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Modulation of inhibitory output is key function of antiobesity hormone

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Scientists have known for some time that the hormone leptin acts in the brain to prevent obesity, but the specific underlying neurocircuitry has remained a mystery. Now, new research published by Cell Press in the July 14 issue of the journal *Neuron* reveals neurobiological mechanisms that may underlie the antiobesity effects of leptin.

"Leptin is a hormone that is secreted by fat cells and acts at its receptor in the brain to decrease food intake and promote energy expenditure," explains senior study author Dr. Bradford B. Lowell from Beth Israel Deaconess Medical Center and Harvard Medical School. "However, despite intensive investigation, the underlying mechanisms responsible for this are poorly understood, in part due to incomplete knowledge regarding leptin-responsive neurons."

Previous studies by Dr. Lowell's group and others pinpointed a region of the brain called the arcuate nucleus as the site of key components related to the control of obesity. In particular, pro-opiomelanocortin (POMC) neurons, which have been shown to play a key role in appetite suppression, reside in this region. Although many POMC neurons express receptors for leptin, direct action of leptin on POMC neurons has not been shown to play a large role in controlling body weight. This suggests that there are likely to be other leptin-responsive neurons that are critical for leptin's antiobesity actions.

In the current study, Dr. Lowell and colleagues took a new approach for identifying these "unidentified" body weight-regulating neurons and

investigated whether leptin's effects are mediated primarily by excitatory (glutamate) or inhibitory (GABA) neurons. "Remarkably, we found that leptin's antiobesity effects are mediated predominantly by GABA neurons and that glutamate neurons play only a small role," says Dr. Linh Vong, a first author on the study. Importantly, the GABA neurons are "upstream" of the POMC neurons and, in response to leptin, the GABA neurons are less active. Conversely, a reduction in leptin levels, such as occurs with fasting, increases the activity of these GABA neurons.

Taken together, the findings suggest that modulation of GABA output is a key aspect of leptin action. "Leptin working directly on GABA neurons reduces inhibitory tone to POMC neurons," concludes Dr. Lowell. "As POMC neurons prevent obesity, their disinhibition by leptin action on upstream GABA neurons likely mediates, at least in part, leptin's antiobesity effects. Further, indirect regulation of POMC neurons by leptin reconciles the known important role of POMC neurons in regulating body weight with the relatively unimportant role played by direct action of leptin on POMC neurons."

Provided by Cell Press