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New master switch found in the brain that regulates appetite and reproduction

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Body weight and fertility have long known to be related to each other – women who are too thin, for example, can have trouble becoming pregnant. Now, a master switch has been found in the brain of mice that controls both, and researchers at the Salk Institute for Biological Studies say it may work the same way in humans.

Findings from the study, published ahead of print in the Aug. 31 online edition of *Nature Medicine*, suggest that variations in the gene that produces this master switch, known as TORC1, could contribute a genetic component to obesity and infertility, and might be regulated with a novel drug.

"This gene is crucial to the daisy chain of signals that run between body fat and the brain," says Marc Montminy, Ph.D., a professor in the Clayton Foundation Laboratories for Peptide Biology, who led the study. "It likely plays a pivotal role in how much we, as humans, eat and whether we have offspring."

It is just as important as leptin, the well-known star regulator of appetite, Montminy says, because leptin turns on TORC1, which in turn activates a number of genes known to help control feeding and fertility.

Judith Altarejos Ph.D., first author on this study, had been trying to understand human energy balance, and what can go awry to promote obesity, diabetes and other metabolic syndromes. In this study, she looked at the signals that travel from body fat to the brain, informing the

brain of how well fed the body is. The primary hormone that performs that function is leptin, which travels through the bloodstream to the hypothalamus in the brain (the appetite center), keeping the brain aware of the body's nutritional status.

"Leptin tells the brain that times are good, your body is full, and that it is not necessary to eat more at the moment," Montminy says. The hormone also is known to play a role in reproduction - although, until this study, no one understood what is was. (Very thin women often do not have periods.)

"Controlling appetite and reproduction together provides a big evolutionary advantage," Montminy says. "If there is no food, the brain believes the body should not reproduce because without body fat, a baby's growth in the womb could be stunted, and without food to replenish the body's energy reserves, there will be nothing to feed the offspring."

"Leptin works remarkably well to give the brain a good indication of how much food has been eaten; 99.9 percent of the time it balances food intake with energy use," he says. "The problem is that no machine works 100 percent of the time, and that slight bit of inefficiency can lead to extra body weight."

Obesity results when the brain becomes "deaf" to the leptin signal, so one goal of Montminy's research is to "try to make a way to make sure the brain signals are being heard." But to do that, he and his research team first have to understand all of the signals involved in the satiety pathway.

Through years of research, they have uncovered a family of genes that act as energy switches, turning other genes on or off. One gene, TORC2, acts like a fasting switch that flips on the production of glucose in the

liver when blood glucose levels run low, usually during sleep. During the day, the hormone insulin normally shuts down TORC2, ensuring that blood sugar levels don't rise too high. Problems along the pathway, however, can help lead to diabetes.

In this study, Altarejos looked at the function of TORC1, which she knew was produced in the brain – unlike TORC2 and TORC3 – but didn't know what its function was. To do this, she created mice that lacked one or both copies of the TORC1 gene – the first such "knock-out" mice to be developed.

Mice born without TORC1 looked fine at birth, but at about eight weeks, they began to gain weight and became persistently obese in adulthood, with two to three times as much adipose fat as normal mice, and they also became insulin resistant. "Their hormones and blood sugar resembled that seen in humans with these disorders," Montminy says.

They also discovered, to their surprise, that mice of both sexes were infertile; the uteri and ovaries in female mice were anatomically dysfunctional, for example. "We don't study infertility, but we put two and two together," he says. "We knew leptin is the critical hormone for regulating body weight, and that it is also very important for regulating reproduction."

Altarejos discovered that TORC1, which is found within nerve cells, responds to signals from leptin, which binds to receptors on the outside of the same cells. TORC1 then turns on a spate of genes, two of which are well known. One is the CART (Cocaine and Amphetamine Regulated Transcript) gene that is known to stifle appetite. The other, KISS1 (named by its discoverers at the Penn State Hershey Medical Center) is required for reproduction; mutations in the gene produce human infertility.

So when leptin binds with its receptor on brain cells, it turns on TORC1, which, in turns activates CART to suppress appetite, because more food is not needed, and KISS1, signaling reproduction can now commence in this well-fed body. Conversely, when leptin is not activating brain receptors, TORC1 is turned off, as are CART and KISS1.

They also discovered that when mice inherit only one TORC1 gene (instead of the normal two, one from each parent), fertility is restored but the mice gain more weight than normal mice. "This suggests that half of the dose of TORC switch is enough to cause problems in leptin signaling in the brain, and it may be that subtle mutations in TORC1 in humans could be responsible for an inheritable risk factor for gaining weight," Montminy says.

Tweaking mutated and inefficient TORC genes may be possible through drug therapy, he adds. "TORC1 is regulated by phosphate handling enzymes called kinases, and kinases often make for very good drug targets," Montminy says.

Source: Salk Institute