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Study reveals new link between brain and fat-burning circuit

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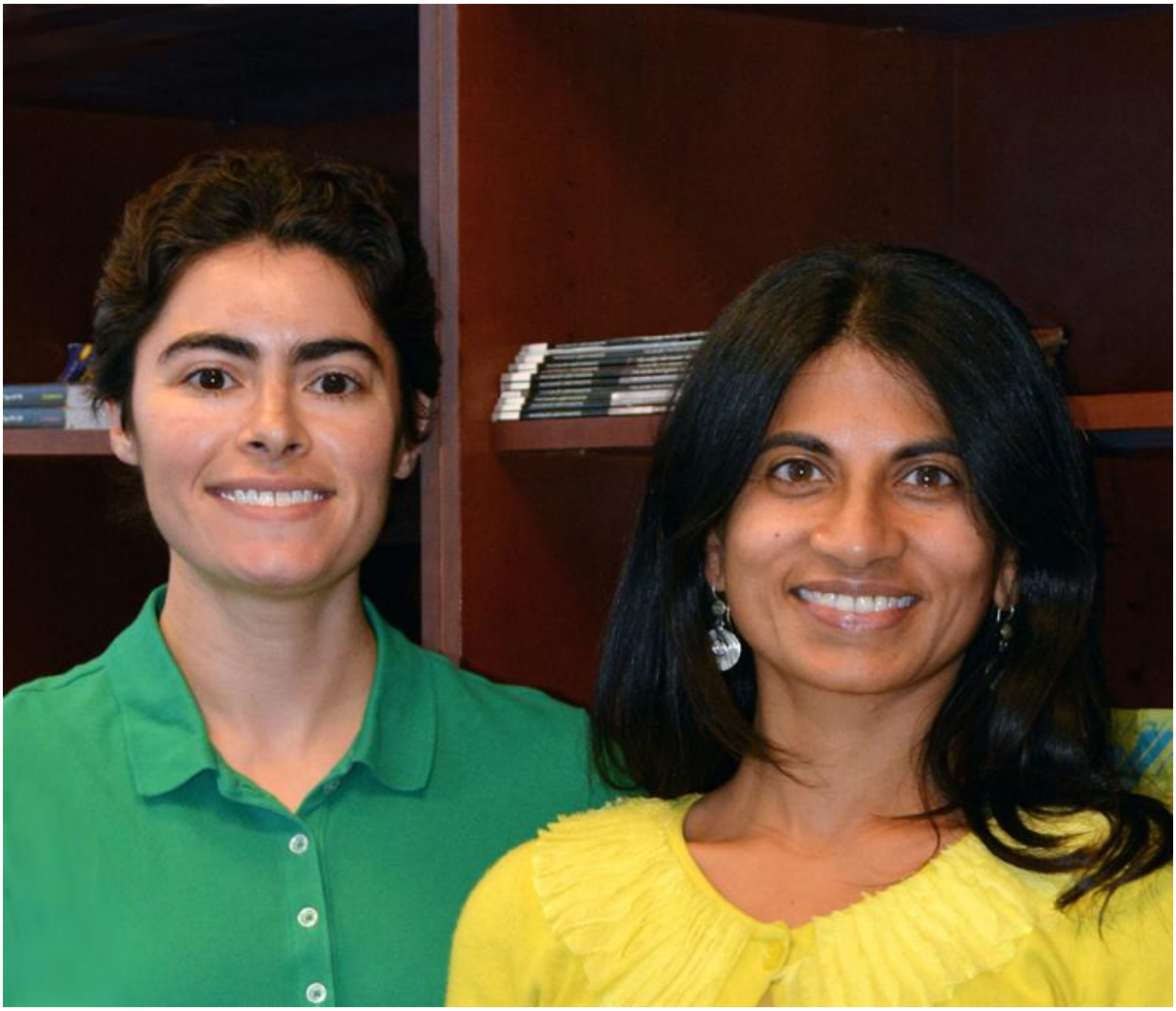

Scripps Research Institute Assistant Professor Supriya Srinivasan (right) authored the new study with Research Associate Emily Witham and colleagues. Credit: The Scripps Research Institute.

A new study in animal models, led by scientists at The Scripps Research Institute (TSRI), is the first to show that oxygen sensing in the brain has a role in metabolism and sensing an organism's internal state.

In a roundworm called *C. elegans*, cues picked up from the environment—specifically, the sensing of oxygen by the brain—determined how quickly the intestine burns fat. Surprisingly, this communication worked both ways, and fat reserves in the intestine could also influence the strength of the fat-burning signal from the nervous system.

"The implications for this are interesting," said TSRI Assistant Professor Supriya Srinivasan, who was senior author of the new study. "If oxygen-sensing neurons change their activity based on how much fat there is in an animal, what other neuronal functions can fat modulate?"

The findings raise the possibility of a similar mechanism in humans that may be dysregulated in diseases such as Bardet-Biedl Syndrome, in which patients with extreme obesity appear to have dysfunctional sensory perception. However, the oxygen sensors in humans are not yet known.

The study was published February 11, 2016 by the journal *Cell Reports.*

A Metabolic Mystery

Food intake is known as an important regulator of metabolism. For example, if consumption of food is low, the body burns fat and makes up for missing nutrients.

But there's growing evidence that fat burning is more complicated than

previously thought. Recent research has shown that the nervous system circuits involved in regulating metabolism are distinct from those regulated by feeding behavior.

"That implies that our metabolism is not a simple consequence of food intake," said Srinivasan.

But if food intake isn't the only player controlling metabolism, what else is?

In the new study, the researchers screened a family of genes known to be important in sensory perception. By deleting these genes one at a time in *C. elegans*, the researchers found that two of these genes were connected to fat metabolism. Interestingly, one of the genes was only expressed in a handful of neurons previously shown to sense oxygen levels in a worm's environment.

"A lightbulb went off in my head—there could be a connection between sensing oxygen and burning fat," said Srinivasan.

Using genetically encoded fluorescent sensors, the researchers found that the amount of fat reserves could affect neuronal activity in response to oxygen.

"This is an interesting, previously unknown role for these neurons," said TSRI Research Associate Emily Witham, who was first author of the new study.

Got Oxygen? Burn Fat

The researchers believe this connection in *C. elegans* might exist as a way of sensing food availability. The worms eat bacteria that consume oxygen, so slightly lower levels of oxygen, compared with normal

atmospheric oxygen, signal that a meal is nearby.

In a follow-up experiment, the researchers found that when oxygen levels were high—indicating no nearby food—the worms would ramp up fat burning. It was as if these worms switched to emergency mode and broke open the reserve rations.

When oxygen levels were slightly lower—indicating nearby food—the worms didn't burn fat as quickly. The worms seemed to sense a meal was coming, so there was no need to switch to emergency fat-burning mode yet.

To their surprise, the researchers found the intestine can also communicate back to the neurons. When fat reserves dipped too low, the neuronal signal to burn fat was dampened. This led the researchers to predict that the intestine was signaling the neurons to lower their activity when there wasn't enough fat available to be burned.

"We think that this is a self-preservation system, which prevents a deleterious fat-burning signal from the neurons in conditions of depleted fat reserves," said Witham.

While it's too soon to say if the insights on fat burning translate to humans, Srinivasan said the findings open new doors to research on metabolism and the mysteries of cross-tissue communication. She said the next step in this research is to identify the molecule that delivers the messages between the intestines and the neurons at play in this study.

"We think a hormone-like factor is secreted," said Srinivasan. "We're chasing down that signal."

More information: "C. elegans Body Cavity Neurons are Homeostatic Sensors That Integrate Fluctuations In Oxygen Availability And Internal

Nutrient Reserves," *Cell Reports,* 2016.

Provided by The Scripps Research Institute

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