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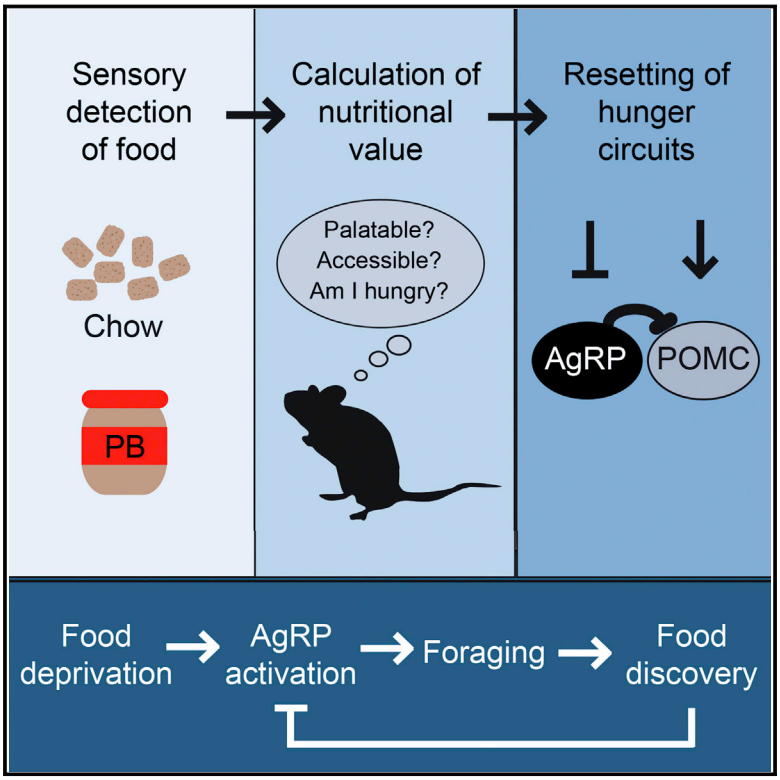
Sensory Detection of Food Rapidly Modulates Arcuate Feeding Circuits

Graphical Abstract



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In Brief

Simply presenting food to a hungry mouse resets the activity of its AgRP and POMC neurons from a pattern associated with energy deficit to one associated with satiety, even if no food is consumed. The extent of the neuronal activity changes depends on the accessibility and palatability of the food.

Highlights

- Sensory detection of food rapidly inhibits AgRP and activates POMC neurons
- Rapid sensory feedback occurs before any food is consumed
- The magnitude of neuronal response depends on food palatability and nutritional state
- AgRP/POMC neurons may play a primary role in driving food discovery

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Sensory Detection of Food Rapidly Modulates Arcuate Feeding Circuits

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SUMMARY

Hunger is controlled by specialized neural circuits that translate homeostatic needs into motivated behaviors. These circuits are under chronic control by circulating signals of nutritional state, but their rapid dynamics on the timescale of behavior remain unknown. Here, we report optical recording of the natural activity of two key cell types that control food intake, AgRP and POMC neurons, in awake behaving mice. We find unexpectedly that the sensory detection of food is sufficient to rapidly reverse the activation state of these neurons induced by energy deficit. This rapid regulation is cell-type specific, modulated by food palatability and nutritional state, and occurs before any food is consumed. These data reveal that AgRP and POMC neurons receive real-time information about the availability of food in the external world, suggesting a primary role for these neurons in controlling appetitive behaviors such as foraging that promote the discovery of food.

INTRODUCTION

Food intake is controlled by evolutionarily hard-wired neural circuits that contain specialized neural cell types. Two cell types in the arcuate nucleus (ARC) of the hypothalamus are known to be particularly important for the control of feeding. These neurons are identified by expression of the neuropeptides Agouti-related Protein (AgRP) and Proopiomelanocortin (POMC) and have opposing functions. AgRP neurons are activated by energy deficit (Hahn et al., 1998) and promote food seeking and consumption. Optogenetic or chemogenetic activation of AgRP neurons induces voracious eating in sated mice (Aponte et al., 2011; Krashes et al., 2011), whereas inhibition or ablation of AgRP neurons results in aphagia (Gropp et al., 2005; Krashes et al., 2011; Luquet et al., 2005). These effects of AgRP neurons are mediated by release of GABA as well as two neuropeptides, AgRP and NPY, that stimulate food intake when delivered into the brain (Clark et al., 1985; Fan et al., 1997; Ollmann et al., 1997; Tong et al., 2008). POMC neurons by contrast are activated by energy surfeit and their activity inhibits food intake and promotes weight loss. These two cell types interact in part through a common set of downstream neural targets that express melanocortin receptors, which are activated by POMC and inhibited by AgRP (Fan et al., 1997; Ollmann et al., 1997; Seeley et al., 1997). Thus, AgRP and POMC neurons are two intermingled, interacting neural cell types that have opposing roles in the control of feeding.

Despite intense investigation of these cells over the past 20 years, their activity dynamics during behavior remain unknown. This knowledge gap reflects the difficulty of recording cell-type-specific neural activity within heterogeneous deep brain structures such as the hypothalamus. As a result, our current understanding of the regulation of AgRP and POMC neurons is based on a combination of approaches that include in vitro electrophysiology, *c-fos* staining, pharmacology, and genetic manipulations. These pioneering studies have revealed a dominant role for circulating hormones and nutrients in the control of these cells (Williams and Elmquist, 2012). AgRP and POMC neurons are modulated by hormones such as ghrelin and leptin (Cowley et al., 2001, 2003; Nakazato et al., 2001; Pinto et al., 2004) as well as circulating nutrients (Blouet and Schwartz, 2010) in part via their metabolic effects on mitochondrial dynamics (Dietrich et al., 2013; Schneeberger et al., 2013). Together, these findings have led to a generally accepted model in which AgRP and POMC neurons function as interoceptors that monitor the concentration of hormones and nutrients in the blood and then gradually adjust their activity in parallel with changes in nutritional state. This model provides a compelling explanation for how nutritional changes can be translated into counterregulatory responses but leaves unanswered the question of whether these neurons are also subject to rapid regulation on the timescale of behavior.

AgRP and POMC neurons also receive abundant synaptic input which provides the potential for more rapid modulation. However, the function of this afferent input is not well understood. Fasting increases excitatory tone onto AgRP neurons (Liu et al., 2012; Yang et al., 2011), and one source of such excitatory input is neurons in the paraventricular hypothalamus (PVH) (Krashes et al., 2014). AgRP neurons also receive inhibitory input from the dorsomedial hypothalamus (DMH) among other sources (Krashes et al., 2014). POMC neurons by contrast receive inhibitory input from cells in the ARC, including neighboring AgRP neurons, as well as excitatory input from the ventromedial hypothalamus (VMH) and other regions (Cowley et al., 2001; Krashes et al., 2014; Pinto et al., 2004; Sternson et al., 2005; Vong et al., 2011). As these circuit connections have only recently been described, their regulation and function are not yet clear. An important open question regards the nature of the information that these presynaptic cells communicate to their AgRP and POMC targets.

In the present study, we have used an optical approach to record the natural activity of AgRP and POMC neurons in awake