Neural circuitry feeding into the lateral hypothalamus, by Matthew Soleiman

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At first blush, eating as a daily behavior may seem fairly straightforward. However, neuroscientists are still getting a handle on the complexities of how the brain controls eating – complexities which may explain how eating goes awry, such as in eating disorders.

Much historical and present-day interest in feeding has revolved around the lateral hypothalamus (LHA), a nucleus that houses genetically diverse neuron populations, and one connected to an intimidating

number of other brain regions. But thanks to current genetic technology, recent work has started to parse out the exact LHA circuitry that regulates feeding in rodents.

A couple years ago, the lab of Garret Stuber (UNC-Chapel Hill) revealed that input from the extended amygdala to excitatory neurons of LHA controls feeding, while earlier this year, both the Stuber and Tye (MIT) labs identified GABA neurons as additional players.

Now, new findings from the lab of Christian Lüscher (University of Geneva) published in *Neuron* unmask another LHA input important for feeding in mice: inhibitory neurons of the nucleus accumbens (NAc, specifically its shell subdivision) expressing the D1 dopamine receptor (D1R).

"This paper is one of the first to link, mechanistically, the nucleus accumbens with other classical feeding-related centers, like the lateral hypothalamus," said Stuber.

Getting permission to eat

Since older studies found that the NAc regulates feeding via the LHA, the authors turned to the question of which circuit mechanisms are at work. "We know that these brain regions contain heterogeneous cell populations, and so we wanted to get at the cellular basis of these observations, taking advantage of the modern neuroscience tool box," wrote lead author Eoin O'Connor in an email, a toolbox that includes genetically modified mice, optogenetics, and electrophysiology.

To this end, the authors began by tracing and molecularly characterizing the projections from the NAc to the LHA. Using genetically modified mice with fluorescently labeled D1 or D2 dopamine receptor-expressing neurons, the authors found that most NAc neurons sending input to the

LHA expressed the D1, but not the D2 receptor. This was confirmed by combining optogenetics and electrophysiology, whereby activating synaptic terminals of these D1R neurons with blue light evoked inhibitory currents in postsynaptic LHA neurons.

To explore the function of this circuitry, the authors again used optogenetics with electrophysiology, but in mice freely eating a palatable, fatty liquid diet. Specifically, they recorded from neurons identified as those expressing D1 or D2 receptors by activating them with blue light. Interestingly, only D1R neurons reliably fell silent during feeding, quickly becoming more active as feeding stopped. It seemed then that their lack of inhibitory input to the LHA permitted feeding. Consistent with this idea, optogenetic inhibition of these neurons' cell bodies increased feeding in well-fed mice.

Under what conditions would feeding be permitted? Asked slightly differently, when would these neurons be activated to not allow feeding? The authors tested a previously proposed idea that NAc neurons use sensory information to adjust ongoing behavior, using a task where an unexpected light and sound were presented to distract the mouse and interrupt feeding. In support of the hypothesis, inhibition of D1R, but not D2R neurons helped the mice ignore the distraction and keep feeding. Therefore, D1R neurons appear to alert an animal to what is going on in the environment during feeding – if there is nothing to worry about, feeding continues.

Next, the authors mimicked how environmental distractors would activate this circuitry by optogenetically activating inputs of D1R neurons to the LHA, finding that indeed the neurons could stop intake of the liquid diet from one lick to the next. "We were amazed to see how quickly the NAc shell to LHA projection can take over," wrote Lüscher. "By measuring licking, we had a precise temporal read out of food intake that is not so easy with solid foods. Since mice lick at about 8-10

Hz, this equates to stopping consummatory actions within approximately 100 ms," O'Connor added.

Downstream targets

Recent studies found that activation or inhibition of LHA GABA neurons increase or decrease feeding, respectively. Hence, the authors asked if D1R inputs to the LHA were able to stop feeding by inhibiting GABA neurons. Again using genetically modified mice, they found evidence for this, observing inhibitory currents specifically in LHA GABA neurons in response to activation of NAc inputs with light. Using additional genetic tools, they confirmed that the inputs were indeed from D1R neurons. Final evidence came from direct optogenetic inhibition of LHA GABA neurons instantly halting food intake, like what was seen with activation of inhibitory D1R inputs.

But LHA GABA neurons are not all the same. Stuber's lab previously found that some GABA neurons are active when animals are working for food, while others are active when animals are feeding. At the moment, Stuber guesses that inputs from D1R neurons are likely to both functional classes. However, "there are a lot of things that are still unknown with respect to this pathway and how it fits in with LHA circuitry," he commented. "The LHA is a pretty large chunk of tissue. We still don't really have a good handle on whether particular levels of the LHA are performing different functions, and whether or not different inputs might be targeting different segments of it," he added.

A more general function?

Although the circuitry was shown to be involved in feeding, the authors do entertain the idea that it may be more broadly involved in behavior, especially since the NAc is implicated in general motivation. Stuber

agrees, saying that future studies should record from these NAc projection neurons or downstream LHA neurons across different behavioral tasks, rather than just during feeding.

Ultimately, the authors argue that the circuit "enables rapid switching between different behavioral states in response to changing external conditions." While their findings show that the circuitry is necessary for environmental changes to stop feeding, well-known projections from the prefrontal cortex to the NAc suggest that the NAc – LHA circuitry may also relay internal states. "The prefrontal cortex could provide top-down control, for example, in enabling choice," stated O'Connor. "Motivation certainly also requires cortical inputs," added Lüscher. Moreover, top-down input could bypass the NAc altogether. "There's some direct cortical projections to the LHA, independent of the NAc," said Stuber.

The next step

As a next step in understanding this circuitry, Lüscher's lab plans to establish models of eating disorders. "We would like to know whether there is evidence for synaptic adaptations in these circuits that could explain symptoms in eating disorders. For example, if the NAc shell to LHA projection is strengthened, that it could lead to excessive inhibition of feeding initiation, which can contribute to anorexia," wrote Lüscher.

More information: Apergis-Schoute, J, Iordanidou, P, Faure, C, Jego, S, Schone, C, Aitta-Aho, T, Adamantidis, A, Burdakov, D (2015) Optogenetic evidence for inhibitory signaling from orexin to MCH neurons via local microcircuits. *J Neurosci.* 35:5435-5441. DOI: 10.1523/JNEUROSCI.5269-14.2015

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