Galef, B.G., Jr. (2003). Social learning of food preferences in rodents: rapid appetitive learning. Curr. Protoc. Neurosci. *Chapter 8*, 5D.

Galef, B.G., Kennett, D.J., and Wigmore, S.W. (1984). Transfer of information concerning distant foods in rats: A robust phenomenon. Anim. Learn. Behav. *12*, 292–296.

Hikami, K., Hasegawa, Y., and Matsuzawa, T. (1990). Social transmission of food preferences in Japanese monkeys (Macaca fuscata) after mere exposure or aversion training. J. Comp. Psychol. *104*, 233–237.

Liu, Z., Chen, Z., Shang, C., Yan, F., Shi, Y., Zhang, J., Qu, B., Han, H., Wang, Y., Li, D., et al. (2017). IGF1-Dependent Synaptic Plasticity of Mitral Cells in Olfactory Memory during Social Learning. Neuron *95*, 106–122.e5.

Martinelli, D.C., Chew, K.S., Rohlmann, A., Lum, M.Y., Ressl, S., Hattar, S., Brunger, A.T., Missler, M., and Südhof, T.C. (2016). Expression of C1ql3 in Discrete Neuronal Populations Controls Efferent Synapse Numbers and Diverse Behaviors. Neuron *91*, 1034–1051.

Shepherd, R., and Raats, M. (2006). The Psychology of Food Choice (CABI Publishing).

Wang, C.Y., Liu, Z., Ng, Y.H., and Südhof, T.C. (2020). A Synaptic Circuit Required for Acquisition but Not Recall of Social Transmission of Food Preference. Neuron *107*, this issue, 144–157.

Understanding the Munchies

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In this issue of *Neuron*, Thoeni et al. (2020) demonstrate that both food restriction and a high-fat diet cause an endocannabinoid-dependent inhibition of D1 medium spiny neuron terminals in the lateral hypothalamus that promotes overeating.

Sporadic munchies leading to a third slice of pizza after a long workday or a midnight chocolate snack during a movie break are delicious treats but, if unregulated, can degrade one's health and lifespan. Acute overeating elicited by prior food restriction is an adaptive behavioral strategy conserved across species that serves to refill depleted energy stores after periods of food restriction. However, chronic overeating triggered by ready availability of hyperpalatable food (i.e., high fat, high sugar) is a risk factor for obesity and is maladaptive (Coccurello and Maccarrone, 2018). The human brain is poorly armed against the constant food seductions that first emerged in western societies, and in many societies, the high prevalence, accessibility, and affordability of hyperpalatable foods as compared to healthy alternatives have caused an obesity epidemic. A better understanding of the brain pathways involved in the development of pathological eating behaviors is important to inform public health strategies against obesity.

The lateral hypothalamus (LH) is interconnected with the brain reward and homeostatic systems, which places the LH at a circuitry control nexus for the regulation of feeding behavior and modulating the hedonic value of food (Coccurello and Maccarrone, 2018). Using optogenetic circuit manipulation, it was recently shown that GABAergic neurons in the bed nucleus of the stria terminalis project to and inhibit glutamatergic neurons in the LH to disinhibit feeding behavior (Jennings et al., 2013). Conversely, GABAergic D1 medium spiny neurons (D1-MSNs) from the nucleus accumbens shell (NAcShell) project to and inhibit LH GABAergic neurons to stop feeding behavior (Connor et al., 2015).

Chronic exposure to high-fat foods that are rich in saturated fatty acids can lead to adaptations in the brain reward system that could further amplify maladaptive eating behavior (Lafourcade et al., 2011).

Although previous optogenetic studies have revealed the importance of LH microcircuits in the real-time control of feeding behaviors, it remained to be discovered which adaptations in these LH circuits could contribute to chronic dysregulation of eating behaviors. In the new study by Thoeni et al. (2020), the authors set out to investigate whether changes in food intake (i.e., overeating after food restriction or overeating due to hyperpalatable food) induce neuroadaptations at the NAcShell D1-MSN-to-LH synapses that induce overeating. To this aim, the authors elegantly combined *in vitro* and *in vivo* optogenetics, whole-cell patch-clamp recordings, tracing studies, and *in vitro* and *in vivo* pharmacology to examine the role of synaptic plasticity at the D1-MSN-to-LH synapses in the regulation of feeding behavior.

In the first set of experiments, Thoeni et al. (2020) probed the capacity of NAcShell D1-MSN-to-LH synapses to undergo long-term potentiation of GABA transmission (i-LTP). D1cre mice were injected with floxed-ChR2 into the NAcShell and whole-cell patch-clamp recordings were performed. Surprisingly, the application of the adenylyl cyclase activator forskolin (FSK) that is known to induce i-LTP at other D1-MSN terminals (Creed et al., 2016) did not induce i-LTP in brain slices from *ad libitum*-fed mice. Since LH neurons are comprised of subpopulations of GABAergic and glutamatergic neurons that maintain opponent control over feeding behavior (Connor et al., 2015; Jennings et al., 2013), the authors speculated that the i-LTP might be only expressed in one of those

subpopulations and would remain undetected unless they discriminated between cell types. Hence, Thoeni et al. (2020) repeated the previously described experiments in vGAT-Cre and vGlut2-Cre mice where GABAergic and glutamatergic cells had been specifically labeled. But still, i-LTP was absent in both subpopulations in *ad libitum*-fed mice.

This form of presynaptic i-LTP had been previously described for D1-MSN GABAergic synapses in the ventral pallidum (VP), as well as in D1-MSN inputs to the ventral tegmental area (VTA) (Creed et al., 2016). Because D1-MSNs from the NAcShell project to the VTA, the VP, and the LH, the authors wondered whether the different basal states of synaptic plasticity are reflected in distinct microcircuits or whether the same D1-MSNs collateralize to the VTA, the VP, and the LH. Accordingly, they performed two elegant experiments involving dual retrograde tracing studies in Drd1a-tdTomato reporter mice using cholera toxin subunit B (CTB) coupled to distinct Alexa fluorophors to quantify the extent of collateralization by the D1-MSNs projecting to the LH, the VP, and the VTA. Interestingly, they found that the NAcShell synapses in the LH arose from D1 MSNs that were largely non-overlapping with D1-MSNs projecting to the VP and the VTA, which provided an anatomical basis for the distinct synaptic plasticity they had observed at these synapses (Figure 1).

Next, the authors probed the presence of i-LTP at D1-MSN synapses in the LH in mice that had been acutely food restricted (AFR) for 24 h. Once this projection was isolated from the other NAcShell D1-MSNs, they found that i-LTP occurred in slices of AFR mice but again was absent in slices of AFR mice that were allowed to recover from their weight loss for one week. This observation led to the million-dollar question: could overeating induced by food restriction and overeating by exposure to highly palatable foods be caused by the same neuroadaptation? To answer this question, mice were provided an exclusively high-fat diet in their home cage for 3 days, which sufficed to induce a significant weight gain in these animals. They prepared brain slices, and the D1-MSN projection to the LH synapse was examined for i-LTP. As predicted, the mice that munched on the high-fat diet showed similar i-LTP as AFR mice, whereas chow-fed control mice did not.

The lack of i-LTP in control mice could indicate that D1-MSN synapses in the LH were already potentiated, thereby occluding further potentiation with FSK. AFR or a high-fat diet could in turn depotentiate these synapses and unmask i-LTP (Figure 1). Given their role in the regulation of synaptic plasticity (Neuhofer et al., 2019) and feeding behaviors (Coccurello and Maccarrone, 2018), the involvement of the endocannabinoid system was tested. And indeed, the CB1R antagonist SR141716A disinhibited D1-MSN synapses in the LH from food-restricted mice whereas it had no effect on the same synapses of *ad libitum*-fed mice. These results indicate a tonic inhibition of these LH synapses by eCBs after food restriction, which allowed for an unmasking of i-LTP. Supporting a role for eCBs, the authors demonstrated that the tonic inhibition of D1-MSN-to-LH synapses was blocked by *in vivo* injection of the cannabinoid receptor antagonist SR141716A, administered at the beginning of food restriction.

These discoveries highlighted the following question: does enhanced eCB signaling at D1-MSN synapses in the LH stimulate overeating *in vivo*? The authors hypothesized that if eCB-LTD at these synapses was involved in overeating, then blocking the induction of eCB plasticity with SR141716A should be sufficient to inhibit overeating. And indeed, Thoeni et al. (2020) were able to show this. In AFR mice, the infusion of the SR141716A into the LH decreased the number licks and bouts for a high-fat solution. Conversely, mice fed *ad libitum* and infused with the CB1R agonist increased their consumption, and mice fed with a high-fat diet for 3 days and injected with SR141716A showed significantly lower high-fat consumption and body weight increase compared to animals that were injected with the vehicle.

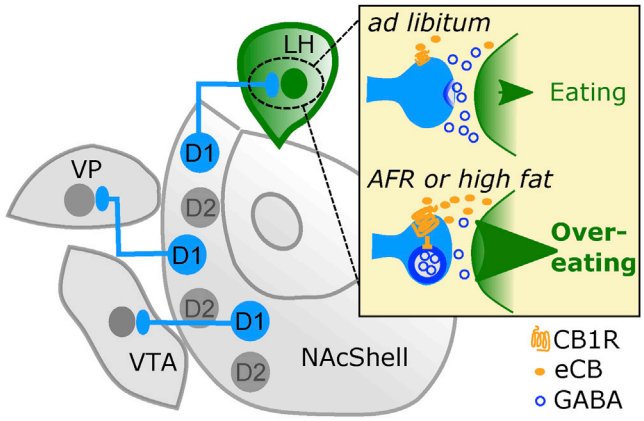

Figure 1. Depression of D1-MSN to Lateral Hypothalamic Synapses Gates Overeating

Both acute food restriction (AFR) and a high-fat diet cause an endocannabinoid-dependent inhibition of GABA release from D1 medium spiny neuron terminals in the lateral hypothalamus that promotes overeating.

Lastly, *in vivo* potentiation of NAcShell D1 synapses in the LH by optogenetic high-frequency stimulation of D1-MSN terminals transfected with a floxed Cheta construct (i.e., an opsin similar to ChR2 but with faster kinetics) significantly reduced the number of licks and bouts for a high-fat solution in food-restricted animals, mimicking the LH infusions of SR141716A to block eCB plasticity.

In conclusion, Thoeni et al. (2020) pinpoint endocannabinoid signaling in the LH as a key long-term modulator of feeding behavior (Figure 1). It comes as a surprise that overeating after food restriction and overeating due to a high-fat diet could be caused by identical neuroadaptations in the LH. These results could indicate that both high-fat food and calorie restriction induce a vicious cycle of overeating and emphasize that a healthy diet is probably the best strategy to fight the spread of obesity in our societies.

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REFERENCES

Coccurello, R., and Maccarrone, M. (2018). Hedonic eating and the "delicious circle": From lipid-derived mediators to brain dopamine and back. Front. Neurosci. *12*, 271.

Connor, E.C.O., Kremer, Y., Lefort, S., Harada, M., Pascoli, V., and Luscher, C. (2015). Accumbal D1R Neurons Projecting to Lateral Hypothalamus Authorize Feeding. Neuron *88*, 553–564.

Creed, M., Ntamati, N.R., Chandra, R., Lobo, M.K., and Lüscher, C. (2016). Convergence of Reinforcing and Anhedonic Cocaine Effects in the Ventral Pallidum. Neuron *92*, 214–226.

Jennings, J.H., Rizzi, G., Stamatakis, A.M., Ung, R.L., and Stuber, G.D. (2013). The inhibitory circuit architecture of the lateral hypothalamus orchestrates feeding. Science *341*, 1517–1521.

Lafourcade, M., Larrieu, T., Mato, S., Duffaud, A., Sepers, M., Matias, I., De Smedt-Peyrusse, V., Labrousse, V.F., Bretillon, L., Matute, C., et al. (2011). Nutritional omega-3 deficiency abolishes endocannabinoid-mediated neuronal functions. Nat. Neurosci. *14*, 345–350.

Neuhofer, D., Spencer, S.M., Chioma, V.C., Beloate, L.N., Schwartz, D., and Kalivas, P.W. (2019). The loss of NMDAR-dependent LTD following cannabinoid self-administration is restored by positive allosteric modulation of CB1 receptors. Addict Biol. https://doi.org/10.1111/adb.12843.

Thoeni, S., Loureiro, M., O'Connor, E.C., and Lüscher, C. (2020). Depression of Accumbal to Lateral Hypothalamic Synapses Gates Overeating. Neuron *107*, this issue, 158–172.