New clues to how the brain and body communicate to regulate weight

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Maintaining a healthy body weight may be difficult for many people, but it's reassuring to know that our brains and bodies are wired to work together to do just that—in essence, to achieve a phenomenon known as energy balance, a tight matching between the number of calories consumed versus those expended. This careful balance results from a complex interchange of neurobiological crosstalk within regions of the brain's hypothalamus, and when this "conversation" goes awry, obesity or anorexia can result.

Given the seriousness of these conditions, it's unfortunate that little is known about the details of this complex interchange. Now research led by investigators at Beth Israel Deaconess Medical Center (BIDMC) provides new insights that help bring order to this complexity. Described in the October 26 issue of the journal *Cell*, the findings demonstrate how the GABA neurotransmitter selectively drives energy expenditure, and importantly, also help explain the neurocircuitry underlying the fat-burning properties of brown fat.

"Our group has built up a research program with the overall goal of unraveling the 'wiring diagram' by which the brain controls appetite and the burning of calories," says senior author Bradford Lowell, MD, PhD, a Professor of Medicine in BIDMC's Division of Endocrinology and Harvard Medical School. "To advance our understanding to this level, we need to know the function of specific subsets of neurons, and in addition, the upstream neurons providing input to, and the downstream neurons receiving output from, these functionally defined neurons. Until recently, such knowledge in the hypothalamus has been largely unobtainable."

A pearl-sized region that directs a multitude of important functions in the body, the hypothalamus is the brain's control center for energy balance. This balance results when the brain receives feedback signals from the body that communicate the status of fuel stores and then integrates this with input from the external world as well as a person's emotional state to modify feeding behavior and energy expenditure.

In this new study, the researchers investigated a unique population of neurons that are located at the base of the brain in the arcuate nucleus of the hypothalamus. "We genetically engineered mice such that they have a specific defect that prevents these neurons from releasing the inhibitory neurotransmitter, GABA," says Lowell. "Mice with this defect developed marked obesity and, remarkably, their obesity was entirely due to a defect in burning off calories," he explains, adding that food intake was entirely unaffected.

By next engineering another group of mice in which these neurons could be selectively turned on at different times, the team went on to show that the arcuate neurons act through a series of downstream neurons to drive energy expenditure in brown fat. Brown fat has been making headlines lately because many recent studies have revealed that, unlike energy-storing white fat, brown fat burns energy to generate heat. This process is called thermogenesis.

"Energy expenditure mediated by brown adipose tissue is critical in maintaining body weight and prevents diet-induced obesity. Its brain-based regulatory mechanism, however, is still poorly understood," says first author Dong Kong, PhD, an Instructor in Medicine in Lowell's laboratory. "Our discovery of a hypothalamus-based neurocircuit that ultimately controls thermogenesis is an important advance," adds Lowell.

The investigators additionally found that when they turned on these neurons, energy expenditure was entirely dependent upon release of GABA. These results reveal that release of GABA from arcuate neurons selectively drives energy expenditure.

"Our findings have greatly advanced our understanding in the control of energy expenditure and have provided novel insights into the pathogenesis of obesity," says Kong.

The unique features of arcuate neurons are important because they could provide an opportunity to experimentally modify the brain's control of energy expenditure. Specifically, neurons receiving GABA-mediated signals from arcuate neurons are likely to play important roles in regulating energy expenditure, but not food intake.

"It is now important to fully delineate the upstream neurons that control these thermogenesis-regulating arcuate neurons, and also the downstream neurons that complete the 'circuit' to brown adipose tissue," Lowell adds. He and his colleagues have identified several specific types of neurons that act downstream of arcuate neurons, but more research is needed to provide a clear and definitive diagram. Such work could uncover new opportunities for pharmacologic interventions that might lead to effective treatments for obesity and its related complications such as diabetes.

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