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Learning and the motivation to eat: Forebrain circuitry

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ABSTRACT

Appetite and eating are not only controlled by energy needs, but also by extrinsic factors that are not directly related to energy balance. Environmental signals that acquire motivational properties through associative learning—learned cues—can override homeostatic signals and stimulate eating in sated states, or inhibit eating in states of hunger. Such influences are important, as environmental factors are believed to contribute to the increased susceptibility to overeating and the rise in obesity in the developed world. Similarly, environmental and social factors contribute to the onset and maintenance of anorexia nervosa and other eating disorders through interactions with the individual genetic background. Nevertheless, how learning enables environmental signals to control feeding, and the underlying brain mechanisms are poorly understood. We developed two rodent models to study how learned cues are integrated with homeostatic signals within functional forebrain networks, and how these networks are modulated by experience. In one model, a cue previously paired with food when an animal was hungry induces eating in sated rats. In the other model, food-deprived rats inhibit feeding when presented with a cue that signals danger, a tone previously paired with footshocks. Here evidence will be reviewed that the forebrain network formed by the amygdala, lateral hypothalamus and medial prefrontal cortex mediates cue-driven feeding, while a parallel amygdalar circuitry mediates suppression of eating by the fear cue. Findings from the animal models may be relevant for understanding aspects of human appetite and eating, and maladaptive mechanisms that could lead to overeating and anorexia.

1. Introduction

The motivation to eat is not only controlled by the physiological signals that convey energy and nutrient needs. Appetite and eating are also driven by environmental and social factors unrelated to homeostasis (for reviews see [1–11]). Notably, cues from the environment that acquire motivational properties through learning exert powerful control over food consumption. Learned cues can override homeostatic regulatory signals to stimulate eating in sated states, or to inhibit eating in states of hunger [12–15]. Such influences are important, and if persistent could lead to dysregulation of eating.

Indeed, environmental rather than metabolic changes are believed to underlie the increased susceptibility to overeating and the rise in obesity in the developed world [10,16–20]. But, the changes that have been reshaping our environment are multifaceted, and could influence eating behavior by exceedingly complex means. Thus, the current obesity models also span across diverse functional systems that contribute to the regulation of feeding beyond the critical homeostatic and metabolic control [21]. Dysfunction in reward processing and the underlying brain systems and similarities with drug addiction have been proposed [22–27]. Other models have focused on the role of stress, or on a relationship between Western diet and cognitive impairments (for reviews see [28–31]). Still, an important facet of our environment is the prevalence of food cues.

Food-associated cues powerfully promote eating in laboratory animals and in humans [12,13,32]. Thus, it is easy to envision how in our environment, which is abundant in easily accessible palatable foods, the ubiquitous images and messages with cues for food that stimulate appetite could aid overeating.

In parallel with obesity, anorexia nervosa and other eating disorders are also more prevalent in Western societies, and have been on the rise [33–36]. Likewise, environmental and social factors are believed to impinge on the genetic background of the vulnerable to increase recruitment to eating disorders. Nevertheless, how environmental cues gain the ability to control feeding, and the underlying brain mechanisms remain largely unknown.

Recently, we developed two behavioral preparations to study how learned cues are integrated with homeostatic signals within functional forebrain networks. We use associative learning, Pavlovian conditioning, to enable initially neutral environmental signals to modulate food intake based on prior associations with either rewarding or aversive events. Thus, in one setting, a cue that signals food based on prior associations with food consumption when an

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animal was hungry, stimulates feeding in sated rats, *food cue induced feeding*. In the other setting, a cue that signals danger based on its prior pairings with an aversive event inhibits feeding in food-deprived rats, *fear cue induced cessation of feeding*.

Here we provide an overview of our recent findings and other evidence that learned cues modulate food consumption, and that the critical forebrain network includes the amygdala, lateral hypothalamus and medial prefrontal cortex. The findings in animals might also be informative for understanding the control of appetite in humans including maladaptive environmental influences that could lead to eating disorders.

2. Learning and the motivation to eat I: Cue-induced feeding

Others and we have shown that a cue that signals food can stimulate eating in stated states, and this ability is acquired through associative learning. We use a preparation that is based on the protocol by Weingarten [13], and work of Zamble [37], and behavioral aspects were described in our recent reviews [14,38–40].

In brief, an initially neutral signal from the environment, such as a tone (conditioned stimulus, CS) is paired with food (unconditioned stimulus, US). That is the tone is repeatedly presented just prior to food delivery to food-deprived rats. The tone (CS) becomes a signal for food and it brings animals to the site of food delivery, the food cup. The amount of time spent at the food cup (conditioned response, CR) is a well-defined measure of associative learning, and during training rats learn to approach the food cup when the cue that predicts food is presented. A control stimulus, typically another auditory cue, such as a noise, that is not followed by food delivery is also presented during training, and that cue does not bring rats to the food cup.

After training, sated rats are tested for food consumption during tests with cues presentations. The cue-induced feeding is evident in such tests; rats consume more food in the presence of the cue that signals food compared to tests with the presentation of the control cue. Importantly, cue-induced eating is not simply a byproduct of the CRs that bring the rats to the food cup. Enhanced eating also occurs in tests when food is presented in a receptacle that is different in appearance and location from the food cup used in training [41–43]. Thus, the cue's ability to stimulate eating is a motivational property acquired through conditioning.

We have typically used discrete cues as conditioned stimuli in our preparations [39]. Recently, we showed that the environment in which food is consumed during training also serve as a conditioned stimulus to promote eating [42]. In that protocol, we trained rats to consume food pellets in a distinct environment (context), while another control group of food-deprived rats were exposed to the same context, but received food pellets in their home cages. Then we tested sated rats for food pellet consumption in the conditioning context. Rats that were previously fed in the conditioning context when hungry consumed more food pellets in the conditioning context during tests compared to the rats in the control group that were never fed in that context. These results showed that contextual conditioned stimuli, similar to discrete cues, could promote food consumption, in agreement with a study in mice [44] and a recent study that used female rats [45].

The rodent cue-induced feeding model is relevant to human eating. Classical conditioning supports cue-driven eating in preschool children. When presented with a distinct song and a flashing light that were previously paired with snacks, sated children begin to eat faster and consume lager amounts compared to their consumption in the presence of another song and light that were not paired with snacks [32]. Additionally, cues associated with the sensory properties of the food itself such as a brief sight, smell, or taste of a food prior to a meal can stimulate sated individuals to eat [12]. This is exaggerated in restrained eaters (dieters) [46], and in obese children [47], suggesting heightened vulnerability in these populations to cue-triggered overeating. In that regard, obese children show bias for food-associated cues (words) [48], and obese women show attentional bias for food images regardless of hunger state [49] and exaggerated brain response (fMRI) to pictures of high-calorie foods compared to controls [50].

Similarities between the rodent and human data underscore that a common, fundamental mechanism supports the ability of learned cues to modulate feeding (also see Section 2.3). This, in turn, underscores the importance of animal models, which allow examination of the brain mechanisms at a level currently impossible with imaging methods in humans. Likewise, findings from human studies provide a valuable guide to future rodent experiments.

There are also some possible translational implications for treatment of overeating. Learning and associative cues serve an adaptive function (see Section 2.3), but are becoming maladaptive, for at least some humans in the developed world. Through these mechanisms, plentiful palatable foods and cues in our surroundings provide constant appetite stimulant. Thus, an obvious, and yet hard to achieve, strategy would be to limit the exposure to the cues for highly palatable, high-calorie foods. Another strategy might be to use associative learning to form new preferences and reminders for "healthy" foods.

2.1. Motivation underlying cue-induced feeding: Appetite for the training food

The motivational basis for feeding under the learned cue is acquired through associative learning, however its exact nature is not known. Recently we showed that it appears to involve specific drive for the training food, rather than a general drive to eat [42,43]. We showed that sated rats enhanced consumption of the training pellets, but not other familiar, or novel foods in the conditioning context [42,43]. These findings suggest that through conditioning the CS becomes a signal for the training food (US) specifically, rather than a signal for feeding.

Other recent studies corroborate our findings [51,52]. In these studies rats were trained with two different CSs (tone or noise) that were each paired with a distinct food, US (sucrose or maltodextrine). Then rats were tested for food consumption during tests with presentations of either the CS that was previously paired with the test food, presentations of the CS for different food, or no CS. The cue-driven feeding occurred only in the presence of the CS for the test food, but not when the CS signaled the other food, in accordance with our findings [42,43].

Collectively, these findings suggest that through associative learning the cue (CS) gains the ability to evoke a sensory-specific representation of the food (US). In turn selective consumption of the signaled food suggests induction of a motivational state similar to appetite, or craving rather than induction of hunger. In that regard, studies in humans that primed subjects with brief food presentations induced specific desires for the food the subject was primed with, and the appetite was correlated with the amounts consumed [12,53].

Additional features suggest parallels with food cravings, although such comparisons should be taken with caution because food cravings are difficult to define in animal models [54]. Nevertheless, both are food selective and can be elicited by exposure to cues associated with food [54,55]. Furthermore, binge eating in humans is associated with cue-elicited cravings, and animals can consume a large amount in a very short time in the context associated with food [42,43,55,56].

2.2. Forebrain circuitry for cue-induced feeding

The cue-induced feeding model provides a framework for analysis of the brain circuitry and plasticity that underlies integration between environmental and homeostatic signals. Our focus has been on the forebrain contribution and specifically the telencephalon communication with the lateral hypothalamus (LHA). Our studies build on the hypothesis that the LHA is an integrative site for signals underlying