Researchers discover new pathway for improving metabolic health

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Blocking the action of an enzyme involved in protein digestion may improve metabolic health, according to a new study published ahead of print in the *American Journal of Physiology—Gastrointestinal and Liver Physiology*. The paper was chosen as an APS*select* article for May.

Trypsin—an enzyme that bonds to proteins—is the primary enzyme responsible for digesting protein in the digestive tract. Drugs (called serine protease inhibitors) that prevent enzymes such as trypsin from working have been found to reduce weight gain, high blood sugar and high cholesterol in rats. However, the process in which serine protease inhibitors improve metabolic health is not well understood.

Researchers from Janssen R&D in Pennsylvania looked at the effects of varied dosages of camostat, a serine protease inhibitor used to treat pancreatitis in Japan, on overweight mice. They found that one week of drug treatment reduced the amount of food the animals ate and led to weight loss. In addition, blood sugar levels and liver function improved when compared to animals that were simply given the same reduced amount of food. This suggested that in addition to caloric restriction, other factors contributed to the metabolic improvements. Bloodwork performed before and after the experiment showed that the mice had higher levels of the hormone fibroblast growth factor 21 (FGF21) during treatment. FGF21 is a hormone that suppresses appetite and manages metabolism, weight loss and glucose levels. In previous studies, FGF21 rapidly increased in mice that followed a protein-restricted diet.

The research team also found that drug treatment activated a signaling pathway called the integrated stress response (ISR), which in turn caused FGF21 levels to rise. ISR can be triggered by a number of physiological stresses, including amino acid or protein deprivation. In this study, however, the dietary protein fed to mice was not restricted, but camostat tricked their bodies into thinking it was, which activated the ISR.

This finding is important because it sheds light on a new mechanism that links ISR and FGF21 in response to trypsin inhibition, the researchers explained. "Trypsin inhibition could be a way to enhance [FGF21 production], resulting in beneficial effects," they wrote.

More information: Kamal Albarazanji et al, Intestinal serine protease inhibition increases FGF21 and improves metabolism in obese mice, *American Journal of Physiology-Gastrointestinal and Liver Physiology* (2019). DOI: 10.1152/ajpgi.00404.2018

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