# Starvation hormone makes for small mice

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Chronically high levels of a recently discovered starvation hormone markedly stunt the growth of mice, reveals a new study in the July issue of *Cell Metabolism*, a publication of Cell Press. The liver-produced hormone known as FGF21 does so by causing the mice to become resistant to growth hormone.

"It was an unexpected finding," said David Mangelsdorf of University of Texas Southwestern Medical Center. "In starvation, [it was known that] growth hormone goes down. This might explain much of the mechanism responsible."

The researchers showed in another *Cell Metabolism* report last year that FGF21 shifts the metabolism of mice to a fat-burning mode and induces a state of energy-conserving torpor. FGF21 has since been shown to act as an insulin sensitizer, as well.

The new findings uncover an even broader physiological role for the hormone in promoting energy conservation when animals go without food, said Mangelsdorf and study coauthor Steven Kliewer, also of the University of Texas Southwestern Medical Center.

They report that mice with higher-than-normal levels of FGF21 are normally sized at birth, but they gain less weight and their bones grow less. That's despite the fact that the animals eat more relative to their body weight than control mice do.

Further study showed that FGF21 reduced concentrations of a growth

hormone-mediating transcription factor (a gene that controls the activity of other genes), leading to a decline in the expression of its target genes, including insulin-like growth factor 1 (IGF-1).

The earlier discovery of FGF21's effects on fat metabolism and insulin response have led to considerable interest in its potential use as a type 2 diabetes drug, Mangelsdorf said. Therefore, it will be important to understand what else the hormone might do.

On the plus side, FGF21's growth hormone actions, along with its insulin effects, support the notion that it might extend life span, a hypothesis Mangelsdorf and Kliewer's team intends to explore. On the other hand, chronically blocking growth hormone could have other ill effects.

The new results might also explain the action of fibrate drugs now in use for treating patients with metabolic syndrome, Mangelsdorf said. Those drugs target a receptor known as PPARa, which is necessary for rise in FGF21 that occurs in fasted mice.

Notably, in clinical studies, the PPARa-agonist bezafibrate significantly lowers IGF-1 levels in patients," the researchers said. "This finding together with data showing that FGF21 expression is induced by PPARa agonists in primary human [liver cells] suggest that the PPARa/FGF21 pathway may be operative and affect IGF-1 signaling in humans."

Source: Cell Press