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Study provides surprising new clue to the roots of hunger

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While the function of eating is to nourish the body, this is not what actually compels us to seek out food. Instead, it is hunger, with its stomach-growling sensations and gnawing pangs that propels us to the refrigerator – or the deli or the vending machine. Although hunger is essential for survival, abnormal hunger can lead to obesity and eating disorders, widespread problems now reaching near-epidemic proportions around the world.

Over the past 20 years, Beth Israel Deaconess Medical Center (BIDMC) neuroendocrinologist Bradford Lowell, MD, PhD, has been untangling the complicated jumble of neurocircuits in the brain that underlie hunger, working to create a wiring diagram to explain the origins of this intense motivational state. Key among his findings has been the discovery that Agouti-peptide (AgRP) expressing neurons – a group of nerve cells in the brain's hypothalamus – are activated by caloric deficiency, and when either naturally or artificially stimulated in animal models, will cause mice to eat voraciously after conducting a relentless search for food.

Now, in a new study published on-line this week in the journal *Nature*, Lowell's lab has made the surprising discovery that the hunger-inducing neurons that activate these AgRP neurons are located in the paraventricular nucleus—a brain region long thought to cause satiety, or feelings of fullness. This unexpected finding not only provides a critical addition to the overall wiring diagram, but adds an important extension to our understanding of what drives appetite.

"Our goal is to understand how the brain controls hunger," explains Lowell, an investigator in BIDMC's Division of Endocrinology, Diabetes and Metabolism and Professor of Medicine at Harvard Medical School. "Abnormal hunger can lead to obesity and eating disorders, but in order to understand what might be wrong – and how to treat it – you first need to know how it works. Otherwise, it's like trying to fix a car without knowing how the engine operates."

Hunger is notoriously complicated and questions abound: Why do the fed and fasted states of your body increase or decrease hunger? And how do the brain's reward pathways come into play – why, as we seek out food, especially after an otherwise complete meal, do we prefer ice cream to lettuce?

"Psychologists have explained how cues from the environment and from the body interact, demonstrating that food and stimuli linked with food [such as a McDonald's sign] are rewarding and therefore promote hunger," explains Lowell. "It's clear that fasting increases the gain on how rewarding we find food to be, while a full stomach decreases this reward. But while this model has been extremely important in understanding the general features of the 'hunger system,' it's told us nothing about what's inside the 'black box' – the brain's neural circuits that actually control hunger."

To deal with this particularly complex brain region – a dense and daunting tangle of circuits resembling a wildly colorful Jackson Pollack painting – the Lowell team is taking a step-by-step approach to find out how the messages indicating whether the body is in a state of feeding or fasting enter this system. Their search has been aided by a number of extremely powerful technologies, including rabies circuit mapping and channelrhodopsin-assisted circuit mapping, which enable their highly specific, neuron-by-neuron analysis of the region.

"By making use of these new technologies, we are able to follow the synapses, follow the axons, and see how it all works," says Lowell. "While this sounds like a relatively straightforward concept, it's actually been a huge challenge for the neuroscience field."

In this new paper, first authors Michael Krashes, PhD, and Bhavik Shah, PhD, postdoctoral fellows in the Lowell lab, employed rabies circuit mapping, a technology in which a modified version of the rabies virus is engineered to "infect" just one type of neuron – in this case, the AgRP neurons that drive hunger. The virus moves upstream one synapse and identifies all neurons that are providing input to AgRP starter neurons. Then, using a host of different neuron-specific cre-recombinase expressing mice (a group of genetically engineered animals originally developed in the Lowell lab) the investigators were able to map inputs to just these nerve cells, and then manipulate these upstream neurons so that they could be targeted for activation by an external stimulus.

"We wanted to know, of all the millions of neurons in a mouse brain, which provided input to the AgRP neurons," explains Lowell. "And the shocking result was that there were only two sites in the brain that were involved – the dorsal medial hypothalamus and the paraventricular nucleus, with the input from the paraventricular neurons shown to be extremely strong."

With this new information, the investigators now had a model to pursue. "We hypothesized that neurons in the paraventricular nucleus were communicating with and turning on the AgRP neurons. We developed mice that expressed cre-recombinase in many subsets of the paraventricular neurons and then, mapping the neurons one-by-one, we determined which was talking to which," says Lowell. Their results revealed that subsets of neurons expressing thyrotropin-releasing hormone (TRH) and pituitary adenylate cylcase-activating polypeptide (PACAP) were in on the neuronal chatter.

Finally, through a chemogenetic technique known as DREADDs – Designer Receptor Exclusively Activated by Designer Drug – the authors used chemicals to specifically and selectively stimulate or inhibit these upstream neurons in the animal models. The fed mice, which had already consumed their daily meal and otherwise had no interest in food, proceeded to search out and voraciously eat after DREADD stimulation. Conversely, the fasting mice – which should have been hungry after a period of no food – ate very little when these upstream neurons were turned off.

"This has led us to the discovery of a novel, previously unknown means of activating AgRP neurons and producing hunger," explains Lowell. "Surprisingly, these hunger-inducing neurons were found in a region of the brain which has long been thought to have the opposite effect – causing satiety. This unexpected discovery, made possible only through the use of the new wiring diagram-elucidating technologies, highlights the importance of following the labeled neuronal lines of information flow. We are getting closer and closer to completing our wiring diagram, and the nearer we come to understanding how it all works, the better our chances of being able to treat obesity and eating disorders, the consequences of abnormal hunger."

Provided by Beth Israel Deaconess Medical Center