A small dose of E. coli wall has big impact on the sweet tooth

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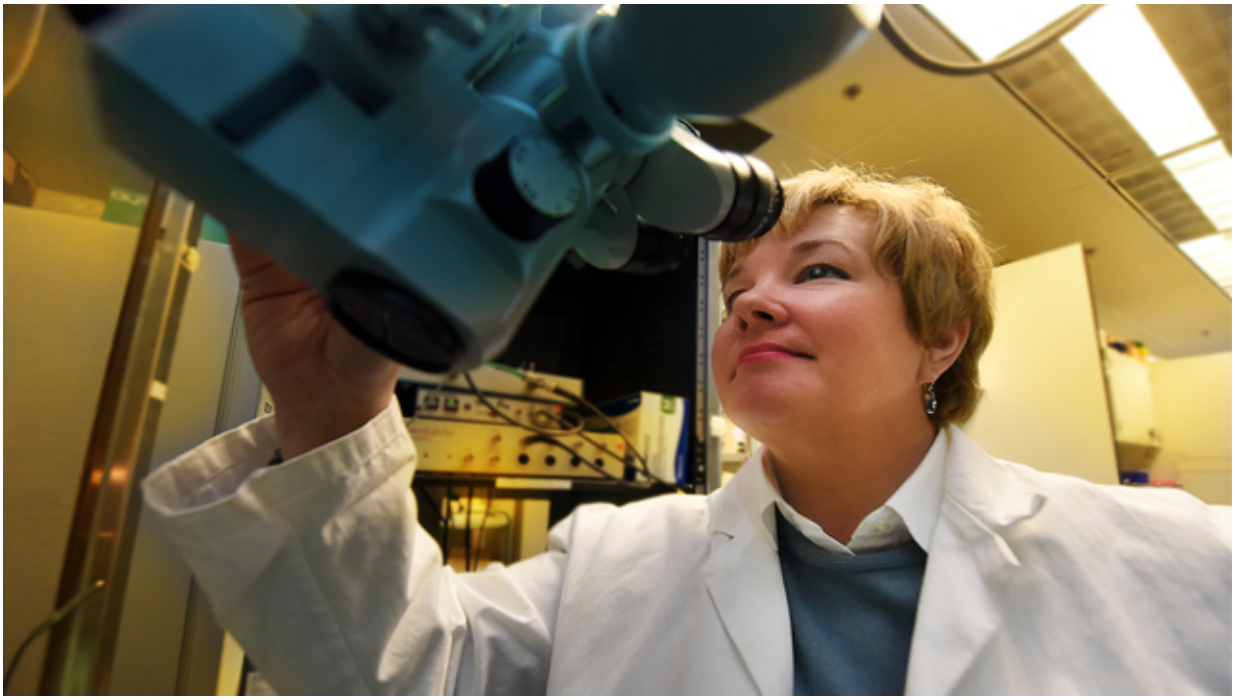

Dr. Lynnette McCluskey, neuroscientist in the Department of Neuroscience and Regenerative Medicine at the Medical College of Georgia at Augusta University. Credit: Phil Jones

Putting just a tiny piece of the wall of detoxified *E. coli* into their gut make mice lose their natural sweet tooth, researchers report.

Fifteen hours after one small dose is placed in the gut, levels of the

satiety hormone leptin go up, and within seven days, the taste for sweets and the number of sweet receptors on the tongue, go way down, said Dr. Lynnette McCluskey, neuroscientist in the Department of Neuroscience and Regenerative Medicine at the Medical College of Georgia at Augusta University.

Mice remain in good health with their taste for other foods, such as salty ones, intact, said McCluskey who presents the findings this week during the Association for Chemoreception Sciences Annual Meeting in Bonita Springs, Florida.

"In our field, we are starting to think about how hormones and different factors affect the taste system, even at the level of the taste buds, and contribute to obesity," she said. "Identifying the taste, whether it's sweet or not, is the first step in feeding. We wanted to know if you change the environment in the gut, what happens to the taste system."

She calls the new finding "a bit serendipitous" as well as proof of principle that just a slight change to the gut's extensive bacterial environment can change the feedback to taste and could one day help reduce unhealthy sweet consumption. "We found that it was surprisingly selective and surprisingly effective," McCluskey said.

Our sense of taste has evolved as a matter of efficiency, so that we can make split-second decisions about whether what we put in our mouths gives us energy or kills us, she said. While associating high-energy sweets with survival worked well at one time, it can mean just the opposite in today's much more sedentary environs where plenty of processed, calorie-laden treats are ready for consumption, McCluskey said.

A little bit of bacteria, may one day go a long way in fending off sweets just for the taste, the new study suggests. Although *E. coli* is often

associated with sickness, only a few strains make us sick, and it's a normal constituent of the billions of bacteria in the gut microbiota that enable us to digest food. But this appears to be the first time *E. coli*'s role in taste has been explored. More typically, a bit of the bacterial wall, called lipopolysaccharide, or LPS, of *E. coli* or some other gut inhabitant is used in vaccines to spur a more general, protective immune response. LPS taken from *E. coli*, minus the stomach-unsettling lipid portion, is a detoxified but potent agent already used in vaccines.

But in the confines of the gut, LPS appears to have a very different and specific effect, prompting more of a "gut-to-tongue" reaction as the additional bacterium somehow triggers higher levels of the hormone leptin, which is known to reduce the taste for sweets, McCluskey said.

While taste cells talking to the gut may seem logical, how the gut signals back is a currently hot - and sometimes controversial - scientific topic that has researchers such as McCluskey looking at hormones, like leptin, which also have a normal home in the gut. Leptin, made by fat cells, also is found in the brain, and recent work has shown it makes its way in the blood to the taste buds where it binds with receptors and dampens the typically positive response to sweets. In fact, in studies of leptin knockouts, even without changing the bacteria balance, other researchers have noted sweet-taste suppression, which is what got McCluskey also looking at leptin in her efforts to connect these two pieces of the taste puzzle.

"We began to think it's triggered by something in the gut and it's feeding back to taste, and what do we know that dampens sweet taste specifically?" she said. Similar to other previous work in leptin knockouts, when she gave a drug to block the leptin receptor in mice, their sweet tooth remained intact - in fact somewhat elevated - when she also gave LPS.

LPS works through Toll-like receptor 4, or TLR 4, present on the surface of many cells, including taste and gut cells as well as immune cells like macrophages, to induce inflammation, which is part of how bacteria make us sick and what ultimately also makes vaccines work. In the tongue, others have shown that LPS signals through TLR 4 to inhibit the proliferation of taste cells.

While directly exposing taste buds on the tongue to LPS didn't seem to have an effect on taste, ingesting LPS did impact the neural response, the researchers found. In the bacterial-laden gut, scientists think LPS also activates TLR 4, which downregulates sweet taste receptor genes in the taste buds. In fact, mice lacking TLR 4 didn't lose their sweet tooth after consuming LPS.

Many unanswered questions remain in this conversation between gut and taste cells, including whether LPS directly acts on leptin and identifying the source of increased leptin levels that occur, not just in the gut, but the blood. "There may be other gut hormones involved as well, but we know that leptin works," McCluskey said. The scientists also want to know more about why the effect on sweet taste takes seven days and why the effect also seems to go away seven days later. They expected any response to be immediate and longer acting, McCluskey said. They also want to give a little LPS daily - as people might take it one day - to measure the response and rebound. She also wants to selectively block TLR 4 in the gut, to double check its role.

Collaborators for the new study include Dr. David Pittman, neuroscientist and coordinator of the Program in Neuroscience, at Wofford College, whose research focus is neural signals sent from the mouth to the brain that affect human and animal feeding behavior.

McCluskey was corresponding author of a 2014 study in the journal *Neuroscience* indicating a very similar response when mice drank LPS

mixed with sucrose overnight. For the newer studies, they gave the mice a more clinically relevant LPS directly into their stomachs with a feeding tube to better control how much they took in.

Researchers from Tokyo Medical and Dental University reported in *Proceedings of the National Academy of Sciences* in 2000 that taste buds were a target for leptin and that the satiety hormone suppressed their response to sugar but not to salty, bitter or sour substances. Some subsequent studies have conflicted with these findings.

Science continues to reveal how the balance is different in the billions of gut microbiota populating obese versus leaner individuals. It's also shown that an individual's population changes over his/her lifespan, likely because of what his/her is exposed to in the environment and diet. "They play a big role in obesity, inflammatory bowel disease and now people are even looking at how they affect the brain for psychiatric disorders like depression," McCluskey said.

Provided by Medical College of Georgia at Augusta University