The neurobiology of food attraction

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Animals use their sense of smell to navigate the world—to find food, sniff out mates and smell danger. But when a hungry animal smells food and a member of the opposite sex at the same time, what makes dinner the more attractive option? Exactly what is it about the odor of food that says, "Choose me?"

Research by investigators at Harvard Medical School illuminates the neurobiology that underlies food attraction and how hungry mice choose to pay attention to one object in their environment over another.

In their study, published in *Nature*, Stephen Liberles and co-author Nao Horio identified the pathway that promotes attraction to food odors over other olfactory cues.

In a series of experiments, the investigators homed in on a signaling molecule called neuropeptide-Y (NPY), secreted by hunger-regulating neurons into a region of the brain known as the thalamus, which regulates a range of physiologic functions, including relaying sensory information to the cortex.

"It turns out that specific neurons 'listen' to hunger state through the release of a neurotransmitter called NPY in the thalamus," said Liberles, professor of cell biology in the Blavatnik Institute at HMS and an investigator at the Howard Hughes Medical Institute.

Deciding between food and romance

"In mice, both food odors and sex pheromones are attractive, but are relevant for different physiological drives," said Horio, a postdoctoral researcher in the Liberles lab. "This suggests that odors activate parallel neural circuits that are shaped by physiological need."

To pinpoint the pathway that enables a mouse to make need-based decisions, Horio constructed an experiment. To start, she placed mice in an enclosure with two odor ports: one that emitted the smell of mouse chow and the other exuding pheromones from a mouse of the opposite sex. Horio noted the length of time a mouse spent lingering over each port, with longer time indicating the animal's preference.

Fed mice with full tummies found food odors and pheromones similarly attractive, but hungry mice displayed a strong preference for food odors, the scientists observed. Fed mice that had been previously exposed to a potential mate showed a distinct preference for the sex pheromones, whereas hungry mice did not. Why did hunger change the choice?

Illuminating the chemistry of food attraction

Neurons in the hypothalamus, a tiny almond-shaped gland buried deep in the brain, emit a molecule known as agouti-related peptide (AGRP). These neurons are known to trigger the drive for food. To study the effect of AGRP-secreting neurons, the researchers used a technique known as optogenetics, which allows scientists to switch neurons on and off by using light. The experiments showed that even in fed animals, AGRP neuronal

activation propelled mice to investigate food odors as though they were famished.

AGRP neurons have branches that spread far and wide, so the researchers wondered which areas of the brain were being stimulated. Further experiments demonstrated that multiple AGRP neuron terminals throughout the brain were activated, but only terminals located in a region known as the paraventricular thalamus changed food odor preference. When they did, mice that were not hungry became attracted to food. Conversely, silencing AGRP projections in this area of the thalamus decreased food-odor attraction in hungry mice.

"This observation led us to believe that the persistent stimulation of AGRP neurons that occurs during fasting enhances food-odor attraction by continually signaling downstream neurons," Liberles said.

The final obstacle was to identify whether any of the three principal neurotransmitters released by AGRP neurons—AGRP, NPY, and GABA—were required for hunger-dependent odor attraction, and if so, which one.

To find out, Liberles and Horio repeated the experiments with three groups of mice—each one genetically modified to lack one of these neurotransmitters.

Hungry mice lacking AGRP and GABA remained attracted to food odor. However, hungry animals that lacked NPY were no longer more attracted to food odors than they were to pheromones. NPY knockout mice, whether their bellies were full or not, retained a lower level of attraction to food odors comparable to their attraction to pheromones. Furthermore, mice lacking a specific NPY receptor, NPY5R, also lost hunger-dependent attraction to food odor.

Moreover, after being exposed to a mate, mice lacking NPY were more attracted to pheromones than food, a finding suggesting that mechanisms other than NPY are involved in tickling the olfactory response to pheromones, Liberles said.

The state of hunger, the study suggests, initiates a complex signaling cascade that, by rendering food aromas appetizing, drives animals to seek nourishment and make food a more attractive option than other alternatives. The experiments demonstrate that the unifying signals in this cascade are NPY and its receptor NPY5R. Moving forward, future research will investigate how NPY acts on some olfactory circuits but not others and how animals learn to associate foods with certain odors.

"It seems likely that different neurotransmitters function as spotlights for other behavioral drives, with the thalamus serving as a switchboard that gives preferential attention to sensory inputs on the basis of physiological need," Liberles said.

More information: Nao Horio et al. Hunger enhances food-odour attraction through a neuropeptide Y spotlight, *Nature* (2021). DOI: 10.1038/s41586-021-03299-4

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