Cell Reports
Preview

AgRP Accountants Compute Caloric Cost

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https://doi.org/10.1016/j.celrep.2017.11.074

The gut-brain communication underlying energy homeostasis has been a topic of interest for years. In two new papers, Beutler et al. (2017) and Su et al. (2017) delve into the mechanisms by which satiation is represented in a well-studied population of orexigenic neurons.

From a human health viewpoint, it is imperative to understand how eating is regulated in the brain. Fasting-activated agouti-related peptide (AgRP) neurons reside at the base of the hypothalamus and are both necessary and sufficient to mediate food seeking and consumption (Aponte et al., 2011; Krashes et al., 2011; Luquet et al., 2005). They were once hypothesized to slowly diminish their activity levels upon discovery and ingestion of calories until satiety is reached. However, paradigm-shifting research demonstrated that this discrete cell type is rapidly and robustly inhibited within seconds of food detection, before actual ingestion (Betley et al., 2015; Chen et al., 2015; Mandelblat-Cerf et al., 2015). Importantly, this population-wide silencing of AgRP dynamics is dependent on ensuing eating and is promptly reset if caloric consumption does not occur (Betley et al., 2015; Chen et al., 2015; Mandelblat-Cerf et al., 2015). These findings suggest that regulation of eating can occur at multiple, interconnected levels, including (1) sensory contingencies of food detection, (2) physical biting, chewing, and swallowing, (3) distension of the stomach, (4) nutrient sensing, and (5) secreted satiety hormones.

Two recent papers employed fiber photometry in AgRP neurons to determine the integrative processes by which AgRP neurons encode hunger through communication with the gut to estimate energy balance. By separately considering the sensory and nutritive properties of food, both groups revealed two distinct properties of AgRP inhibition: a transient, sensory-mediated anticipatory response and a sustained, calorie-dependent response. In this issue of *Cell Reports*, Su et al. (2017) assessed the contribution of sensory aspects (taste, sight, and smell) of food in AgRP regulation by providing animals with a non-caloric gel and found the neural response was reduced over trials due to the lack of calories. Remarkably, this devaluation was promptly reversed upon presentation of a caloric gel with nearly identical visual, olfactory, and gustatory profiles, convincingly demonstrating that AgRP neurons learn the nutritive value of novel foods in a single trial. Concordantly, both studies found that sustained inhibition of AgRP neurons requires caloric consumption.

To identify the neural underpinnings of this calorie-conditional suppression, both groups equipped mice with intragastric catheters for direct infusion of nutrients into the stomach while recording AgRP population dynamics. Strikingly, gastrointestinal calorie detection durably inhibited AgRP activity within minutes in a manner proportional to the number of calories infused. Furthermore, this rapid reduction was independent of macronutrient identity. Isovolemic and isocaloric solutions of glucose, lipids, or amino acids all reduced AgRP activity with similar magnitudes and temporal resolution. This response was independent of osmotic, stretch, and taste signaling in the gut, as water, hypertonic saline, methylcellulose, and sucralose failed to influence AgRP network dynamics.

Whereas AgRP neuronal activity in sated mice is not regulated by external sensory cues (Betley et al., 2015; Chen et al., 2015), Beutler et al. (2017) surprisingly found that AgRP activity in fed mice is further reduced by direct delivery of intragastric nutrients. This reveals a calculative role of these neurons in dictating food intake based on current nutritional state. Supporting this ability of AgRP neurons to predict the number of calories to be consumed, gastrointestinal nutrients or toxins that evoke sickness reduced the sensory response of AgRP neurons to subsequently presented food. Individual animal analyses showed a tight correlation between the level of AgRP reduction and the quantitative value of food consumed.

Nutrient detection and distension in the gut spark the release of a host of satiety hormones to provide interoceptive feedback to ensure proper energy balance (Clemmensen et al., 2017). Both labs challenged animals with a set of anorectic peptides and found that cholecystokinin (CCK) caused a rapid but transient reduction in AgRP activity, an effect specific for lipid detection as revealed by pharmacological blockade of CCK-A receptors, whereas peptide tyrosine tyrosine (PYY) induced a delayed, sustained response. While Beutler et al. (2017) observed a similar fast and brief inhibition via 5-hydroxytryptamine, they failed to detect the AgRP neuron changes in response to amylin reported by Su et al. (2017), perhaps due to technical disparities or different sources/batches of peptide. Nonetheless, together the labs found that glucagon, glucagon-like peptide-1, gastrin-releasing peptide, enterostatin, obestatin, oxyntomodulin, and leptin had no acute effect on AgRP activity. However, elegant work by Beutler et al.

(2017) showed that leptin generates a slow modulation, likely involving transcription-dependent synaptic plasticity (Pinto et al., 2004) of both AgRP and POMC activity with diametrical control that is required to restrain feeding. Optogenetic AgRP photostimulation experiments in leptin-deficient mice support a model in which the site of action of this well-studied hormone is centered on or upstream of AgRP neurons (Garfield et al., 2016).

While these results vastly enhance our understanding of feeding circuits, they also pave the way for further studies. A major limitation of photometry is the inability to directly correlate increased calcium levels with a numerical increase in action potentials, although this could be achieved via *in vivo* electrophysiological or optical voltage-sensor recordings. Furthermore, photometry relies on bulk population activity, making it impossible to investigate heterogeneity in the AgRP subfield to different nutrients and satiety peptides. This caveat can be addressed by sharpening the specificity of photometry recordings through discrete axonal projection monitoring (Chen et al., 2015) or using miniaturized endoscopy to visualize individual AgRP cells (Betley et al., 2015).

These studies establish that AgRP suppression is a consequence of nutrient detection in the gut. It is, however, unclear whether effects of nutrient detection and resultant satiety peptide secretion act directly or indirectly on AgRP neurons. Several avenues can identify the pathways by which these cells receive nutritional information. Selective vagotomy could pinpoint the necessity of ascending neural pathways and establish a causal link between gut-brain connections. Genetically powered, cell-type- or region-specific knockouts of peptide receptors could target the neural populations and/or location of action of these manipulations. In concert, satiety hormones and/or their corresponding antagonists could be administered to individual brain regions through cannula implants.

Given that these papers reveal that inhibition of AgRP activity is inversely proportional to increasing calorie intake, it would be interesting to probe whether corresponding sensory modulation of AgRP activity could be mediated via reward prediction error. Moreover, it will be interesting to uncouple the role of oropharyngeal signals generated during eating from caloric detection in the stomach using classic gastric emptying methods. Another compelling future direction is to assess the effects of caloric but otherwise non-palatable tastants on AgRP activity, since tolerance for bitter compounds and spoiled food is positively correlated with starvation grade. Similarly, would illness-eliciting caloric foods be devalued if encountered again, and if so, would this depreciation occur with temporal dynamics similar to the devaluation of palatable foods not meeting proper caloric criteria?

Although the response properties of AgRP neurons to the sensory detection of food is unchanged in leptin-deficient mice, it would be insightful to probe the population dynamics in this and other genetically obese models in response to direct gut infusions and peptide challenges. Perhaps it would be even more relevant to our current obesity epidemic to explore the properties of AgRP neurons in diet-induced obese animals. Given the growing number of patients undergoing gastric bypass surgery, determining the gastrointestinal sites that most potently reduce AgRP activity when infused with micronutrients may have important implications for our understanding of the cellular and molecular basis of weight loss after this procedure. These two papers markedly expand our understanding of this complex system and open multiple directions for future exploration.

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