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Hormone Ignites the Body's Fat-Burning Furnace

Researchers have identified a master hormone that allows the body to fuel itself with stored fat during times of fasting. The hormone mobilizes lipids from fat cells, and then directs the liver to transform those lipids into energy-rich molecules that circulate throughout the body.

The researchers said their findings reveal a more complete picture of the far-reaching role of the hormone, fibroblast growth factor 21 (FGF21), which is already in development as a treatment for type 2 diabetes. In addition to switching the body to a fat-burning mode, the team found FGF21 induces the hibernation-like state of torpor that conserves energy in fasting animals.

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— David J. Mangelsdorf

FGF21's unexpectedly broad role in fat-burning was reported in two papers published in the June, 2007, issue of the journal *Cell Metabolism*. One paper was from the laboratory of Steven Kliewer and Howard Hughes Medical Institute investigator David Mangelsdorf at the University of Texas Southwestern Medical Center. Coauthors on the paper are Kliewer and Mangelsdorf's colleagues at UT Southwestern and scientists from Van Andel Research Institute and New York University School of Medicine. The other *Cell Metabolism* paper was by Eleftheria Maratos-Flier of Harvard University and colleagues.

The Kliewer-Mangelsdorf group wanted to find out how a protein called peroxisome proliferator-activated receptor α (PPAR α) regulates the fasting response. Other researchers had found that PPAR α switches on genes central to this response, but the identity of those genes was not known, said Kliewer. Although no link had yet been found between PPAR α and FGF21, Kliewer

and Mangelsdorf suspected the hormone might be involved because of its extraordinarily wide range of action in the body.

FGF21 seems to have these almost magical properties, said Kliewer. It improves insulin sensitivity, making insulin in the body work more efficiently. It lowers lipid levels, triglyceride levels, and cholesterol levels, and induces weight loss. So, FGF21 was at the top of our list of hormones that might be regulated by PPAR α . FGF21's insulin-sensitizing properties have led Eli Lilly & Co. to explore developing the hormone as a diabetes treatment, Kliewer noted.

In experiments with mice, the researchers showed that during fasting, PPAR α directs the liver to produce FGF21. The hormone then stimulates the breakdown of stored fat into triglycerides that can travel to the liver. In the liver, FGF21 triggers the transformation of those triglycerides into energy-rich ketone bodies.

These experiments told us that FGF21 works on several levels, said Kliewer. It works in the white adipose tissue signaling the body to send fats to the liver. And at the same time it causes the liver to metabolize fatty acids. The most unexpected aspect of this study, however, is that FGF21 sends signals from the liver to the adipose tissue. While molecules such as leptin are well known signals from the adipose tissue to the liver, FGF21 is the first I am aware of that signals the other way.

The finding that members of the FGF family function as hormones and are targets of nuclear receptors opens up an entirely new and virtually unexplored area of endocrinology, Mangelsdorf added.

FGF21 also induces a behavioral response to fasting called torpor, the researchers found. Mice engineered to have high levels of FGF21 showed dramatically reduced body temperature and activity, key characteristics of torpor.

It was a big surprise that many of the body's responses to fasting and starvation can be mimicked simply by administering FGF21 by itself, Mangelsdorf said. This opens up the intriguing possibility of using FGF21 as a drug to drive energy expenditure. Since PPAR α is a target of cholesterol- and lipid-lowering drugs called fibrates, FGF21 may mimic some of those drugs' positive effects.

Kliewer, Mangelsdorf, and their colleagues plan to further explore the receptors that FGF21 activates in various tissues in the body and how they produce its diverse physiological effects.

One area we are keen on exploring is the other actions that FGF21 may have on the body, Mangelsdorf said. Since it circulates as a hormone, and its receptors are found in other tissues, it stands to reason that FGF21 may have other actions. We would also like to show that this system is conserved in humans by monitoring FGF21 levels during fasting or starvation.

In the accompanying *Cell Metabolism* paper, Maratos-Flier and colleagues report on their discovery of FGF21's role through a complementary experimental approach. They fed mice a diet high in fat and low in carbohydrates and found that the diet triggered production of FGF21. They also identified FGF21 as the regulator of the physiological response to that diet of converting the body to fat as an energy source, just as does fasting.