Obesity treatment could offer dramatic weight loss without surgery or nausea

March 29 2023

Credit: Pixabay/CC0 Public Domain

Imagine getting the benefits of gastric bypass surgery without going under the knife—a new class of compounds could do just that. In lab animals, these potential treatments reduce weight dramatically and lower blood glucose. The injectable compounds also avoid the side effects of nausea and vomiting that are common with current weight-loss and diabetes drugs. Now, scientists report that the new treatment not only

reduces eating but also boosts calorie burn.

The researchers will present their results today at the spring meeting of the American Chemical Society (ACS). ACS Spring 2023 is a hybrid meeting being held virtually and in-person March 26–30.

"Obesity and diabetes were the pandemic before the COVID-19 pandemic," says Robert Doyle, Ph.D., one of the two principal investigators on the project, along with Christian Roth, M.D. "They are a massive problem, and they are projected to only get worse."

Gastric bypass and related procedures, known collectively as bariatric surgery, offer one solution, often resulting in lasting weight loss and even remission of diabetes. But these operations carry risk, aren't suitable for everyone and aren't accessible for many of the hundreds of millions of people worldwide who are obese or diabetic. As an alternative, Doyle says, they could tackle their metabolic problems with a drug that replicates the long-term benefits of surgery.

Those benefits are linked to a post-bypass-surgery change in the gut's secretion levels of certain hormones—including glucagon-like peptide-1 (GLP-1) and peptide YY (PYY)—that signal fullness, curb appetite and normalize blood sugar. Current drugs that aim to replicate this effect primarily activate cellular receptors for GLP-1 in the pancreas and brain. That approach has shown great success in reducing weight and treating type 2 diabetes, drawing a lot of social media postings from celebrities in recent months. But many people can't tolerate the drugs' side effects, says Doyle. "Within a year, 80 to 90% of people who start on these drugs are no longer taking them." Doyle is at Syracuse University and SUNY Upstate Medical University, and Roth is at Seattle Children's Research Institute.

To address that drawback, various researchers have designed other

treatments that interact with more than one type of gut hormone receptor. For example, Doyle's group created a peptide that activates two receptors for PYY, as well as the receptor for GLP-1. Dubbed GEP44, this compound caused obese rats to eat up to 80% less than they would typically eat. By the end of one 16-day study, they lost an average of 12% of their weight. That was more than three times the amount lost by rats treated with liraglutide, an injected drug that activates only the GLP-1 receptor and that is approved by the U.S. Food and Drug Administration for treating obesity. In contrast to liraglutide, tests with GEP44 in rats and shrews (a mammal that, unlike rats, is capable of vomiting) revealed no sign of nausea or vomiting, possibly because activating multiple receptors may cancel out the intracellular signaling pathway that drives those symptoms, Doyle says.

In its latest results, his team is now reporting that the weight loss caused by GEP44 can be traced not only to decreased eating, but also to higher energy expenditure, which can take the form of increased movement, heart rate or body temperature.

GEP44 has a half-life in the body of only about an hour, but Doyle's group has just designed a peptide with a much longer half-life. That means it could be injected only once or twice a week instead of multiple times a day. The researchers are now reporting that rats treated with this next-generation compound keep their new, slimmer physique even after treatment ends, which often isn't the case with currently approved drugs, Doyle says.

But weight loss isn't the only benefit of the peptide treatments. They also reduce blood sugar by pulling glucose into muscle tissue, where it can be used as fuel, and by converting certain cells in the pancreas into insulin-producing cells, helping replace those that are damaged by diabetes. And there's yet another benefit: Doyle and Heath Schmidt, Ph.D., of the University of Pennsylvania, recently reported that GEP44 reduces the

craving for opioids such as fentanyl in rats. If that also works in humans, Doyle says, it could help addicts quit the illicit drugs or fend off a relapse.

The researchers have filed for patents on their compounds, and they plan to test their peptides in primates. They will also study how the treatments change gene expression and rewire the brain, and what that could mean for these compounds, as well as other types of medication.

"For a long time, we didn't think you could separate weight reduction from nausea and vomiting, because they're linked to the exact same part of the brain," Doyle says. But the researchers have now uncoupled those two pathways—and that has implications for chemotherapy, which causes similar side effects. "What if we could maintain the benefit of chemotherapy drugs but tell the part of the brain that causes vomiting and nausea to knock it off? Then we could dose patients at a higher level, so they would have a better prognosis, and they would also have a better quality of life while undergoing chemotherapy," he says.

More information: ACS Spring 2023: Peptide triagonists of the GLP-1-, neuropeptide Y1- and neuropeptide Y2- receptors for glycemic control and weight loss, www.acs.org/meetings/acs-meetings/spring-2023.html

Provided by American Chemical Society

Citation: Obesity treatment could offer dramatic weight loss without surgery or nausea (2023, March 29) retrieved 21 November 2023 from https://medicalxpress.com/news/2023-03-obesity-treatment-weight-loss-surgery.html