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Neural Control and Modulation of Thirst, Sodium Appetite, and Hunger

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Abstract

The function of central appetite neurons is instructing animals to ingest specific nutrient factors that the body needs. Emerging evidence suggests that individual appetite circuits for major nutrients—water, sodium, and food—operate on unique driving and quenching mechanisms. This review focuses on two aspects of appetite regulation. First, we describe the temporal relationship between appetite neuron activity and consumption behaviors. Second, we summarize ingestion-related satiation signals that differentially quench individual appetite circuits. We further discuss how distinct appetite and satiation systems for each factor may contribute to nutrient homeostasis from the functional and evolutionary perspectives.

Introduction

Ingestion of the appropriate amount of each nutrient factor is crucial for maintaining body homeostasis (Andermann and Lowell, 2017; Fitzsimons, 1998; Geerling and Loewy, 2008; Lemieux and Ashrafi, 2015; Scott, 2018). Improper nutritional balance has been linked to a wide spectrum of disorders (Berthoud and Morrison, 2008; Bourque, 2008; Morrison and Ness, 2011). For example, too much feeding leads to obesity, while a high-sodium diet poses a risk of cognitive and cardiovascular disorders (Berthoud and Morrison, 2008; Faraco et al., 2018; Milan et al., 2002). Repeated dehydration in the body could damage kidney functions chronically (Johnson and Sánchez-Lozada, 2013). Thus, optimized ingestive behavior is important for survival and well-being. Modern neurotechnologies have brought us a better understanding of neural circuits underlying body fluid and energy balance at the anatomical and functional level (Gizowski and Bourque, 2018; Ichiki et al., 2019; Lowell, 2019). As summarized in this review, appetite circuits for different nutrients (energy, water, and sodium) receive unique combinations of sensory modulation that arise from different parts of the body (Andermann and Lowell, 2017; Augustine et al., 2018b; Johnson and Thunhorst, 1997; Zimmerman et al., 2017). These signals—chemosensory, hormonal, and gut-to-brain afferent pathways—play key roles in appetite induction and satiation. This review will focus on three major appetites, hunger, thirst, and sodium craving, and explain how nutrient-

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related sensory signals regulate our ingestive behavior. In particular, we will discuss sensory modulation and operating timescale of individual appetite circuits. We propose that appetite and satiation signals are specifically tailored for each nutrient factor based on its internal nutritional need. More broadly, the activity of central appetite circuits defines “what” to ingest, while sensory modulation from the body determines “how much” to consume of a given nutrient.

Feedback and Feed-Forward Regulation of Appetite

One of the major drives of appetite is homeostatic regulation, a concept adopted by Walter Cannon in the 1930s. In this model, appetite is viewed as a passive process, with nutrient depletion being the major driving factor and nutrient absorption being the quenching factor (post-absorption signals) (Cannon, 1929). Another line of evidence in behavioral and psychophysical experiments suggested that central appetite circuits are actively regulated by sensory signals from the periphery prior to nutrient absorption (pre-absorption signals) (Kim et al., 2018; Ramsay et al., 1991; Wolf et al., 1984). From the behavioral perspective, both pre- and post-absorptive regulations are feedback signals because they are the consequences of ingestive behaviors. From the homeostatic perspective, post-absorption factors are feedback signals whereas pre-absorptive factors are feed-forward because it precedes changes in homeostatic state (Andermann and Lowell, 2017; Lowell, 2019). For clarity of terminology, we will use the terms from the homeostatic standpoint throughout this review.

Operating Timescale of Appetite Neurons

Thirst

There are dedicated neurons and brain circuits underlying major appetites: water, sodium, and energy (food). The common function of these neural circuits is to drive animals toward foraging and consuming specific nutrient factors. However, rapid neural manipulation paradigms (e.g., optogenetics) revealed drastic differences in the operating time of individual appetite neurons (Figure 1), which could have profound effects on our ingestive behavior. A brain structure called lamina terminalis (LT) in the mammalian forebrain is the primary site that regulates thirst. In the LT, neurons that control water intake are housed in three anatomically linked nuclei—the subfornical organ (SFO), the organum vasculosum of LT, and the median preoptic nucleus (MnPO). The former two structures lack the blood brain barrier and directly sense the internal water balance (Johnson and Thunhorst, 1997; McKinley et al., 2003). Thirst neurons are mainly excitatory neurons that express genetic markers such as nitric oxide synthase (nNOS) (Abbott et al., 2016; Allen et al., 2017; Augustine et al., 2018a; Betley et al., 2015; Leib et al., 2017; Oka et al., 2015; Zimmerman et al., 2016). A series of studies demonstrated that the activity of thirst neurons has a time-locked causal relationship with drinking behavior (Abbott et al., 2016; Allen et al., 2017; Augustine et al., 2018a; Betley et al., 2015; Chen et al., 2016; Gizowski et al., 2016; Matsuda et al., 2017; Oka et al., 2015; Zimmerman et al., 2019; Zimmerman et al., 2016). For instance, optogenetic stimulation of SFO thirst neurons rapidly drives water intake within a few seconds. Conversely, once the stimulation is turned off, animals rapidly stop water intake (Chen et al., 2016; Oka et al., 2015; Zimmerman et al., 2016). The rapid on and

off effects were observed in various thirst-related brain nodes including other LT nuclei and their projection sites (Abbott et al., 2016; Allen et al., 2017; Augustine et al., 2018a; Leib et al., 2017; Matsuda et al., 2017). These findings demonstrate that water-seeking and drinking behavior is precisely time-locked to thirst neuron activity in the brain.

Sodium Appetite

A similar temporal relationship between neural activity and behavior was observed for sodium appetite circuits. Internal sodium depletion increases a combination of hormonal secretion: aldosterone and angiotensin II (Richter, 1936; Sakai et al., 1986). These signals directly stimulate interoceptive neurons located in both the LT and the nucleus solitary tract (NTS) (Fitzsimons, 1998; Geerling and Loewy, 2008; McKinley and Johnson, 2004). In particular, 11-beta-hydroxysteroid dehydrogenase type 2 (HSD2)-positive neurons in the NTS respond to aldosterone and angiotensin II (Geerling et al., 2006; Resch et al., 2017). Recent studies demonstrated that activation of HSD2 neurons or a subset of SFO neurons increases preference toward sodium through their downstream sites (Jarvie and Palmiter, 2017; Matsuda et al., 2017; Resch et al., 2017). In HSD2 neurons, sodium deficiency increases spontaneous pacemaker-like activity that correlates with enhanced gene expression of several cation channels (Resch et al., 2017). Further studies revealed that interoceptive signals from HSD2 neurons are transmitted to a subset of excitatory neurons in the pre-locus coeruleus (pre-LC) (Jarvie and Palmiter, 2017; Lee et al., 2019; Resch et al., 2017). These neurons, characterized by the expression of prodynorphin (PDYN) and *Foxp2*, are causally linked to sodium ingestion in mice (Geerling et al., 2011; Lee et al., 2019). Similar to thirst neurons, stimulation of PDYN neurons with optogenetics immediately induces sodium intake in fully sated animals. Termination of light illumination rapidly ceased sodium ingestive behavior (Lee et al., 2019). Therefore, the ongoing activity of thirst and sodium appetite neurons is closely linked to water and sodium intake.

Hunger

Another key appetite, hunger, runs on a quite different operating scheme. Need-based feeding is mainly regulated by GABAergic neurons that express agouti-related peptide (AgRP) in the hypothalamic arcuate nucleus (ARC). These interoceptive neurons detect internal energy deficiency through hormonal signals such as ghrelin (Cowley et al., 2003; Friedman, 2014; Nakazato et al., 2001; Saper et al., 2002). Similar to LT neurons, AgRP neurons are exposed to circulation due to the lack of the blood brain barrier (Olofsson et al., 2013; Yulyaningsih et al., 2017). Several studies have demonstrated that artificial stimulation of AgRP neurons triggers voracious feeding behavior in energy-sated animals via downstream neural circuits (Aponte et al., 2011; Atasoy et al., 2012; Betley et al., 2013; Chen et al., 2016; Krashes et al., 2011; Livneh et al., 2017). Moreover, cell-type-specific ablation studies showed that AgRP neurons are required for need-based feeding behavior (Gropp et al., 2005; Luquet et al., 2005; Tan et al., 2014). These topics have been covered in exquisite detail by several excellent reviews (Andermann and Lowell, 2017; Lowell, 2019; Sternson and Eiselt, 2017). Importantly, AgRP neurons are known to be “slow” operating neurons for several reasons. First, unlike thirst and sodium appetite circuits, AgRP neuron stimulation does not immediately initiate feeding behavior. Instead, several minutes of delay is reported from the onset of neural stimulation to the ingestive behavior (Aponte et al.,

2011). Second, the termination of AgRP neuron stimulation does not promptly stop eating behavior. Indeed, pre-stimulation of this neural population with ChR2 causes sustained feeding behavior for 30–60 min after stimulus termination (Chen et al., 2016). These studies revealed persistent feeding regulation by AgRP neurons. At the physiological level, a single light pulse to AgRP neurons induces asynchronous and continuous (up to 1 s) postsynaptic currents at downstream projection sites (Atasoy et al., 2012). At the molecular level, neuropeptide Y (NPY) is required for this sustained behavior. Optogenetic stimulation of AgRP neurons in NPY^{-/-} mice induces time-locked feeding without persistent activity (Chen et al., 2019). These results suggest that NPY is uniquely required for sustained hunger, but how NPY affects the neural circuit activity remains unknown. Either NPY signals at AgRP downstream sites or recurrent activation circuits may contribute to the sustained ingestive phenotype. It should be noted that not all feeding-related neurons are necessarily slow operating; acute feeding could be triggered through GABAergic neurons in a few brain areas including the zona incerta and lateral hypothalamus (Hao et al., 2019; Jennings et al., 2013; Zhang and van den Pol, 2017). Optogenetic manipulation of these neurons or projections results in acute feeding regulation within several seconds that resembles binge eating behavior. It is unclear whether these fast-operating neurons are related to homeostatic regulation. However, these studies show that feeding behavior involves complex and heterogeneous regulatory processes (Rossi and Stuber, 2018), among which slow behavioral kinetics is a distinct characteristic of AgRP-related neural circuits.

Taken together, appetite for water, sodium, and energy are each regulated by specific interoceptive neurons in the LT, NTS-related nuclei, and ARC, respectively. They share a common function to process internal state information and drive appetite. However, the operating timescales are vastly different: time-locked control for thirst and sodium appetite and delayed control for feeding (Figure 1). This neural activity behavior relationship likely affects the pattern and duration of ingestive behavior toward different nutrients. One caveat of appetite kinetics is that the observations are largely based on acute optogenetic manipulation. While this is a powerful experimental approach, it is still unclear how precisely such artificial stimulation can recapitulate natural circuit functions in response to endogenous signals (Allen et al., 2015; Häusser, 2014). Nevertheless, the results from acute stimulation offer an opportunity to investigate the exact neural and molecular mechanisms underlying a distinct timescale for individual appetites.

Nutrient-Specific Satiety Signals from Peripheral Sensory Systems

Generally, nutrient absorption by the body is a relatively slow process that takes several minutes to hours, but much less time is required for consuming necessary amounts of nutrient. Therefore, if animals only rely on homeostatic feedback to terminate ingestive behaviors, they will end up eating and/or drinking too much. To solve this conundrum, the brain has evolved feed-forward satiety mechanisms (Andermann and Lowell, 2017). Imagine that you are extremely thirsty after exercising. Drinking a bottle of water should rapidly alleviate your thirst. This process takes less than a minute, even though the osmotic environment of the body has not changed by that point. From behavioral observations like this in the past decades, it became obvious that animals cease ingestive behaviors before the body absorbs nutrients (Osborne et al., 1987; Saker et al., 2014; Thrasher et al., 1981).

However, only recently did we begin to understand how the brain processes these pre-absorptive satiation signals. A series of studies in the past five years demonstrated that central appetite neurons receive rapid feed-forward modulations as summarized below (Figure 2).

Oropharyngeal and Gastrointestinal Modulation of Thirst Circuits

Once thirst neurons in the LT are stimulated by angiotensin II or hyperosmotic signals, it drives water intake behavior (Fitzsimons, 1998; Johnson and Thunhorst, 1997). Multiple lines of evidence suggest that water intake stimulates rapid satiation signals that quench thirst. The initial checkpoint of drinking exists in the throat (Saker et al., 2014; Thrasher et al., 1981). *In vivo* optical recording studies demonstrated that stimulation of the oropharyngeal area by liquid gulping inhibits thirst neurons of the LT (Augustine et al., 2018a). Intriguingly, these responses are triggered by rapid ingestion of liquid, but not solid materials. For example, water intake strongly suppresses thirst neuron activity, but eating the same amount of hydrogel (98% water) does not induce this effect (Augustine et al., 2018a). These data suggest that the brain somehow “knows” that animals have drunk liquid and anticipates future water balance. Tactile signals through vagal or other cranial nerves likely mediate gulping-induced initial thirst satiation (Augustine et al., 2018a). The second checkpoint is in the gut that senses osmolality changes. Once liquid passes through the throat, the brain waits for the next satiation signals from the gastrointestinal area to confirm that the ingested liquid will indeed rehydrate the body. Studies in awake-behaving animals have shown that SFO thirst-neuron activity is drastically suppressed by hypoosmotic stimuli in the gut (Augustine et al., 2019; Zimmerman et al., 2019). Although the precise mechanisms remain unknown, the vagal pathway was suggested to transmit gut osmolality signals to the brain (Berthoud and Neuhuber, 2000; Zimmerman et al., 2019). Importantly, oropharyngeal- and gut-mediated sensory signals work in series after water intake (Ramsay et al., 1991; Thrasher et al., 1981). Liquid-selective gulping signals initially inhibit thirst neurons. They are followed by osmolality-dependent sustained signals from the gut. In the brain, these two satiation signals are represented by different GABAergic neural populations in the LT that express glucagon-like peptide 1 receptor (GLP1r). A subpopulation of GLP1r-positive MnPO neurons are activated during drinking behavior, particularly by gulping action (Augustine et al., 2018a; Zimmerman et al., 2019). Conversely GLP1r-positive SFO neurons respond to gut osmolality change (Augustine et al., 2019). Thus, specific and independent pathways from the body to the brain appear to mediate individual thirst satiation signals.

Taste Modulation of Sodium Appetite Circuits

Sodium appetite neurons also receive feed-forward inhibition after sodium intake. Similar to water intake, animals rapidly terminate need-based sodium intake before sodium absorption by the body (Osborne et al., 1987; Wolf et al., 1984). Recent dissection of sodium appetite circuits has shed light on the mechanisms of feed-forward satiation signals. *In vivo* recording of neural dynamics in the pre-LC showed that taste signals are the major feed-forward signals from the periphery; the activity of sodium appetite neurons (PDYN neurons) were rapidly suppressed upon oral sodium contact in depleted animals (Lee et al., 2019). This effect was sodium taste dependent because of the following: (1) suppression of PDYN

neurons was only observed with sodium ions, (2) blocking sodium taste receptor, ENaC, by amiloride abolished this suppression (Chandrashekar et al., 2010; Heck et al., 1984; Oka et al., 2013), and (3) gastric sodium infusion (bypassing oral contact) had no inhibitory effect. Thus, for this particular nutrient, oral chemosensory signals play a pivotal role in pre-absorptive satiation. This idea is supported by previous studies showing that oral sodium detection is a critical factor in quenching appetite for sodium. Taste signals are transmitted from the tongue to the brain through facial nerves, but how they modulate sodium appetite neurons is unknown.

Pre- and Post-ingestive Modulation of Hunger Circuits

Feed-forward regulation also impacts hunger circuits. An elegant set of studies have shown that AgRP neurons are rapidly suppressed by sensory detection of food as well as gut caloric detection. Any food-associated cues, including visual, olfactory, and taste, are sufficient to suppress AgRP neuron activity (Betley et al., 2015; Beutler et al., 2017; Chen et al., 2015; Su et al., 2017). The association between caloric and sensory cues can be formed even after a single eating episode (Livneh et al., 2017; Su et al., 2017). However, this cue-induced suppression is temporal because AgRP neuron activity bounces back if no caloric is detected in the gut (Betley et al., 2015; Beutler et al., 2017; Chen et al., 2015; Su et al., 2017). Thus, it is now clear that caloric sensing in the gut is a primary pre-absorptive satiation signal that persistently suppresses AgRP neurons. Importantly, the amplitude of neural suppression is proportional to caloric contents in the gut. How are these satiation signals transmitted to the brain? A piece of evidence suggests that peripheral injection of anorexic hormones inhibit AgRP neurons (Beutler et al., 2017; Su et al., 2017). Some of these hormones (e.g., CCK) stimulate vagus nerves, implying that rapid feed-forward signals are mediated by neurons in the nodose ganglia (Alhadeff et al., 2019; Bai et al., 2019; Han et al., 2018; Kaelberer et al., 2018; Williams et al., 2016). Alternatively, since the ARC is exposed to circulation, the hormonal effects may be transmitted through the blood circulation. One study investigated the neural basis of feed-forward AgRP suppression and identified a genetically defined population that expresses leptin receptor in the dorsal medial hypothalamus (Garfield et al., 2016). These neurons are a GABAergic inhibitory population, rapidly activated upon foraging and feeding, and monosynaptically connected to AgRP neurons. Thus, leptin receptor-positive neurons, at least in part, convey feed-forward modulation to AgRP neurons. Although one neural substrate for rapid satiation is uncovered, many questions remain unanswered. For example, just seeing food does not suppress our craving for food (Hill et al., 1984; Lambert et al., 1992), but hunger neurons are suppressed by the same stimulus. Thus, the perception of hunger and eating behavior itself may be regulated by related but distinct mechanisms. Another question is the gut-to-brain signal transmission. It was suggested that different hormonal signals are involved in fat-, sugar-, and protein-induced satiation signals from the gut (Beutler et al., 2017; Su et al., 2017). In other species, including humans, *Drosophila*, and *C. elegans*, element-specific appetite has been well documented, although the precise feedback and feed-forward mechanisms remain to be discovered (Griffioen-Roose et al., 2012; Lemieux and Ashrafi, 2015; Liu et al., 2017; Stubbs et al., 2001; Yang et al., 2018). Further studies will clarify whether and how peripheral detection of individual nutrient components modulates brain appetite circuits.

This review exclusively focused on feed-forward aspects of appetite modulation. It is, however, important to note that homeostatic feedback signals also play crucial functions for ingestive termination on a longer timescale. For instance, intravenous infusion of water or caloric contents can alleviate thirst and hunger, respectively, without apparent feed-forward signals (Nicolaidis and Rowland, 1974; Walls and Koopmans, 1992). Similarly, gastric sodium load provides little satiation effects in the order of minutes. However, a few hours after loading, sodium intake is significantly suppressed because of feedback signals (Lee et al., 2019; Wolf et al., 1984). Therefore, nutrient absorption itself carries satiation signals to inhibit central appetite circuits. In reality, sensory-based feed-forward signals and homeostatic-based feedback signals work together to regulate animals' daily ingestive behavior. How these two sources of signals modulate each other is an important area of future study.

Need-Based Neural Circuit Architecture for Appetite and Satiation

Different appetite circuits drive ingestion over distinct timescales and receive unique sensory modulations from the periphery. What is the evolutionary benefit of having dedicated regulations for each appetite instead of a single mechanism? We propose that operating time of appetite neurons and feed-forward signals are specifically evolved to meet the nutrient's need. The requirement of nutrient factors widely varies. Humans roughly consume 2–5 L of water and 1500–3000 kcal of energy while we need only approximately 1.5 g of sodium daily (Geissler and Powers, 2017; National Academies of Sciences, Engineering, and Medicine, 2019; Popkin et al., 2010). Laboratory mice also consume widely variable amounts of nutrients (Bachmanov et al., 2002; Council, 1995). How does the brain adjust ingestive behavior in order to meet variable and unique nutrient needs of the body? Compared with other major nutrients, the sodium requirement is minimal because of sodium retention in the kidney (DiBona, 2005). Correspondingly, sodium appetite neurons are fast operating: their activity is precisely time-locked to ingestive behavior (Lee et al., 2019). The activation is rapidly quenched upon sodium detection in the oral cavity. We speculate that the combination of acute appetite induction and satiation allows ingestion of a minimum but necessary amount of sodium. Conversely, animals need to consume a larger quantity of food through slow chewing or biting processes. This would require longer behavioral control by the brain after the onset of eating. In fact, major hunger satiation signals arise from the gut, which are much slower to take effect compared with taste signals. Consequently, these delayed signals allow animals more time to consume food. Importantly, as mentioned above, AgRP neurons drive persistent feeding even after the activity is quenched. This slow and persistent behavioral regulation may contribute to maximizing food consumption. Thirst is somewhere in between because thirst neuron activity corresponds well with drinking behavior, but major satiation signals derive from oropharyngeal and gut areas (Augustine et al., 2019; Augustine et al., 2018a; Zimmerman et al., 2019; Zimmerman et al., 2016). This combination may allow animals to consume enough water before satiation signals terminate the behavior. Altogether, these functional analyses of major appetite circuits suggest that feed-forward signals associated with ingestion are a key factor to determine the amount of ingestion. If these speculations are correct, then interrupting feed-forward signals should affect ingestive behavior. Recent studies on the thirst circuit addressed the functional

relevance of feed-forward signals to drinking. When thirst satiation neurons (GLP1r-positive neurons) in the LT are functionally silenced, animals spend an unusually long amount of time drinking (Augustine et al., 2019; Augustine et al., 2018a). Apart from the LT, several candidate neurons that may encode feed-forward signals have been identified. GLP1r-positive neurons in the paraventricular hypothalamus are activated by food cues and caloric contents (Li et al., 2019). Stimulation of these neurons bidirectionally regulates feeding behavior. Oxytocin receptor-positive neurons in the parabrachial nucleus are acutely activated by fluid intake, suggesting roles in fluid satiation (Ryan et al., 2017). Broader analysis of satiation circuits will provide further insights into the roles of pre-absorptive satiation signals in ingestive control.

When we get thirsty, our natural instinct is to look for liquid water and gulp it down. However, nutrient availability is not equal for all species. A typical example is water sources: although some species like laboratory mice or humans drink liquid water, it is rarely available for animals in arid climates. Indeed, these animals generally eat instead of drink to gain water (McManus, 1972; Schmidt-Nielsen and Schmidt-Nielsen, 1952; Vanderweele, 1974). To deal with this nutrient pressure, desert species have adapted their body (e.g., kidney morphology and function) for better water conservation (Vimtrup and Schmidt-Nielsen, 1952). In the nutrient-specific feed-forward model, we predict that central appetite and satiation circuits have co-evolved to deal with nutrient availability in the environment. More specifically, liquid-based feed-forward satiation mechanisms (i.e., gulping) may have been replaced by other mechanisms, and thirst circuit activity may be innately linked to eating behavior in arid species. In this regard, it would be interesting to compare appetite and satiety circuits in laboratory mice and desert animals that rarely drink water throughout life and investigate how their behavior and neural functions adapted to their living environment.

Concluding Remarks

In the past decade, cell-type-specific analysis has seen great success in unveiling the function of interoceptive neurons and their immediate downstream neural circuits (Andermann and Lowell, 2017; Gizowski and Bourque, 2018; Lowell, 2019; Sternson and Eiselt, 2017; Zimmerman et al., 2017). These studies have revealed appetite regulation mechanisms for major nutrient factors: water, sodium, and energy. First, thirst and sodium appetite circuits are fast operating, in that neural activity drives appetite and ingestive behavior rapidly (Figure 1). Conversely, need-based hunger circuits seem to have slower behavioral kinetics after neural firing. Second, all appetite neurons receive feed-forward satiation signals before nutrient absorption. However, the sources of these signals are quite different. As summarized in Figure 2, thirst, sodium appetite, and hunger circuits are modulated by distinct combinations of pre- and post-consumption signals from the periphery. Recent studies suggest that a unique appetite induction and satiation mechanism may contribute to optimal nutrient ingestion and homeostasis.

Despite better understanding of appetite regulation, there are still many missing puzzle pieces in understanding the basis of ingestive regulation. For one thing, it remains unknown how signals from interoceptive neurons modulate our perception of nutrient, motivational

state, and behavioral output. For another, the precise neural pathways and/or mechanisms underlying feed-forward appetite regulation awaits further investigation. Expanding neurotechnologies, including transcriptomics and gene editing, should provide a springboard to tackle these key questions.

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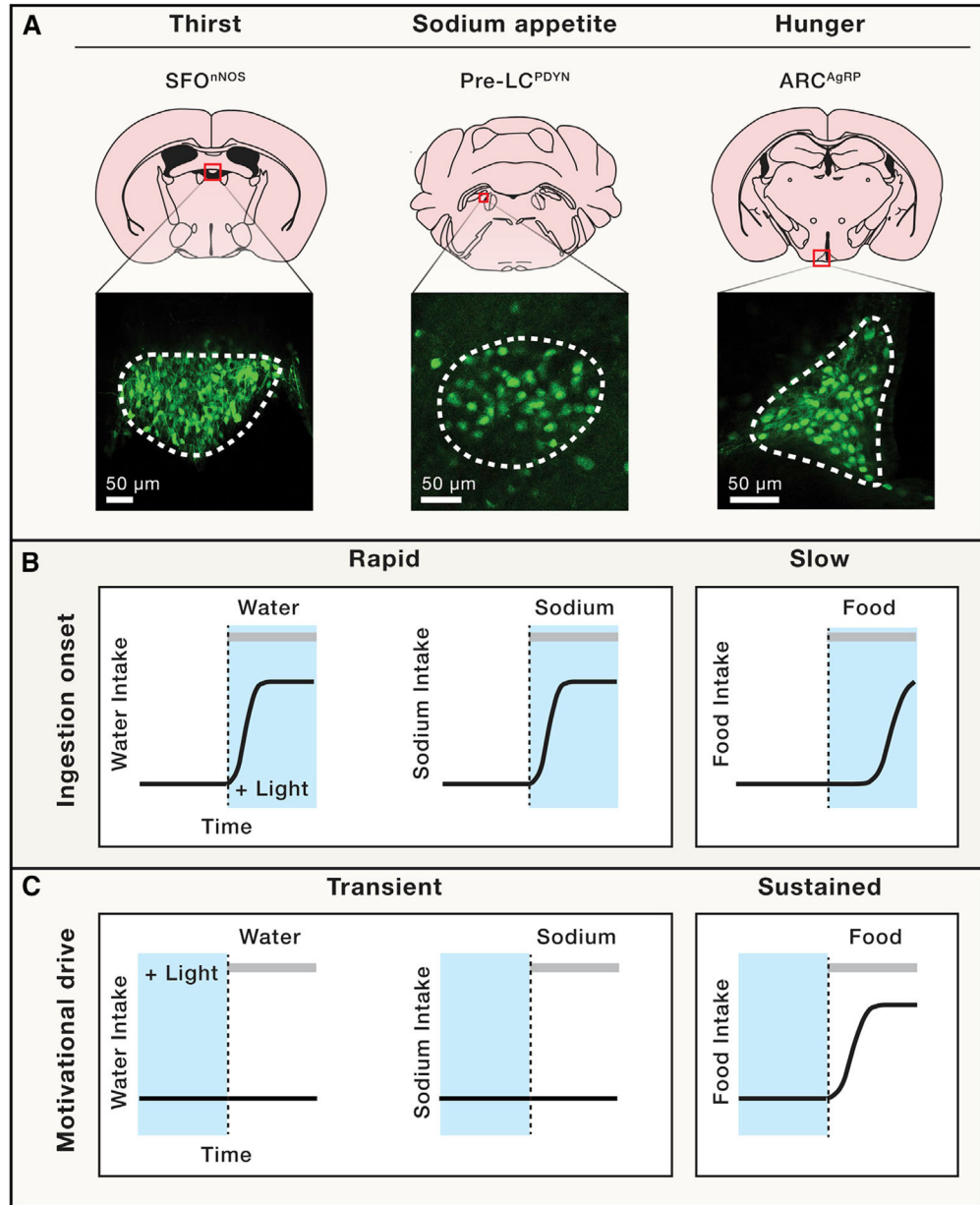


Figure 1. Operating Timescale of Distinct Appetite Neurons
 (A) Representative neuronal populations that regulate thirst (left), sodium appetite (middle), and hunger (right) visualized with fluorescence reporters. Shown are coronal sections of mouse brain containing individual neural populations (upper panels), and magnified images (lower panels). Scale bars, 50 μ m.
 (B) Temporal relationship between neural stimulation and nutrient consumption. The onset of ingestion upon optogenetic activation of appetite neurons. The x axis shows the time before and after neural stimulation, and the y axis shows nutrient consumption. Stimulation of thirst (left) and sodium appetite (middle) neurons induces rapid consumption. Conversely, hunger neurons (right) drive feeding with a longer latency. Photo-stimulation periods are shaded in blue, and nutrient access is indicated by gray bars.

(C) Motivational drive after continuous stimulation of appetite neurons. In the absence of ongoing thirst (left) and sodium appetite (middle) neuron activities, animals do not consume water and sodium, respectively. By contrast, robust food consumption is induced after the termination of hunger neuron stimulation (right). Although AgRP-related homeostatic feeding regulation is a slow process, not all feeding circuits are slow-operating. For example, stimulation of GABAergic neurons in a few brain areas drives acute feeding (Hao et al., 2019; Jennings et al., 2013; Zhang and van den Pol, 2017).

Abbreviations are as follows: AgRP, agouti-related protein; ARC, arcuate nucleus; nNOS, neuronal NO synthase; PDYN, prodynorphin; pre-LC, pre-locus coeruleus; SFO, subfornical organ.

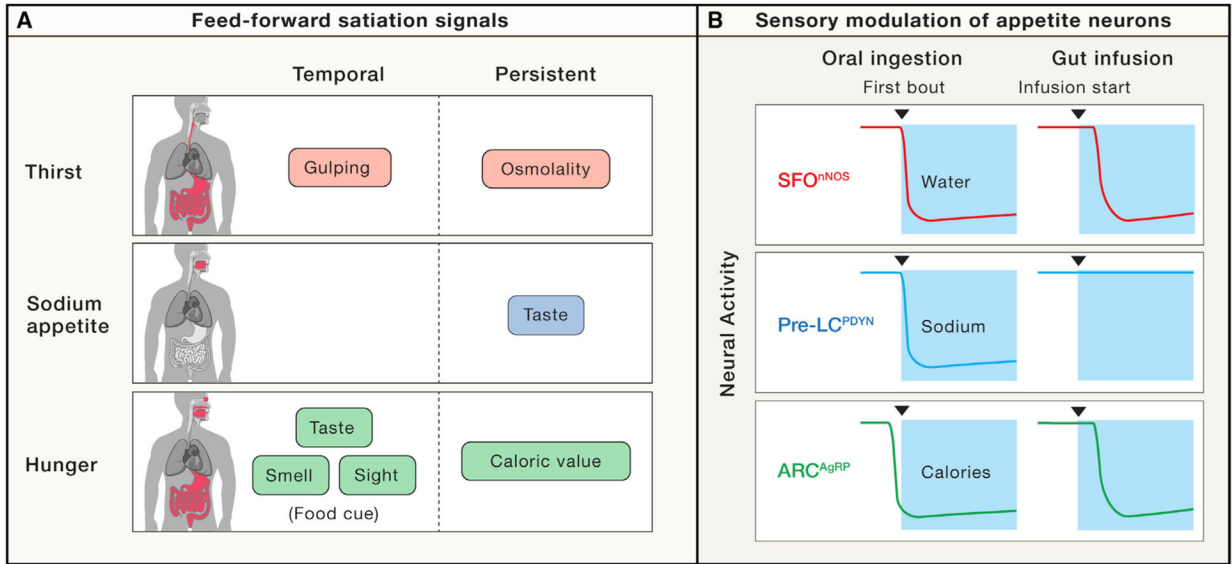


Figure 2. Feed-Forward Regulation of Appetite Circuits

(A) Temporal and persistent feed-forward factors regulating thirst (top), sodium appetite (middle), and hunger (bottom). Thirst circuits are temporally inhibited by liquid gulping through signals derived from the oropharyngeal area, while persistent inhibition stems from the gut based on the osmolality of the ingested fluid. Sodium taste signals arising from the mouth persistently inhibit sodium appetite circuits. Various food-related cues like vision, smell, or taste contribute to temporal inhibition of hunger neurons in the ARC. Persistent modulation of hunger neurons is caused by caloric detection by the gut.

(B) Sensory modulations of appetite neurons. Shown are schematic calcium dynamics of thirst (red), sodium appetite (blue), and hunger neurons (green) after oral and intragastric nutrient administration. Each neural population receives unique sets of sensory modulation from the periphery after nutrient ingestion.