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# New brain target for appetite control identified

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Researchers at Columbia University Medical Center (CUMC) have identified a brain receptor that appears to play a central role in regulating appetite. The findings, published today in the online edition of *Cell*, could lead to new drugs for preventing or treating obesity.

"We've identified a receptor that is intimately involved in regulating food intake," said study leader Domenico Accili, MD, professor of Medicine at CUMC. "What is especially encouraging is that this receptor is belongs to a class of receptors that turn out to be good targets for drug development, making it a highly 'druggable' target. In fact, several existing medications already seem to interact with this receptor. So, it's possible that we could have new drugs for obesity sooner rather than later."

In their search for new targets for obesity therapies, scientists have focused on the hypothalamus, a tiny brain structure that regulates appetite. Numerous studies suggest that the regulatory mechanism is concentrated in neurons that express a neuropeptide, or brain modulator, called AgRP. But the specific factors that influence AgRP expression are not known.

The CUMC researchers found new clues to appetite control by tracing the actions of insulin and leptin. Both hormones are involved in maintaining the body's energy balance, and both are known to inhibit AgRP. "Surprisingly, blocking either the insulin or leptin signaling pathway has little effect on appetite," says Dr. Accili. "We hypothesized

that both pathways have to be blocked simultaneously in order to influence feeding behavior."

To test their hypothesis, the researchers created a strain of mice whose AgRP neurons lack a protein that is integral to both insulin and leptin signaling. As the researchers hypothesized, removing this protein — Fox01 — had a profound effect on the animals' appetite. "Mice that lack Fox01 ate less and were leaner than normal mice," said lead author Hongxia Ren, PhD, associate research scientist in Medicine. "In addition, the Fox01-deficient mice had better glucose balance and leptin and insulin sensitivity — all signs of a healthier metabolism."

Since Fox01 is a poor drug target, the researchers searched for other ways to inhibit the action of this protein. Using gene-expression profiling, they found a gene that is highly expressed in mice with normal AgRP neurons but is effectively silenced in mice with Fox01-deficient neurons. That gene is Gpr17 (for G-protein coupled receptor 17), which produces a cell-surface receptor called Gpr17.

To confirm that the receptor is involved in appetite control, the researchers injected a Gpr17 activator into normal mice, and their appetite increased. Conversely, when the mice were given a Gpr17 inhibitor, their appetite decreased. Similar injections had no effect on Fox01-deficient mice.

According to Dr. Accili, there are several reasons why Gpr17, which is also found in humans, would be a good target for anti-obesity medications. Since Grp17 is part of the so-called G-protein-coupled receptor family, it is highly druggable. About a third of all existing drugs work through G-protein-coupled receptors. In addition, the receptor is abundant in AgRP neurons but not in other neurons, which should limit unwanted drug side effects.