

Hungry for Pleasure, Hungry for Food

Our drive to eat can be based on physical hunger or desire. The two aren't as separate as once thought.

IMAGINE YOU HAVEN'T EATEN IN DAYS. THEN, SOMEONE PLACES TWO plates in front of you. One holds a chocolate truffle, the other, a large turkey sandwich. No matter how much you adore chocolate, you will likely opt for the more filling sandwich. But given the choice in a different situation—after a big dinner, for example—the chocolate might look vastly more appealing. Are these choices due to pure reasoning or an innate desire mediated by chemicals in your brain?

New research suggests the latter. Your level of hunger affects how much pleasure you'll get out of eating chocolate or a turkey sandwich. In a recent experiment, mice placed a higher reward value on a calorie-rich drink than on an artificially sweetened drink after they'd been deprived of food. It's the first experiment to show that hunger levels affect the reward value of food.

The choice to eat something is influenced by a mélange of messages: how good something tastes and smells, the time since your last meal, your mood, what emotions or memories you associate with a food.

"Our new findings provide an experimental approach for studying how feeding pathways, including those that sense hunger and pleasure, are wired together into one grand circuit," says HHMI investigator Jeffrey Friedman, who led the study.

Friedman, at the Rockefeller University, studies the complex chemical signaling in the brain that controls hunger, appetite, and eating behaviors. In 1994, he published results describing his discovery of leptin, a hormone that controls appetite. When a mouse loses weight or hasn't eaten recently, the leptin levels in its blood fall, making it hungry and likely causing it to eat. After a large meal or weight gain, leptin levels rise, and the mouse loses its appetite and eats less.

There is a separate aspect of appetite, however: the desire to eat based on pleasure. When someone consumes food that tastes good, neurons fire in the brain's reward center, the same area that's activated by sex and nicotine. This process explains how food can be addictive, and why people get so much joy out of eating good food.

Friedman and research associate Ana Domingos turned to mice to test the interactions between the hunger and pleasure pathways. They wanted to see whether leptin—and therefore starvation or obesity—could change the pleasure associated with food.

To control the activity of dopamine neurons associated with pleasure, Friedman and Domingos used a technique called optogenetics that was developed by HHMI early career scientist Karl Deisseroth at Stanford University. It allows researchers to use tiny lasers to selectively boost firing of specific neurons in the brain.

Friedman's team offered mice different combinations of choices between three drinks: water; liquid sweetened with natural, calorie-rich sucrose; and liquid sweetened with the calorie-free, artificial sweetener sucralose. They measured how long the mice drank each liquid.

Normally, if mice can choose between water, sucrose, and sucralose, they consume more of the drink with sucrose than of the one with sucralose. And they take more sips of either sweet beverage than of the water. But by using optogenetics to



turn up the activity of dopamine neurons, Friedman and his colleagues could change how much pleasure the mice experienced from each drink.

When the researchers activated dopamine neurons every time the animals lapped up sucralose, the mice began to prefer the artificial sweetener to natural sugar. In other words, the enhanced pleasure changed their normal preferences. Next, to test whether hunger made a difference, Friedman and Domingos repeated the experiment with mice that hadn't eaten in 24 hours. This time, activation of dopamine neurons to encourage sucralose preference didn't work; the mice drank more of the

sucrose drink. When the scientists injected leptin into the hungry animals, however, mimicking a state of satiety, the sucralose once again became more appealing.

"This experiment suggests that the leptin is actually changing the hedonic value, the reward value, of the food," says Friedman. Since the dopamine neurons were being activated with the same intensity during each experiment, the scientists could rank the pleasure the mice got from each drink. And hunger, they concluded, changes these pleasure ratings.

"We can also use this method to test preferences for other nutrients, like fat or protein," says Friedman, "because it allows

us to separate taste from reward. We can deliver pure taste through the sucralose or pure reward through the laser. Neither of these alone is more appealing to a mouse than sucrose, but together they are."

For humans, the results shed light on the interplay between metabolic signals that convey hunger and sensory inputs that convey pleasure. But further experiments are needed to show exactly how this system plays out in patients with obesity, which is associated with insensitivity to leptin.

One thing is for sure: if a food tastes better when you eat it after a period of undereating, it's not just your imagination.

■ - SARAH C.P. WILLIAMS