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# Researchers identify and block protein that interferes with appetite-suppressing hormone

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Ever since the appetite-regulation hormone called leptin was discovered in 1994, scientists have sought to understand the mechanisms that control its action. It was known that leptin was made by fat cells, reduced appetite and interacted with insulin , but the precise molecular details of its function —details that might enable the creation of a new treatment for obesity—remained elusive.

Now, University of Texas Medical Branch at Galveston researchers have revealed a significant part of one of those mechanisms, identifying a protein that can interfere with the brain's response to leptin. They've also created a compound that blocks the protein's action—a potential forerunner to an anti-obesity drug.

In experiments with mice fed a high-fat diet, scientists from UTMB and the University of California, San Diego explored the role of the protein, known as Epac1, in blocking leptin's activity in the brain. They found that mice genetically engineered to be unable to produce Epac1 had lower body weights, lower body fat percentages, lower blood-plasma leptin levels and better glucose tolerance than normal mice.

When the researchers used a specially developed "Epac inhibitor" to treat brain-slice cultures taken from normal laboratory mice, they found elevated levels of proteins associated with greater leptin sensitivity. Similar results were seen in the genetically engineered mice that lacked the Epac1 gene. In addition, normal mice treated with the inhibitor had significantly lower levels of leptin in their blood plasma—an indication

that Epac1 also affected their leptin levels.

"We found that we can increase leptin sensitivity by creating mice that lack the genes for Epac1 or through a pharmacological intervention with our Epac inhibitor," said UTMB professor Xiaodong Cheng, lead author of a paper on the study that recently appeared on the cover of *Molecular and Cellular Biology*, available on the journal's Web site at http://mcb.asm.org/content/33/5.toc. "The knockout mice gave us a way to tease out the function of the protein, and the inhibitor served as a pharmacological probe that allowed us to manipulate these molecules in the cells."

Cheng and his colleagues suspected a connection between Epac1 and leptin because Epac1 is activated by cyclic AMP, a signaling molecule linked to metabolism and leptin production and secretion. Cyclic AMP is tied to a multitude of other cell signaling processes, many of which are targeted by current drugs. Cheng believes that understanding how it acts through Epac1 (and another form of the protein called Epac2) will also generate new pharmaceutical possibilities—possibly including a drug therapy that will help fight obesity and diabetes.

"We refer to these Epac inhibitors as pharmacological probes, and while they are still far away from drugs, pharmaceutical intervention is always our eventual goal," Cheng said. "We were the first to develop Epac inhibitors, and now we're working very actively with Dr. Jia Zhou, a UTMB medicinal chemist, to modify them and improve their properties. In addition, we are collaborating with colleagues at the NIH National Center for Advancing Translational Sciences in searching for more potent and selective pharmacological probes for Epac proteins."

Provided by University of Texas Medical Branch at Galveston