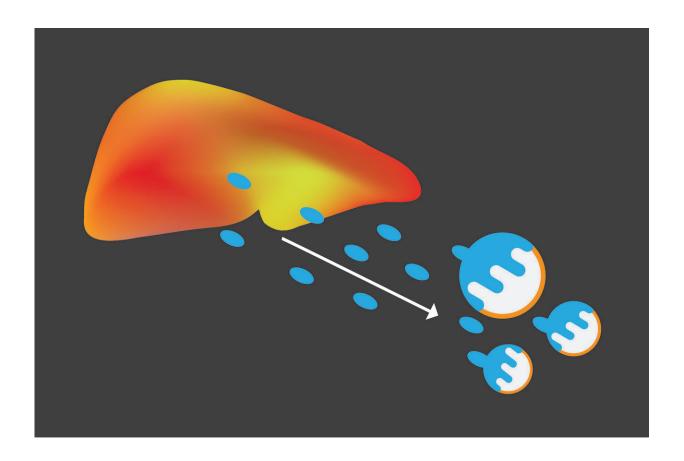


When the body's in overdrive, this liver hormone puts the brakes on metabolism

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Researchers at the University of Michigan have identified a liver hormone that puts a brake on metabolism in mice by dampening their ability to burn fat. The research reveals a potential target for treating metabolic disorders. Credit: Stephanie King, LSI multimedia designer.

Researchers at the University of Michigan Life Sciences Institute have



identified a hormone produced by the liver that tells the body to downshift its metabolism when it's expending a lot of energy.

The research, scheduled to be published Jan. 14 in *Nature Metabolism*, reveals a potential target for treating <u>metabolic disorders</u>.

Our bodies use several systems to maintain precise control of energy homeostasis—balancing the amount of energy we use and the calories we consume. The hormone leptin, for example, signals the brain to suppress appetite and increase burning of calories when energy stores are high.

"But much less is known about the other side of this equation: energy expenditure," said <u>Jiandie Lin</u>, professor at the LSI and senior study author. "How does the body sense rapid depletion of energy, and how does it tell the brain to adjust the body's metabolism and maintain homeostasis? That's the question we set out to answer."

By parsing gene expression data in mouse tissues, Lin and his colleagues found a hormone that was elevated when mice were burning a lot of energy, such as when they needed to maintain body temperature in a cold environment. This hormone, tsukushi (or TSK), is excreted primarily by the liver—a central player in nutritional, metabolic and hormonal pathways.

"We think that TSK is somehow dampening energy expenditure," said Lin, who is also a professor of cell and developmental biology at the U-M Medical School. "When there is a rapid loss of energy, it puts a brake on metabolism. If we remove this brake, our prediction was that the mice would have accelerated burning of calories. And that turned out to be the case."

When mice temporarily went without food, those lacking TSK lost



significantly more weight than normal mice. The mice without TSK also tended to have a higher body temperature than normal mice, indicating that their bodies were burning more energy when the TSK brake was removed.

The researchers also tested metabolic responses in mice given a <u>high-fat</u> diet. Normal mice approximately doubled in weight; the mice that lacked TSK, however, experienced only about a 30 percent increase in weight and displayed better metabolic parameters than the <u>normal mice</u>.

"We saw substantial protection against obesity," said Qiuyu Wang, a <u>postdoctoral fellow</u> in Lin's lab and lead author of the study. "And it comes with better glucose levels, reduced lipids, reduced fatty liver—really the whole package is improved."

The researchers believe the hormone achieves these effects by acting on the nerves that stimulate the activity of so-called brown fat, or thermogenic fat—which creates heat by burning energy. Lin and his colleagues next hope to investigate how TSK sends signals to the nerves to control fat burning and to explore strategies to dial down the TSK brake to treat metabolic disease.

An accompanying study from the Lin lab, published Dec. 15 in the journal Molecular Metabolism, showed that TSK deficiency also protects mice from diet-induced fatty liver disease. These findings illustrate the multifaceted beneficial effects of blocking TSK in preventing or treating metabolic disease, Lin says.

More research is needed to determine whether and how this hormone could be used to treat human metabolic disorders. But this latest research opens a potential new strategy for understanding and improving metabolic homeostasis.



The *Nature Metabolism* paper is titled "The hepatokine tsukushi gates energy expenditure via brown fat sympathetic innervation."

More information: Qiuyu Wang et al. The hepatokine Tsukushi gates energy expenditure via brown fat sympathetic innervation, *Nature Metabolism* (2018). DOI: 10.1038/s42255-018-0020-9

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