Researchers reveal how a single gene mutation leads to uncontrolled obesity

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Researchers at Georgetown University Medical Center have revealed how a mutation in a single gene is responsible for the inability of neurons to effectively pass along appetite suppressing signals from the body to the right place in the brain. What results is obesity caused by a voracious appetite.

Their study, published March 18th on Nature Medicine's website, suggests there might be a way to stimulate expression of that gene to treat obesity caused by uncontrolled eating.

The research team specifically found that a mutation in the brain-derived neurotrophic factor (Bdnf) gene in mice does not allow brain neurons to effectively pass leptin and insulin chemical signals through the brain. In humans, these hormones, which are released in the body after a person eats, are designed to "tell" the body to stop eating. But if the signals fail to reach correct locations in the hypothalamus, the area in the brain that signals satiety, eating continues.

"This is the first time protein synthesis in dendrites, tree-like extensions of neurons, has been found to be critical for control of weight," says the study's senior investigator, Baoji Xu, Ph.D., an associate professor of pharmacology and physiology at Georgetown.

"This discovery may open up novel strategies to help the brain control body weight," he says.

Xu has long investigated the Bdnf gene. He has found that the gene produces a growth factor that controls communication between neurons.

For example, he has shown that during development, BDNF is important to the formation and maturation of synapses, the structures that permit neurons to send chemical signals between them. The Bdnf gene generates one short transcript and one long transcript. He discovered that when the long-form Bdnf transcript is absent, the growth factor BDNF is only synthesized in the cell body of a neuron but not in its dendrites. The neuron then produces too many immature synapses, resulting in deficits in learning and memory in mice.

Xu also found that the mice with the same Bdnf mutation grew to be severely obese.

Other researchers began to look at the Bdnf gene in humans, and large-scale genome-wide association studies showed Bdnf gene variants are, in fact, linked to obesity.

But, until this study, no one has been able to describe exactly how BDNF controls body weight.

Xu's data shows that both leptin and insulin stimulate synthesis of BDNF in neuronal dendrites in order to move their chemical message from one neuron to another through synapses. The intent is to keep the leptin and insulin chemical signals moving along the neuronal highway to the correct brain locations, where the hormones will turn on a program that suppresses appetite.

"If there is a problem with the Bdnf gene, neurons can't talk to each other, and the leptin and insulin signals are ineffective, and appetite is not modified," Xu says.

Now that scientists know that BDNF regulates the movement of leptin and insulin signals through brain neurons, the question is whether a faulty transmission line can be repaired.

One possible strategy would be to produce additional long-form Bdnf transcript using adeno-associated virus-based gene therapy, Xu says. But although this kind of gene therapy has proven to be safe, it is difficult to deliver across the brain blood barrier, he adds.

"The better approach might be to find a drug that can stimulate Bdnf expression in the hypothalamus," Xu says. "We have opened the door to both new avenues in basic research and clinical therapies, which is very exciting."

Provided by Georgetown University Medical Center