BEHAVIOR

A new brain circuit in feeding control

Components of a neural circuit that regulates body weight are found

By **Sabrina Diano**[1,2]

The discovery of the anorexigenic (loss of feeding) adipose-derived hormone leptin (*1*) and its action on part of the brain, the central melanocortin system (*2*), confirmed earlier predictions of a crucial role of peptides produced by the neurons in this system, neuropeptide Y (NPY) and proopiomelanocortin (POMC), in the control of appetite and feeding (*3*). Further studies reaffirmed the relevance of these circuits in metabolism regulation by the use of increasingly sophisticated methods (*4*, *5*). On page 76 of this issue, Luo *et al.* (*6*) reveal the unsuspected role of another hypothalamic neuronal population in control of feeding, consisting of cells that express the neuropeptide somatostatin (SST), in the nucleus tuberalis lateralis (NTL). This finding adds to the neurological components that regulate food intake and thus body weight.

Luo *et al.* observed that after overnight food deprivation or the administration of the hunger hormone ghrelin in mice, SST-expressing neurons in the hypothalamic NTL expressed the immediate early gene *Fos*, a marker of neuronal activation. This suggested a potential role for these neurons in feeding regulation. To investigate this possibility, Luo *et al.* used selective activation of NTL SST$^+$ neurons either by means of DREADD (designer receptor exclusively activated by designer drug) or optogenetics. Either approach increased cumulative eating time and frequency. Conversely, inhibition of SST$^+$ neurons by use of DREADD or optogenetics significantly reduced feeding. To assess their long-term effect on metabolism, elimination of SST$^+$ neurons in mice resulted in decreased daily food intake and decreased body weight gain over time. To explore the efferent signaling involved in this process, they traced SST$^+$ collateral neuronal projections to several brain areas, including the hypothalamic paraventricular nucleus (PVN), the bed nucleus of the stria terminalis (BNST), the central amygdala, and the periaqueductal gray. The PVN and the BNST were found to be the main projection sites of the NTL SST$^+$ neurons, and only their axonal stimulation from optogenetics increased food intake (see the figure). This effect on food intake was blunted by local administration of the γ-aminobutyric acid ($GABA_A$) receptor antagonist bicuculline, indicating that GABAergic inhibitory signaling of the NTL SST$^+$ neurons is important. In line with this, both enzymes involved in GABA production, glutamate decarboxylase 1 (GAD1) and GAD2, were found to be expressed in these neurons.

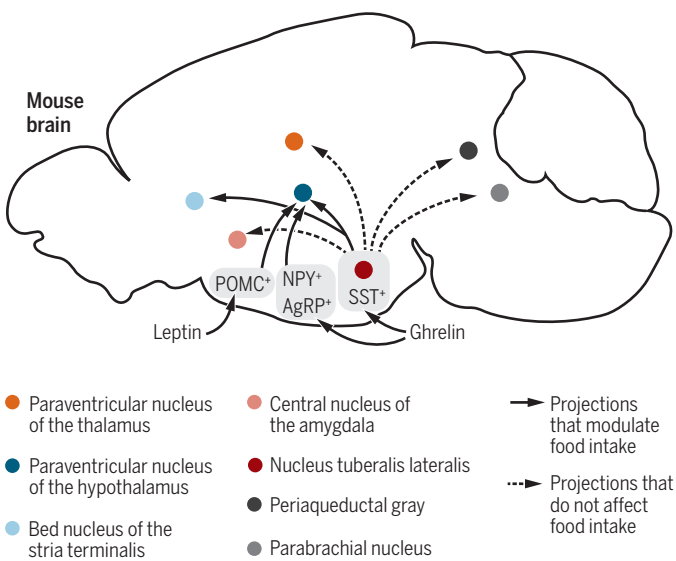
These findings add another player to the increasing number of nodes in the brain that affect homeostatic feeding. To date, the efforts to modulate feeding and aberrant feeding behavior—for example, in association with obesity or anorexia nervosa—have proven futile to control body weight and related impairments in physiology. Because food intake is a crucial aspect of survival, and because the neurological control of executions of complex, goal-oriented behaviors assures survival, it is not surprising that many brain regions are involved in the control of feeding. Indeed, multiple brain areas, from "lower" to "higher" function–related brain regions, have been shown to affect various aspects of eating. These include multiple hypothalamic nuclei, the BNST in the basal forebrain, the parabrachial nucleus in the hindbrain, the amygdala, the hippocampus, as well as the prefrontal cortex (*7*).

However, there are several caveats with all these observations, including the one by Luo *et al.* Regardless of the increasing sophistication of the experimental tools, such as optogenetics and chemogenetics, activation or inactivation of cells are both arbitrary from the perspective of the size of the cell population, the timing, and type and amounts of interference with neuronal activity. For example, what are the physiological triggers for the activation of these cells? What are the intracellular and extracellular adaptations that enable firing of these cells at a time of declining glucose and increasing fatty acid availability? Could lipid utilization as well as mitochondrial and synaptic adaptations drive the activation of SST$^+$ cells under hunger conditions, similar to what was found for hypothalamic NPY$^+$ neurons that also produce Agouti-related peptide (AgRP) (*8*–*10*)?

Another interesting question is whether these NTL SST$^+$ neurons that are involved in feeding control may also affect other complex behaviors. For example, hypothalamic NPY$^+$AgRP$^+$ neurons drive complex behaviors beyond feeding, such as reward seeking (*11*), anxiety, locomotion, and repetitive

Neurological circuits in appetite

Hypothalamic neuronal populations (POMC$^+$, NPY$^+$AgRP$^+$, and SST$^+$) regulate appetite and food intake through multiple neurological circuits. Activation of NTL SST$^+$ neurons increases feeding time and frequency. Modulating this circuit may help overcome the aberrant feeding behavior of obesity and anorexia nervosa.



GRAPHIC: V. ALTOUNIAN/*SCIENCE*

[1]*Department of Obstetrics, Gynecology and Reproductive Sciences, Section of Comparative Medicine, and Department of Neuroscience, Yale University School of Medicine, 310 Cedar Street FMB302A, New Haven, CT 06520, USA.* [2]*Department of Clinical Medicine and Surgery, University of Naples "Federico II," Via Pansini 5, Naples 80131, Italy. Email: sabrina.diano@yale.edu*

behavior (*12*, *13*). Because hunger evokes multiple well-coordinated efferent outputs in the brain, it is likely that NTL SST$^+$ neurons will affect multiple behavioral outputs as well. In this regard, it is notable that the NTL has been less defined in rodents. Intriguingly, and arguing for a potential role for these neurons in complex behaviors, neuronal loss in the NTL has been shown to occur in Huntington's disease (*14*), whereas SST production in NTL neurons is reduced in Alzheimer's disease (*15*).

The physiological and pathophysiological implications of the study by Luo *et al.* need future investigations to confirm the role of these circuits in humans. This is further confounded by the fact that our understanding of the homology between mouse and human circuits affecting feeding behavior is currently limited. Nevertheless, because most discoveries on neurological control of human feeding behavior originated in animal studies, the current finding of a role for NTL SST$^+$ neurons in feeding regulation in mice warrants investigations in human subjects as well. The human studies that followed the discovery of leptin and melanocortin signaling in mice were a notable success of these comparative approaches. Whether such endeavors pursuing the NTL SST$^+$ circuit will deliver insights and potential therapies for metabolic disorders in humans is yet to be seen.

"This finding adds to the neurological components that regulate food intake and thus body weight."

Luo *et al.* have introduced a new player in the sandbox of neuronal nodes that affect feeding. Their observations open up a new vista in the control of eating and other goal-oriented complex behaviors and peripheral tissue functions. ■

REFERENCES

1. Y. Zhang *et al.*, *Nature* **372**, 425 (1994).
2. M. A. Cowley *et al.*, *Nature* **411**, 480 (2001).
3. T. L. Horvath *et al.*, *Endocrinology* **131**, 2461 (1992).
4. S. Luquet *et al.*, *Science* **310**, 683 (2005).
5. M. L. Andermann, B. B. Lowell, *Neuron* **95**, 757 (2017).
6. S. X. Luo *et al.*, *Science* **361**, 76 (2018).
7. M. J. Waterson, T. L. Horvath, *Cell Metab.* **22**, 962 (2015).
8. Z. B. Andrews *et al.*, *Nature* **454**, 846 (2008).
9. M. O. Dietrich *et al.*, *Cell* **155**, 188 (2013).
10. S. Pinto *et al.*, *Science* **304**, 110 (2004).
11. L. S. Zweifel *et al.*, *Nat. Neurosci.* **14**, 620 (2011).
12. M. O. Dietrich *et al.*, *Cell* **160**, 1222 (2015).
13. S. L. Padilla *et al.*, *Nat. Neurosci.* **19**, 734 (2016).
14. H. P. Kremer, *Prog. Brain Res.* **93**, 249 (1992).
15. H. J. L. M. Timmers *et al.*, *Brain Res.* **728**, 141 (1996).

10.1126/science.aau1419

CHEMICAL PHYSICS

Molecular movies filmed at conical intersections

Electron diffraction maps atomic motions that result from photoexcitation of CF_3I molecules

By **Helen H. Fielding**

How molecules respond to ultraviolet (UV) light is not only a fundamental issue but has relevance in nature (such as in photosynthesis) and technology (such as with solar cells). Many spectroscopic methods have been developed for the study of photoexcited molecules in the gas phase, free from interactions with any environment, because these conditions allow the intrinsic properties of the molecule to be studied in exquisite detail and to be compared directly with theory. Many spectroscopic methods rely on measuring observables from which it is possible to infer the positions of the individual atoms of the molecule but do not directly measure molecular structure. On page 64 of this issue, Yang *et al.* (*1*) report the use of ultrafast gas-phase electron diffraction (GED) and high-level calculations to probe the movements of individual atoms in the prototypical molecule CF_3I after the absorption of UV light.

When a molecule absorbs UV light, it is promoted to an electronically excited state in which the individual atoms are no longer in their equilibrium positions. Their resulting excess potential energy can be redistributed in a variety of ways. For example, a molecular bond may break, or the atoms may rearrange to form a new molecular structure in which the excited electronic state and another electronic state become degenerate (a conical intersection between potential energy surfaces). Such conical intersections provide particularly efficient "funnels" for transferring molecules from an electronically excited state to a lower-lying excited electronic state or back to the ground state.

A molecular bond typically breaks or relaxes through a conical intersection in a few tens of femtoseconds. Spectroscopic measurements on these time scales became possible in the late 1980s with the advent of femtosecond lasers. Zewail and co-workers carried out the first pioneering experiments, using femtosecond laser pulses to record spectroscopic signatures of molecular bonds breaking and rearranging (*2*). After the pump pulse, a series of precisely timed probe pulses interrogate the electronic or molecular structure of the excited molecule. One approach is femtosecond time-resolved photoelectron spectroscopy, which has proved to be a powerful detection technique for probing ultrafast electronic relaxation processes in neutral molecules (*3*, *4*) and molecular anions (*5*–*7*) in the gas phase. The related techniques of femtosecond pump-probe velocity-map ion imaging (*8*) and time-resolved photoelectron-photoion imaging (*9*) have also proved valuable for monitoring the fragments of dissociation reactions. However, these techniques probe the evolution of the electronic wave function or the products of dissociation reactions and rely on complementary quantum chemistry calculations to deduce the corresponding molecular geometries after the absorption of the photon or after dissociation.

Time-resolved x-ray and electron diffraction techniques, on the other hand, are now emerging as exciting new methods for real-time measurement of molecular structure after absorption of UV light (molecular movies) (*10*, *11*). Yang *et al.* used the ultrafast GED setup at the SLAC National Accelerator Laboratory to record a molecular movie of photoexcited CF_3I molecules. A femtosecond UV pump pulse promoted the molecules to electronically excited states. Ultrashort pulses of electrons were then fired at the photoexcited molecules at a series of precisely timed intervals after the UV pump pulse. The resulting interference patterns arising from electron waves being scattered from the nuclei and electron clouds of the molecule were recorded at each time interval. Each diffraction pattern effectively provides a snapshot of the movie of molecular structures at the time each was recorded.

Yang *et al.* used a single UV photon to initiate C–I bond dissociation on an excited electronic state. This process has been the subject of several femtosecond pump-probe experiments, and the electronic states involved and time scale for dissociation are well characterized (*12*). The velocity and angular distributions provide information on the multiphoton pathways and the potential

Department of Chemistry, University College London, 20 Gordon Street, London WC1H 0AJ, UK. Email: h.h.fielding@ucl.ac.uk

A new brain circuit in feeding control

Sabrina Diano

Science **361** (6397), 29-30.
DOI: 10.1126/science.aau1419