Journal Club

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When to Stop Eating: An Auxiliary Brake on Food Consumption from the Nucleus Accumbens

Ben Yang

Departments of Psychiatry & Behavioral Sciences and Physiology, Feinberg School of Medicine, Northwestern University, Chicago, Illinois 60611
Review of Bond et al.

Feeding is not only driven by homeostatic needs, but is also regulated by other factors, such as environmental sensory inputs, cognitive processes, emotions, and learning. For example, in the presence of palatable foods, feeding can be prolonged to store excess energy. However, in the presence of a predator, feeding must be terminated to ensure survival from the imminent threat. The nucleus accumbens (NAc), which integrates motivational and sensory signals to guide motor output (Mogenson et al., 1980; Kelley et al., 2005), contributes to such context-dependent regulation of feeding. Indeed, >2 decades of study, much of it spearheaded by the late Ann Kelley and colleagues, has led to the idea that the medial shell of the NAc (mNAcSh) plays the role of a “sensory sentinel” in the regulation of feeding in response to motivational and sensory signals (Kelley et al., 2005). For example, pharmacological activation of mNAcSh neurons suppresses feeding, whereas inhibiting these neurons promotes feeding (for review, see Kelley et al., 2005). Consistent with this model, NAc neurons are inhibited by palatable taste stimuli and activated by aversive taste stimuli (Roitman

et al., 2005). Furthermore, *in vivo* recording and stimulation confirmed that a pause in NAc neuron firing is required for the initiation and maintenance of feeding (Krause et al., 2010), which is in agreement with a permissive role for NAc inhibition in feeding.

What are the cell types and circuits that mediate the feeding-suppression effect of NAc activation? The mNAcSh is populated by two major classes of spiny projection neurons (SPNs): one that expresses D₁ dopamine receptors (D₁-SPNs); and another that expresses D₂ dopamine receptors (D₂-SPNs; Gerfen and Surmeier, 2011). The mNAcSh-D₁-SPNs primarily innervate the ventral tegmental area (VTA), the ventral pallidum (VP), and the lateral hypothalamus (LH), while D₂-SPNs project primarily to the VP and LH, but weakly to the VTA (Kupchik et al., 2015; O'Connor et al., 2015; Yang et al., 2018). Classical pharmacology experiments suggest that NAc projection to the LH inhibits feeding (for review, see Kelley et al., 2005). In agreement, a recent study using optogenetics showed that activating mNAcSh-D₁-SPN projections to the LH rapidly inhibits feeding in response to sensory alerts (O'Connor et al., 2015). The same group further showed that depression of mNAcSh projection to the LH promotes overeating (Thoeni et al., 2020). These observations support the hypothesis that mNAcSh subserves the sensory sentinel function that was proposed a decade ago.

In addition to NAc projection to the LH, classical pharmacology experiments suggest that its projection to the VTA

may regulate feeding (Will et al., 2003). Consistent with this, in a recent issue of the *Journal of Neuroscience*, Bond et al. (2020) used an optogenetic approach to show that mNAcSh-D₁-SPN projections to the VTA suppress feeding. Bond et al. (2020) found that the activation of mNAcSh projection in the VTA, which is predicted to inhibit VTA dopaminergic neurons, reduced feeding, but did not affect locomotion, motivation toward food, or valence associated with food. The latter finding was surprising as rich literature showed that activation of VTA dopaminergic neurons and dopamine release in the NAc increase locomotion, motivation, and positive valence (Kelley et al., 2005; Boekhoudt et al., 2017; Heymann et al., 2020). Furthermore, although the NAc → VTA circuit has been shown to be part of a neural network that regulates palatable food consumption (Will et al., 2003), Bond et al. (2020) showed that activation of the NAc → VTA circuit suppressed the feeding of both palatable (high-fat pellets) and nonpalatable (regular chow) food to a similar extent when the foods were presented together. These contrasting findings suggest that VTA and NAc neurons are involved in multiple circuits that regulate different aspects of feeding.

Next, the authors asked whether inhibition of the mNAcSh projection to the VTA increases feeding, using the inhibitory opsin eNPHR3.0. Because optogenetic inhibition of axonal projections can lead to paradoxical increases in neurotransmitter

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Correspondence should be addressed to Ben Yang at yang@u.northwestern.edu.

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release (Mahn et al., 2016), the previous study examining the role of NAc projection to the LH in feeding regulation (O'Connor et al., 2015) used optogenetic inhibition of the soma, which inhibited all mNacSh-D₁-SPNs, not just those projecting to the LH. Therefore, it was not clear whether the increase in food consumption and the prevention of feeding suppression caused by distracting sensory stimuli (O'Connor et al., 2015) were mediated by the inhibition of LH-projecting neurons or by the inhibition of other populations of mNacSh-D₁-SPNs. To circumvent this problem, Bond et al. (2020) took a pathway-specific approach to inhibition, by injecting a retrogradely transported virus expressing Cre into the VTA and a Cre-dependent virus expressing eNPHR3.0 into the mNacSh. Because the VTA-projecting and LH-projecting mNacSh-D₁-SPNs are distinct (Gibson et al., 2018), this led to selective expression of eNPHR3.0 in mNacSh neurons that project to the VTA. Optical inhibition of VTA-projecting neurons significantly increased food consumption and prevented the inhibition of feeding induced by distracting stimuli.

The study by Bond et al. (2020) on the mNacSh → VTA circuit is very similar in nature to the previous study on the mNacSh → LH circuit in feeding regulation (O'Connor et al., 2015; Fig. 1). In both studies, when excitatory opsin was used, channelrhodopsin 2 was expressed in the mNacSh and axonal projections were stimulated in the LH (O'Connor et al., 2015) or VTA (Bond et al., 2020). However, this approach has its own technical limitations. For instance, a recent study on LH GABAergic neurons, the presumptive target of mNacSh-D₁-SPNs, showed that optical activation of their projections in the VTA promoted feeding, but this effect did not result from the inhibition of VTA neurons, but from the activation of LH axons passing by the VTA and projecting more caudally to dorsomedial locus coeruleus (LC) GABAergic neurons (Marino et al., 2020; Fig. 1). Thus, feeding suppression induced by activating the mNacSh projections in the LH and VTA may not stem from the inhibition of local neurons, but rather from the activation of mNacSh axons passing by the LH and VTA that project to more caudal targets, such as the raphe, periaqueductal gray, pedunculopontine nucleus, or even the LC (Groenewegen and Russchen, 1984; Fig. 1). When inhibitory opsin was used, although Bond et al. (2020) used a retrograde labeling strategy, this approach also

Figure 1. Circuit connections between the mNacSh and its caudal projection targets that are involved in feeding regulation. All projections are GABAergic. Red and blue represent neurons/projections that promote or inhibit feeding (or food reward), respectively, when activated. Black represents neurons/projections that either don't affect feeding or have unknown effects on feeding. The connections shown here are simplified, and many additional connections (e.g., an LH glutamatergic projection to VTA) are not shown. Note VTA neurons innervated by the LH and mNacSh seem to be largely nonoverlapping (Soden et al., 2020) and the functions of LC and peri-LC neurons in feeding are beginning to be revealed (Gong et al., 2020; Marino et al., 2020; Yang et al., 2021). D₁ and D₂, D₁- and D₂-SPNs; Glu, glutamatergic neurons; GABA, GABAergic neurons; DA, dopaminergic neurons; NA, noradrenergic neurons; mVTA, medial VTA, IVTA, lateral VTA.

has its own technical limitations, as virus may be taken up by passing NAc axons projecting more caudally and the VTA-projecting SPNs may form collateral projections to other more caudal nuclei. Therefore, further studies are required to test whether one or more efferent targets of mNacSh mediate overlapping or different aspects (e.g., homeostatic vs hedonic, locomotion, motivation, and valence) and different phases of feeding.

If the VTA does in fact mediate feeding suppression in response to the signal from the mNacSh, which VTA neurons are targeted by the mNacSh? The mNacSh projections to the VTA form synapses with similar strength on both dopaminergic and GABAergic neurons (Yang et al., 2018). Their synapses on GABAergic neurons promote reward seeking (Gibson et al., 2018), most likely by reducing the inhibition of dopaminergic neurons. Indeed, the activation of VTA GABAergic neurons inhibits dopaminergic neurons and rapidly inhibits sucrose solution licking in food-restricted animals (van Zessen et al., 2012). Nonetheless, the effects of mNacSh projection on dopaminergic neurons are more inhibitory than disinhibitory (Yang et al., 2018). Therefore, mNacSh-D₁-SPNs likely suppress feeding by inhibiting VTA dopaminergic neurons.

One subpopulation of VTA dopaminergic neurons that may be of particular importance in feeding is the leptin receptor-expressing VTA neurons (VTA^{Lepr}). Leptin is a circulating hormone that

inhibits feeding and VTA dopaminergic neuron firing. Notably, knocking down leptin receptors in VTA increases feeding and locomotion (Hommel et al., 2006). Unlike other VTA neurons that project primarily to the NAc (Boekhoudt et al., 2017), VTA^{Lepr} neurons send relatively minor projections to the NAc, but stronger projections to the central nucleus of amygdala and interstitial nucleus of the posterior limb of the anterior commissure (Leshan et al., 2010). A recent study showed that subpopulations of amygdala neurons (Kim et al., 2017), which could be potential targets of VTA^{Lepr} neurons, regulate feeding. Details of circuit connections and functions of VTA^{Lepr} neurons require further investigation. Other populations of VTA neurons, such as those expressing serotonin 2C receptor (Xu et al., 2017) and those expressing oxytocin receptors (Mullis et al., 2013), have also been shown to regulate feeding. Characterizing VTA neurons innervated by the mNacSh is therefore critical to understanding the mechanisms by which this circuit influences feeding.

Fifteen years have passed since it was proposed that mNacSh plays a sensory sentinel role in feeding. But, precisely how this role is fulfilled has largely been a mystery. The study by Bond et al. (2020) provides some key clues about how mNacSh carries out this role, but important knowledge gaps remain. First, the circuit mechanisms underlying NAc-induced hedonic feeding are still unclear, but Bond et al.

(2020) suggested the mNacSh → VTA circuit likely is not involved. Second, although projections to both the LH and VTA have been shown to inhibit feeding, projections to more caudal targets have not been studied, and a loss-of-function study (e.g., lesion of local target neurons) has not been performed. Whether these different circuits play overlapping or distinct roles in feeding regulation requires further investigation. Third, the molecular and electrophysiological properties of target VTA neurons are not clear. An in-depth characterization of receptors and ion channels expressed in target neurons will help with the development of therapeutic targets for feeding disorders. Finally, how stress, and pathologic and psychiatric conditions that cause eating disorders and obesity influence the intrinsic excitability and synaptic plasticity in these neural circuits remain important topics for future investigation (Thoeni et al., 2020).

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