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Eat more, weigh less: Worm study provides clues to better fat-loss therapies for humans

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Scientists at The Scripps Research Institute (TSRI) have discovered key details of a brain-to-body signaling circuit that enables roundworms to lose weight independently of food intake. The weight-loss circuit is activated by combined signals from the worm versions of the neurotransmitters serotonin and adrenaline, and there are reasons to suspect that it exists in a similar form in humans and other mammals.

"Boosting serotonin signaling has been seen as a viable strategy for weight loss in people, but our results hint that boosting serotonin plus adrenaline should produce more potent effects—and there is already some evidence that that's the case," said TSRI Assistant Professor Supriya Srinivasan, who was principal investigator for the study, published online before print on October 10, 2013 by the journal *Cell Metabolism*.

Serotonin signaling, which can be increased artificially by some diet and antidepressant drugs, has long been known to reduce weight. Until recently, scientists assumed that it does so largely by suppressing appetite and food intake. However, Srinivasan reported in 2008—while she was a postdoctoral fellow at the University of California, San Francisco—that serotonin changes food intake and fat levels via separate signaling pathways. "We could make the animals we studied lose fat even as they ate more," she said. Her experiments were conducted on *C. elegans* roundworms, whose short lifespans and well-characterized nervous systems make them a preferred species for quick-turnaround lab studies. Indeed, other researchers soon found that serotonin's food-intake-

suppressing and weight-loss effects are separable in mammals, too.

Now with her own laboratory at TSRI, Srinivasan has been examining the *C. elegans* weight loss circuitry in more detail. In the new study, Srinivasan and her colleagues, first author Research Assistant Tallie Noble and graduate student Jonathan Stieglitz, used a series of gene-blocking experiments to identify some of the circuit's key elements.

Their most surprising discovery was that serotonin isn't the sole driver of this weight-loss pathway, but works in concert with another neurotransmitter, octopamine—the *C. elegans* version of adrenaline (also called epinephrine) in mammals. "That was a very interesting finding, especially since other studies suggest that these two neurotransmitters tend to oppose each other's functions," said Noble.

The team mapped out a self-reinforcing network of serotonin and octopamine-producing neurons in the worms that send the lose-weight signal to the body. This network includes a set of serotonin-sensitive neurons known as URX neurons, which have access to the worm circulatory system and apparently release a still-to-be-identified signaling molecule. The downstream result of this signal, the researchers found, is a boost in the production of a key enzyme in the worm intestine. The enzyme, known as adipocyte triglyceride lipase 1 (ATGL-1), literally cuts fat molecules in a way that leads to their further metabolic breakdown. ATGL-1 also has a very similar counterpart in mammals.

Srinivasan and her colleagues plan in future work to identify the long-range molecular signal that boosts ATGL-1 production and to better delineate the serotonin-octopamine network that produces the signal. Eventually, they would like to map out the corresponding fat-loss network in a closer evolutionary relative of humans, such as the mouse.

However, Srinivasan noted that the human experience with weight-loss drugs already hints that mammals may have such a fat-loss circuit. Serotonin-plus-adrenaline boosting therapies, the most prominent of which was fenfluramine-phentermine ("fen-phen"), have tended to do better at cutting weight than serotonin-boosting therapies alone. Unfortunately, the serotonin-boosting elements of these compounds have often been blamed for cardiovascular side effects—fenfluramine, for example, was banned by the FDA in 1997—but in principle, future combination therapies could be designed to avoid producing such side effects.

"We wonder if boosting not just serotonin but serotonin plus a little bit of adrenaline is the real key to more potent weight loss," Srinivasan said.

More information: "An Integrated Serotonin and Octopamine Neuronal Circuit Directs The Release of An Endocrine Signal to Control C. elegans Body Fat," *Cell Metabolism*, 2013..

Provided by The Scripps Research Institute

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