Published in final edited form as:
Physiol Behav. 2013 September 10; 121: . doi:10.1016/j.physbeh.2013.03.024.

Forebrain networks and the control of feeding by environmental learned cues

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Abstract

The motivation to eat is driven by a complex sum of physiological and non-physiological influences computed by the brain. Physiological signals that inform the brain about energy and nutrient needs are the primary drivers, but environmental signals unrelated to energy balance also control appetite and eating. The two components could act in concert to support the homeostatic regulation of food intake. Often, however, environmental influences rival physiological control and stimulate eating irrespective of satiety, or inhibit eating irrespective of hunger. If persistent, such maladaptive challenges to the physiological system could lead to dysregulated eating and ultimately to eating disorders. Nevertheless, the brain mechanisms underlying environmental contribution in the control of food intake are poorly understood. This paper provides an overview in recent advances in deciphering the critical brain systems using rodent models for environmental control by learned cues. These models use associative learning to compete with the physiological control, and in one preparation food cues stimulate a meal despite satiety, while in another preparation fear cues stop a meal despite hunger. Thus far, four forebrain regions have been identified as part of the essential cue induced feeding circuitry. These are telencephalic areas critical for associative learning, memory encoding, and decision making, the amygdala, hippocampus and prefrontal cortex and the lateral hypothalamus, which functions to integrate feeding, reward, and motivation. This circuitry also engages two orexigenic peptides, ghrelin and orexin. A parallel amygdalar circuitry supports fear cue cessation of feeding. These findings illuminate the brain mechanisms underlying environmental control of food intake and might be also relevant to aspects of human appetite and maladaptive overeating and undereating.

Keywords

Animal Models; Amygdala; Anorexia; Anxiety; Conditioning; Eating Disorders; Fear; Feeding; Ghrelin; Hippocampus; Hypothalamus; Learning; Memory; Motivation; Obesity; Orexin; Prefrontal Cortex

1. Introduction

Hunger drives appetite and eating, while satiety halts them. But, we also eat when not hungry and we cease eating when not sated. That is, the motivation to eat is not only controlled by the basic energy and nutrient needs, but also by other factors that are not

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directly related to energy homeostasis. Food consumption is regulated by internal, physiological signals from the body (e.g., deficit signals, hormones, circadian rhythm), as well as by external, environmental signals (i.e., sensory, reward, experiential, cognitive, emotional, social) [1–10]. Both physiological and environmental drivers therefore influence how much is consumed in a meal, and which one prevails ultimately depends on their strengths and the state and susceptibility (genetic background and prior experience) of the individual. Nevertheless, the stronger the non-physiological influences are, the harder it is for the homeostatic regulatory system to maintain constancy.

In the contemporary, developed world the environmental contribution to the control of food intake is becoming increasingly more powerful, and as such has an impact on eating dysregulation. Environmental influences are believed to promote overeating and susceptibility to weight gain at least in some individuals, and as such ultimately contribute to the rise in obesity in Western and other developed countries [3, 5, 11–14]. Environmental and social factors also enhance vulnerability to anorexia nervosa and other eating disorders [15–18]. Deciphering how the contemporary environment (and lifestyle) challenges our physiological systems and why fewer and fewer of us remain resilient to such challenges, are among the most difficult questions puzzling diverse fields of inquiry—from physiology, medicine and neuroscience, social and clinical psychology, to economy and public health and policy.

One of the fundamental questions is how the environmental influences are integrated with the physiological regulatory control and the brain mechanisms that orchestrate it. The focus of this review is on recent advancements in our understanding of the critical neural networks that support one form of non-physiological control of food intake—the control by feeding by environmental learned cues. Learned cues are initially arbitrary cues from the environment that gain the ability to control feeding through associations with rewarding or punishing events. Food predictive cues can stimulate eating despite of satiety, while fear cues can inhibit eating despite of hunger.

These preparations have therefore provided a framework for analyses of the brain mechanisms underlying the motivation to eat controlled not by hunger, but by environmental cues. The focus has been on the forebrain networks and this paper provides an overview of the findings that the amygdala, prefrontal cortex, hippocampus and lateral hypothalamus form a system that is an essential, minimal circuitry.

Rats have typically been used in these studies because the rat is an established model for mammalian brain structure and function [19], and the behaviors of interest are conserved across mammalian species and highly relevant to humans. Notably, recent work has extended these preparations to mice [20] [21, 22], which provides a promising avenue for future work with genetic mice models in identifying the critical molecular substrates. The findings from rodent studies are therefore relevant to our understanding of the fundamental principles of mammalian brain function in regulation of feeding behavior, as well as to understanding aspects of human eating and dysregulation.

2. The control of feeding by environmental learned cues

Towards a long-term aim to decipher the brain mechanisms underlying environmental (non-physiological) motivation to eat, we and others have been designing behavioral preparations suitable for brain imaging and manipulations. The basis for these paradigms is associative learning. Through Pavlovian conditioning procedures rats are trained to associate an initially neutral cue from the environment with a biologically significant event (i.e., an event that is rewarding or aversive). Then, these learned, predictive cues are used to induce motivational states that oppose the existing physiological drive.

In one set of preparations rats are repeatedly presented with a cue (tone or contextual conditioned stimulus, CS) immediately prior to food delivery (unconditioned stimulus, US). Through these associations the CS becomes a signal for the food US, and as such gains the capability to stimulate feeding even in sated states. In another set of preparations rats are repeatedly presented with a CS immediately prior to delivery of mild, electric foot shocks (US). Through these associations the CS becomes a signal for the shocks (US) and as such a "fear cue", which inhibits feeding even in hungry states.

It is beyond the scope of this paper to review other aspects of Pavlovian appetitive conditioning, or studies in which associative learning supports instrumental actions towards food (for recent review on these topics see Holland, 2005 #1598}). That includes important work on formation of preferences or aversions to foods and their cues based on taste and post-ingestive effects (for reviews see [23–26]). Similarly notable is the work on reward processes and hedonic aspects of food consumption, including formation of habits through associative processes (e.g., [27–29]).

2.1. Cue induced feeding

The cue induced feeding phenomenon was originally shown about three decades ago, first in rats and then in humans [30] [31, 32] (for recent reviews see [33, 34]. In these preparations, a cue that signals food can stimulates eating despite satiety based on its prior association with food consumption when an organism was hungry. Discrete cues (e.g., tone, light) have been typically used in these preparations, however recent studies have demonstrated that the environment in which food is consumed (feeding context) can also stimulate subsequent intake in sated rats on its own (i.e., without any discrete cues) [35] [36]. Through a few pairings with food consumption the feeding environment was shown to acquire the ability to later motivate eating, and it did so in a highly selective manner (see 2.1.1.) [35, 36]. Thus, both discrete and contextual cues associated with prior food consumption could later modulate intake demonstrating that cue induced feeding is not bound to the type of stimuli used, but rather it is a fundamental result of learning. These findings are in agreement with a study in mice [20] and a study that used female rats [37]. These results also contribute to substantial literature on the role of context in associative learning and to prior findings on the effects of ambience on food intake (for reviews see [9, 38, 39]).

The finding that a feeding environment could motivate intake independent of physiological hunger was hypothesized to have important implications to human eating [35]. The environment in which we consume food has been changing substantially over the last few decades, and now we consume a much larger portion of our daily intake outside home and often in distinct settings including 'fast food' restaurants [40]. In particular, 'fast food' and other 'chain' restaurants provide good opportunities for specific food-context associations because they typically offer limited menu choices and they are easily recognized and uniform across different locations. Based on the findings from the animal model, it was hypothesized that such food–context associations would enable those places to later stimulate appetite and consumption independent of physiological hunger. Nevertheless, future studies are needed to investigate how cues associated with such feeding environments might contribute to food choices and consumption in humans.

2.1.1. Food cues drive selective appetite for the signaled food, not basic hunger—Many features of eating driven by learned food cues suggest that the induced state is unlike a general state of hunger. Food cues stimulate consumption of the signaled food, but not consumption of other foods. The drive in these circumstances is therefore selective and specific and as such similar to induction of appetite, or even craving, rather than induction of a more general state of hunger. This was originally observed by

Weingarten [41] and more recently shown in two studies that used the feeding context as a CS. The conditioning context enhanced rats' consumption of the training food, but it did not change their consumption of other familiar or novel foods [35, 42]. Later studies replicated and extended these results using preparations with multiple CSs and USs [43] [44]. In those studies, rats that were conditioned to associate two distinct cues with two different foods showed selective consumption of the cued food; that is, at testing each cue stimulated consumption of only the food it was previously associated with [43] [44].

Studies with humans also showed induction of selective appetites and consumption when subjects were primed with food cues prior to a meal. In those studies subjects reported increased appetite and craving for the cued food, which was then followed by increased consumption of that food [45, 46]. In agreement, a recent study also showed selective enhancement of the consumption of the training food pellets, but not the consumption of the other available food option in rats primed with the cue for the pellets [47]. Nevertheless, in some settings, if the signaled food is absent, rats could be stimulated by learned cues to eat the food that is provide to them [37].

In addition to the food selectivity, another feature of eating under the learned cue in rats suggests that the underlying mechanism might be somewhat similar to cue induced cravings in humans, with an obvious caveat that cravings are difficult to define in animals [48]. Cue elicited cravings are associated with binge-eating in humans, and similarly in rats food cues have been shown to stimulate consumption of large amounts of food in a short period of time, in a binge-like manner [35–37].

2.1.2. Food cues stimulate persistent eating—Food cues enable an organism to consume a large meal when not hungry, but how long such appetites might last is unclear. Also unclear is whether the consumption stimulated by food cues in the absence of hunger is appropriately compensated for in later meals. A recent study began to characterize potential long-term effects of food cues on feeding, and examined the extent of the effect during 4-hour long tests and its persistence through repeated testing [47]. In that study rats were conditioned to associate a tone with food pellets distinct from their regular chow, and then were tested along with controls for food consumption following tone presentations. The study found that after an initial rapid and substantial consumption conditioned rats stimulated with the tone (food cue) continued to eat large amounts of food pellets (comparable to the amounts consumed by the controls) for the duration of the tests. The high intake persisted in four tests that occurred over two weeks.

Nevertheless, there were no differences in body weights between the conditioned and control groups, likely due to the intermittent testing schedule. These observations are consistent with the findings from other rat models of binge eating that found stable body weights with periodic versus chronic regimens of palatable food intake [49, 50]. Thus, chronic stimulation with food cues might provide a setting for potential weight gain over time.

In that regard, the study above that tested rats during long tests, also measured daily intake post-tests and found no evidence of a compensatory decrease in eating [47]. The chow consumed during a 24hr period subsequent to the tests was similar between the conditioned and control groups of rats. Therefore, it was hypothesized that if not compensated for metabolically, consumption gains driven by the food cue could result in a caloric surplus. These would be small gains, which nevertheless could accumulate over time if uncompensated for. These speculations are in agreement with prior observations that small fluctuations in intake are not accounted for properly by the homeostatic system, and as such could compound to weight gain over time [12]. Nevertheless, whether repeated food cue

stimulated consumption would remain undetected over long periods sufficient to result in weight gain remains to be determined.

2.2. Cue induced inhibition of feeding

Cues that predict danger (fear cues) inhibit feeding and other ongoing behaviors as part of a coordinated preparatory defensive response to the signaled threat. Among often-studied fear cue triggered behaviors in rodents, are the expression of freezing behavior and an enhancement of the acoustic startle reflex [51–53]. Conditioned aversive cues also suppress ongoing appetitive and consummatory feeding behaviors, including food approach and instrumental actions towards food, as well as suppression of licking (e.g., [54] [55–59]). In contrast, the effects of fear cues on the consumption of food, other than suppression of sucrose solution licking, have been largely unexplored since the classic studies of Cannon [60] and later work of Schachter [61].

Recently, we began developing behavioral preparations to study the brain substrates underlying fear cue effects on food consumption. These preparations complement cue induced feeding work and together aid in our pursuit of the brain mechanisms underlying environmental (non-physiological) control of food intake. These paradigms are based on well-known fear conditioning protocols (e.g., [53, 62–64]. In fear conditioning preparations, a discrete cue (typically tone, or light) or a contextual stimulus (CS) is paired with an aversive event (typically an electric footshock; US). After conditioning the CS alone produces fear-related behavioral responses (e.g., freezing behavior, startle reflex enhancement). Our interest is in the control of feeding, and we use these cues to modulate food intake.

Using these preparations we have shown in two different studies that a tone cue that signals mild electric footshocks effectively inhibits eating in hungry rats (food-deprived prior to testing) [65, 66]. Recently, we have shown that the training environment in which the shocks are administered (conditioning context), can alone (i.e., in the absence of any discrete cues) serve as a CS to inhibit feeding in food-deprived rats [67]. Thus, such fear cues induce a competing motivational state that overrides the physiological drive to eat. The brains circuitry that supports the competition of fear and hunger motivational states is currently under investigation in our laboratory (see section 3.2.).

As mentioned above, part of the species-typical fear response in rodents is the expression of freezing behavior, which is characterized as a complete immobility except for the movement required for breathing [51, 52]. Importantly, we have shown that cessation of feeding is not mediated by freezing behavior, even though both are triggered by the same fear cue. That is, the cessation of feeding is not simply a consequence of rats' inability to get to the food due to immobility.

In two studies we prevented the expression of conditioned freezing and showed that even though rats were not freezing in response to the CS, and therefore were capable of approaching the food, they still inhibited eating. In one study conditioned freezing was eliminated by lesions of the ventrolateral region of the periaqueductal gray [68], and in the other by lesions of the basolateral amygdala [65]. In another recent study dissociation of freezing and inhibition of feeding induced by the same CS was also observed. Female rats continued to inhibit feeding during tests with tone (CS) presentations even after they have extinguished freezing behavior induced by the same CS [66] (also see 2.3.1).

2.3. Sex differences in the control of feeding by environmental learned cues

Women are more susceptible to eating disorders, and other psychiatric illnesses than man, and yet, female subjects are greatly underrepresented in basic research and in clinical trials

[69, 70] [71]. Consequently there is an urgent need to study female subjects and to examine the differences between the sexes in relevant behavioral preparations. A recent discovery of a pronounced sex difference in the fear cue inhibition of feeding preparation (2.3.1.) prompted us to begin to systematically compare male and female rats in various tasks with associative learning and feeding (e.g., [67, 72]).

Behavioral characterization of intact, adult female and male rats is a necessary step towards future work that will examine the underlying brain substrates and the role of circulating sex hormones. This work aims to complement other research areas that study sex differences in cognitive and behavioral tasks relevant to associate learning, energy homeostasis, reward motivated behaviors, stress, and anxiety (for reviews, see [73–78].

2.3.1. Sex differences in fear cue inhibition of feeding—Our recent study examined learning and feeding behavior of intact, adult male and female rats in the fear cue induced inhibition of feeding preparation (see section 2.2.) and found sex differences [66]. In that study, males and females learned similarly well the association between a tone and foot shocks, as determined by freezing behavior during testing. The extent of food intake inhibition by the tone (fear cue) was also similar for the two sexes during the first test. A pronounced sex difference emerged during extinction, when female rats showed sustained inhibition of feeding compared to males [66]. That is, male rats extinguished inhibition of food intake much more rapidly than females. During the second test, male rats in the experimental group ate the same high amounts of food as the controls, while it took females in the conditioned group two additional tests to reach the consumption levels similar to that of the controls.

These finding providing a novel framework for investigation of sex differences in the control of feeding and the underlying brain substrates. Ongoing studies in our laboratory are examining the critical brain substrates underlying these sex differences (see section 3.3.). This animal model may be also informative about aspects of eating dysregulation in humans. Particularly, the potential contribution of fear in the maintenance of low food intake in anorexia nervosa was hypothesized [66].

Anorexia nervosa (anorexia) is a complex eating disorder that is characterized by relentless maintenance of extremely low body weight through restricted eating, often combined with excessive exercise and purging [16–18, 79]. The ability to maintain restricted eating in emaciated states is paradoxical, and occurs even with increased physiological hunger signals [18, 80]. We have hypothesized that sustained fear might facilitate the maintenance of restricted eating in anorexia [66]. Indeed, obsessive fear of weight gain despite being underweight is a core symptom of anorexia [79]. Furthermore, anorexia shows high co-morbidity with anxiety disorders (reviewed in [18]), and dysfunction in fear network regions (amygdala and prefrontal cortex) have been found in recent imaging studies with anorexia nervosa patients [81–84].

Anorexia afflicts women disproportionately more than men, and elucidating the role of fear might be also relevant to the mechanisms underlying enhanced susceptibility of the female sex. The findings from the animal model for sustained cessation of feeding in females suggest a biological vulnerability that would be manifested under threat. It is intriguing to speculate that our environment provides a maladaptive setting in that regard. Our world is saturated with alarming and fearful news and messages, as well as many other cues that might be fearful specifically to the anorexia population. Indeed, excessive images of idealized female bodies and relentless food advertisements, both of which are perceived as threating by anorexia population are notoriously abundant in Western societies.

3. Forebrain networks and the control of feeding by environmental learned cues

Food intake regulation involves complex interactions between the body and the brain, and elaborate computations of bodily energy states and needs and their translation into hunger and appetites. Proper detection and response to even seemingly simple perturbations, such as food deprivation, require complex coordination of the hypothalamic-brainstem circuitry regulating behavioral, visceral and endocrine output components [2]. These circuitries also communicate with the telencephalic networks responsible for encoding internal states and rewards with emotional and cognitive processes.

These telencephalic networks in turn regulate the hypothalamic-brainstem feeding circuitry through similarly complex mechanisms and exceedingly elaborate connections. Behavioral models for the control of consumption by environmental learned cues have provided a helpful framework for investigation of the functional circuitries within this distributed connectional net, and evidence from those studies is presented next.

3.1. The forebrain circuitry for cue induced feeding

The cue-induced feeding phenomenon was originally shown about three decades ago (see 2.1.), but the brain mechanisms were not investigated systematically until much later. In the last decade, studies in rodents that applied brain lesions, pharmacological, genetic and functional neuroanatomical methods have identified four regions within the forebrain network that supports cue-induced feeding. These are telencephalic areas crucial for associative learning, memory encoding and decision-making, the amygdala, hippocampus and medial prefrontal cortex, and an area which functions to integrate feeding, reward, and motivation, the lateral hypothalamus.

The first evidence that the basolateral area of the amygdala (includes basolateral, basomedial and lateral nuclei) is critical for cue induced feeding was initially found in the early 1990es [85]. This finding was later replicated [86, 87] and extended to the analysis of the circuitry through which it acts to regulate feeding [36, 88–91].

Subsequent studies that examined the circuitry for the amygdala action on feeding showed that the basolateral amygdala-lateral hypothalamic system is essential [88, 91]. The basolateral amygdala can communicate with the lateral hypothalamus via direct, and indirect pathways, and one of the areas well positioned to relay the information between the two areas is the ventral medial prefrontal cortex [92–95]. Two studies then examined whether the ventral medial prefrontal cortex is an essential component of the critical forebrain system. The first study showed that the amygdalar and medial prefrontal cortex neurons that send direct pathways to the lateral hypothalamus were selectively activated (measured with induction of immediate early genes) by the learned food cue that stimulates eating [91]. Then in the second study, that region of the medial prefrontal cortex was targeted with bilateral, neurotoxic lesions, which produced impairment in cue induced feeding [36], and confirmed its necessity in the critical forebrain circuitry.

The evidence for the hippocampal involvement in cue induced feeding is very recent and it specifically involves its ventral region [96] (also see section 3.1.1.). Nevertheless, a role of the hippocampus in the control of feeding has been established previously [97, 98]. Furthermore, the ventral hippocampus is extensively connected with the basolateral amygdala, medial prefrontal cortex and the lateral hypothalamus, and therefore well placed to participate in processing within the cue induced feeding circuitry (for reviews see [95, 99, 100]).

Recent work has begun to further dissect the forebrain circuitry for cue induced feeding in terms of sub-architecture (3.1.3) and peptide regulators involved (3.1.1 and 3.1.2.). Findings from those studies are reviewed next.

3.1.1. Food cue integration with the lateral hypothalamic orexigenic peptides —As discussed above, prior work provided support that the telencephalon-lateral hypothalamic system is critical for cue induced feeding; however, the specific neuronal mediators within the lateral hypothalamus remained unknown. Recently, we examined whether the underlying mechanism involves recruitment (measured by induction of immediate early gene *c-fos* protein, Fos) of the lateral hypothalamic neurons with neuropeptides that stimulate feeding, orexin/hypocretin (ORX) and melanin-concentrating hormone (MCH) [101]. The ORX and MCH are expressed in separate neuronal populations [102–105], and their functions in the control of food intake are also distinct. The critical regulatory role in energy homeostasis has been established for MCH (e.g., [106–108]). In contrast, ORX's role in feeding is more complex. While it has a stimulatory effect on feeding (e.g., [109–111]), ORX is also critical for wakefulness and arousal (e.g., [112–116]), and is important for other motivated behaviors driven by food and drug rewards (e.g., [117–122]), for reviews see [123, 124]). Thus our goal was to test whether one or both of these orexigenic lateral hypothalamic neurons are recruited by a learned food cue.

The study used a preparation in which sated rats were tested independent of the training context, and in the absence of food. This was done because the training context, as well as food presentation and consumption, could stimulate Fos induction in the hypothalamic neurons. Nevertheless, in a group of rats that were allowed access to food in the same setting, the cue for food stimulated consumption. Using fluorescent immunohistochemistry method for combined detection of Fos and characterization of ORX and MCH neurons, the study showed that the cue for food (tone) selectively induced Fos in ORX but not in MCH neurons. Thus, a learned food cue selectively recruited ORX, but not MCH neurons, in a preparation that stimulates feeding in sated rats. Therefore, these results suggest a role for ORX in cue induced feeding that occurs in the absence of physiological hunger [101].

This was the first study to show that a discrete learned food cue recruits ORX neurons in the absence of food or physiological hunger. Nevertheless, these findings are in agreement with prior work with contextual cues associated with food in the conditioned place preference task [117, 121, 123, 125].

These findings are also in agreement with prior rodent studies that examined Fos induction and found selective recruitment of ORX, but not MCH neurons across different behavioral preparations [126–130]. Nevertheless, almost all of these studies were conducted under non food-deprived conditions and the lack of MCH recruitment might have been due to the physiological state. Indeed, fasting dramatically upregulates MCH expression [106], and might be required for MCH recruitment. In that regard, the acquisition phase of cue-induced feeding occurs under food-restricted conditions and MCH might be important during that stage. In agreement, recent experiments showed that functional MCH receptor signaling was necessary for cue-induced feeding in mice [21].

The evidence for ORX neurons' recruitment by a food cue offers appealing functional implications for ORX involvement in cue induced feeding mechanisms. This recruitment might reflect ORX's role in anticipatory motivational mechanism induced by the food cue that primes an organism to eat. This postulation is in agreement with ORX's role in arousal and its proposed role in coordinating behavioral responses according to the current motivational state ([131]; for reviews see [114, 132, 133]). The exact inputs and substrates that recruit ORX or the circuitry through which ORX then acts to mediate anticipatory

motivational mechanisms induced by food cues, are unknown. Nevertheless, the extensive distribution of ORX neurons' outputs and its receptors [104, 134–136] allows for communication with forebrain and brainstem areas critical for feeding, arousal, and motivation [2, 6].

Regarding ORX inputs, the amygdala and prefrontal cortex are the key candidates given their critical role in cue induced feeding. In that regard, the regions of the basolateral area of the amygdala that send direct projections to the lateral hypothalamus (basomedial and basolateral nuclei) do not reach the perifornical area, and instead innervate the ventrolateral region of the lateral hypothalamus [91, 99, 137]. On the other hand, the ventromedial prefrontal cortex innervates the perifornical area, and thus might be able to directly influence ORX neurons [138, 139]. In that regard, stimulation of μ-opioid system within the ventromedial prefrontal cortex was recently shown to drive palatable food (carbohydrate) intake in sated rats [140]. Whether that system acts via ORX neurons remains to be determined, nevertheless it offers an intriguing possibility.

One of the potential key substrates might be ghrelin, which was recently shown to be critical for cue induced feeding (see section 3.1.2.). Ghrelin is the only currently known physiological hunger signal and therefore its implication in feeding driven by learned food cues is particularly intriguing. Ghrelin is a peptide released by the stomach before meals, and it acts through the vagus nerve to reach the brain, where its substrates include neurons that also produce ghrelin [141, 142]. Ghrelin production and signaling in the body and in the brain therefore support its function in the homeostatic food intake and body weight regulation, as originally demonstrated with systemic and central ghrelin injections that stimulated food intake and body weight gain [143].

Additionally, a role for ghrelin in anticipatory and reward-mediated aspects of feeding behavior as well as a role in learning and memory has also been shown (e.g., [144–146] [147]). Such diverse ghrelin functions are supported by the widespread distribution of its receptor (growth hormone secretagogue receptor) within the hypothalamic and brainstem feeding areas as well as within the telencephalon, including the amygdala and hippocampus [148, 149]. Importantly, homeostatic and non-homeostatic ghrelin functions involve orexin (e.g., [145, 150, 151]), and similarly a ghrelin-orexin subsystem might be involved in cue induced feeding.

3.1.2. Cue induced feeding requires ghrelin signaling—Two recent studies offer compelling evidence that ghrelin signaling is necessary for learned food cue induced feeding [22, 96]. The first study showed that ghrelin delivery into the ventral hippocampus increased meal initiation in sated rats in response to a food cue [96]. Ghrelin action through the ventral hippocampal neurons, therefore enhanced food cue stimulated feeding. That study is the first to show evidence for the involvement of the ventral hippocampus in cue induced feeding (see discussion in section 3.1).

The second study showed that mice with ghrelin receptor deficiency induced pharmacologically or genetically, were impaired in cue induced feeding. A treatment with a ghrelin receptor antagonist during the cue-food learning phase later blocked enhanced eating in response to the cue for food at testing; control mice ate more when primed with the food cue compared to their consumption when primed with a control cue, while mice that had blocked ghrelin receptors showed similar low consumption under both cues. In another experiment in the same study, ghrelin receptor null mice were also impaired in cue induced feeding, but they showed enhanced eating in response to both the food cue and to the control cue. In accordance with their non-selective enhanced eating the ghrelin receptor null mice

also had increased immediate early gene induction in the basolateral amygdalar neurons in response to both cues [22].

The findings from these studies demonstrate the importance of ghrelin signaling in cue induced feeding, and highlight the ventral hippocampus as a critical site of its action. Future studies are needed to determine the exact function ghrelin supports in cue induced feeding and whether it acts through multiple sites within the critical circuitry.

3.1.3. Amygdalo-prefrontal-lateral hypothalamic circuitry—Previous work showed that the basolateral area of the amygdala, the medial prefrontal cortex, and their connections with the lateral hypothalamus are essential for cue induced feeding (see section 3.1). The basolateral area of the amygdala communicates with the lateral hypothalamus through a direct pathway, as well as through indirect routes, including relays via the medial prefrontal cortex. Whether the same or different amygdala neurons give rise to the pathways to the lateral hypothalamus and to the pathways to the medial prefrontal cortex is unclear.

Recently, we began to characterize these pathways with neuroanatomical tract tracing methods. We used double retrograde tracers approach to examine whether the same neurons in the basolateral area of the amygdala send pathways to the lateral hypothalamus and to the medial prefrontal cortex. Preliminary findings from that study showed that almost completely separate populations of amygdala neurons contribute to the pathways to the medial prefrontal cortex and to the pathways to the lateral hypothalamus, suggesting that the amygdala communicates with the prefrontal cortex and the lateral hypothalamus via separate routes [137, 139]. These findings have important implications for the organization of the amygdalo-prefrontal-hypothalamic networks in the control of feeding.

In that regard, ongoing projects in our laboratory are mapping functional activation (Fos induction) of the amygdalo-medial prefrontal cortex pathway during the acquisition of cue-food association that supports cue induced feeding. Other related studies have begun to map functional activation within the critical forebrain regions during early and late stages of cue-food learning to determine network plasticity underlying cue-food association [152].

3.2. The forebrain substrates for cue driven inhibition of feeding

The role of the amygdala in aversive associative learning is well known, and its central nucleus and the basolateral area comprise a circuit critical for conditioned fear learning [53, 64, 153–155]. Therefore, we examined whether each of these regions is also critical for the inhibition of feeding by a fear cue. The study found that the central nucleus of the amygdala, but not the basolateral area is necessary for fear cue cessation of eating [65]. Bilateral, neurotoxic lesions of the central amygdala, but not bilateral, neurotoxic lesions of the basolateral amygdala, abolished fear cue induced feeding cessation, while lesions of either of the two structures abolished fear cue induced freezing behavior [65]. The finding determined the amygdala substrate for cessation of feeding by an aversive CS, and also revealed that dissociable amygdalar subsystems support CS's influence on feeding and CS-induced freezing (also see discussion on freezing and cessation of feeding dissociation in section 2.2.).

The central nucleus of the amygdala is well positioned to block feeding and to help prioritize defensive behavioral response via distributed connectional network with the hypothalamic and brainstem areas coordinating the expression of these behaviors. It could exert its action on feeding via direct pathways to the brainstem, lateral hypothalamus, and bed nuclei of the stria terminalis targets [95, 156, 157], and via indirect pathways to the paraventricular nucleus of the hypothalamus [156, 158]. Ongoing experiments in our laboratory are examining these critical targets using imagining methods (Fos induction maps).

Initially, our efforts are focused on the lateral hypothalamic substrates. The central nucleus of the amygdala provides a dense innervation of the lateral hypothalamus [99], including the perifornical region where its targets include ORX and MCH neurons [136, 159]. Based on anatomical evidence the input to the ORX and MCH neurons from the central amygdalar neurons is inhibitory [159], which would suggest a mechanism for inhibition of feeding via direct blockade of these two orexigenic drivers. Future studies will examine additional targets within the feeding network and the plasticity that underlies learned fear cue inhibition of feeding [2, 5, 6, 8, 95, 160–162]. Additional studies are also needed to test whether repeated exposure to fear cue might contribute to long-term suppression of eating and changes in body weight.

3.3. The brain substrates underlying sex differences in the control of feeding by learned cues

Current work in our laboratory is examining the brain substrates underlying the sex differences found in fear cue induced inhibition of feeding (see 2.3.1.). This is an ambitious project that is mapping brain activation patterns (Fos induction) in male and female rats across different stages of extinction of fear cue inhibition of feeding. The ultimate aim is to determine the brain substrates mediating prolonged fear cue driven inhibition of feeding in females.

The initial focus is on two brain areas. One is the central nucleus of the amygdala, which prior work in males showed was necessary for fear cue inhibition of feeding [65], and which has extensive access to the hypothalamic and brainstem feeding systems [95, 99]. The other is the medial prefrontal cortex, which is critical for extinction of fear [162] and is also important for food regulation [36, 140], and which sends substantial input to the central nucleus [92, 93]. These experiments are therefore testing the hypothesis that the medial prefrontal cortex-central amygdalar nucleus system is critical for the prolonged fear effects on feeding observed in females. This work will continue with additional brain analysis and as well as manipulations of circulating sex hormones.

4. Concluding remarks

This review discussed recent advancements in our understanding of the brain mechanisms underlying environmental control of food intake. The focus was on two behavioral models that use associative learning to control food consumption independent of ongoing physiological hunger-satiety state. In one preparation learned environmental cues for food are used to stimulate consumption in sated states, while in the other preparation learned fear cues are used to inhibit feeding in hungry states. As such these behavioral models have provided a useful framework for analyses of the brain mechanisms underlying the motivation to eat controlled not by hunger, but by environmental cues.

Based on the evidence from studies with these models the essential circuitry for cue induced feeding is formed by the basolateral amygdala, the medial prefrontal cortex, the ventral hippocampus and the lateral hypothalamus. The circuitry for fear cue inhibition of feeding requires the central nucleus of the amygdala, but the rest of the system is yet to be revealed. Indeed, mapping the critical brain circuitries remains an important step in deciphering the brain mechanisms underlying environmental control of food intake and body weight. The findings reviewed provide a blueprint for future work on the role of the telencephalon in the control of feeding by environmental cues, including maladaptive influences that could lead to overeating and anorexia.

Acknowledgments

I am very grateful for the exceptional honor of being selected as a recipient of the Alan N. Epstein Research Award, and would like to thank the Society for the Study of Ingestive Behavior and the committee who supported my nomination. I am also very grateful to the many mentors and collaborators who have shaped my scientific development over the years and who continue to guide and inspire my research. Supported by the National Institute of Health Grant (DK085721).

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Highlights

- Food cues stimulate feeding in sated states (cue induced feeding model).
- Cue feeding circuitry: Amygdala-prefrontal cortex-hippocampus-lateral hypothalamus
- Fear cues inhibit feeding in hungry states (fear induced anorexia model).
- Fear cue-induced feeding cessation depends on the central nucleus of the amygdala.