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Applying the Brakes: When to Stop Eating

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The nucleus accumbens regulates consummatory behaviors, such as eating. In this issue of *Neuron*, O'Connor et al. (2015) identify dopamine receptor 1-expressing neurons that project to the lateral hypothalamus as mediating rapid control over feeding behavior.

Survival is dependent on balancing conflicting needs by identifying opportunities to obtain palatable food while avoiding noxious food or acute threats such as predators. Homeostatic energy balance controls food-seeking behaviors over long timescales, but food consumption also must be regulated on a momentary basis. Eating is elicited by environmental cues that signal food availability (Weingarten, 1983), and it is equally important that feeding has a rapid braking system to prevent consumption during dangerous circumstances. This function appears to be mediated by the nucleus accumbens shell (NAcSh), which is a ventral part of the striatum that has been referred to as a "sensory sentinel" for consummatory behavior (Kelley et al., 2005).

Pharmacological suppression of neuron activity in the NAcSh induces robust food consumption (Stratford and Kelley, 1997), and activation of the nucleus accumbens suppresses food intake (Kandov et al., 2006). Correspondingly, palatable and aversive tastes inhibit and activate neurons in the NAcSh, respectively (Roitman et al., 2005). Taken together, these studies indicate that a subset of NAcSh neurons detect foul food, increase firing rate, and inhibit feeding. Conversely, rewarding stimuli, such as sweet tastes, inhibit NAcSh neurons and promote food intake.

In this issue of *Neuron*, O'Connor et al. (2015) identify a molecularly defined cell type in the NAcSh that vetoes food consumption. The NAcSh is comprised of two major classes of projection neurons that are defined by expression of dopamine receptor 1 (D1R) or dopamine receptor 2 (D2R). The authors performed in vivo electrophysiological recordings of D1R and D2R neurons in the NAcSh. For cell-type identification, they combined extracellular recordings with cell-type-selective expression of channelrhodopsin-2 in each neuron population in order to identify single units showing light-evoked responses that corresponded to spike waveforms observed under natural conditions. $NAcSh^{D1R}$ neurons reduced action potential firing during consumption of a sucrose solution, while the activity pattern of $NAcSh^{D2R}$ neurons was mostly unchanged. Correspondingly, in optogenetic behavioral experiments, they found that photoinhibition of $NAcSh^{D1R}$ neurons increased feeding bouts. Neuroanatomy experiments showed that ~40% of $NAcSh^{D1R}$ neurons, but only ~5% of $NAcSh^{D2R}$ neurons, send projections to the lateral hypothalamus (LH), a brain region well established to elicit food consumption. O'Connor et al. (2015) examined the behavioral consequences of activity perturbations of axon projections to this brain area, finding that inhibition of $NAcSh^{D1R} \rightarrow LH$ axon projections increased eating. Inhibition of this circuit also reduced the ability of a distractor to interrupt feeding, demonstrating that $NAcSh^{D1R} \rightarrow LH$ (but not $NAcSh^{D2R} \rightarrow LH$) fulfills the predicted role as "sensory sentinel." Conversely, selective photoactivation of these neurons and their projection to the LH stopped consumption of a

palatable solution, even during homeostatic energy deficit.

Recent studies have found that food consumption was suppressed by inhibiting GABA-releasing LH^{VGAT} neurons (VGAT: vesicular GABA transporter, *Slc32a1*) (Jennings et al., 2015). O'Connor et al. (2015) show that NAcSh^{D1R} neurons selectively inhibit LH^{VGAT} neurons to halt feeding (Figure 1). These experiments reveal a circuit that may be responsible for controlling behavioral responses necessary for survival in a changing environment.

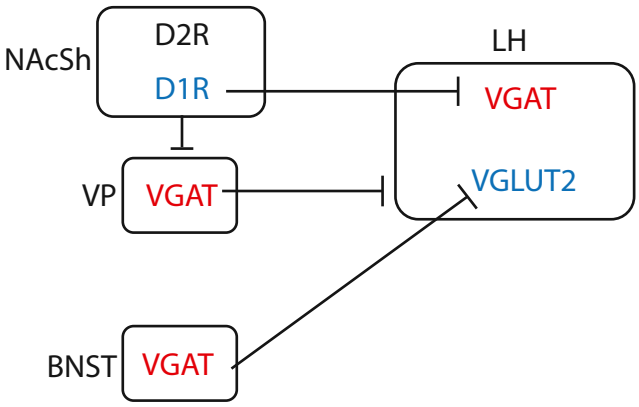

Figure 1. Circuit Interactions between Cell Types that Have Been Implicated in Acute Regulation of Food Intake via Axon Projections to the LH

Red and blue represent neurons that increase or decrease food intake, respectively, when activated. All circuit interactions shown here release GABA. Diagram of connectivity is highly simplified, and many additional connections are not shown.

This ventral striatal→hypothalamic system complements another circuit interaction in which inhibitory neurons of the bed nucleus of the stria terminalis (BNST) project to the LH and increase appetite. BNST^{VGAT} neurons target glutamate-releasing LH^{VGLUT2} neurons (VGLUT2: vesicular glutamate transporter 2, *Slc17a6*) (Jennings et al., 2013), and direct inhibition of LH^{VGLUT2} neurons elicits feeding (Jennings et al., 2013). Therefore, LH ^{VGLUT2} and LH^{VGAT} cell populations oppositely regulate feeding and are selectively targeted by inhibitory circuits from BNST^{VGAT} and NAcSh^{D1R} neurons, respectively (Figure 1).

One other component of the appetite-regulating circuit involving NAcSh^{D1R} neurons that was not explored by O'Connor et al. (2015) is a GABA-releasing inhibitory projection to the ventral pallidum (VP). GABA receptor blockade of the VP (loosely corresponding to blockade of NAcSh→VP input) has been shown to also increase food consumption, and the VP appears to increase appetite through an inhibitory projection to the LH (Stratford and Wirtshafter, 2013). Therefore, a pause in the NAcSh^{D1R} neurons associated with increased eating would be expected to activate the inhibitory VP→LH projection (Tindell et al., 2004). The LH cell types targeted by this VP→LH connection are not yet well established, but they are presumably not the LH^{VGAT} neurons inhibited by the NAcSh^{D1R} projections. One possibility is that VP neurons inhibit the LH^{VGLUT2} neurons targeted by the BNST^{VGAT} neurons (Figure 1). To resolve these issues, the approaches used by O'Connor et al. (2015) could also be applied to reveal the cell types in the VP→LH circuit.

Systems that evolved to help procure food under conditions of scarcity can lead to overeating in the abundant food environment of modern society. The identification of NAcSh^{D1R} neurons as a sensory sentinel provides a neural entry point into an ethologically and potentially therapeutically important neural circuit that has the ability to modulate food intake. Further refinement of the cell types in the NAcSh and LH remains a challenge. Molecular markers such as VGAT and VGLUT2 label large populations of neurons in the LH and other regions. NAcSh^{D1R} neurons did not appear to target more restricted molecularly defined LH populations expressing hypocretin/orexin or melanin concentrating hormone that have been implicated in appetite (O'Connor et al., 2015). Increasing the precision for defining neuronal subpopulations in the NAcSh and the LH will refine the neural substrate underlying behavioral, pharmacological, and environmental factors that regulate feeding. This is an important area for future investigation because these circuits provide a neural entry point to understand how environmental changes are integrated with internal state to influence behavior.

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