Layers of signals that regulate appetite
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All meals come to an end. This is because eating and drinking generate feedback signals that communicate to the brain what and how much has been consumed. Here we review our current understanding of how these feedback signals regulate appetite. We first describe classic studies that surgically manipulated the gastrointestinal tract and measured the effects on behavior. We then highlight recent experiments that have used in vivo neural recordings to directly observe how ingestion modulates circuit dynamics in the brain. A general theme emerging from this work is that eating and drinking generate layers of feedback signals, arising sequentially from different tissues in the body, that converge on individual neurons in the forebrain to regulate hunger and thirst.

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Current Opinion in Neurobiology 2020, 64:79–88
This review comes from a themed issue on Systems neuroscience
Edited by Dan Feldman and Kristin Scott
For a complete overview see the Issue and the Editorial
Available online 20th April 2020
https://doi.org/10.1016/j.conb.2020.03.007
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Introduction
Eating and drinking are fast processes, but their physiologic effects are slow and delayed. For example, drinking can quench thirst in just a few minutes, even though tens of minutes are required for the ingested water to be absorbed into the bloodstream and reestablish fluid balance \([1–3]\). This phenomenon—loss of appetite before ingested food or water is absorbed—is known as satiation, and implies that the brain uses pre-absorptive signals to dynamically control eating and drinking.

In this review, we summarize recent progress towards understanding how pre-absorptive feedback signals regulate appetite. We discuss the various kinds of sensory information that are encoded by these signals, where and when they are represented in the brain, and how they influence behavior. To organize this discussion, we first describe classic experiments that surgically manipulated the gut and measured the effects on behavior. These experiments led to the hypothesis that an interaction between pre-gastric and gastrointestinal feedback is responsible for the tight control of eating and drinking. We then review recent work that has used techniques for neural recording to observe these feedback signals directly, as they emerge sequentially in the brains of behaving animals.

Sham ingestion revealed the pre-gastric and gastrointestinal controls on appetite
The key role of pre-absorptive feedback signals in satiation was first established by experiments using sham feeding and drinking (Figure 1). In this procedure, an opening (fistula) is surgically created in the esophagus, stomach, or intestines so that any ingested food or water drains from the animal before it can pass further. As early as 1856, Claude Bernard described such a sham drinking experiment in a thirsty dog equipped with a gastric fistula \([4]\). He reported that the dog drank voraciously when given water, but that “... the thirst was not abated. The animal ... drank until it was fatigue. A moment later, when he had rested, he started again, and so on” (p. 50–51, Ref. \([4]\)). This revealed that pre-gastric signals alone cannot durably satiate thirst.

In the 1930s, Roland Bellows and Edward Adolph repeated Bernard’s experiment, this time using quantitative measurements of behavior \([1,2]\). They found that dogs engaging in sham drinking exhibited a distinctive behavior, in which they would rapidly drink a large volume of water and then pause for 10–30 min before recommencing drinking. This cycle of drinking and pausing led Bellows to hypothesize that there are “two factors concerned in the satisfaction of thirst”: a fast signal that arises from the mouth or throat and temporarily quenches thirst when water is drunk, and a slower signal that arises from elsewhere in the body and enables the durable suppression of thirst (p. 96–97, Ref. \([2]\)).

A decade later, Henry Janowitz and Morton Grossman made strikingly similar observations with sham feeding in dogs \([5]\). They showed that dogs with open esophageal fistulas could temporarily suppress their hunger by simply chewing and swallowing food, even though the food would drain out of the fistula. However, the dogs ate much less food if the fistula was closed and the food

\[\text{Reference}\]
Effects of gastrointestinal manipulations on eating and drinking behavior.

(a) Two experimental techniques—sham ingestion and intragastric infusion—allow investigators to manipulate the contents of the gastrointestinal tract during eating and drinking. Today, both techniques frequently rely on a surgical procedure called catheterization, in which one end of a catheter is permanently attached to an animal’s stomach while the other end remains outside the body. Earlier experiments—often employing dogs or other large animals—used a similar procedure called fistulization, in which a portion of the esophagus, stomach, or intestines is ruptured and surgically attached to the animal’s exterior (either directly or via a steel cannula) so that tubing can be temporarily attached during experiments. (b) During sham feeding or drinking, the external end of the catheter is left open so that any ingested food or water drains from the animal before reaching the stomach. This has two striking effects. First, animals consume much larger meals than they would during normal ingestion. Second, while animals will eventually pause eating or drinking, this inhibition is only transient. These observations suggest that pre-gastric signals alone can produce temporary (but not persistent) satiation. (c) During intragastric infusion, the external end of the catheter is used to infuse food or water directly into the stomach, bypassing the mouth and throat altogether. Infusions into hungry or thirsty animals dramatically (sometimes completely) reduce intake when food or water is subsequently presented. This suggests that post-ingestive signals are sufficient to durably satiate hunger and thirst. However, the exact nature of these signals (what sensory information they convey, where in the gut they are generated) cannot be determined from behavioral observations alone. In (b), the listed water intake is the volume sham drunk (fistula open) relative to the volume drunk normally (fistula closed) [2], and the listed food intake is the time spent sham feeding (after fistulization) relative to the time spent feeding normally (before fistulization) [5]. In (c), the listed water intake is the volume sham drunk after intragastric infusion (water was presented 20 min after the dog’s entire fluid deficit was infused; the dog refused to drink) relative to the volume sham drunk without prior infusion [2], and the listed food intake is the amount eaten normally after intragastric infusion (food was presented 20 min after ~43% of the dogs’ normal meal size was infused) relative to the amount eaten without prior infusion [5]. In the schematics in (b) and (c), the horizontal axis represents time and the vertical axis represents rate of ingestion. These schematics are based on many of the references cited, although it is important to note that these are generalizations and that observations have varied across studies and species. We direct the reader to Chapters 2–4 of Ref. [80] and Chapter 19 of Ref. [81] for a more thorough discussion. The illustrations in (a) are adapted with permission from Figures 27 and 56 of Ref. [4] (public domain, https://gallica.bnf.fr/ark:/12148/bpt6k6214318x) and from Figures 2 and 3 of Ref. [82] (copyright 2012, Springer Nature).
allowed to enter the stomach. Later experiments showed that this pre-gastric inhibition of feeding underwent extinction if animals sham fed on successive days [6], implying that it is learned based on post-ingestive feedback. These and subsequent behavioral studies [7–14] suggested that the satiation of hunger and thirst follow a similar logic. First, temporary satiation is produced during ingestion by rapid pre-gastric (oropharyngeal or extraneous) signals. Later, more durable satiety is produced by signals arising from the stomach, intestines, or post-absorptive tissues.

The precise identity of the pre-gastric mechanisms that drive satiation remains unclear, although gustatory, olfactory, somatosensory, and visual cues are all likely involved. For gastrointestinal feedback, two mechanisms have received the most attention [15] (Figure 2). The first centers around enteroeoendocrine cells (EECs), which are rare epithelial cells that reside in the mucosal layer of the gastrointestinal tract [16]. EECs express on their surface a variety of transporters and receptors that sample the chemical composition of the gut lumen and, upon detection of nutrients or other substances, trigger the release of hormones such as cholecystokinin (CCK), glucagon-like peptide-1 (GLP1), peptide tyrosine tyrosine (PYY), and serotonin [17*]. These hormones feedback to inhibit food intake and modulate autonomic reflexes such as gastric emptying. This feedback is mediated by a combination of endocrine effects on the brain, paracrine effects on nearby tissues and nerve fibers, and direct synaptic connections between EECs and the adjacent axon terminals of sensory neurons [18,19**,20**].

In addition to EECs, vagal afferents comprise a second important class of sensory cells that regulate satiation. Vagal afferents have cell bodies located in the nodose ganglion and axons that bifurcate into two branches, one of which innervates the abdominal viscera and the other of which terminates in the nucleus of the solitary tract and area postrema of the brainstem [21]. Vagal sensory neurons are robustly activated by both mechanical and chemical signals associated with ingestion [22], and stimulation of vagal afferents can inhibit food intake [23,24*,25**]. Mechanical signals, such as distension of the stomach or intestines, directly activate vagal neurons that have specialized sensory endings known as intraganglionic laminar endings (IGLEs) and intramuscular arrays (IMAs), while chemical signals are thought to activate vagal neurons primarily indirectly via communication with EECs in the mucosal villi [21]. Recent work has begun to identify genetic markers for subtypes of vagal neurons that detect specific chemical and mechanical signals and have distinct patterns of visceral innervation [25**,26].

Like the vagus nerve, spinal afferents innervate the abdominal viscera and therefore represent a third potential mechanism for gastrointestinal feedback during eating and drinking. However, the diversity of gut-innervating spinal afferents is not well characterized, and key questions about how they might regulate appetite—including what signals they encode and how that information is transmitted to the brain to influence behavior—remain largely unexplored.

Neural control of appetite: from inference to observation

Our understanding of eating and drinking has been deeply influenced by experiments that measured the effects of gastrointestinal manipulations on behavior (Figure 1). Yet this strategy cannot teach us everything we want to understand about the regulation of appetite, because behavior is many steps removed from the underlying neural processes. This creates three challenges.

The first challenge relates to specificity. When a manipulation inhibits food intake, we often do not know why an animal has decided not to eat. This could be due to a specific change in a satiation-promoting feedback signal or have a more general cause (such as malaise or fatigue), and behavior alone cannot always distinguish between these possibilities. A second challenge relates to redundancy. Ablation of most gastrointestinal hormones has little or no behavioral phenotype [27], presumably because eating and drinking are robust to loss of individual feedback signals. How do we determine what information these individual signals are conveying under physiologic conditions? A third challenge relates to timing. Animals eat and drink at variable rates, and for this reason ingestive behavior must often be measured over tens of minutes to detect a meaningful effect of a perturbation. Yet on this timescale eating and drinking can generate numerous different feedback signals that arise in close succession. How can we disentangle these layers of rapid feedback?

One way to address these challenges is to monitor the activity of the neurons that control appetite, and thereby observe directly the information that the brain receives during eating and drinking. Traditionally, Fos immunohistochemistry has been an important method to do this, enabling brain-wide visualization of neural responses to gastrointestinal manipulations and identification of relevant brain regions [28–30]. However, Fos histology is limited by the fact that it is slow (integrates neural activity over tens of minutes), unidirectional (only detects activation), and enables only one measurement per animal. For this reason, there is the potential for considerable additional insight by using methods that record neural activity in real-time and during behavior.

Microdialysis measurements of dopamine release

Eating [31,32] and drinking [33,34] stimulate the release of dopamine in the striatum. This dopamine release is
**Pathways for gut–brain communication.**

(a) The vagus nerve densely innervates the gastrointestinal tract and transmits sensory information to the brain. Vagal afferents are characterized by the types of sensory endings that they form in the gut, as well as by their gene expression profiles and response properties. Mechanosensitive vagal afferents innervate the muscle layers of the stomach and intestines, where they form IGLEs and IMAs to directly detect distension. In contrast, chemosensitive vagal afferents predominantly innervate the mucosa, where they monitor nutrients and other chemical signals via communication with nearby EECs. (b) Ingestion triggers the release of hormones by sensory cells, such as EECs, throughout the gastrointestinal tract. These hormones are released in response to specific nutrient, chemical, and other stimuli, and can directly influence local tissues and nerve fibers (paracrine effects) as well as distant tissues like the brain (endocrine effects). In addition to the vagus nerve and the endocrine action of hormones, information from the gut is also transmitted to the brain by spinal nerves. However, the gastrointestinal signals that are encoded by subtypes of spinal afferents—and how those signals might influence ingestion—have not been well characterized. Abbreviations: EECs, enteroendocrine cells; IGLEs, intraganglionic laminar endings; IMAs, intramuscular arrays.
mediated by exterosensory cues, such as the sight and smell of food [35,36], and oropharyngeal signals, such as sweet taste [37,38] or mouth wetness [39]. However, the fact that sham feeding stimulates less dopamine release than natural feeding [37,40,41] implies that post-ingestive signals are also involved.

To investigate how gastrointestinal signals modulate the dopamine system, several studies have monitored striatal dopamine levels by microdialysis while infusing nutrients into the stomachs of behaving mice [42–45] (Figure 3). Although microdialysis is slow (temporal resolution of several minutes), it has the important advantage relative to Fos in that it enables continuous recordings in a single animal [46]. These experiments showed that intragastric infusion of sugars [42,45] or fats [43,44] causes a rapid increase in dopamine in the dorsal striatum (DS). In contrast, a broader array of signals—including exterosensory [35,36], oral [37,38,41], and post-ingestive sugar [38,42,45] cues—appears to drive dopamine release in the adjacent nucleus accumbens (NAc) during feeding, suggesting that the DS may be more specifically involved in gastrointestinal nutrient responses. These effects of nutrients on dopamine release are proposed to be transmitted by the vagus nerve and to mediate the rewarding effects of post-ingestive nutrient detection [24*,47*]. Recent work using optical dopamine sensors [48,49] has reproduced some of these microdialysis findings at higher temporal resolution [50].

Dopamine is critical for helping animals learn to associate foods with their post-ingestive consequences [51,52], and

**Figure 3**

**Microdialysis measurements of striatal dopamine release.** (a) Coronal representation of the midbrain dopamine system. The colormap highlights the broad anatomical organization of mesostriatal dopamine projections, although it is noteworthy that dopamine neurons—including their inputs, outputs, and response properties—are very heterogeneous. (b) In this experiment, hungry rats were given access to a sugar (sucrose) solution for 20 min while dopamine release was measured by microdialysis. Natural feeding stimulates intense dopamine release [40], while sham feeding results in a much smaller increase (despite greater intake) [37]. Similar results were obtained with rats sham feeding a fat (corn oil) solution [41]. These observations suggest that post-ingestive signals must contribute to dopamine release during feeding. (c) Left: In hungry mice, intragastric infusion of sugar rapidly stimulates dopamine release [42,45]. Right: Intragastric infusion of fat has a similar effect [43,44]. These experiments showed the first gut-to-brain sensory responses in behaving animals, and demonstrated that nutrient signals in particular drive dopamine release in the DS. The gray shaded area in (b) indicates the availability of food, and the black vertical lines in (c) indicate the start of intragastric infusion. The data in (b) are adapted with permission from Figure 1 of Ref. [40] (copyright 2001, Elsevier) and from Figure 3 of Ref. [37] (copyright 2004, American Physiological Society). The data in (c) are adapted with permission from Figure S3 of Ref. [44] (copyright 2013, American Association for the Advancement of Science) and from Figure S1 of Ref. [45] (copyright 2016, Springer Nature). Abbreviations: DS, dorsal striatum; NAc, nucleus accumbens; SNc, substantia nigra pars compacta; VTA, ventral tegmental area.
in this way dopamine microdialysis has provided important insight into how animals develop preferences for foods and bias feeding choices across meals. On the other hand, dopamine does not appear to play a critical role in the generation of hunger or thirst or in the suppression of those drives by eating and drinking [53]. Investigation of these processes requires monitoring neural circuits with a more specific role in appetite.

**Optical recordings of hypothalamic hunger neurons**

Early electrophysiological recordings found neurons in several hypothalamic nuclei that respond to gastrointestinal signals [54–56], but interpretation of these findings was limited by an inability to determine the identity or function of the recorded neurons, or to monitor their activity in awake animals. A breakthrough came with the development of fiber photometry [57,58] and microendoscope imaging [59], two approaches that made it possible for the first time to monitor the activity of genetically defined neurons deep in the brains of awake, behaving mice.

These tools were first applied to agouti-related peptide (AgRP) neurons, a small population of hypothalamic neurons that are activated by food deprivation and critical for hunger [60,61]. Based on their sensitivity to hormones such as leptin, it was long thought that the activity of AgRP neurons would gradually fluctuate in unison with changes in circulating hormones and nutrients. However, in vivo recordings revealed that these neurons are instead rapidly inhibited in the moment that a hungry animal sees and smells food [62–64]. This rapid, pre-gastric inhibition predicts how much food an animal will eat in the forthcoming meal [65], suggesting that AgRP neurons can anticipate the physiologic effects of impending behavior.

The rapid inhibition of AgRP neurons by the sight and smell of food is reversed if the food is not consumed [62–64], implying that it is contingent on subsequent post-ingestive signals. To test this directly, AgRP neurons were monitored while nutrients were infused directly into the stomachs of behaving mice, thereby bypassing any oral or exterosensory cues [65,66] (Figure 4a,b). This revealed that intragastric nutrients inhibit AgRP neurons on a timescale of minutes as they are progressively infused into the stomach, in a manner proportional to their caloric content but largely independent of their macronutrient identity. On longer timescales (tens-of-minutes to hours) AgRP neurons are modulated by the hormone leptin [65], which circulates at levels proportional to body fat stores. Thus, AgRP neurons receive layers of signals that report on future, current, and past ingestive behavior, which they integrate to estimate the animal’s need for energy.

The pathway by which nutrient signals from the gut are transmitted to AgRP neurons is unclear but likely involves the enteroendocrine–vagal system. The evidence for this includes the fact that AgRP neurons are inhibited by administration of hormones that are naturally released by EECs (CCK, PYY, serotonin) [65,66] as well as by infusion of nutrients directly into the duodenum (which stimulates release of these same hormones) [25**]. Moreover, the inhibition of AgRP neurons by dietary fat requires CCK [65*], and surgical vagotomy blocks the ability of CCK or intragastric fat to inhibit AgRP neuron activity [50]. Recently, the role of specific vagal cell types in modulating AgRP neurons has been investigated by stimulating vagal neurons using DREADDs while simultaneously monitoring AgRP neuron activity by fiber photometry [25**]. This revealed that AgRP neurons are inhibited by CCK A receptor (CCKAR)-expressing vagal mechanoreceptors innervating the stomach or intestines, but surprisingly not by putative chemosensory vagal afferents that innervate the intestinal mucosa (and express even higher levels of CCKAR) [25**]. This revealed that AgRP neurons are sensitive to mechanical signals from the gut. It also suggested that information about nutrients (e.g., through CCK) and meal volume (from distension) that is transmitted to the forebrain may already be integrated at the level of vagal afferents [22].

**Thirst circuits integrate signals from the oropharynx, gut, and blood**

Thirst is triggered by activation of glutamatergic neurons in the subfornical organ (SFO) and organum vasculosum of the lamina terminalis (OVLT) [67,68]. Because these neurons lie outside the blood–brain barrier and are directly activated by increases in blood osmolality, it was long assumed that their activity would gradually fluctuate in unison with changes in the blood. However, in vivo neural recordings revealed that thirst-promoting SFO neurons [3] and their downstream targets [69,70] also receive rapid anticipatory signals from the oropharynx during eating and drinking. For example, SFO thirst neurons are progressively inhibited each time a mouse takes a lick of water, in a way that tracks the cumulative volume of water consumed [3]. This pre-gastric modulation allows thirst neurons to anticipate changes in blood osmolality before ingested water is absorbed and thereby terminate drinking pre-emptively.

The oropharyngeal signal described above allows thirst neurons to track the volume of fluids consumed, but provides no information about their composition [3]. Recent work has shown that this missing information is provided by a signal from the gut that tracks fluid osmolality [71**,72] (Figure 4c,d). For example, SFO thirst neurons and their downstream targets are rapidly inhibited when water is infused into the stomach and are rapidly activated when hypertonic fluids are infused, in direct proportion to the osmolarity of the infused solution [71**]. This gastrointestinal modulation functions to control thirst satiation, by either stabilizing the transient...
Optical recordings of neurons that control hunger, thirst, and salt appetite.

(a) Sagittal representation of the brain’s hunger circuit, highlighting the projections of AgRP neurons. (b) Left: AgRP neurons are rapidly inhibited when hungry mice are presented with food, before feeding begins [62]. Right: AgRP neurons are rapidly inhibited by intragastric infusion of the liquid diet Ensure [65], which is a complex mixture of fats, proteins, and sugars. (c) Sagittal representation of the brain’s thirst circuit, highlighting the projections from the lamina terminals (SFO, MnPO, and OVLT). (d) Left: SFO thirst neurons are rapidly inhibited when thirsty mice drink water, in a manner that is time-locked to ingestion [3]. Right: SFO thirst neurons are rapidly inhibited by intragastric infusion of water, and are activated by infusion of hypertonic solutions (not shown) [71**]. (e) Sagittal representation of the brain’s salt appetite circuit, highlighting the projections of aldosterone-sensitive HSD2 neurons. The pre-LC neurons that drive salt appetite project broadly throughout the brain (including to the BNST), although the functions of these projections have not yet been annotated. (f) Left: Pre-LC neurons are rapidly inhibited when salt-deprived mice drink sodium solutions [74]. Right: In contrast, pre-LC neurons are not modulated by intragastric infusion of NaCl [74]. The black vertical lines in (b), (d), and (f) indicate the start of food, water, or salt (0.15 M NaCl) availability, and the gray shaded areas indicate the duration of intragastric infusion. The data in (b) are adapted with permission from Figure 5 of Ref. [62] (copyright 2015, Elsevier) and from Figure 1 of Ref. [65] (copyright 2017, Elsevier). The data in (d) are adapted with permission from Figure 2 of Ref. [3] (copyright 2016, Springer Nature) and from Figure 1 of Ref. [71**] (copyright 2019, Springer Nature). The data in (f) are adapted with permission from Figure 4 of Ref. [74] (copyright 2019, Springer Nature).

Abbreviations: AgRP, agouti-related peptide; ARC, arcuate nucleus; BNST, bed nucleus of the stria terminalis; CeA, central amygdala; HSD2, 11β-hydroxysteroid dehydrogenase type 2; LH, lateral hypothalamus; MnPO, median preoptic nucleus; NTS, nucleus of the solitary tract; OVLT, organum vasculosum of the lamina terminalis; PAG, periaqueductal gray; PBN, parabrachial nucleus; pre-LC, pre-locus coerulescens; PVH, paraventricular hypothalamus; PVT, paraventricular thalamus; SFO, subfornical organ; SON, supraoptic nucleus.

Inhibition of thirst neurons produced by oropharyngeal signals when water is drunk or by causing thirst neuron activity to rebound when hypertonic fluids are consumed [71**]. While the specific cell types and pathways mediating this gut–brain communication are largely unknown, the vagus nerve [71**] and key forebrain GABAergic interneurons that suppress thirst [71**,72] have been shown to be involved. On longer timescales (tens-of-minutes to hours) ingested fluids can modulate SFO thirst neurons directly, through their effects on the volume and...
osmolarity of the blood. Thus, forebrain thirst neurons integrate layers of signals that report on ingestion and its physiologic effects in order to generate a running estimate of the body’s need for water.

In contrast to the regulation of thirst, gut osmosensing does not appear to play a major role in salt appetite. Early behavioral studies showed that sodium detection in the mouth, but not the gastrointestinal tract, satiates the innate desire for sodium in salt-deprived animals [73], and fiber photometry recordings have confirmed that salt appetite-promoting neurons in the pre-locus coeruleus (pre-LC) do not respond to intragastric sodium [74] (Figure 4e,f). Recently, key neurons in two other brain regions that control ingestive behavior—the parabrachial nucleus [75,76,77]** and insular cortex [78,79]**—have also been observed by calcium imaging, demonstrating that these cells respond to both interoceptive and exteroceptive cues. Investigation of the specific gastrointestinal signals that regulate these hindbrain and cortical cell types should generate important new insight in the near future.

**Layers of feedback converge on forebrain neurons that control appetite**

The experiments described above have made it possible to observe how eating and drinking modulate key neurons that control appetite. A major finding has been that these cells receive layers of feedback signals, which begin the moment that food or water is detected and then emerge sequentially as ingestion proceeds (Figure 4). These signals are remarkably diverse—spanning, for example, the smell of food, the nutrient content of the gut, and the level of body fat reserves—yet are seamlessly integrated within individual neurons to track changes in bodily state. This reveals how the feedback control of appetite is represented in the key circuits that control eating and drinking. Our ability to monitor these cells while systematically manipulating their inputs, whether they arise from within the body or from the outside world, creates an exciting new opportunity to probe the logic underlying ingestive behavior.

**Conflict of interest statement**

Nothing declared.

**Acknowledgements**

We thank members of the Knight laboratory for comments on the manuscript and Julia Kuhl for illustrations. C.A.Z. acknowledges support from the NSF Graduate Research Fellowship (DGE-1144247), UCSF Discovery Fellowship, Genentech Foundation Predoctoral Fellowship, and NIH National Research Service Award (F31-HL137383). Z.A.K. is a Howard Hughes Medical Institute Investigator and acknowledges support from the New York Stem Cell Foundation, American Diabetes Association Pathway Program, Rita Allen Foundation, McKnight Foundation, Alfred P. Sloan Foundation, Brain and Behavior Research Foundation, Esther A. and Joseph Klingenstein Foundation, UCSF Program for Breakthrough Biomedical Research, and UCSF Nutrition Obesity Research Center. This work was also supported by an NIH Director’s New Innovator Award (DP2-DK109533), R01-DK106399, and R01-N5094781.

**References and recommended reading**

Papers of particular interest, published within the period of review, that have been highlighted as:

- of special interest
- **of outstanding interest


This study characterized the chemosensory properties of enterochromaffin cells (an EEC subtype) in the small intestine and colon and showed that these cells form serotonergic synapses with peripheral sensory neurons.

This study showed that nutrient-sensory EECs (CCK cells in the small intestine and PYY cells in the colon) form glutamatergic synapses with vagal and spinal sensory neurons.


This study showed that activation of vagal sensory neurons broadly innervating the upper gastrointestinal tract suppresses feeding and intragastric fat administration, and drives dopamine release and reinforcement.


This study reported a cellular atlas of the vagus nerve that connects the genetic identity of vagal cell types to their anatomy and function. It further showed that stimulation of a vagal subtype that forms IGLE mechanoreceptors innervating the intestines potently suppresses feeding and inhibits AgRP neurons. This revealed a role for intestinal mechanosensation in the regulation of hunger.


This study showed that individual midbrain dopamine neurons are activated by intragastric sugar infusion, and that this activation involves the hepatic branch of the vagus nerve.


55. Brimble MJ, Dyball REJ: Characterization of the responses of oxytocin- and vasopressin-secreting neurons in the


This study showed that AgRP neurons are inhibited in a minutes-time-scale by gastrointestinal nutrients and EEC-released hormones and on a hours-timescale by leptin. It further showed that CCK is specifically required for the effect of dietary fat on these neurons.

This study showed that eating caloric (but not non-caloric) foods entrains anticipatory inhibition of AgRP neurons to associated sensory cues like sight and smell.


This study showed that thirst and vasopressin neurons are bidirectionally modulated by gastrointestinal osmolarity, and that this signal controls thirst satiation and involves the vagus nerve. It further showed that individual thirst neurons integrate feedback signals arising from the oropharynx, gut, and blood.


This study showed that hindbrain salt appetite neurons are inhibited by oral sodium taste but are not modulated by gastrointestinal signals.


This study identified a subpopulation of PBN neurons that is activated by mechanosensory signals from the upper digestive tract (mouth, esophagus, and stomach) during ingestion, and showed that gastric distension signals are transmitted to these cells by the vagus nerve. It further showed that activation of these neurons suppresses feeding, drinking, and salt intake.


This study showed that neurons in insular cortex not only respond to food- and water-predicting cues but also track slower changes in internal state. It further showed that the state-dependence of food and water cue responses involves a hypothalamus—thalamus—amygdala—cortex pathway.

