Researchers discover obesity-related hormone in fruit flies

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Researchers have discovered in fruit flies a key metabolic hormone thought to be the exclusive property of vertebrates. The hormone, leptin, is a nutrient sensor, regulating energy intake and output and ultimately controlling appetite. As such, it is of keen interest to researchers investigating obesity and diabetes on the molecular level. But until now, complex mammals such as mice have been the only models for investigating the mechanisms of this critical hormone. These new findings suggest that fruit flies can provide significant insights into the molecular underpinnings of fat sensing.

"Leptin is very complex," said Akhila Rajan, first author on the paper and a postdoctoral researcher in the lab of Norbert Perrimon, James Stillman Professor of Developmental Biology at Harvard Medical School. "These types of hormones acquire more and more complex function as they evolve. Here in the fly we're seeing leptin in its most likely primitive form."

These findings will be published September 28 in *Cell*.

In order for an organism to function normally under varying conditions, its organ systems must learn to maintain a steady state, or "homeostasis." Coordinating food intake and nutrient stores with energy requirements is a key homeostatic mechanism referred to as energy homeostasis. Leptin regulates energy homeostasis by linking the organisms's fat stores with caloric intake. It is the hormone that tells the brain, "You've had enough."

Researchers have known for the better part of a decade that molecules secreted by the fruit fly's fat tissue communicate such nutrition status reports throughout the fly's entire body. However, they have not known the identity of these molecules, or the nature of the signals they transmit. Rajan hypothesized that this signaling molecule most likely resembles the leptin hormone in humans, since flies and mammals share similar nutrient-sensing pathways.

Researchers had predicted that three molecules in flies were likely to be structurally similar to leptin. When Rajan knocked out one of them, a protein called Upd2, the flies behaved, on a metabolic level, as though they were starving—despite consuming their normal caloric content.

"Since leptin is a nutrient sensor, this makes sense," said Rajan. "If you knock out the molecule that senses nutrients, the body thinks there are no nutrients. Blocking this molecule copied the phenotype of starvation."

Further tests showed that when flies were actually starving, levels of Upd2 went down, and when they received adequate nutrition, levels went up. This provided further evidence that, like leptin, Upd2 is a nutrient sensor.

Next, the researchers found that Upd2 uses a neural circuit similar to that of leptin to traffic nutrition information between the brain and fat tissue. When Upd2 reaches the brain, it regulates insulin secretion, in effect "telling" the fly to store nutrition and expend energy on growth.

Finally, Rajan and colleagues engineered a fly that lacked Upd2 altogether and inserted the human leptin gene in its place. The fly fully incorporated this mammalian molecule, and all normal nutrient-sensing functions resumed.

"The key significance here is that we can now take full advantage of the

sophisticated genetic tool kit available in fly genetics to address profoundly complex questions pertaining to leptin biology," said Perrimon. "This is good news to scientists studying obesity at the molecular level."

Interestingly, the amino acid sequence of leptin diverges from that of Upd2. However, the proteins produced by each gene share many structural similarities. "There are very few examples of this in the literature," Perrimon said.

"Now that we've identified Upd2 as a fly's nutrient sensor and have begun to work out the brain circuitry, the next step is to go deep into the mechanisms," added Rajan.

Provided by Harvard Medical School

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