HHS Public Access

Author manuscript

Neuron. Author manuscript; available in PMC 2021 June 14.

Published in final edited form as:

Neuron. 2021 March 03; 109(5): 746–747. doi:10.1016/j.neuron.2021.02.008.

Dissecting the neural circuitry of fear-induced appetite suppression

Jessica Shaw[1], **Mariella De Biasi**[1,*]

[1]Department of Psychiatry, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA 19104, USA

Abstract

The circuit that links stress and fear to feeding behavior is poorly understood. In this issue of *Neuron*, Yang et al. detail a trisynaptic, cannabinoid-dependent circuit that underlies appetite suppression in response to a fearful stimulus and provide evidence of noradrenaline and glutamate co-transmission in locus coeruleus.

In the lab, alone at night and famished while waiting to finish your experiment, you hear the tell-tale *beep, beep, beep* of a −80°C freezer rising above temperature. Fearing the loss of your life's work, you rush to the freezer. but, distracted by hunger, you lose focus. Will you let your samples warm to room temperature and lose it all to pursue your dream of a late dinner?

In this situation appetite suppression would be advantageous, while in other situations addressing fear rather than hunger can become maladaptive. For example, loss of appetite is a common symptom of post-traumatic stress disorder, in which patients may experience fear in response to reminders of the initial traumatic experience(s). In this issue of *Neuron*, Yang et al. (2021) carefully dissect the circuitry underlying fear-induced appetite suppression using a combination of classical fear conditioning, electrophysiology, and genetic manipulations.

The authors first established the circumstances under which a fearful stimulus suppresses appetite using a Pavlovian fear conditioning paradigm, where a tone acts as a cue for an electrical foot shock. While the experience of the foot shock itself did not alter appetite, recollection of the foot shock in response to the tone/cue effectively suppressed consumption of all but the most palatable foods in hungry mice (so while broccoli may not be an effective distraction, chocolate mousse might). This was true both when the tone was played *during* food access and when it was played in a separate context *before* food access, suggesting that the memory of the associated shock—or anticipation of its recurrence—was sufficient to suppress appetite. Having thus determined the conditions of fear-induced appetite suppression, Yang et al. focused first on the parabrachial nucleus (PBN) and its afferents from the locus coeruleus (LC). Using chemogenetics, they found that exciting the LC

*Correspondence: marielde@pennmedicine.upenn.edu.

suppressed feeding, consistent with recent research (Sciolino et al., 2019) and with the LC's well-established roles in stress and arousal.

One of many areas that receive input from the LC, the PBN is heavily implicated in feeding behavior, and disruption of the area results in severe feeding abnormalities, including anorexia (Wu et al., 2012). Using optogenetics, Yang and colleagues demonstrated that the LC provides an excitatory input to the PBN that is sensitive to both glutamatergic and adrenergic antagonism. Surprisingly, this appears to result from co-transmission of glutamate and noradrenaline (norepinephrine). Complementary approaches using transgenic mice and a viral vector showed that some LC neurons possess both noradrenergic and glutamatergic machinery. Potential co-transmission of glutamate and noradrenaline in the LC is somewhat controversial, with evidence both supporting (Fung et al., 1994) and refuting (Stornetta et al., 2002) the phenomenon. Yang and colleagues provided strong evidence for co-transmission in LC neurons projecting to the PBN by optogenetically activating noradrenergic neurons, which produced a post-synaptic current in PBN neurons that was also sensitive to glutamate antagonism.

The PBN also receives inhibitory afferents from the central nucleus of the amygdala (CeA), which has in turn been implicated in both fear and feeding. Consistent with the overall finding that increased excitation of the PBN appears to suppress feeding, Yang et al. found that mice exposed to the fear conditioning paradigm show a reduction in CeA inhibition of PBN neurons and an increase in the paired-pulse ratio, suggesting that fear conditioning decreased presynaptic release probability from CeA projections. Fear conditioning also induced long-term depression (LTD) in these synapses, which was found to be at least partially mediated by cannabinoid 1 receptors (CB1Rs). A CB1R agonist given to naive mice recapitulated some of the effects observed with fear conditioning, while an inverse agonist of CB1Rs—rimonabant—seemed to prevent the reduction in CeA inhibitory input to the PBN. This latter finding is particularly important, as it suggests that fear-induced plasticity at CeA-PBN synapses relies on CB1R function. LC stimulation also induced LTD at CeA-PBN synapses, an effect that was inhibited by blocking CB1Rs. The phenomenon was mimicked by bath application of a α1AR agonist or mGluR activation, demonstrating that LC stimulation induces a cannabinoid-dependent LTD on PBN-CeA synapses—that is, a trisynaptic, LC→PBN←CeA circuit. Notably, although adrenergic transmission was dominant in inducing LTD, a subset of PBN neurons relied on glutamatergic transmission, leading to the hypothesis that co-transmission of glutamate and noradrenaline may control stability of LTD at the CeA synapse and the duration of the suppression of feeding induced by LC activation.

Finally, the authors moved from circuit back to system, demonstrating the necessity of CeA CB1Rs for fear-induced suppression of feeding. Hypothesizing that silencing LC neurons or blocking LTD at the PBN should disinhibit feeding in response to fear, they first used inhibitory DREADDs to reduce LC activation during fear conditioning. When testing for feeding suppression during the fear retrieval test, they found that mice with inhibited LC did not display the expected feeding suppression. Downregulation of CB1Rs on CeA neurons recapitulated this effect, establishing the importance of cannabinoid-mediated CeA synapses on PBN neurons in the appetite-suppressive response to LC input.

This work fills gaps in the scientific knowledge of LC-PBN-CeA connectivity and provides important information on the complex neurocircuitry underlying a relatively complex behavior. Most research investigating the relationship between fear/stress and feeding behavior has focused on the observation that chronic stress increases appetite, with only limited explicit investigations of fear-induced appetite suppression. The results from Yang et al. are consistent with a wider literature suggesting that hyperactivity of the locus coeruleus underlies hypervigilance, a symptom observed in patients with post-traumatic stress disorder. Further, the authors integrate observations in the LC with those in lateral PBN, contributing to ongoing efforts to understand how the brain functions as a system. Finally, although not the focus of the study, Yang and colleagues also make a significant contribution to the understanding of complex neural systems by detailing both new evidence of noradrenaline and glutamate co-transmission and its possible consequences. The ultimate functional outcomes of this co-transmission have yet to be determined and present an intriguing path for future research.

REFERENCES

Fung SJ, Reddy VK, Liu RH, Wang Z, and Barnes CD (1994). Existence of glutamate in noradrenergic locus coeruleus neurons of rodents. Brain Res. Bull 35, 505–512. [PubMed: 7859108]

Sciolino NR, Mazzone CM, Plummer NW, Evsyukova I, Amin J, Smith KG, McGee CA, Fry SA, Yang CX, Powell JM, et al. (2019). A role for the locus coeruleus in the modulation of feeding. bioRxiv. 10.1101/2019.12.18.881599.

Stornetta RL, Sevigny CP, and Guyenet PG (2002). Vesicular glutamate transporter DNPI/VGLUT2 mRNA is present in C1 and several other groups of brainstem catecholaminergic neurons. J. Comp. Neurol 444, 191–206. [PubMed: 11840474]

Wu Q, Clark MS, and Palmiter RD (2012). Deciphering a neuronal circuit that mediates appetite. Nature 483, 594–597. [PubMed: 22419158]

Yang B, Sanches-Padilla J, Kondapalli J, Morison SL, Delpire E, Awatramani R, and Surmeier DJ (2021). Locus coeruleus anchors a trisynaptic circuit controlling fear-induced suppression of feeding. Neuron 109, this issue, 823–838. [PubMed: 33476548]