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Hormone helps mice ‘hibernate,’ survive starvation

DALLAS – June 5, 2007 – A key hormone enables starving mice to alter their metabolism and “hibernate” to conserve energy, revealing a novel molecular target for drugs to treat human obesity and metabolic disorders, UT Southwestern Medical Center researchers have found.

The starvation-fighting effects of the hormone, called fibroblast growth factor 21 (FGF21), are described for the first time in a study appearing online today in *Cell Metabolism*.

FGF21, triggered in starving mice by a specific cellular receptor that controls the use of fat as energy, spurs a metabolic shift to burning stored fats instead of carbohydrates and induces a hibernation-like state of decreased body temperature and physical activity, all geared to promote survival.

“This hormone changes the metabolism and behavior of mice in the face of inadequate nutrition,” said Dr. Steven Kliewer, professor of molecular biology and pharmacology at UT Southwestern and the study’s senior author. “We hope to manipulate this hormone-receptor signaling pathway to craft the next generation of drugs to combat human obesity and other conditions.”

Mammals on the brink of starvation normally shift their main fuel source from carbohydrates to stored fats, promoting survival during foodless periods. Some mammals also enter a hibernation-like state of regulated hypothermia, known as torpor, which conserves energy.

The molecular driver behind this reaction to starvation, however, had been unknown.

To find an answer, UT Southwestern researchers and other scientists examined potential molecular cues and cellular interactions at play during starvation and fasting.

They focused on a nuclear receptor – a protein that turns genes on and off in the body – called peroxisome proliferator-activated receptor alpha, or PPAR-alpha, which is known to control the use of fat as energy. Starving mice without PPAR-alpha become hypoglycemic and quickly die.

In analyzing the molecular impact of PPAR-alpha in mice, the researchers found that it stimulates production of FGF21, a member of a hormone family that has been shown to lower blood glucose levels in diabetic and obese mice.

FGF21, in turn, stimulates the use of stored fats as energy and causes torpor.

In properly fed mice, FGF21 is not normally active; however, when the researchers introduced

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'Hybernate' hormone – 2

FGF21 into these mice, the animals' metabolism changed.

"When mice were given this hormone, their metabolism appeared as if they were starved, even after they had just eaten," said Dr. Kliewer.

Because limiting food consumption is known to have a range of beneficial effects, such as lowering blood pressure, cholesterol and glucose levels in the blood, Dr. Kliewer is interested in understanding how FGF21 impacts these processes.

"We want to see if we can get some benefits of eating less without actually eating less," he said.

Manipulating the PPAR-alpha-FGF21 signaling pathway might ultimately prove to be a vital part of the ongoing search for new therapies for human obesity and other metabolic conditions, Dr. Kliewer said.

"Given that the PPAR-alpha receptor already is the target of drugs that work to boost high-density lipoproteins, or the 'good' cholesterol, and reduce the amount of fat in the blood, we believe this new pathway may lead to a new class of drugs that will impact many human conditions," he said.

Other UT Southwestern researchers involved in the study were Drs. Takeshi Inagaki, Guiziang Zhao, Xunshan Ding and Laurent Gautron, postdoctoral researchers; Paul Dutchak, graduate student; Dr. Vinay Parameswara, instructor of internal medicine; Drs. Victoria Esser and Robert Gerard, associate professors of internal medicine; Dr. Joel Elmquist, professor of internal medicine; Dr. Shawn Burgess, assistant professor in the Advanced Imaging Research Center; Dr. Robert Hammer, professor of biochemistry; and Dr. David Mangelsdorf, chairman of pharmacology. Researchers from New York University School of Medicine and the Van Andel Research Institute in Michigan also were involved.

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