

# Orally administered liquid salt helps prevent fat absorption and slow down weight gain in rats

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Obesity, which affects more than one-third of American adults, is more than just an uncomfortable excess of weight—it is a driver of several,

often fatal diseases like high blood pressure, diabetes, asthma, stroke, and congestive health failure, making it one of the most significant public health threats. The cost of treating and managing obesity-related diseases is expected to double every decade, ballooning to account for about 16% of all US healthcare costs by 2030.

While genetics plays a role, eating [high-calorie foods](#) rich in carbohydrates and fats is a major cause of this epidemic, and though doctors and nutritionists recommend a healthy, balanced diet as a prevention strategy, many people simply lack affordable access to fresh foods. Several weight-loss drugs that reduce weight by about 10% have been approved by the FDA over the last few decades, but they come with significant side effects including headaches, diarrhea, severe liver injury, birth defects, sleep apnea, pancreatitis, and suicidal thoughts.

Now, a new study from Harvard's Wyss Institute for Biologically Inspired Engineering and John A. Paulson School for Engineering and Applied Sciences (SEAS) has found that an orally administered [liquid salt](#) called Choline and Geranate (CAGE) can physically reduce the absorption of fats from food with no discernable side effects in rats, and reduces total body weight by about 12%. The research is reported in *PNAS*.

"A reduction in body weight of 12% is like getting a human from 200 pounds down to 176, which is a significant change," said first author Md Nurunnabi, Ph.D., a former Postdoctoral Fellow at the Wyss Institute and SEAS who is now an Assistant Professor of Pharmaceutical Sciences at The University of Texas at El Paso. "Our goal is to translate this work into a product that can help people maintain a healthier weight, and this study marks the very beginning of that journey."

## **Turning a bug into a feature**

CAGE, which is a salt in its liquid state, was created a few years ago by Wyss Core Faculty member Samir Mitragotri, Ph.D. as part of an effort to improve the body's absorption of medicines. Last year, his lab published a paper describing CAGE's ability to enhance the uptake of insulin when given orally. However, in their study of CAGE's properties, they found that there was one molecule that was not helped by the liquid: a small hydrophobic molecule. Mitragotri's team had a hunch that CAGE was somehow binding to this molecule and preventing it from being absorbed.

"That observation led us to wonder if there were any contexts in which we would want to prevent the uptake of this type of molecule. We realized that fats are small and hydrophobic, and that CAGE could potentially be of interest as a [medical treatment](#) for obesity," said Mitragotri, who is also the Hiller Professor of Bioengineering and Hansjörg Wyss Professor of Biologically Inspired Engineering at SEAS.

The researchers got to work evaluating CAGE's interactions with fats by mixing the liquid with an omega-3 fat called DHA and water. They saw that the DHA formed large particles about 3-4 microns in length, about the size of a cell's nucleus. DHA molecules mixed with water alone formed much smaller particles in the range of 50-400 nanometers, suggesting that there is some interaction between the CAGE and DHA molecules that causes them to aggregate into larger particles.

The team then added the DHA-CAGE mixture to healthy rat intestines *ex vivo*. Compared to intestines that were only injected with DHA, the inclusion of CAGE significantly reduced the permeation of DHA into the intestinal tissue over the course of six hours.

## **Helping rats resist obesity**

To evaluate the performance of CAGE in living organisms, the

researchers prepared capsules with a mixture of DHA and CAGE and gave them orally to rats. After six hours, the amount of DHA absorbed into their blood from the mixture was about half the amount that was absorbed when they were given DHA alone. Biodistribution studies showed that giving CAGE along with the DHA increased its concentration in the rats' stomachs and intestines two-fold and reduced its presence in their livers, suggesting that CAGE prevents DHA from leaving the gastrointestinal tract.

They then studied the effect of CAGE on fat uptake in rats who were fed a high-fat diet, which has 20% more fat than a regular diet, for 30 days. A daily, 10-microliter dose of CAGE caused rats to gain 12% less weight than rats that received either a 5-microliter dose or no CAGE. The untreated rats usually ate about 10 grams of food every day, whereas the high-dose CAGE cohort ate about 8 grams of food, suggesting that CAGE might also have an effect on enzymes that regulate digestion, and/or increase the feeling of fullness after a meal.

Importantly, over the 30-day time period, no side effects were observed in the rats treated with CAGE, and there were no signs of inflammation or differences in the animals' organ structure or function. There was also no trace of CAGE's components in the body following treatment.

Pull quote: "Our goal is to translate this work into a product that can help people maintain a healthier weight, and this study marks the very beginning of that journey."—Md Nurunnabi

"This is the first proof-of-concept that orally administered ionic liquids can help reduce fat uptake and body mass, and this approach has significant clinical potential given that it is simple, fast, and much less invasive than liposuction or bariatric surgery and, because its mechanism of action is physical rather than chemical, it lacks the side effects observed with other drugs," said Mitragotri.

The team is now pursuing answers to the more mechanistic questions about CAGE, including exactly how CAGE binds to fats, how long its effects last, what its potential interactions with the obesity-associated leptin signaling pathway are, and where the unabsorbed fat goes.

"This study is a perfect example of the potentially transformative innovations that can come from looking at an unexpected result in the lab as a solution rather than a problem. We love simple solutions here at the Wyss Institute," said Wyss Founding Director Donald Ingber, M.D., Ph.D., who is also the Judah Folkman Professor of Vascular Biology at Harvard Medical School and the Vascular Biology Program at Boston Children's Hospital, as well as Professor of Bioengineering at SEAS.

**More information:** Md Nurunnabi et al., "Oral ionic liquid for the treatment of diet-induced obesity," *PNAS* (2019).

[www.pnas.org/cgi/doi/10.1073/pnas.1914426116](http://www.pnas.org/cgi/doi/10.1073/pnas.1914426116)

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