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Feast or famine: Researchers identify leptin receptor's sidekick as a target for appetite regulation

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A study by researchers at Mayo Clinic's campus in Florida and Washington University School of Medicine adds a new twist to the body of evidence suggesting human obesity is due in part to genetic factors. While studying hormone receptors in laboratory mice, neuroscientists identified a new molecular player responsible for the regulation of appetite and metabolism.

In the Jan. 11 online issue of *PLoS Biology*, the authors report that mice engineered not to express the lipoprotein receptor LRP1, in the brain's hypothalamus, began to eat uncontrollably, growing obese as well as lethargic. They found that LRP1, a major transporter of lipids and proteins into brain cells, is a "co-receptor" with the leptin receptor — meaning that both the leptin and LRP1 receptors need to work together to transmit leptin signals.

Leptin decides whether fat should be stored or used, resulting in lethargy or energy. When working properly, the hormone, which is made when body cells take in fat from food, travels to the brain to tamp down appetite.

"If a person is born with too little gene expression in the leptin pathway, which includes its receptors, or the circuitry is not functioning well, then leptin will not work as well as it should," says the study's lead investigator, neuroscientist Guojun Bu, Ph.D., of Mayo Clinic. "Appetite

will increase, and body fat will be stored."

Given these results, Dr. Bu says it may be possible to develop a treatment that increases gene expression in one or both of the protein receptors, which then increases the messages meant to decrease appetite sent to the brain.

The serendipitous findings were born out of Dr. Bu's primary research focus, Alzheimer's disease. He has been studying how cholesterol, essential to the smooth functioning of neurons, is carried from star-shaped astrocytes to the surface of neurons by apolipoprotein E (APOE). There are two major receptors for APOE on brain neurons, and LRP1 is one of them.

Inheriting one version of APOE — APOE4 — is a known risk factor for development of Alzheimer's disease, and Dr. Bu has found that APOE4 is less effective at transporting cholesterol. To understand what role LRP1 plays in bringing APOE4 into neurons, he created a knockout mouse model with no expression of LRP1 in its forebrain neurons; the rest of its body expressed the receptor normally.

He found neurons lacking LRP1 had even less ability to absorb cholesterol, and that they lost synaptic contact with other neurons, impairing their ability to retain memory.

But Dr. Bu was surprised to find the mice suddenly gained weight. "This is the opposite of what had been observed in mice who did not have the receptor in their body fat cells," he says. "Those animals became skinny because they couldn't absorb enough lipoproteins."

The knockout mice were indistinguishable from control mice for the first six months of life but then gained weight rapidly, a phenomenon that correlated with a decrease in LPR1 expression in the central nervous

system. At 12 months old, the genetically engineered mice had twice as much body fat as control mice, lacked energy, and were insulin resistant. "Together, these results indicate that LRP1, which is critical in lipid metabolism, also regulates food intake and energy balance in the adult central nervous system," Dr. Bu says.

Provided by Mayo Clinic