Hate to diet? It's how we are wired

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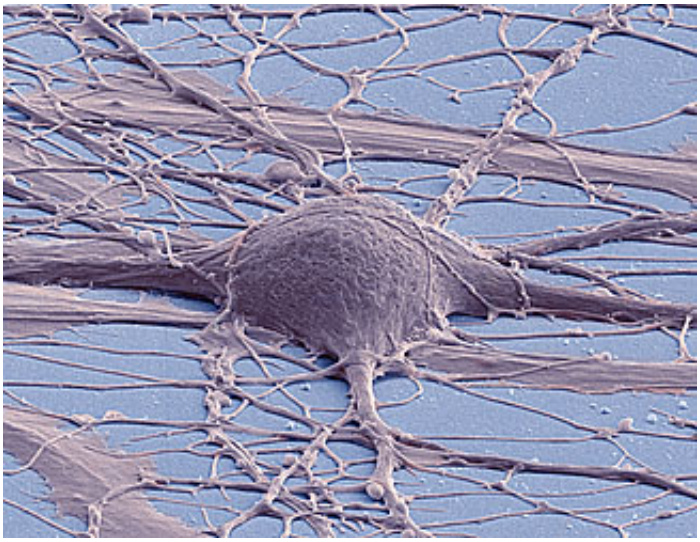

This is a scanning electron micrograph (false color) of a human induced pluripotent stem cell-derived neuron. Credit: Thomas Deerinck, UC San Diego

If you're finding it difficult to stick to a weight-loss diet, scientists at the Howard Hughes Medical Institute's Janelia Research Campus say you can likely blame hunger-sensitive cells in your brain known as AGRP neurons. According to new experiments, these neurons are responsible for the unpleasant feelings of hunger that make snacking irresistible.

The negative emotions associated with hunger can make it hard to maintain a diet and lose weight, and these neurons help explain that struggle, says Scott Sternson, a group leader at Janelia. In an environment where food is readily available, their difficult-to-ignore

signal may seem like an annoyance, but from an evolutionary point of view, they make sense. For earlier humans or animals in the wild, pursuing food or water can mean venturing into a risky environment, which might require some encouragement. "We suspect that what these neurons are doing is imposing a cost on not dealing with your physiological needs," he adds.

AGRP neurons do not directly drive an animal to eat, but rather teach an animal to respond to sensory cues that signal the presence of food. "We suspect that these neurons are a very old motivational system to force an animal to satisfy its physiological needs. Part of the motivation for seeking food is to shut these neurons off," says Sternson, whose team also demonstrated that a different set of neurons is specialized to generate unpleasant feelings of thirst. Sternson and his colleagues published their findings in the journal *Nature* on April 27, 2015.

Hunger affects nearly every cell in the body, and several types of neurons are dedicated to making sure an animal eats when energy stores are low. But Sternson says that until now, what scientists had learned about those neurons had not completely matched up to something we already know: hunger is unpleasant.

"There was an early prediction that there would be neurons that make you feel bad when you were hungry or thirsty. This made sense from an intuitive point of view, but all of the neurons that had been looked at seemed to have the opposite effect," he says. In earlier studies, researchers found that neurons that promoted eating did so by increasing positive feelings associated with food. In other words—not surprisingly—hunger makes food tastes better.

Some scientists had begun to suspect their ideas about a negative signal in the brain motivating hunger might be wrong. But their knowledge of the system was incomplete. AGRP neurons, located in a regulatory area

of the brain known as the hypothalamus, were clearly involved in feeding behaviors: When the body lacks energy, AGRP neurons become active, and when AGRP neurons are active, animals eat. But no one had yet investigated those cells' strategy for generating that motivation.

Postdoctoral researcher Nicholas Betley and graduate student Zhen Fang Huang Cao began to address the question with a series of behavioral experiments. In the first, they offered well-fed mice two flavored gels - one strawberry and the other orange. Neither gel contained any nutrients, but the hungry mice sampled them both. Then the scientists' manipulated the hunger signals in the animals' brains by switching AGRP neurons on while they consumed one of the two flavors. In subsequent tests, the animals avoided the flavor associated with the false hunger signal.

In a reverse experiment, the scientists switched AGRP neurons off while hungry animals consumed a particular flavor. The animals developed a preference for the flavor choice that led to silencing of AGRP neurons, suggesting they were motivated to turn off the cells' unpleasant signal. In further experiments, the scientists found that mice also learn to seek out places in their environment where AGRP neurons had been silenced and avoid places where those cells were active.

Next, postdoctoral researcher Shengjin Xu used a tiny, mobile microscope to peer inside the brains of hungry mice and monitor the activity of AGRP neurons. As expected, the cells were active until the mice found food. What was surprising, Sternson says, is that mice did not actually have to eat to quiet the neurons. Instead, the cells ceased activity as soon as an animal saw food - or even a signal that predicted food. And their activity remained low while the animal was eating.

That wouldn't make sense if the job of AGRP neurons was to make food taste better or if they directly controlled the individual actions that go into eating, which were two possibilities, Sternson says. But to encourage

eating, a negative signal would need to turn off when an animal consumed food. So their imaging experiments further supported what they had learned in their previous experiments.

The team later conducted similar experiments in which they manipulated thirst-sensitive neurons instead of AGRP neurons. Those neurons, found in a part of the brain known as the subfornical organ (SFO) behaved similarly: animals avoided places where the SFO neurons had been active, indicating that the cells generated a negative feeling. Again, the findings were consistent with everyday experience: "There's a similar motivational quality to hunger and thirst," Sternson says. "You want them to end." But although AGRP and SFO neurons motivate similar behaviors, their goals are very specific: AGRP neurons only drive animals to eat and SFO neurons only drive animals to drink. Recent independent work by HHMI researcher Charles Zuker at Columbia University has also shown that a circuit in the SFO regulates thirst.

In further experiments, Sternson's team will investigate similarities and differences between the two groups of cells. In addition, his group is interested in understanding more about how to interfere with the functions of AGRP neurons, which, in the future, might make it easier to keep those extra pounds off next time you go on a diet.

More information: Neurons for hunger and thirst transmit a negative-valence teaching signal, *Nature*, DOI: 10.1038/nature14416

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