Learning and the motivation to eat: Forebrain circuitry

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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.

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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
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 larger 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 maltodextrin). 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
the motivation to eat that include the physiological signals from the body (“intrinsic”), and “extrinsic”, such as environmental, emotional, and cognitive signals.

The LHA receives the inputs that could relay the physiological signals relevant for food intake regulation via the arcuate nucleus of the hypothalamus and other hypothalamic and brainstem areas, and the inputs from the telencephalic areas related to motivation, emotion, and cognition [2,4,57,58]. In turn, the LHA sends widespread outputs to the brainstem and forebrain. Thus, the LHA is well positioned to contribute to its historically assigned functions, the initiation of feeding, reward, and motivation (for reviews see [2,4,59]).

Within the telencephalon, areas well known for their roles in associative learning and decision-making, the amygdala and medial prefrontal cortex, respectively, send substantial input to the LHA. We examined each of these areas and showed that cue-driven food consumption critically depends on an intact basolateral area of the amygdala (BLA, includes basolateral, basomedial, and lateral nuclei), the ventromedial prefrontal cortex (vmPFC, includes infralimbic, prelimbic and ventral medial orbitofrontal areas), and the BLA–LHA communications [41,43,60,61].

The BLA communication with the LHA includes direct, and indirect pathways, and we used a preparation that disconnected both types of relays to show that the BLA–LHA system is necessary for cue-induced eating [61]. The vmPFC receives inputs from the BLA and in turn sends outputs to the LHA and is thus, well positioned to relay the information between the BLA and LHA [57,62–64]. Therefore, we examined whether the vmPFC and BLA neurons that send direct pathways to the LHA are functionally activated (immediate early gene induction) during the cue-induced feeding tests. To accomplish this we applied a combination of immediate early gene induction imaging method with detection of a retrograde tracer within the vmPFC and BLA after injections into the LHA. We showed that subpopulations of neurons within the vmPFC and BLA that send input to the LHA (retrogradely labeled) were selectively activated during the cue-induced feeding tests [65].

Then we targeted the vmPFC with bilateral, neurotoxic lesions, and found that the lesions abolished conditioned context-driven food consumption [43]. The vmPFC lesions in that study also produced changes in food consumption in novel settings. The vmPFC-lesioned rats consumed less than controls when fed in a novel environment, or when a novel food was first presented in a familiar environment. Importantly, the vmPFC-lesions deficits were specific to food consumption during tests and did not impact food intake in the home cage or body weight. Similarly, a recent study found no changes in body weight after lesions of the vmPFC region somewhat overlapping with the lesioned area in our study [66]. Collectively, these results suggest that the vmPFC might not be critical for the homeostatic control of food intake and body weight. Instead, it might be critically recruited when evaluation of environmental signals based on prior experience is required to guide goal-directed behaviors, such as eating under the learned cue or in a novel setting.

The specific roles of the basolateral amygdala, and prefrontal cortex in cue driven feeding remain unknown. Our lesions were made before behavioral training, and thus could have interfered with the learning acquisition, memory recall, or behavioral expression phase of the cue-induced feeding. The basolateral amygdala and prefrontal cortex are engaged differently in other tasks that are similar to our paradigm in that they also rely on CS properties acquired through associative learning to modulate behavior (devaluation task, and second order conditioning; [39]). The basolateral amygdala is needed during the acquisition phase, but not when the flexible use of the CS acquired value is used to modulate behavior in the devaluation task, and in the second order conditioning [67,68]. In contrast, a region of the prefrontal cortex (the lateral orbitofrontal cortical area) is needed during both the acquisition, and expression phase in the devaluation task [68]. In that regard, the lateral orbitofrontal cortex encoding, and updating of the acquired associative value of the CS depends on communications with the BLA [69,70].

Similar dissociable roles for the BLA and vmPFC have been shown in aversive conditioning. The vmPFC’s responses to aversive CSSs [71], and cannabinoid potentiation of learning plasticity within the vmPFC requires BLA input during the acquisition, but not once the association has been formed [72]. Thus, the basolateral amygdala plays a role in guiding prefrontal cortical responses during the learning acquisition based on the incentive value acquired through the association between environmental signals and rewards or punishments. This general framework might apply to the BLA–vmPFC system in cue-induced feeding.

The anatomical connections between the BLA, vmPFC, and LHA support this possibility. The BLA and vmPFC share extensive bidirectional connections and each send direct pathways to the LHA [62–64,73–76]. Thus, the BLA and vmPFC could modulate the LHA processing via direct pathways, as well as through the communications with each other.

Additional complexity in this system is provided by heterogeneity within the vmPFC. The distinct regions within the vmPFC (the infralimbic, ventral prelimbic, and ventro-medial orbitofrontal areas) might serve different functions in the appetitive processing, and associated motivation for food and drugs [77,78]. For example, the initial choice to explore novel food, and responding to conflicting information guided by context is attributed to the prelimbic area [79,80]. On the other hand the infralimbic area, which is critical for extinction of aversive CSSs, also supports functions associated with extinction of appetitive CSSs [81–83]. Notably, cue-induced cravings for food and drugs in humans are attributed to the medial orbitofrontal area [84,85–87], a region that appears somewhat homologous to the ventro-medial orbitofrontal area in rats [43]. Nevertheless, whether the ventral medial orbitofrontal area might be necessary for the cue memory recall and subsequent induction of the drive to eat remains to be determined.

2.3. Learning and the homeostatic control

In our preparations we pit learned cues against homeostatic signals to stimulate eating in sated states or inhibit feeding in states of hunger. However, associative learning endows an organism with an adaptive function to facilitate regulation of feeding and other goal-directed behaviors.

As such associative learning supports acquisition of preferences and aversions to foods and associated cues and environments based on taste and post-ingestive consequences (for reviews see [38,88–90]). Associative learning and memory are also critical in reward processing mechanisms that contribute to regulation of feeding, and much has been elucidated about the underlying brain systems (for reviews see [23,91–94]).

Importantly, learning and associated anticipatory motivation function in concert with the homeostatic regulation [95–97]. The ability to predict a meal, and the anticipatory motivation prepare the body for the incoming nutrients, and as such assist homeostatic regulation [95–97]. The well-known example is control of insulin, a hormone released by the pancreas that peripherally regulates glucose metabolism, and acts as an adiposity signal in the brain [98].

Insulin is regulated by both the physiological and anticipatory signals. Its release is triggered by a meal-induced increase in blood glucose, as well as by the cues that predict a meal [95], and gain control through conditioning [99]. The anticipatory insulin release (“cephalic insulin”) is regulated by the brain via the vagus nerve, and is an adaptive response that helps prevent hyperglycemia that would otherwise occur because of the delay in meal-induced insulin cascade [95,100].
Other physiological signals and associated brain regulatory substrates are also under anticipatory control. A recent study examined the role of ghrelin in food anticipatory functions with ghrelin-receptor deficient mice [101]. Ghrelin is an orexigenic peptide released by the stomach before meals that acts through the vagus nerve to reach the brain substrates including ghrelin-producing neurons [102,103]. Thus, ghrelin receptors in the body and the brain are necessary for ghrelin homeostatic signaling and function. Interestingly, Davis and colleagues found that ghrelin-receptor signaling is also necessary for adaptive, food anticipatory activity, and modulation of spatial memory [101].

Finally, the brain feeding regulatory systems can be conditioned to function independent from the physiological signals that normally regulate them. This was shown in a recent study [104] with exogenous manipulation of a potent feeding stimulant, the neuropeptide Y (NPY) [105]. In the study of Drazen and colleagues, NPY was injected into the brain repeatedly at the same time of the day, and then at testing the injection was omitted to examine the consequences of anticipation of the NPY burst based on the time cue [104].

The anticipation of the NPY burst induced eating that was comparable to that produced by the actual NPY injection. Thus, the learned cue (injection time) was able to recruit the NPY input-dependent substrates to initiate feeding in the absence of the physiological signals.

In turn, these findings might provide insights into the mechanisms underlying food-cue driven feeding that also occurs in the absence of physiological hunger. In particular the plasticity within the NPY input system is of interest. In that regard, the NPY is important for the motivation to eat [106], and can initiate feeding under sated conditions. Importantly, its ability to stimulate feeding in satiated rats is mediated via the LHA [107].

2.3.1. Cue integration with the hypothalamic homeostatic system

As follows from the above discussion, the NPY input system within the lateral hypothalamus might be important for convergence between the telencephalic influences and homeostatic regulatory control. The anatomical evidence supports this possibility. The NPY neurons from the ARH send input to the LHA, where they end on the neurons that express orexigenic neuropeptides, melanin concentrating hormone (MCH) and orexin/hypocretin (ORX) [3,108]. The BLA, and vmPFC also send direct pathways to the LHA [58,62–64,109], and the vmPFC innervates the area with ORX- and MCH-neurons [2,58,108–110].

The two orexigenic peptides appear to sub serve different functions in the control of food intake. The MCH role in the homeostatic regulation is well established. The MCH injections induce feeding and its mRNA is increased by fasting, and is over expressed in genetically obese (ob/ob) mice [111]. Genetic manipulations that eliminated [112] or enhanced MCH production [113] confirmed its importance in food intake and body weight regulation.

On the other hand, the role of ORX system in feeding [114] might be related to adaptive functions that complement homeostatic control. The ORX system, which is critical for control of wakefulness, mediates arousal in response to fasting, and contributes to other functions that depend on behavioral states, including reward [115–117]. Accordingly, neurons that produce ORX, which are located exclusively in the LHA, have the capability to influence diverse brain systems via widespread pathways, and similarly broadly distributed receptors [110,118,119].

Importantly, the ORX system is involved in processing of food and drug rewards via circuitry that engages the LHA, nucleus accumbens, ventral tegmental area, and the prefrontal cortex (e.g., [120–124]). Notably, ORX neurons have been shown to respond to contextual cues for food and drugs in the conditioned place preference task [122,125]. Similarly, a recent study showed that the ORX neurons located in the perifornical area responded to the contextual cues that were previously paired with food [126]. Interestingly, the ORX neurons responded regardless of the type of food the context signaled, while the prefrontal cortex was selectively activated when the context signaled palatable food (chocolate), but not when the context signaled an ordinary meal (lab chow) [126]. These findings highlight the role of ORX neurons in food anticipatory mechanisms, and suggest that communication with the prefrontal cortex, and other forebrain and brainstem targets, might be important for dissociation between general and specific food motivations.

In accordance, our preliminary findings suggest that the ORX neurons are also important for cue-induced feeding (unpublished observations). Thus, we have begun work that examines whether the ORX and MCH neuron are engaged (immediate early gene induction) by the learned cue that stimulates feeding.

Other hypothalamic regions that are under telencephalic influences via indirect pathways might also be important for cue-driven feeding. A polysynaptic pathway could allow the BLA influence on the arcuate nucleus of the hypothalamus [127], which is considered a primary sensory area for the physiological signals related to energy needs [3]. Similarly, the amygdala and prefrontal cortex could reach another critical node of the hypothalamic feeding circuitry, the paraventricular nucleus of the hypothalamus [2–4] via indirect pathways through the bed nuclei of the stria terminalis [57,58,64,128].

3. Learning and the motivation to eat II: Fear cue induced cessation of feeding

In parallel with cue-induced feeding we have been developing a preparation that uses learned cues to inhibit feeding. In that protocol a cue that predicts danger (fear cue) inhibits food intake in food-deprived rats [15,40]. Similar to food cue’s ability to stimulate feeding in satiated states, fear cue’s ability to inhibit feeding in hungry states is acquired through associative learning. As such both behavioral preparations provide models for integration between the environmental and homeostatic signals, and for mapping of the underlying brain networks.

Our fear-induced feeding cessation model builds on well-established aversive, fear conditioning paradigms (e.g., [129–132]). In these preparations an initially neutral, environmental signal such as a tone (conditioned stimulus, CS) is paired with an aversive event such as a mild, electric, foot-shock (unconditioned stimulus, US). Through associative learning the tone becomes a predictor for the shock, and this is manifested in its acquired ability to produce fear-related behavioral responses (conditioned responses, CRs).

We use aversive conditioning to modulate feeding. In our preparation, rats receive tone-shock pairings during aversive training sessions, and are given food pellets that they consume during appetitive training sessions. The aversive and appetitive training sessions occur in alternating order, and are conducted in distinct environments (contexts). After training, rats are tested for food consumption during tests with tone (CS; fear cue) presentations in the appetitive context. Prior to testing rats are food deprived, and accordingly rats in the control condition (that did not receive tone-shock pairings during training) consume substantial amounts of food during the tests. Rats that previously received tone-shock pairings consume much less food than rats in the control condition. Thus, the fear cue effectively competes with the homeostatic signals induced by food deprivation to inhibit feeding.

We also measure CS-induced freezing behavior during food consumption tests. Freezing is a species-typical defense response that has been extensively studied in rodent fear conditioning paradigms. It is an easily recognized behavior, characterized by the absence of all movement except that required for breathing [133,134]. During our food consumption tests with tone (CS) presentations, rats show both behavioral responses, the freezing behavior and the
inhibition of feeding. Importantly, the CS-induced feeding cessation is not merely a consequence of immobilization due to CS-induced conditioned freezing behavior. We showed previously that the CS-induced feeding cessation and CS-induced freezing are dissociable behavioral responses induced by the same CS. Brain lesions that abolished conditioned freezing left inhibition of eating intact—lesions of the ventrolateral region of the periaqueductal gray [135], an area critical for conditioned freezing [136], or lesions of the basolateral amygdala [15]. Thus, the CS’s influence on feeding is not directly dependent on CS-induced freezing, and engages somewhat dissociable amygdalar and brainstem substrates.

Nevertheless, cessation of eating and freezing behavior are both components of a preparatory motivational system critical for defensive behavior triggered by the CS. Cessation of eating in anticipation of danger is an adaptive response that prepares an organism for an imminent threat, but could become maladaptive when persistent. Sustained fear is associated with anxiety, and its effects on food intake might relate to aspects of disordered eating in humans.

Anorexia nervosa is an eating disorder characterized by relentless maintenance of extremely low body weight through restricted eating, which is often combined with excessive exercise and even purging [34–36,137]. The ability to maintain restricted eating in emaciated states is paradoxical, and occurs in conflict with physiological hunger signals [36,138]. We hypothesize that another core symptom of anorexia nervosa might be invasive, the obsessive fear of weight gain despite being underweight [137].

Fear inhibits food intake [139,140]. Thus, the sustained fear might not only be the key symptom, but also an important contributor that facilitates the maintenance of restricted eating in anorexia. In that regard, anorexia nervosa shows high co-morbidity with anxiety disorders (reviewed in [36]), and support for fear network dysfunction has been found in recent imaging studies with anorexia nervosa patients.

Within the amygdala, abnormal functioning, and a decrease in its volume were found in anorexia patients [141,142]. Enhanced medial prefrontal cortex activity was associated with responses to food images that the patients with eating disorders (anorexia and bulimia) found threatening and disgusting [143]. Similarly, greater amygdala activation was found among anorexia patients when confronted with a threatening, symptom-provoking cue—their distorted body image [144]. Interestingly, amygdala recruitment was also correlated with increased anxiety in non-eating disordered young women when viewing pictures of slim, idealized female bodies [145].

Thus, our fear cue-induced feeding cessation rodent model is relevant to human eating, and provides a behavioral framework for defining the critical brain substrates. We have begun the analysis of the brain systems that allow fear cues access to the feeding circuitry, and the findings are discussed next.

3.1. The forebrain circuitry for fear cue feeding cessation

We began to delineate the forebrain circuitry underlying fear cue-induced feeding cessation in a study that examined the involvement of amygdalar subregions. The central nucleus (CEA) and the BLA are necessary components of the conditioned fear circuit [129–132,146], and have been linked to a range of functions that rely on associative learning to control goal-directed behaviors (for reviews see [92,129–132,146–148]). Furthermore, relevant to fear cue-mediated regulation of feeding the BLA and CEA could both influence hypothalamic and brainstem functions via distributed network of direct and indirect connections [58,64]. Thus we examined whether one or both of these structures are critical.

We found that bilateral, neurototoxic lesions of the central amygdala, but not bilateral, neurototoxic lesions of the basolateral amygdala, abolished CS-induced feeding cessation [15]. On the other hand, lesions of each of the structures abolished CS-induced freezing behavior. Thus, both the BLA- and CEA-lesioned rats greatly reduced freezing compared to the control (sham-lesioned) rats, but only the CEA-lesioned rats failed to inhibit feeding during the same test. Thus, the data showed that the CS’s influence on eating is independent of CS-induced freezing, and engages dissociable amygdalar and brainstem substrates.

The CEA influence on food consumption could be accomplished via complex output network that reaches multiple components of the feeding system via direct and indirect pathways. The CEA sends direct projections to the brainstem, lateral hypothalamus, and bed nuclei of the stria terminalis [64,128,149], as well as indirect pathways to the paraventricular nucleus of the hypothalamus [128,150]. Thus, future studies will examine where within the distributed feeding network the CEA exerts its action, and the plasticity that underlies learned cue inhibition of feeding [3–6,10,64,81,151].

Similarly, future studies are needed to address whether repeated exposure to aversive events, and associated fear and anxiety, might contribute to long-term suppression of eating and changes in body weight. The fear cue model presented here, therefore, provides a framework for future brain and behavioral analyses.

4. Conclusion

In summary, we have developed two behavioral preparations that rely on associative learning to acquire motivational powers to modulate feeding independent of existing hunger-satiety state. In one preparation a cue becomes a signal for food and gains the ability to stimulate consumption of that food in sated states. In the other preparation a cue becomes a signal for an imminent danger and gains the ability to powerfully inhibit feeding in hungry states. As such these models are helpful for analysis of the integration between the systems that process associative learning (the amygdala, prefrontal cortex and associated network) and the hypothalamic and brainstem feeding regulatory systems.

Thus far, our work has identified several critical components of the forebrain circuitry for cue-induced feeding. Nevertheless, the entire network, which is undoubtedly complex, and highly interconnected, remains unknown. Even less is known about the circuitry through which fear and anxiety inhibit feeding. Thus, determining the critical brain circuitries remains an important step in illuminating the mechanisms underlying environmental contribution to the regulation and dysregulation of food intake and body weight.

On a higher level, these models should provide a framework for understanding the role of the telencephalon in control of feeding and other goal-directed behaviors in the context of learning and anticipatory motivation. Ultimately they should help elucidate how the amygdala and its associated network processes biologically relevant sensory stimuli and modulates behavior accordingly.

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