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The role of the opioid system in binge eating disorder

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Abstract

Binge eating disorder is characterized by excessive, uncontrollable consumption of palatable food within brief periods of time. Excessive intake of palatable food is thought to be driven by hedonic, rather than energy homeostatic mechanisms. However, reward processing does not only comprise consummatory actions; a key component is represented by the anticipatory phase directed at procuring the reward. This phase is highly influenced by environmental food-associated stimuli which can robustly enhance the desire to eat even in the absence of physiological needs. The opioid system (endogenous peptides and their receptors) has been strongly linked to the rewarding aspects of palatable food intake, and perhaps represents the key system involved in hedonic overeating. Here we review evidence suggesting that the opioid system can also be regarded as one of the systems regulating the anticipatory incentive processes preceding binge eating hedonic episodes.

Introduction

Binge eating disorder (BED) is characterized by recurrent-persistent episodes of excessive and uncontrollable food consumption within a short period of time. Although individuals with BED generally have a higher than average body mass index (BMI), weight and BMI are not diagnostic criteria for BED. The aberrant eating behaviour behind this disorder is characterized by a subjective sense of loss of control, distress, uncomfortable fullness and

intense feelings of disgust and embarrassment¹, without the inappropriate compensatory behaviours of bulimia nervosa². Episodes of binge eating, associated with at least three specific features (e.g. eating more rapidly than normal, eating until uncomfortably full, eating a large amount when not hungry, eating alone because of embarrassment, feeling disgusted, depressed, or guilty about overeating) occur both in BED and in bulimia nervosa with an average frequency of at least once a week, over three months².

The lifetime prevalence of frequent binge eating in the United States is about 1.5% with a median age of onset of about 12.5 years^{3,4}. About 35% of those who regularly binge are overweight or obese⁵. Additionally, individuals reporting to engage in binge eating behaviours have been shown to regain weight at a faster rate than those who do not⁶. Interestingly, among those who binge approximately 76% of adults and 85% of adolescents experience psychiatric co-morbidities such as anxiety, mood, and substance use disorders³, as well as other disorders such as obesity, diabetes, and cardiovascular diseases⁷. Based on the growing evidence of high prevalence and clinical significance^{8,9}, the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) has now designated BED as a psychiatric illness distinct from other eating disorders with a specific formal diagnosis² and the only pharmacological treatment for BED, lisdexamfetamine dimesylate, has just recently been approved by the Food and Drug Administration (FDA)¹⁰. On the other hand, medications that have been reported to reduce binge eating in clinical studies, e.g. topiramate^{11,12}, are associated with a variety of adverse side effects, which may result in discontinuation of therapy¹³.

Unlike individuals with bulimia nervosa, individuals with BED typically do not show marked or sustained dietary restriction designed to influence body weight and shape between binge-eating episodes. They may, however, report frequent attempts at dieting.. Therefore, a widely accepted hypothesis about the etiology of binge eating is based on the sequential

access to foods with different hedonic value, as occurs in restrained eaters^{14,15}. Highly palatable foods are typically rich in sucrose and fat and they are commonly perceived as ‘forbidden’ between binges because they are calorie-dense^{16,17}. Therefore, selection of low energy-dense foods in chronic dieters^{18–20} may instead increase craving for more appetitive palatable foods, and makes individuals more vulnerable to behavioural excess and overeating²¹. Highly palatable foods are more likely to be consumed for reasons beyond hunger, and their high palatability make it more difficult to limit and to control their intake^{22,23}.

The opioid system (endogenous peptides and their receptors) has been strongly linked to rewarding impact of palatable food intake, and it represents one of the key systems regulating hedonic overeating²⁴. Opioid receptor agonist administration increases food intake while opioid receptor antagonists decrease it²⁵. Among the different opioid receptor subtypes, μ -opioid receptors have been strongly involved in the modulation of hedonic feeding in general and more specifically in pathological overeating observed in BED²⁴. Motivated behaviours are not only characterized by hedonic mechanisms leading to consummatory episodes. Anticipatory incentive processes by which an individual comes to expect contact with palatable food, e.g. the exposure to cues associated with that specific food, also play a fundamental role. A cue may be successfully resisted many times, but on some occasions it may trigger irresistible temptation^{26,27}. Clinical data have suggested that some individuals may attribute a higher motivational value to food-cues compared to others and, therefore, these may be more likely to overeat^{28,29}. Indeed, food craving has been reported to be a major precipitant of binge episodes^{30,31}.

While emphasizing the results obtained in animal models of binge eating, the present review will focus on the role of the opioid system both in the hedonic component of

consummatory behaviour and more specifically in anticipatory incentive processes preceding binge-eating hedonic episodes.

Hedonically-driven eating behaviour

Because consumption of large volumes of palatable food in brief periods of time is the key diagnostic criterion for BED, animal models of this disorder have been developed to mimic this essential maladaptive behavioural outcome. Table 1 summarizes the most predictive binge eating preclinical models, divided into three major classes, as a function of the procedures used to induce binge eating in animals: *i*) binge eating induced by cycles of food deprivation and renewed access to a sucrose solution; *ii*) binge eating induced by cycles of stress and food restriction/refeeding; *iii*) binge eating induced by limiting access to a highly palatable diet.

Abundant evidence implicates the brain opioid systems in the regulation of food intake and the rewarding impact of palatable food intake²⁴. Hedonic pleasure reactions have been operationalized in animals through ‘liking’ reactions to sweetness, which are affective orofacial expressions (tongue and lateral tongue protrusions) that are homologous in human infants, monkeys, horses and rats³². The neural mechanisms associated with hedonic responses to palatable foods have been investigated by using selective μ -opioid receptor ligands to identify ‘hotspots’ in the basal ganglia, especially in the ventral pallidum (VP) and the nucleus accumbens (NAc)^{33,34}. It has been shown that the ability of μ -opioid receptor agonists to increase food intake is restricted to a specific portion of the NAc shell (the rostradorsal quadrant of NAc medial shell), which shows high μ -opioid receptor density³³. Recently, it has been shown that within the same μ -opioid receptor hotspot stimulation of δ -opioid receptor a subtype of opioid receptor having a prominent role in emotional processing, can also amplify hedonic reactions to sweetness³⁵.

The NAc sends projections to the VP, which also projects back to the NAc, and each structure is embedded in complex mesocortico-limbic circuits involving the lateral hypothalamus, the ventral tegmental area, the prefrontal cortex and the amygdala. Each of these areas is fundamental in reward and motivational processes. Similar to the NAc, the VP has been shown to contain a hedonic hotspot, specifically in the posterior portion³⁴.

Based on these mechanisms, μ -opioid receptor agonists have been demonstrated to increase the intake of palatable food with a high sugar or fat content and to increase the consumption of more preferred food when presented at the same time with less preferred food³⁶. μ -opioid receptor antagonists, on the other hand, reduce binge episodes for highly palatable food^{17,19,37-39}, confirming the critical involvement of this system in the hedonic and consummatory aspects of ingestive behaviour. For example, the preferential μ/k opioid-receptor antagonist nalmefene, an effective and approved treatment for heavy alcohol drinking⁴⁰, has been successfully tested in a binge-eating paradigm¹⁷. In this study, adolescent female Wistar rats were food deprived for 2 h a day and then offered 10-min access to a feeder containing chow followed sequentially by 10-min access to a highly preferred, but macronutrient-comparable, sucrose-rich diet. Those exposed to chow and high sucrose diet developed experience-dependent binge-like hyperphagia of the diet as well as anticipatory hypophagia of the less preferred alternative. ‘Binges’ were reduced dose-dependently by systemically injected nalmefene¹⁷, supporting the hypothesis that the endogenous opioid system promotes hedonic intake. Using the binge-eating procedure described above, the behavioural effects of a novel, selective μ -opioid receptor antagonist GSK1521498, currently in clinical development for the treatment of compulsive eating disorders and obesity, was tested in comparison with naltrexone (NTX), a preferential μ -opioid receptor antagonist clinically approved for alcoholism³⁷. Both GSK1521498 and NTX reduced binge-like palatable food hyperphagia and food intake after instrumentally working to obtain it,

confirming the key role that the opioid system plays in hedonic eating behaviour. The same compound, GSK1521498, was tested for 4 weeks in binge-eating obese subjects and resulted in reduced hedonic preference, specifically for higher concentrations of sugar and fat, and markedly reduced calorie intake in an *ad libitum* buffet, particularly for more palatable foods³⁹.

Incentive salience in eating behaviour

Reward processing comprises two dissociable components: an anticipatory (or appetitive) phase, which is directed at procuring the reward, and a consummatory phase. The anticipatory phase can be associated with stimuli (contextual, visual, auditory or food-associated) or the food *per se*. These stimuli can have a great impact on the eating behaviour, as they can increase it. It has been shown, for example, that learned contextual cues potentiate eating in rats⁴¹. Berridge's group has also demonstrated that hedonic reactions to palatable food can be dissociated from the motivation process regulating its intake ('wanting'), showing that food intake can be stimulated without enhancing 'liking' reactions⁴².

In animal studies, food-associated cues have been operationalized and thoroughly studied in the context of both Pavlovian and instrumental conditioning⁴³. After repeated pairings of a cue, such as the presentation of a stimulus light (conditioned stimulus, CS) with the delivery of palatable food (unconditioned stimulus, US), the learned cue itself becomes salient, triggers intense urges to obtain the associated reward, and also acts as a conditioned reinforcer able to maintain instrumental seeking even in absence of food presentation. Importantly, cues paired with the delivery of palatable food become capable of promoting consumption even when the animals are not deprived (CS-potentiated feeding)⁴⁴. Even in fully sated rats, CSs strongly promote feeding compared to neutral stimuli^{45,46}. Both associative learning and prediction contribute to motivation for rewards. The conditioned stimuli gain salience and elicit incentive motivation even in absence of physiological needs.

Evidence from the influence of Pavlovian stimuli on instrumental behaviour is provided by experiments based on the specific Pavlovian-instrumental transfer (PIT) effect where appetitive CSs (associated with positive reinforcers such as food) can greatly enhance instrumental responding for the same reinforcer when presented unexpectedly (independent of the instrumental response). Training consists of three phases: in the first, a Pavlovian association is acquired between a cue and a reinforcer; in the second, an instrumental response is trained for the same reinforcer (without any cue); in the third, the cue is presented during the performance of instrumental behaviour in extinction (without any reinforcer). Such a procedure has shown that appetitive Pavlovian stimuli can greatly enhance instrumental responding for the same reinforcer (specific PIT effect). PIT has been interpreted as evidence that CSs can exert a motivational influence over instrumental performance⁴⁷ (Figure 1A).

An additional useful procedure for measuring the impact a CS may have over instrumental performance is the second-order schedule of reinforcement, where a stimulus that acquires its reinforcing properties by being paired with other, generally primary, reinforcers such as food or drugs, can act as a conditioned reinforcer⁴⁸ to enhance and maintain high levels of instrumental responses over protracted periods of time even in the absence of the primary reinforcer. This procedure, used previously to study the seeking of a sexual reward as well as cocaine, heroin, and alcohol seeking, has been adapted in order to measure, in terms of instrumental responses, the motivation for the opportunity to binge on a palatable food, as well as the impact that ingestion of that food has on subsequent food seeking⁴⁹. The procedure has temporarily distinct intervals that enable the separate assessment of motivational influence of the food-related CS over instrumental response before and after food ingestion, respectively. This allows the dissociation between pharmacological effects on response to food cues (during the interval before food ingestion) and effects on hedonic impact of the food reward (during the interval(s) after food ingestion)^{37,50} (Figure 1B).

A different way to study anticipatory incentive processes preceding consummatory behaviours mediated by hedonic mechanisms consists of analysing the phenomenon known as ‘anticipatory negative contrast’⁵¹. Evidence suggests that binge hyperphagia of ‘forbidden’ foods is linked with the refusal of otherwise acceptable alternatives in humans⁵². The phenomenon has been operationalized in preclinical models by exposing the animals to less preferred, but perhaps healthier, foods followed by highly palatable foods for restricted periods of time^{17,37,53}: as described above, 10-min brief access to a standard chow diet, followed by a 10-min access to a highly palatable food^{17,37}, promotes binge eating of the highly palatable food, and self-restriction of the otherwise acceptable chow diet (Figure 1C).

The role of the opioid system in incentive motivation for palatable food

The mesolimbic dopamine system has long been implicated in the motivational aspects of feeding behaviour. Exposure to either drugs or palatable food as well as to food-associated stimuli promotes dopamine release in the striatum. Dopamine has been demonstrated to be fundamental in the stimulus–reward learning that is specifically associated with the attribution of incentive salience to reward cues⁵⁴. It is widely accepted, although quite simplistic, that motivated behaviours for food are dopamine-mediated and that hedonic reactions to food are opioid-mediated. Indeed, dopaminergic manipulations within or outside the NAc shell hotspot consistently fail to enhance positive hedonic reactions to sweet tastes^{55,56} but potentially alter motivated ‘wanting’ for the food rewards⁴².

Although there is much less consensus, it has been proposed that opioid mechanisms can also regulate incentive motivational processes that underlie the propensity to seek palatable foods.

Striatum

It has been shown that opioid receptor agonists in the NAc increase motivation for food⁵⁷. Recently, selective stimulation of the three major subtypes of opioid receptors via agonist microinjections [μ (DAMGO), δ (DPDPE), or κ (U50488H)] in the NAc shell hotspot has been employed, to construct anatomical maps for functional localization of consequent changes in hedonic ‘liking’ (assessed by affective orofacial reactions to sucrose taste) versus ‘wanting’ (assessed by changes in food intake). In line with results from other groups that demonstrated that the NAc shell contributes not only to the hedonic impact of sensory pleasure, but also to the incentive motivation to consume foods⁵⁷, δ - and μ -opioid receptor stimulation enhanced the ‘wanting’ to eat more food. The real distinction between ‘wanting’ and ‘liking’ emerged from the effects of μ - and κ -opioid receptor stimulation: although they both increased the ‘liking’, only the μ -opioid receptor stimulation increased the incentive motivation for food.

In contrast, opioid receptor antagonists have been shown to reduce the anticipatory incentive processes preceding the consummatory episodes of highly palatable food. The non-selective opioid receptor antagonist, nalmefene, for example, blocked the anticipatory negative contrast in the binge-eating procedure as well as highly palatable food binge eating¹⁷. Additionally, the μ -opioid receptor antagonist GSK1521498 exerted a more specific effect on the impact of the hedonic value of the food and intake than did NTX, reducing the anticipatory chow hypophagia, before the highly palatable food was available for ingestion. Although the paradigm used did not include any discrete stimulus (i.e. a light), several cues might have served as conditioned stimuli predictive of imminent preferred food availability, including the test environment, the deprivation period, or even the preceding first feeder (chow) presentation.

A different anticipatory contrast paradigm has been developed by Katsuura and Taha⁵³, in which separate groups of rats were presented sequentially with 4% sucrose and then either

20% or 0% sucrose (Group 1: 4-20%, Group 2: 4-0%). Similar to the paradigm described above^{17,37}, daily training in this paradigm produced robust intake of 20% sucrose (binge) preceded by learned hypophagia during access to 4% sucrose (anticipatory negative contrast). The authors then tested the effects of NTX, naltrindole (a δ -opioid receptor antagonist) and β -funaltrexamine (a μ -opioid receptor antagonist) in the NAc shell on sucrose consumption. NTX and β -funaltrexamine infused into the NAc shell significantly reduced sucrose intake in both groups, but the suppressive effects were strongly selective and dependent upon the relative value of sucrose solutions within each group. Thus, they reduced sucrose consumption in the 4-0% group, but they decreased the 20%, and not the 4%, sucrose solution consumption in the 4-20% group. Although the authors interpreted the results as a demonstration that endogenous opioid signaling promoted consumption of the preferred food, since the μ -opioid receptor antagonists tested blocked the learned hypophagia (anticipatory negative contrast) and reduced the sucrose hyperphagia (binge); therefore, it would have been interesting to test the compounds on a group of animals exposed to 4% sucrose during both phases of the session, rather than 4-20%. In that case, a specific effect of the μ -opioid receptor antagonists on the anticipatory negative contrast could have resulted in an increase of 4% sucrose solution intake in the first phase associated with a decrease of the 20% sucrose solution intake in the second phase.

External food-related cues precipitate a desire for food items, resulting in food craving independently of energy-homeostatic needs. In this context, opioid receptor antagonists have been tested in animal models aiming at investigating the role of a conditioned stimulus on instrumental response. In a study comparing dopamine and μ -opioid receptor stimulation in enhancing cue-triggered motivation for reward in PIT²⁶, it was shown that opioid stimulation caused increased cue-triggered ‘wanting’ as well as ‘linking’ at nearly all NAc sites. Thus, μ -opioid receptor stimulation has been shown possibly to have effects functionally identical to

dopamine stimulation: they both elevated 'wanting'. Additionally, the μ -opioid receptor antagonist GSK1521498 has been tested in comparison with NTX on food seeking under second-order schedule of chocolate-flavoured pellet reinforcement, in which a CS associated with chocolate ingestion supports high levels of instrumental-seeking behaviour over delays to the delivery of a large chocolate reward³⁷. Although both compounds reduced food intake, only GSK1521498 reduced the seeking responses for chocolate before its delivery for ingestion, suggesting the additional effect the opioid system has on incentive motivational mechanisms controlling food seeking. The higher potency of GSK1521498 compared with NTX has been hypothesized to be due to its increased selectivity at μ -opioid receptors and/or its specific action on appetitive processes underlying food selection. Several putative neural sites at which μ -opioid receptor antagonism may cause decreases in the propensity to seek food have been hypothesized. It has been shown that the dopaminergic transmission in the NAc has a major role in incentive motivational processing for food³⁴. Therefore, μ -opioid receptors localized on the GABAergic interneurons in the VTA may provide one site at which GSK1521498 might act to decrease dopamine release in the NAc to reduce food seeking and incentive motivation for food.

Additional studies confirmed the role of the striatum and the basal ganglia, specifically putamen and pallidum which are brain regions involved in the motivational mechanisms underlying eating behaviour, in cue-induced responses for highly palatable food³⁸. For example, a 28 day treatment with GSK1521498 in obese individuals with moderate binge eating and was associated with reduction in pallidum/putamen responses to pictures of high-calorie food and a reduction in motivation (measured as grip force) to view images of high-calorie food, confirming its potential as a treatment aiming at reducing compulsive food seeking behaviour.

Amygdala

The amygdala is the brain area hypothesised to encode the association of initially motivationally neutral environmental stimuli with motivationally relevant outcomes in a Pavlovian manner⁵⁸. This structure is divided into several subnuclei, including the central (CeA) and the basal and the lateral nuclei often group as the basolateral amygdala (BLA), and it has connections with both the hypothalamus, striatum and medial and orbital prefrontal cortical areas⁵⁸. The CeA has been hypothesized to mediate more generalized associations based upon the motivational valence of the reinforcer^{59,60}, whereas the BLA has been shown to be required for selective cuing effects related to the identity of a particular outcome⁶¹.

Incentive specific rewards has been shown to increase when the mesocortico-limbic brain systems are activated⁶². Although Petrovich and colleagues reported that enhancement of eating by an appetitive CS is dependent on the integrity of the BLA, but not CeA^{63,64}, specific stimulation of the μ -opioid receptor circuit in the CeA has been shown to produce elevation of incentive salience in rats. Specifically, μ -opioid receptor stimulation (using DAMGO infusions) in the CeA caused elevated incentive motivation in subjects naturally attracted by a predictive cue (sign-trackers) and in those naturally attracted by a reward contiguous goal cue (goal-trackers)^{65,66} but also elevation in 'wanting' under PIT⁶⁷. These findings may have strong clinical implications in compulsive pursuit disorders involving intense motivations for a specific target, which is the case in binge eaters that want food and perhaps a particular food.

Cortex

It has been shown that the medial prefrontal cortex (mPFC), projecting to the amygdala and the lateral hypothalamus, is activated selectively by a cue that stimulates eating behaviour in sated rats⁶⁸. Moreover, it has been shown that the mPFC mediates enhanced food consumption driven by contextual conditioned cues⁶⁹.

μ -Opioid receptors within the mPFC have been shown to mediate an important function in overeating⁷⁰. Naltrexone microinfused into the mPFC selectively reduced the consumption and the motivation to obtain highly palatable food, but not standard chow¹⁹.

In humans, the μ -opioid receptor antagonist GSK1521498 was tested for 4 weeks in obese adults with moderate to severe binge eating and resulted in a significant reduction in attentional bias for food-related stimuli, quantified using objective indices of cognitive prioritisation of food (e.g. the visual dot probe task) and shown to be associated with the activation of the lateral PFC⁷¹, supporting the central role of μ -opioid receptors in reward-related cognitive functions⁷². Additionally, a functional magnetic resonance imaging study showed that naltrexone decreased the response in the anterior and dorsal anterior cingulate cortex, an area involved in the processing of rewarding stimuli including food, to the rewarding sight and taste of chocolate⁷³.

Conclusions

Recent evidence suggests that loss of control over food intake is the primary indicator of BED severity. Deficits in cognitive⁷⁴ function and inhibitory control⁷⁵ are considered a possible risk and maintenance factor for binge eating, and so are the hypersensitivity to motivational stimuli with high incentive salience producing a bias in attentional processing toward drug-related cues⁷⁶. Obese versus lean individuals report greater sensitivity to reward⁷⁷ and elevated responses to food cues in regions of the brain that encode the sensory properties of food. The opioid system has been extensively demonstrated to be involved in the hedonic and consummatory aspects of ingestive behaviour. Here in reviewing the existing literature we discuss the importance of the opioid system in mediating the impact of palatable food-conditioned stimuli on the incentive motivation for food. Drugs inhibiting opioid system activity may have utility in treatments intended to reduce maladaptive, palatability-driven

eating behaviour by reducing the motivational properties of stimuli that elicit the binge eating strongly associated with obesity^{20,78}.

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Tables

	Features	Binge-eating episodes
History of dieting and sucrose exposure model	12-h food deprivation is followed by 12-h access to sucrose solution ^{79,80} .	After few days, subjects escalate sucrose intake during the first hour of access.
History of dieting and stress model	Repetition of cycles of food-restriction and refeeding. At the end of each cycle, subjects are exposed to a stressor ⁸¹⁻⁸⁶ .	After three restriction/refeeding stress cycles, stressed subjects escalate their palatable food intake.
The limited access model	Subjects are never food deprived. They are given sporadic, time limited access to either vegetable fat ^{87,88} or sucrose diet ^{17,19,37,89-91} .	Subjects with sporadic access to palatable food escalate their intake.

Table 1: Summary of the most predictive binge eating preclinical models, divided into three major classes, as a function of the procedures used to induce binge eating in the animal.

Drugs	Effects	Reference
Nalmefene	↓binge-like eating; ↑negative contrast	Cottone et al. ¹⁷
GSK1521498	↓binge-like eating; ↑negative contrast; ↓CS-controlled food seeking; ↓attentional bias for food-related stimuli	Giuliano et al. ³⁷ ; Ziauddeen et al. ³⁹
Naltrexone	↓binge-like eating; ↑negative contrast	Giuliano et al. ³⁷ ; Ziauddeen et al. ³⁹ ; Katsuura et al. ⁵³
DAMGO	↑liking; ↑wanting	Peciña et al. ²⁶ ; Zhang et al. ⁵⁷ ; Mahler et al. ^{65,67} ; DiFeliceantonio et al. ⁶⁶
DPDPE	↑liking; ↑wanting	Zhang et al. ⁵⁷
U50488H	↑liking	Zhang et al. ⁵⁷
Naltrindole	↑liking	Katsuura et al. ⁵³

Table 2: Summary of the drugs targeting the opioid system tested on binge-eating paradigms, their effects, and the relative references.

Legends

Figure 1: Incentive salience in eating behaviour has been operationalized in the context of both Pavlovian and instrumental conditioning through the use of:

A) Specific Pavlovian-Instrumental Transfer, which consists of three phases: 1, a Pavlovian association between cue-food; 2, an association between instrumental response-food; 3, the instrumental response in the presence of the cue.

B) Second-Order Schedule of Reinforcement, which consists of two temporarily distinct phases: 1, during the first interval, each 10th active lever press (ALP) is associated with a brief 1-sec CS presentation; 2, during the interval(s) following the first one, the 10th active lever press is associated with a 20-sec CS and food delivery.

C) Anticipatory Negative Contrast, which develops in a procedure consisting of: 1, two-hour food deprivation; 2, 10-min brief access to a standard chow diet; 3, 10-min brief access to a highly palatable food.