."

Davies noted that the researchers also observed effects of the

compounds in the liver, suggesting that it may be possible to use modified bacteria to deliver therapeutics beyond the [gut](#).

The investigators are currently working on strategies to address regulatory issues related to containing the bacteria, for example by knocking out genes required for the [bacteria](#) to live outside the treated host.

More information: *Journal of Clinical Investigation*,
www.jci.org/articles/view/72517

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