Cell

The Hunger Games

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http://dx.doi.org/10.1016/j.cell.2015.02.028

Although AgRP and POMC neurons in the hypothalamus have long been associated with regulation of food intake, in this issue of *Cell*, Chen et al. use direct imaging in vivo to demonstrate rapid changes in their activity upon food presentation. The rapidity of their altered responses challenges classic notions of their functions and raises new hypotheses.

Food is essential to an organism's survival, and consequently, considerable neural circuitry is dedicated to directing and regulating ingestive behaviors. Hypothalamic AgRP and POMC have been known as the yin/yang of food intake regulation for over a decade (Schwartz et al., 2000). They are targets of molecules indicating energy status such as leptin, ghrelin, and nutrients, with AgRP neurons promoting feeding and POMC neurons decreasing feeding. However, approaches to measuring the activity of these neurons have been technically limited in terms of monitoring them during the act of eating itself.

In the current edition of *Cell*, all of this changes. Chen et al. (2015) used fiber photometry to visualize the activity of both AgRP and POMC neurons while hungry mice began to eat palatable food or interact with food odors in their environment. Given that activating AgRP neurons is thought to cause a robust and rapid increase in food intake (Aponte et al., 2011), a logical expectation might have been that AgRP neuronal activity would be high when animals began to eat, remain high during the early portion of the meal, and gradually decline during eating as appetite ebbed. The exact opposite pattern would be expected in POMC neurons—a low start followed by a gradual rise during eating. What Chen et al. found, however, was that while AgRP neuronal activity was high in fasted mice before encountering food, their AgRP neuronal activity decreased in mere seconds as soon as food was presented and just as eating began. Conversely, POMC activity, while low as expected in hungry mice, rose almost immediately as soon as the mouse began to eat, even though mice continued to eat avidly for some time more without being inhibited by the initial rise in POMC neuronal activity. If the chow pellet was removed midway through the meal, the AgRP neurons increased again in activity, and the POMC neurons declined. Moreover, if mice were given access to more attractive food, such as chocolate or peanut butter, the rapid decrease in AgRP activity and increase in POMC activity were even more pronounced.

These observations have a number of important implications. The rapid changes in the activity of these neurons could not be the result of signals coming from the body about fuel status. That is, the early POMC rise could not be a physiological satiety signal, nor could the early AgRP decline mean that appetite had disappeared (since the mice continued to eat avidly for some time after both signals changed). At least, if the initial POMC rise were a satiety signal that stops eating, it was a remarkably ineffective one because most of the avid eating occurred afterward. Rather, these changes must reflect inputs onto these neurons that process information about the immediate availability and attractiveness of food in the environment.

What does that mean for understanding the regulatory roles of AgRP or POMC neurons? Chen et al. (2015) suggest one possibility. They note that hunger would promote foraging in addition to eating food actually found and propose that the role of AgRP neurons is specifically the former. A sudden drop in in AgRP as soon as food was discovered, they suggest, "provides a mechanism to rapidly inhibit foraging upon the discovery of food." In that case, AgRP and POMC would have a role in appetitive food seeking and foraging behaviors but not so much in the consummatory eating phase of actual biting, chewing, and swallowing. Splitting appetite into separate effects on foraging and consummatory behaviors is certainly one way of potentially solving this puzzle. However, that split raises a further puzzle of why earlier studies reported that AgRP and POMC manipulations do powerfully control food consumption, and so it is not limited to foraging behavior (Aponte et al., 2011).

A second way of looking at the rapid changes in activity is that AgRP may still promote the act of eating and intake, and POMC activity inhibits intake, but these signals are only the first links in a long chain. By that view, the rapid changes in AgRP and POMC neuronal activity are not sufficient to inhibit intake on their own but might act as the first topple in a chain of dominos. After some delay, the final domino might be another mechanism that successfully inhibits eating.

A third way of looking at the rapid response of AgRP and POMC neurons is the alternative view that perhaps these signals do not drive eating directly, but rather these neurons modulate and receive powerful input from brain reward circuitry that reacts to cues and foods in the environment and that mediates current motivation to eat (Figure 1). That is, high AgRP (and low POMC) may prime the reactivity of mesocorticolimbic circuitry to the sight, smell, and taste of food, which generates high incentive motivation to eat, rather than simply

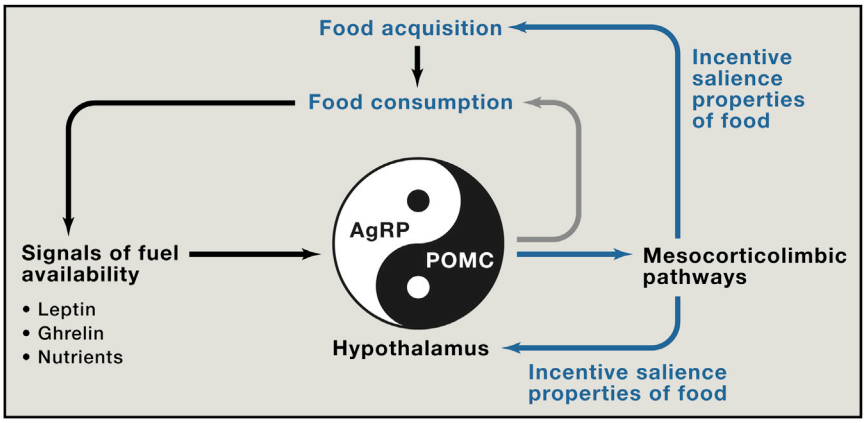

Figure 1. Integrated Model for the Roles for AgRP and POMC Neurons in Food Responsiveness and Energy Homeostasis

Traditional models of hypothalamic regulation of food intake (blue arrows) hypothesize that AgRP and POMC neurons in the hypothalamus are regulated by signals of fuel availability and, in turn, that AgRP activation directly drives eating, whereas POMC activation inhibits eating (hatched blue arrow). Chen et al. (2015) challenge this view and show that these neurons' activity is often disconnected with the act of eating itself. Incorporating findings of Chen et al. (2015) into the incentive interpretation we describe, the activity of these neurons instead primes the motivational/incentive salience mesocorticolimbic circuitry to react to food stimuli, which sustains continued eating, and feeds back to immediately and potently regulate hypothalamic neuronal activity (yellow arrows). This embeds hypothalamic function to regulate eating into larger circuitry that also incorporates mesocorticolimbic pathways and regulates the varied behaviors involved in acquiring and consuming food in a complex environment.

causing a hunger drive that more directly powers eating. Once eating is triggered by that amplified mesocorticolimbic reaction to food, the high AgRP could be superfluous to appetite and eating behavior and is able to decline without suppressing behavior. Higher mesocorticolimbic reactivity could sustain eating by its own continuing activation, such as by higher dopamine levels or related neuronal signals in nucleus accumbens or related targets (see Figure 1). In turn, by this view, mesocorticolimbic circuitry must send feedback signals that food is encountered to hypothalamus, causing the early changes in AgRP and POMC neurons, so that their activity immediately reflects the incentive value of food in the moment.

Other data support this modulatory incentive hypothesis. For example, starvation signals similarly increase mesocorticolimbic reactivity to food in both humans and rats (Berthoud, 2012; DiLeone, 2009; Farooqi et al., 2007; Figlewicz and Sipols, 2010) (though compare Fulton et al. [2006]). Incentive-related feedback from mesocorticolimbic circuitry may also explain another finding of Chen et al. (2015)—namely, that the rapid AgRP and POMC activity changes triggered by mouse chow can be blocked if the mouse has just eaten a morsel of chocolate or peanut butter 10 min earlier. If the order is reversed, however, eating chow first does not block the neural responses to a subsequent chocolate or peanut butter treat. Eating chocolate first would reduce the incentive value of chow, but that should not occur in reverse, and so the rapid AgRP and POMC changes accordingly remain robust to both foods.

This incentive hypothesis of hypothalamic interaction with mesocorticolimbic circuitry leads to some further predictions. For example, neutral cues in the environment can gain motivational value when paired with food and activate mesocorticolimbic systems as effectively as food itself. The current findings would predict that such previously neutral stimuli would also serve as potent stimuli to rapidly alter the activity of AgRP and POMC neurons if they have been learned as food cues.

The bottom line is that psychologists and neuroscientists have spent decades investigating the relationship between neural activity and key aspects of our behavior, including motivation, reward, and hunger. Chen et al. (2015) have ushered in a new chapter where molecular markers of activity for the neurons one wishes to observe can be directly related to ingestive behavior. Here, we have learned that these specific neuronal populations respond more rapidly than previously suspected to information about the quality of food in their environment. Given the importance of these neurons beyond ingestive homeostasis (Dietrich et al., 2012; Matarese et al., 2013), the implications for this work extend to understanding not only how food intake is regulated but to a wide swath of topics around the relationship between brain and behavior.

ACKNOWLEDGMENTS

R.J.S. has received research support from Novo Nordisk, Boehinger Ingelheim, Eisai, Givaudan, and Ethicon Surgical Care. He has also served as a paid consultant for Novo Nordisk, Boehinger Ingelheim, Sanofi, Novartis, Circuit Therapeutics, Nestle, and Takeda.

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