Study: Gut hormones' regulation of fat production abnormal in obesity, fatty liver disease

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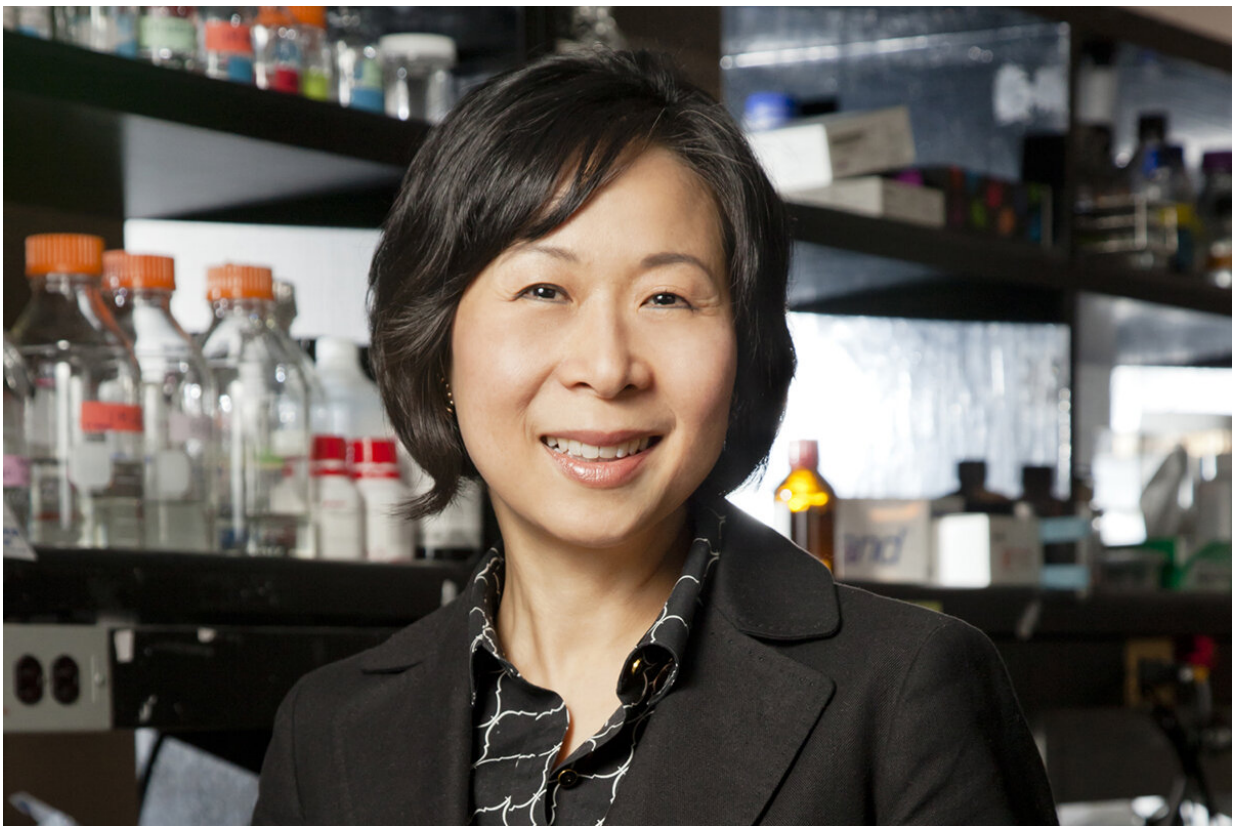

The gut releases hormones hours after eating that prompt the liver to stop storing fat, but the process is dysregulated in obesity and fatty liver disease, a study led by Illinois professor Jongsook Kim Kemper found. Credit: L. Brian Stauffer

Gut hormones play an important role in regulating fat production in the body. One key hormone, released a few hours after eating, turns off fat production by regulating gene expression in the liver, but this regulation is abnormal in obesity, researchers at the University of Illinois Urbana-Champaign found in a new study.

The study, led by molecular and integrative physiology professor Jongsook Kim Kemper and research scientist Young-Chae Kim, was published in the journal *Nature Communications*.

After eating, the pancreas produces insulin, which triggers the liver to convert digested foods into fat for storage in a process known as lipogenesis. A few hours later, when the body begins the transition to fasting mode, the liver slows fat production. While the insulin pathway has been thoroughly studied, the pathway by which lipogenesis is turned off has largely remained unknown, Kemper said.

In the new study, Kemper's team found that the gut hormone FGF15 in mice and its human counterpart FGF19 turn off fat-producing genes in the liver. The hormones are released a few hours after eating, when the body transitions from feeding to fasting. FGF15/19 activate regulatory molecules to enter the nucleus, the center of the cell where DNA is stored, and inhibit gene expression.

"This gut hormone actually acts as a breaker of insulin action, and specifically inhibits lipogenesis in the liver so that it's tightly regulated," Kemper said. "For example, with the holidays coming up, if you eat some cookies, the body will release insulin, which promotes lipogenesis. If lipogenesis is not reduced later when the body enters the fasting state, excess fat will accumulate in the liver, so the FGF19 hormone puts the brakes on fat production."

Furthermore, in experiments involving mice with obesity and human

patients with nonalcoholic fatty liver disease, the researchers found that the pathway for turning off fat production was dysregulated. The genes that the gut hormone regulates were highly active, the FGF15/19-activated regulatory molecules did not even enter the cell's nucleus and the suppression markers were not added to the genes.

"This study could be very important for understanding this pathway and investigating how it is abnormal in obesity and nonalcoholic fatty liver disease," Kemper said. "It adds to our understanding of obesity, nonalcoholic fatty liver disease and other metabolic disorders. It also could have implications for other diseases such as diabetes or certain cancers, for which obesity is a risk factor.

"Based on this study, we potentially could search for therapeutic treatment options to target this pathway and increase regulatory function."

More information: Young-Chae Kim et al, Intestinal FGF15/19 physiologically repress hepatic lipogenesis in the late fed-state by activating SHP and DNMT3A, *Nature Communications* (2020). DOI: 10.1038/s41467-020-19803-9

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