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Eating beyond metabolic need: how environmental cues influence feeding behavior

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Animals use current, past, and projected future states of the organism and the world in a finely tuned system to control ingestion. They must not only deal effectively with current nutrient deficiencies, but also manage energy resources to meet future needs, all within the constraints of the mechanisms of metabolism. Many recent approaches to understanding the control of ingestive behavior distinguish between homeostatic mechanisms concerned with energy balance, and hedonic and incentive processes based on palatability and reward characteristics of food. In this review, I consider how learning about environmental cues influences homeostatic and hedonic brain signals, which may lead to increases in the affective taste properties of food and desire to over consume. Understanding these mechanisms may be critical for elucidating the etiology of the obesity epidemic.

Introduction

What drives us to eat? An answer might encompass a need to survive, routines or well-established patterns of feeding behavior (e.g., eating at particular times of day), and because we mostly like the taste and pleasurable consequences of eating. Although historically feeding research has been dominated by interest in the hormonal regulation of hypothalamic and hindbrain systems involved in energy regulation [1,2], roles for forebrain circuits in learning, memory, reward, and decision-making are now more widely appreciated [3–5]. Such processes may influence eating by cueing or guiding food procurement and in establishing food preferences and aversions [6]. Thus, cues that predict the availability of food become able to activate brain reward systems, much like the food itself. On a related note, learning is involved in mapping the hedonic (see Glossary) properties of food in brain reward systems, which in turn influences feeding behavior [5]. Indeed, many recent reviews of the control of feeding behavior describe two parallel systems; one homeostatic and sensitive to energy balance, the other hedonic driven by the palatability and rewarding properties of food, which can influence feeding without regard to energetics [7–9] (Figure 1). Moreover,

Glossary

Allostasis and homeostasis: both terms refer to the maintenance of stability of internal states. Traditionally, homeostatic regulation was described as reactive to deviations in state, and involving single, low-level physiological systems, often with fixed set points, whereas allostasis embraced proactive changes, coordinated action of multiple systems, and is generally less reliant on individual set points.

Conditioned reinforcement: the ability of a stimulus to serve as a reinforcer acquired through learning. For example, a mouse will learn to press a lever that yields presentation of a tone-conditioned reinforcer that had previously been paired with food, but not a lever that produces a tone that had not been paired with food.

Hedonic and hedonic hotspots: hedonic properties of food are those that humans describe as evoking pleasure or 'liking', even before postingestive processing. Hedonic hotspots are brain sites that amplify pleasure or 'liking' responses when stimulated.

Instrumental conditioning: learning procedure in which presentation of a reinforcer is contingent on the performance of a response; sometimes used to refer to the outcome of that procedure or a process by which that outcome occurs.

Licking microstructure analysis: detailed examination of the temporal characteristics of licking that relate to the variables that influence consumption of fluid reinforcers. For example, hedonic valuation independent of postingestive processes is indicated by the initial lick rate because it reflects intake before gastrointestinal absorption, and the duration of continuous bouts of licking (i.e., burst or cluster size) because this measure is unaffected by sham-feeding procedures.

'Liking' and 'wanting': 'liking' refers to a measurable hedonic reaction observed neurally or behaviorally (see 'taste reactivity'), often accompanied (in humans) by a subjective experience of pleasure. 'Wanting' refers to conditioned incentive salience or motivation for reward produced by reward-associated cues, often accompanied (in humans) by subjective desires.

Pavlovian conditioning: learning procedure in which presentation of a reinforcer is contingent on the presentation of another stimulus (i.e., the 'conditioned stimulus') regardless of the performance of the subject; sometimes used to refer to the outcome of that procedure or a process by which that outcome occurs.

Pavlovian-instrumental transfer (PIT): modulation of instrumentally trained responding by a separately trained Pavlovian CS, often attributed to learned incentive. For example, a tone previously paired with food often enhances the rate of instrumental lever pressing separately rewarded with that same food.

Progressive ratio: reinforcement schedule in which the number of responses (e.g., on a lever) required to obtain a reinforcer is systematically incremented following the delivery of each reinforcer. Typically, rats will cease responding once the number of responses exceeds a certain threshold (breakpoint), which is thought in part to reflect the motivation or willingness of the animal to respond for the reinforcer.

Reinforcer devaluation experiment: used to explore the contents of learned associations. For example, after training in which a rat learns to associate one cue with sucrose and another with maltodextrin, the value of sucrose is reduced (by selective satiation on that food, or pairing it with an illness-inducing agent). This results in immediate and selective reductions in learned responses to the cue previously paired with sucrose, as though the performance of the rat was controlled by the current value of the anticipated outcome.

Taste reactivity responses: stereotyped behavior patterns normally produced by oral presentations of flavors characterized as positive (accepted) or negative (rejected). These behavior patterns are observed even in very young animals and are somewhat homologous across species.

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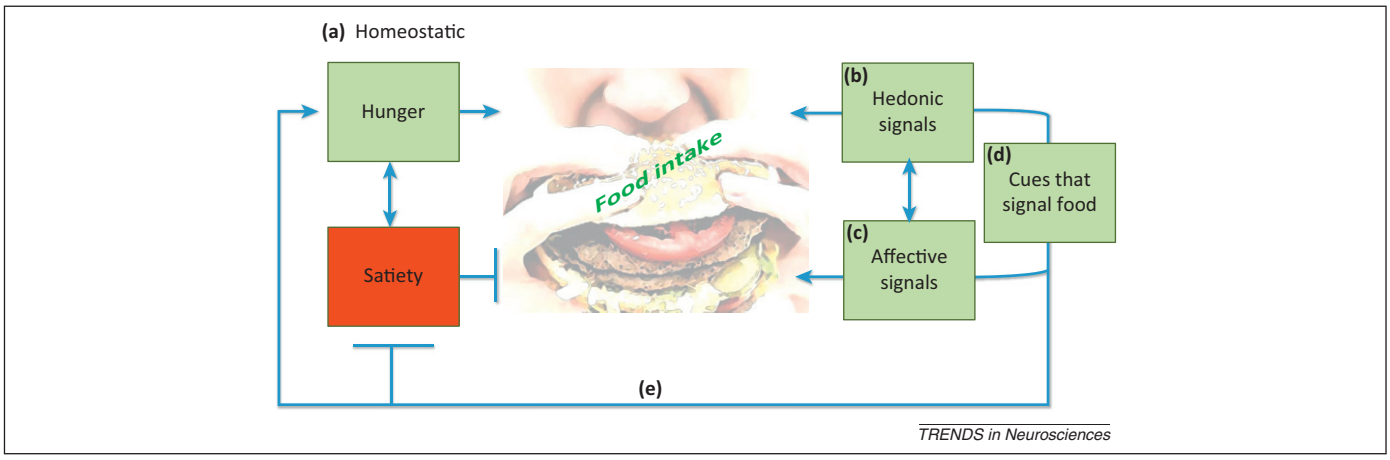

Figure 1. Signals that may influence food intake. **(a)** Homeostatic systems include interactions between circulating hunger (i.e., ghrelin) and satiety (e.g., leptin) signals, which drive and inhibit food intake, respectively [1,2,4]. These hormonal signals of energy balance mediate activity in hypothalamic and hindbrain systems. In addition to these homeostatic energy signals, reward signals also play significant roles in driving feeding behavior. These signals may include: **(b)** the hedonic aspects of food intake, such as palatability and reward characteristics of food itself and **(c)** affective (motivational) signals, which collectively drive activity in a variety of brain regions, including the prefrontal cortex, amygdala, striatum, and midbrain [5,7–9]; and **(d)** various discrete (e.g., radio jingle), contextual (e.g., restaurant), and temporal (e.g., time of day) food-associated cues, which through learning can acquire cognitive, affective, and behavioral control over the individual, resulting in food intake [3,5,13–15,17]. These cues may encode detailed sensory information (e.g., hedonic taste features) as well as more general affective properties (e.g., desirability) of food [3,5,17]. **(e)** These reward signals may drive food intake by influencing regulatory signals (e.g., by increasing feelings of hunger or inhibiting internal satiety mechanisms). Green boxes indicate appetite-stimulating effects, red box indicates inhibitory effects on appetite.

some authors have suggested that homeostatic systems are better understood within a framework of allostasis [10,11] in which, through learning, animals come to anticipate their needs rather than simply reacting to them.

In this review, I consider how feeding and food procurement behavior can be triggered by cues in the environment, and elucidate the potential mechanisms that allow cues to exert their influence on feeding behavior.

Learning about the food environment

Initially meaningless stimuli, such as sights, sounds, smells, locations and time intervals, can acquire new cognitive, affective, and behavioral functions when they occur in predictive relations with food. In this way, learning involves associations between different internal and external events. For example, most of us have learned that the GoldenArches™ (a cue) signals the availability of fast food. In laboratory Pavlovian conditioning experiments, food-predictive cues may come to direct attention [12], provide information about detailed properties of the impending food [13], acquire affective or incentive properties [5], and elicit a range of discrete skeletal and autonomic responses.

Each of these can have important effects on feeding. For example, various discrete, contextual, and temporal cues associated with meals have been shown to influence the release of gut hormones, such as ghrelin and insulin [14–16]. These gastrointestinal signals by their action within regulatory systems, affect both relatively immediate and longer-term consumption of food. One may therefore be more susceptible to visiting fast-food locations at certain times of the day or in certain places based on 'triggers' in the environment (e.g., food advertisements) that interact with physiological mechanisms of regulatory control (Figure 1). Cues that predict food also acquire incentive (or 'rewarding') properties [17]: cues that signal the likelihood of food support active food procurement behaviors [e.g., Pavlovian-instrumental transfer (PIT) [18]] and can also strengthen new behavioral strategies (e.g., conditioned reinforcement [19]). That is, visiting a new place when hungry and seeing the GoldenArches™ cue is enough to increase the likelihood of your repeating that behavior in the future, or developing different strategies to acquire the food (e.g., sitting in a restaurant or driving to a drive through). Moreover, results from a number of experimental paradigms [20], including reinforcer devaluation [21], PIT [22], and others [20,23,24], show that such cues may activate acquired representations of expected food outcomes. Importantly, this may include detailed sensory information (e.g., how the food tastes) as well as more general affective properties (e.g., the desirability of food). Thus, food seeking appears to be guided by detailed and affective representations of expected food outcomes that combine knowledge of where and how those foods can be obtained, with information about the current need for, or desirability of, those foods. Considerable investigation has shown that, across a range of species, a circuit including (but not limited to) the basolateral amygdala, medial and orbitofrontal cortex, medial and ventral striatum, and midbrain is critical for the formation and use of such associatively activated food representations [20,25–29].

Cue-potentiated feeding

Many of us experience sudden cravings for particular foods when exposed to sights or smells, or perhaps menu descriptions or advertisements for those foods, even when we are otherwise food sated (not hungry). These cravings may lead us to unplanned (and unnecessary) food consumption. Food-related cues have been shown to induce eating in food-sated human adults [30] and children [31]. These effects are in part based on our experiences with food cues in the obesogenic environment (they are all around us). For instance, a study in young children revealed that the capacity of McDonald's packaging to drive food preferences

was associated both with the number of television sets found in the household and the frequency of visits to this fast-food chain [32]. Thus, greater exposure to food advertisements (and the positive consequences that they predict) may have enhanced the likelihood for these cues to acquire control over food preferences.

The influence of food-paired cues on food preference and overeating has been studied in laboratory rats and mice using cue-potentiated feeding (CPF) (Figure 2). In one version of this task [33,34], food-deprived mice received separate presentations of two initially neutral cues (e.g., readily discriminable auditory stimuli), which either led to the delivery of a sucrose solution (the conditioned stimulus; CS+) or not (the unconditioned or control stimulus; CS–). Following extended satiation (i.e., free feeding) on laboratory chow in their home cages, the mice were returned to the training chambers, where sucrose was freely available. When consumption in the presence of the CS+ and CS– was then assessed (in short separate sessions), a majority of sated mice over-consumed during the CS+ but not CS–. Notably, the CS+ did not potentiate feeding simply by waking the animals or eliciting approach to the recessed food cup (a trained location), because a separate study found that rats also overate when the associated food was available in a new location on the opposite side of the chamber and the recessed food cup was empty [18]. CPF has been obtained under a variety of different settings, with discrete or contextual cues and foods of varying degrees of nutrition and palatability [33,35–37]. These effects are typically uncompensated for by internal regulatory mechanisms, because rats will fail to reduce (daily) chow consumption to account for the overeating elicited by a food-paired cue [38,39].

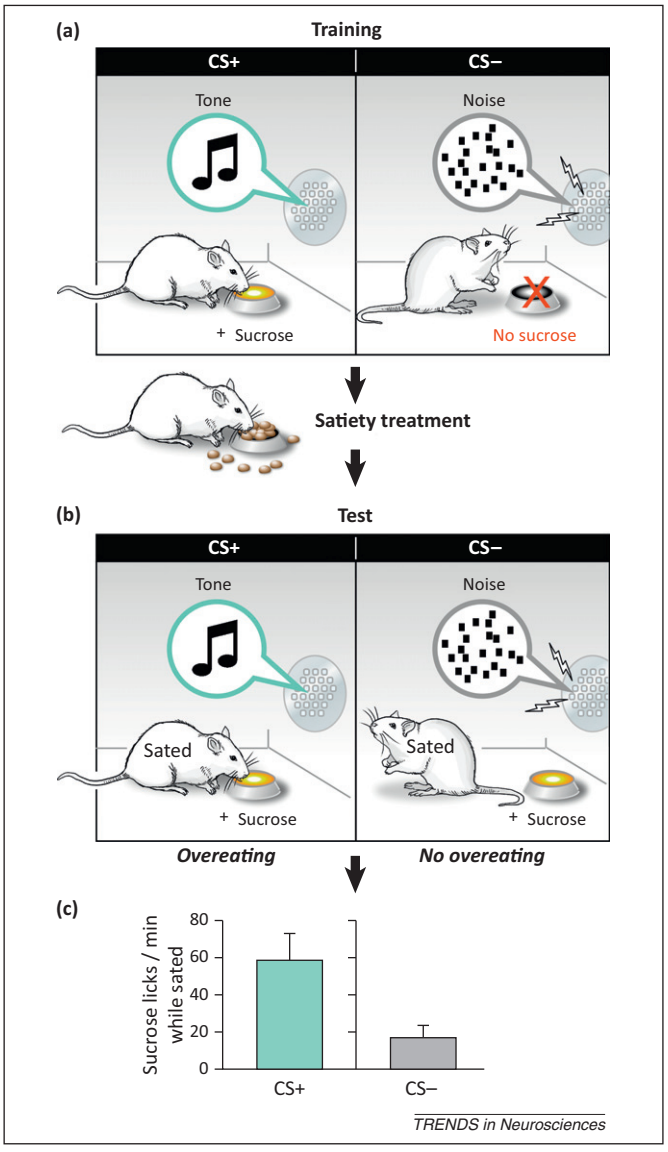

Figure 2. An example of cue-potentiated feeding (CPF). Rodents are food deprived by limiting access of laboratory chow to a single daily meal. **(a)** Training is carried out in conditioning chambers, during which sucrose is delivered only during presentations of a tone (i.e., conditioned stimulus, CS+) but not white noise (i.e., unconditioned stimulus, CS–). Following training, rodents are sated for a prolonged period of time (≥ 3 days) by providing unlimited access to their laboratory chow in their home cages (i.e., satiety treatment). **(b)** Subsequently, rodents are tested in the conditioning chambers, where they receive unlimited access to a sucrose solution. Given that the rodents are sated, they eventually avoid the sucrose during periods when no stimuli are presented. However, during presentation of the tone CS+, sated animals show voracious intake of the solution, as evidenced by an increase lick rate for the sucrose **(c)**. This CPF effect is due to learning of the prior Pavlovian associations, because no overeating is seen in response to the CS– cue [33,34,41].

Neuronal mechanisms of cue-potentiated feeding

The first brain region identified as playing a role in this form of overeating was the basolateral amygdala (BLA), which is a structure critically involved in associating food cues with the incentive properties of foods [20,21]. Although neurotoxic lesions to the BLA disrupted CPF, these rats were still able to acquire the initial Pavlovian associations in training, and displayed appropriate conditioned responses (such as approaching the food cup) during the test [35].

Subsequent examinations focused on BLA connections with the lateral hypothalamus (LH), which is a region traditionally linked to homeostatic and reward mechanisms [40]. Contralateral functional disconnection of the BLA from the LH, achieved by making unilateral lesions of BLA in one hemisphere and of LH in the other, also abolished CPF [41]. Given that BLA outputs are mostly ipsilateral, the contralateral disconnection disrupted signaling between BLA and LH, but left intact other functional circuits involving each of these structures. By contrast, rats that received unilateral lesions of both regions in one hemisphere (i.e., producing a similar degree of neural damage to the contralateral group but restricted to one brain hemisphere) showed overeating elicited by the CS+ to the same extent as sham (control) rats [41]. These disconnection studies suggest that intact signaling between hypothalamic homeostatic and amygdala reward centers is necessary for CPF.

Subsequent studies using anatomical tract tracing and immediate-early gene (IEG) activation techniques [42,43] revealed additional neuronal systems that underlie this feeding network. These studies took advantage of the distinct activity profile of nuclear mRNA for two IEGs: the activity-regulated cytoskeletal (*Arc*) gene and Homer 1a (*H1a*). *Arc* is transcribed in the cell nucleus within 5 min of synaptic activity, whereas *H1a* is present in the cell nucleus 30 min after synaptic activity, by which point the *Arc* nuclear signal will have degraded into the cytoplasm

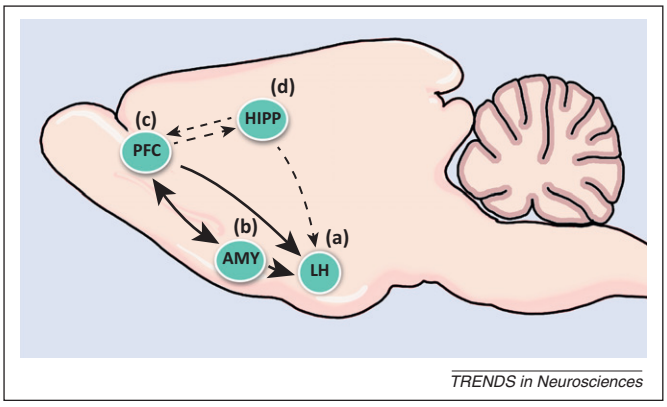

Figure 3. Basic circuitry for cue-potentiated feeding (CPF). Neurotoxic lesions to either **(a)** lateral hypothalamus (LH), **(b)** basolateral nucleus of the amygdala (AMY) comprising the lateral, basal, and basomedial areas, or **(c)** ventromedial prefrontal cortex (PFC), including infralimbic, prelimbic, and medial orbitofrontal cortex, disrupt CPF [35,41–43,45]. **(d)** Microinjections of the gastric peptide ghrelin into the ventral hippocampus (HIPP) elicit CPF in rats [76]. Thus far, ghrelin [33,76] and melanin-concentrating hormone (MCH) [34] are the only regulatory signals identified as critical to CPF. Ghrelin immunoreactive neurons project to the LH and its receptor, growth hormone secretagogue receptor (GHSR), is expressed in AMY and HIPP (but not PFC [33]). MCH is synthesized in LH and its receptor, MCH-1R, is expressed in PFC, AMY, and HIPP [59–61]. Solid lines depict known pathways that mediate CPF. Broken lines indicate known connections between regions, which have yet to be studied in CPF.

[44]. CPF tests can be designed such that the presentation of the CS+ (e.g., 30 min before sacrificing the animal) and CS– (e.g., 5 min before sacrificing the animal) can be arranged to correspond with the activity profile of these two IEGs [42,43]. This allows for the detection of those neurons that were activated by the CS+ (e.g., *H1a*) but not by the CS– (e.g., *Arc*). Neurons with direct inputs to LH (as defined by the retrograde tracer FluroGold) from both BLA and ventromedial prefrontal cortex (vmPFC) became activated while the rats consumed during the CS+ (but not CS–) [42]. A role for vmPFC in CPF was later confirmed in a lesion experiment [45]. Finally, in a separate tract tracing and IEG study, additional CS+ activated neurons were identified, projecting from the vmPFC to the BLA [43].

The brain regions identified in this network (Figure 3) may be capable of driving CPF in several ways: encoding cue-evoked representations or memories of the specific sensory features (e.g., taste, smell, or texture) of foods (via the BLA) [21]; integrating physiological, gastrointestinal, and sympathetic peripheral signals with exogenous signals (e.g., motivational or cognitive) to mediate the desire to eat (via the LH) [40]; and influencing decision-making, which may include recruiting information from our experiences with food in the environment to influence preference (via the vmPFC) [46].

The decision to overeat in cue-potentiated feeding

There are many reasons why CPF may result in the decision to overeat. Choosing to avoid fast food is all well and good, until one sees or smells the food, then temptation takes over, and one's decision not to indulge may wane. The idea is that cues associated with the food trigger interactions between the homeostatic and reward circuits of the brain, which contributes to overeating. Two influences of food cues, based on their capacity to potentially alter our perception (i.e., our hedonic evaluation) of food, and the motivation to consume it, are discussed below. These dissociable (but related) influences on overeating may be mediated by different regulatory systems.

Hedonics, evaluation, and cue-potentiated feeding

The hedonic taste qualities associated with palatable food are capable of driving feeding behavior [9,47]; that is, we like to eat certain tasty snacks even when not hungry. As contact is made with these palatable foods, various subtle responses are emitted that can be assessed. For instance, during consumption of palatable taste solutions, rodents will emit a rich array of orofacial and licking responses that vary in nature, probability, duration, and number [17,48,49]. It is possible to capture these responses via slow-motion video analysis of rats as they consume the liquid reinforcer. Similar to facial reactions in humans (including infants), these appetitive taste reactivity (TR) measures have been found to correlate positively with palatability or 'liking' [17,50] in many species. In addition to these orofacial reactions, rodents will emit various patterns and fluctuations in their licking behavior, which correspond to the orosensory-positive features of food [48,49]. Thus, consumption of a highly palatable solution is characterized by significantly large bursts or bouts of licking, which increase with the palatability of food, but are unaffected by other variables that can influence food intake. Notably, food-paired cues result in an increase in positive TR measures [51]. In addition, increased consumption during the CS+ in CPF has been accompanied by increased licking microstructural measures associated with food palatability [34].

The possibility that CPF is mediated by enhancement in associated food palatability is consistent with the highly food-specific nature of CPF. When two separate CS+ cues lead to the delivery of two readily distinguishable but equally preferred reinforcers, CPF is observed only when the CS+ is presented in combination with the reinforcer that it predicts (i.e., the congruent but not incongruent food) [22,52]. This reinforcer specificity of CPF would be expected if it were mediated by enhancement of sensory-hedonic processing (i.e., 'liking'; [5,17]) of the food item, rather than by inducing a generic appetitive motivational state (i.e., 'wanting'; [17,40]). This suggests that the cues present when consuming fast food (e.g., signs or wrapping) enhance the taste of the associated food (e.g., hamburger), which may lead to eating beyond current metabolic need.

If cues are able to acquire the capacity to enhance how food tastes, this suggests that a transfer of hedonic properties occurs between the associated food and the CS that predicts its occurrence. More generally, a variety of studies support the idea that experiences with food alter its palatability [6]. An intriguing example comes from a recent effort-based study [53]. In this study, mice were trained to respond using two separate levers. Pressing one of the levers (low effort) resulted in the presentation of a particular auditory cue and the delivery of a particular food. The other lever (i.e., high effort) had to be pressed 15 times (not one) to affect the delivery of a different auditory cue and different food. When mice were later given free access to both foods in their home cage, they exhibited increased

consumption and preference for the reinforcer that was previously associated with the high-effort lever. A subsequent test showed that the auditory cue associated with the high-effort lever acquired greater conditioned reinforcement value than did the low-effort auditory cue. Supposing that the attractiveness of (such auditory) cues (and their potency to strengthen behavior) is related to the value of the reinforcers they predict, then working hard increases the incentive value of the food procured. In a separate experiment in the same study, examination of licking microstructure revealed that the augmented intake of the high-effort food reflected features of licking thought to indicate orosensory stimulation [48,53]. The observation that 'working hard for food enhances its taste' implies that the changes in reinforcing value and preference of food may have derived from palatability changes induced by the contrasting schedules of reinforcement. Thus, learned changes in food palatability could have broad effects on the procurement of food and its intake.

What might the physiological mechanisms be that mediate palatability modulation in CPF? One potential candidate is the melanin-concentrating hormone (MCH). This orexigenic (appetite-stimulating) peptide is synthesized in the LH and zona incerta. Acting through its G protein-coupled receptor MCH-1R, this orexigenic peptide becomes upregulated during periods of food withdrawal or in hypoleptinemic obese *ob*/*ob* mice [54,55]. Central infusions of this orexigen increased food intake in rodents [56,57] and led to marked hyperphagia following transgenic overexpression [58]. Although MCH cells are restricted to the LH, MCH-1R is densely expressed within the BLA and vmPFC areas (Figure 3) [59,60]. Thus, via LH activity, MCH cells may modulate the action of other brain regions involved in CPF [59,61]. Notably, a recent series of studies has investigated the role of MCH in CPF and other incentive phenomena [34,62]. Wild type mice that received lateral ventricle infusion of an MCH-1R antagonist failed to show sated overeating to a sucrose solution during CS+ presentations [34]. A similar result was obtained using MCH-1R-knockout mice [34]. Again, as with the lesion studies [18], these mice showed normal performance in training and food cup approach behaviors under test, supporting a selective deficit in CPF. When the dynamics of licking behavior were assessed, the genetically or pharmacologically manipulated mice displayed a significant reduction in the mean number of licks emitted during each burst compared with controls [34]. This suggests that MCH may drive CPF by encoding hedonic properties of the associated food with the CS+ and/or retrieving this information under conditions of satiety.

Although much work is needed to elucidate the complicated network modulating CPF, in addition to the MCH, candidate signals of palatability modulation in CPF include the endocannabinoid system. Notably, by activating cannabinoid CB1 receptor signaling, this system has been shown to increase spike frequency and depolarize MCH neurons via presynaptic attenuation of GABA release from adjacent hypothalamic GABA neurons [61,63]. Interestingly, the CB1 receptor has been shown to affect both the hedonic valuation of foods (i.e., 'liking') [64] and learning phenomena that depend on associatively activated representation of detailed reinforcer features [65,66], a characteristic shared by CPF. It remains to be seen whether this system is capable of influencing CPF via the engagement of similar mechanisms.

Motivation to procure and over consume food

As a result of pairing with food, cues can acquire a range of incentive capabilities that may modulate food intake based on increasing our motivation to consume. There are several notable contrasts with mechanisms of incentive [67,68] and those responsible for hedonic evaluation [17,48]. In addition to motivating eating behavior (and procurement) based on the specific features of food elicited by the cue (e.g., craving a particular food), food paired cues may also drive motivation by increasing nonspecific arousal [69]. An example of this multimodular capacity for CSs to motivate behavior is seen in PIT rodent and human studies [18,69,70]. In one version of this task, rats were presented with two cues that led to the delivery of different food reinforcers. In separate sessions, the same rats were required to respond using two separate levers for the two different foods. During the test phase, they were presented for the first time with both cues and levers simultaneously (but no food), resulting in increased selective responding (i.e., selective PIT) on the lever that was associated with the food that the cue predicts. For rats to 'solve' this task, they had to use CS-evoked sensory representations of the foods to signal the direction of lever responding. However, under certain conditions (e.g., if a single reinforcer is used in training; [18]), the CS may elicit a nonspecific arousal to facilitate ongoing lever responding at test. This general PIT may occur even if the CS+ and lever signal different (incongruent) foods [69]. Thus, CSs are not only capable of directing motivated responding by the selective features of food, but may also elicit a general motivational drive, akin to increases in 'wanting', but not 'liking' food [17]. Notably, transfer that enhances motivational arousal relies on different neural structures [i.e., central nucleus of the amygdala (CeA), nucleus accumbens (NAc) core, and ventral tegmental area (VTA)] compared with those regions involved in selective PIT [i.e., BLA, NAc shell, and orbitofrontal cortex (OFC) [23,69,71,72]].

The above discussion suggests that CSs may drive consumption based on temporarily increasing hunger ('wanting') for food, which would be expected to elicit nonspecific sated feeding as revealed under certain, cue-induced feeding preparations [38]. Interestingly, the appetite-enhancing effects of the gastric signal ghrelin are thought to reflect motivation to eat independent of hedonic valuation [73]. Rats that received lateral ventricle infusions of ghrelin consumed more of an appetizing food solution, without changes in their patterns of licking microstructure that reflect palatability [73]. This suggests that ghrelin has its action over food intake in a relatively nonspecific manner (e.g., by increasing hunger and motivation to eat; i.e., 'wanting' [17]) and, thus, may facilitate the desire to consume. Indeed, ghrelin enhanced progressive ratio responding for sucrose [73], which is a procedure thought to reflect 'wanting' mechanisms. These latter effects of ghrelin were suppressed following treatment with a dopamine (D1 receptor) antagonist (SCH-23390)

[73], consistent with a well-characterized role for this neurotransmitter in learned incentive salience [67].

Ghrelin is notable in that it is so far the only gastric feeding signal that has been discovered [74]. Following secretion from the gastric mucosa into the circulation, the expression of this peptide and its receptor [growth hormone secretagogue receptor (GHSR)] throughout the brain (e.g., amygdala, hippocampus, and VTA [74,75]) renders it capable of influencing a variety of functions, including CPF [33,76]. In the first of a series of recent studies, infusion of ghrelin into the ventral hippocampus resulted in the initiation of CPF [76]. Although the hippocampus has traditionally been associated with spatial and declarative memory, its ventral regions in particular are now known to influence a variety of behaviors, including feeding [77,78]. In a second recent study, (before each training session) control mice were treated intraorally with a compound designed to antagonize the actions of GHSR [33]. This led to a deficit in CPF even when mice were tested in the absence of the GHSR inhibitor. This finding suggests that ghrelin is involved in encoding, but not the retrieval of, the learned associations that mediate CPF. Finally, using a similar procedure to the aforementioned rat studies [42,43], these investigators arranged presentation of the CS+ and control cues to coincide with transcription of the IEGs *Arc* and *H1a* (i.e., 5 min and 30 min, respectively), which confirmed encoding of CS+ in the BLA of control mice [33].

Many questions remain as to the role of ghrelin in CPF. However, based on the above discussion, ghrelin is known to modulate motivation to eat food but not hedonic evaluation, and interacts with mesolimbic 'wanting' circuitry [73,75]. Moreover, it is notable that, in patients with Prader–Willi syndrome, food CSs increased nonspecific arousal of ongoing instrumental behavior (i.e., general PIT) to a greater extent than in control subjects [79]. This syndrome is associated with elevated circulating ghrelin levels and profound hyperphagia [80,81]. These findings suggest that these patients are particularly vulnerable to overeating based on increased 'wanting' of food [79]. Thus, it is tempting to speculate that ghrelin may similarly mediate CPF by influencing motivation or 'wanting'. This may in turn help to account for the somewhat indiscriminate and voracious eating habits of these patients [80,81]. Moreover, several features of the aforementioned ghrelin CPF studies [33,76], such as testing under subthreshold conditions (that required ghrelin to initiate CPF [76]) and the use of bland food pellets as the reinforcer (to minimize hedonic influences; [33]), are to some extent more consistent with CPF mechanisms that would support the motivation to drive and initiate responding [73], than with those for hedonic valuation [34]. This would suggest expanding further the highlighted putative circuit (Figure 3), perhaps to include certain portions of mesolimbic circuitry (e.g., VTA) [82].

Neural system dissociations of cue-potentiated feeding and other incentive phenomena

Although CPF has features in common with other phenomena ascribed to learned incentive, such as conditioned reinforcement, PIT, and reinforcer devaluation, it also exhibits unique features, which may in part relate to modulation of hypothalamic feeding systems in CPF. For example, although both CPF and conditioned reinforcement require the integrity of the BLA [35,83], these phenomena are mediated by different BLA projections. Whereas BLA–LH disconnection prevents CPF, it has no effect on second-order conditioning, an example of conditioned reinforcement [41]. By contrast, communication between the BLA and the ventral striatal NAc is necessary for second-order conditioning [84], but not for CPF [3]. This is consistent with the observation that NAc neurons that project to the LH are not engaged in CPF [42]. The apparent lack of involvement of NAc–LH projections in CPF is especially notable given the many demonstrated effects of manipulations of NAc function on other incentive phenomena (e.g., [66]) and the presence of 'hedonic hotspots' in the NAc shell, which are known to play critical roles in hedonic control of eating to NAc [85,86]. These findings suggest that regions other than the NAc (e.g., the vmPFC; [87]) may modulate CPF via hedonic valuation [17]. In addition, neurons in the OFC respond to food valuations [26,88], and lateral OFC dysfunction in rodents and primates impaired conditioned reinforcement [89,90] and reinforcer devaluation [28,29]. However, CPF only minimally activated OFC neurons [42] and OFC lesions left CPF unaffected [23]. Finally, the CeA (which shares connections with LH [43]) in part modulates incentive salience, but not CPF driven by appetitive cues [18,69,91].

Concluding remarks: implications for obesity

This review has attempted to couch the influence of environmental cues on feeding behavior in the context of basic learning mechanisms in rodents. Similar neuroanatomical systems are found in humans and the findings herein discussed have important implications for the obesity epidemic. Two different types of behavioral, neural, and regulatory influence by food-paired cues are outlined; one driven by (food-specific) hedonic valuation and orosensory stimulation via MCH interactions [34], and a second possibly driven by incentive (e.g., food general) and based on increasing arousal and drive to eat [33,76], via ghrelin. Hence, the success of fast-food advertisement campaigns to attract business might reflect their capacity to manifest cravings (e.g., thoughts of hamburgers and chicken nuggets) and evoke a general drive to eat (e.g., a feeling of hunger).

As obesity rates rise, an increasing proportion of human food consumption may be attributable reward (i.e., hedonic and incentive) influences on ingestive behavior. Although central systems responsible for metabolic control and those involved in hedonic valuation, reward, and incentive are continually interacting to allow individuals to respond and anticipate metabolic need [11], they also dispose us to external influences present in the current obesogenic environment [92]. Thus, there are many reasons why we overeat in the presence of obesogenic cues; these may be elucidated by subtle psychological, neuronal and molecular manipulations in CPF. Unfortunately, in comparison to the study of other hedonic and incentive phenomena [17,24–29,68,93], relatively fewer studies have investigated mechanisms of CPF. The paucity in data is surprising

given the many characteristics that are common between the laboratory model of CPF and studies of human eating. For example, the rapid consumption of large amounts of food in rodents while not hungry [45] characterizes binge-eating disorder [94], which in some cases can lead to obesity. More generally, food-paired cues can direct feeding behavior and preference in children [31,32], adolescents [95], and adults [30,96], both in selective [95,96] and non-specific [32] ways, which is perhaps consistent with the modulation of overeating by dissociable but interrelated CPF mechanisms [33,34,36,38].

CPF and related phenomena highlight the complexity of the relation between mammals and their food environments. Reward learning and incentive mechanisms that may have evolved to promote species survival in environments of at least intermittent scarcity may now produce overeating outside of metabolic requirements, leading to obesity and its many physical comorbidities (e.g., diabetes and heart disease) as well as quality-of-life issues. That is to say, our hunter-gatherer forbearers would be well advised to learn that the GoldenArches™ signal the availability of food and survival, but modern man is bombarded with 'eat now' cues at every turn that promote overeating and weight gain.

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