Researchers determine hormone linked to improved glucose metabolism activates browning of fat

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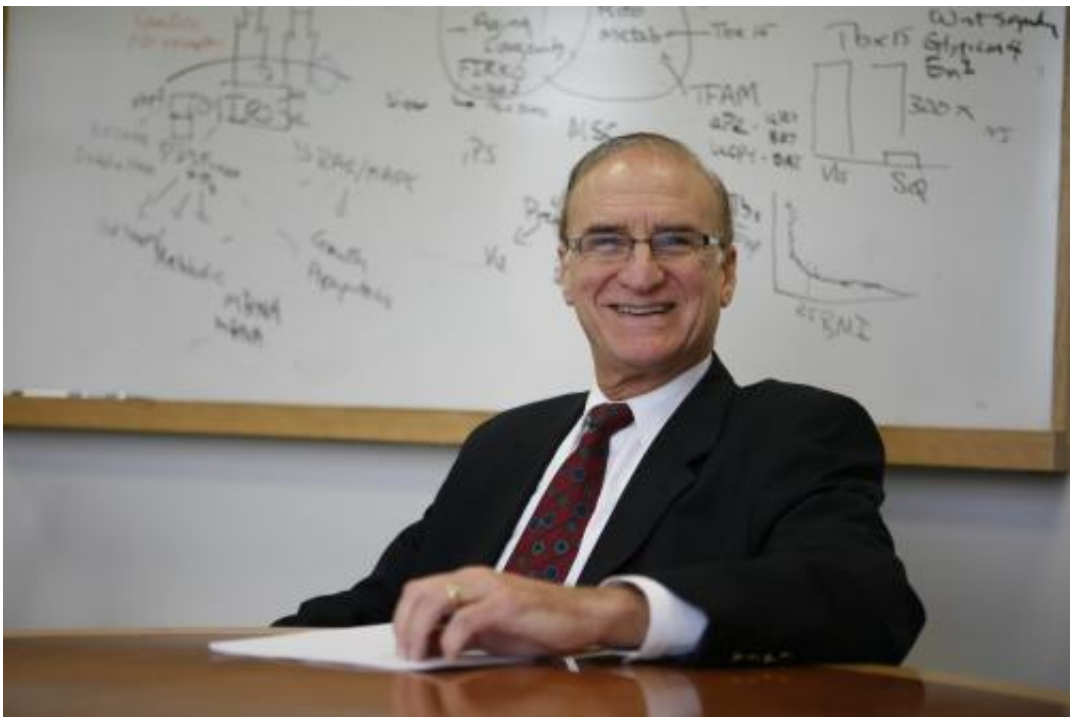

C. Ronald Kahn, M.D., is Chief Academic Officer at Joslin Diabetes Center. Dr. Kahn is co-head of the section on Integrative Physiology & Metabolism and the Mary K. Iacocca Professor of Medicine at Harvard Medical School. Credit: John Soares

Researchers at Joslin Diabetes Center have discovered that a hormone long associated with weight loss and improved glucose metabolism is

linked to activation of calorie-burning brown fat. This finding could have implications for production of new medications for type 2 diabetes and obesity. The results are published in the January issue of the *Journal of Clinical Investigation* in a paper titled "Interplay between FGF21 and Insulin Action in the Liver for the Regulation of Metabolism."

For the past decade, FGF21 has been known to play a role in metabolic regulation. Its mechanism of action, however, remained unidentified.

"So what we were interested in learning is how does FGF21 stimulate both weight loss and improve glucose metabolism," said C. Ronald Kahn, M.D., Chief Academic Officer at Joslin Diabetes Center, Mary K. Iacocca Professor of Medicine at Harvard Medical School, and the corresponding author on the paper. "And this study shows that one big factor in this is the ability of FGF21 to stimulate what's called browning of white fat, that is where the white fat becomes more energetically active and begins to burn energy rather than store energy."

Brown fat, shown to exist in humans in 2009 by researchers at Joslin, burns calories to produce heat. White fat can act in a similar manner when stimulated, a process known as "browning." Determining stimulation mechanisms can provide researchers with a first step towards using brown fat as a treatment for obesity and type 2 diabetes.

FGF21 is secreted from the liver, prompting the researchers to question if its metabolic-related activity depended on molecular interactions within the liver tissues. They tested this using insulin resistant animal models created through two different methods—in one model, they created obesity-induced insulin resistance through a high fat diet; in the other, they knocked out the insulin signaling in liver tissues.

They then introduced FGF21 to the system continuously for two weeks via an inserted pump. During that time, they monitored weight, blood

glucose levels, and lipid levels. After the two weeks ended, they harvested liver tissues to analyze their makeup.

"What we found was that even without insulin signaling in the liver, FGF21 could still improve glucose metabolism," said Dr. Kahn. To determine that the improvements were due to the browning of white fat, rather than the activation of brown fat, they surgically removed the pads of brown fat found in the animals, so that any fat-based energy burning would surely have to be a result of white fat browning.

"So in those animals, where most of the brown fat is removed, FGF 21 still works on the remaining white fat because of browning," he said.

FGF21 also regulates lipid metabolism, and that function was determined to be dependent on functioning insulin signaling in the liver.

Proving that FGF21 activates the browning of white fat is a large step forward in understanding the process of how variations of brown fat assist in metabolic regulation. Identifying this hormone as a major player in this activation has implications for the eventual creation of a brown fat stimulating drug.

"As with any new drug or hormone, of course we need to learn not only its good effects, but also any potential side effects," said Dr. Kahn. "And I think that's where a lot of the effort is now…by pharmaceutical companies."

Drug creation aside, Dr. Kahn thinks this discovery is interesting from a basic biology point of view.

"FGF 21 wasn't even known to exist until 10 years ago, and now we know it is a new circulating hormone, that is regulated in feeding and fasting," he said. "And I think that this is another piece of evidence that

we don't understand all there is to know yet about metabolic regulation even though people have been studying it for literally hundreds of years."

Provided by Joslin Diabetes Center