MedicalXpress

Researchers find a novel signaling pathway involved in appetite control

January 20 2015, by Tim Stephens

Agouti-related protein regulates feeding behavior, illustrated here in the Eastern chipmunk. Credit: Ed Reschke with permission from The American Biology Teacher

A new study has revealed important details of a molecular signaling system in the brain that is involved in the control of body weight and metabolism. The study, published January 19 in *Nature*, provides a new understanding of the melanocortin pathway and could lead to new treatments for obesity.

Coauthor Glenn Millhauser, a distinguished professor of chemistry and biochemistry at UC Santa Cruz, said the findings are very exciting and have broad biomedical implications. "We are getting to the real molecular features of what's controlling this important signaling system in the brain," Millhauser said.

The study, led by researchers at Vanderbilt University, focused on a receptor embedded in the membranes of nerve cells called the melanocortin-4 receptor, or MC4R. It belongs to a class of receptors known as G-protein coupled receptors (GPCRs), which typically act like on-off switches, signaling over short time frames, according to Roger Cone, who led the study at Vanderbilt.

"This finding identifies a molecular mechanism for converting an on-off switch into a rheostat," Cone said. "This could help explain slow, sustained biological processes that also are mediated by GPCRs, such as tanning or weight regain after dieting."

Millhauser's lab has done extensive research on proteins that bind to the MC4R receptor, such as agouti-related protein (AgRP). AgRP is a potent appetite stimulant. Its role in regulating energy balance is to suppress metabolism and increase feeding when the body needs to put on weight and store energy, Millhauser said. His lab has developed modified versions of the AgRP protein that alter its activity. In the new study, the modified proteins from Millhauser's lab helped researchers identify a previously unsuspected effect of AgRP.

Millhauser's previous studies have shown that a single dose of AgRP given to laboratory animals can stimulate daily food intake for up to 10 days. This observation didn't fit with the traditional "on-off" signaling model for the receptor it binds to, MC4R. G-protein coupled receptors can only take so much stimulation before they shut down, and this phenomenon, called desensitization, often happens rapidly.

Cone's lab discovered a companion protein—a potassium channel in the membrane called Kir7.1—that couples to the MC4R receptor and acts independently from G-protein signaling. The researchers found that AgRP induces MC4R to open the potassium channel, which "hyperpolarizes" and inhibits neurons that are involved in blocking appetite.

"Moreover, with modifications to AgRP discovered previously by our lab, we can increase or decrease this coupling of the receptor to the potassium channel," Millhauser said. "These concepts could ultimately lead to new generations of therapeutics for treating metabolic disorders, including obesity, anorexia, and cachexia, the wasting condition that often occurs in cancer treatment."

More information: G-protein-independent coupling of MC4R to Kir7.1 in hypothalamic neurons, *Nature* (2015) DOI: 10.1038/nature14051

Provided by University of California - Santa Cruz