



# Food Cues and Obesity: Overpowering Hormones and Energy Balance Regulation

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## Abstract

**Purpose of Review** In the modern obesogenic environment, food cues play a crucial role in the development of obesity by disrupting hormone and energy balance mechanisms. Thus, it is critical to understand the neurobiology of feeding behaviors and obesity in the context of ubiquitous food cues. The current paper reviews the physiology of feeding, hormonal regulation of energy balance, and food cue responses and discusses their contributions to obesity.

**Recent Findings** Food cues have strong impact on human physiology. Obese individuals have altered food cue-elicited responses in the brain and periphery, overpowering hormone and energy balance regulation. Disrupted homeostasis during food cue exposure leads to continued food intake, unsuccessful weight management, and poor treatment outcomes, which further contributes to obesity epidemic.

**Summary** Findings from the review emphasize the crucial role of food cues in obesity epidemic, which necessitates multidimensional approaches to the prevention and treatment of obesity, including psychosocial interventions to reduce food cue reactivity, along with conventional treatment.

**Keywords** Obesity · Food cues · Brain activity hormone · Energy balance

## Introduction

### Obesity Today

A marked steady increase in the prevalence of obesity has been observed in the end of last century. Population weight status has been tracked by the National Health and Nutrition Examination Survey (NHANES) from the National Center for Health Statistics since 1960, and a sharp increase was noted in the 1970s (Fig. 1) [1]. In 2000, more than two-thirds of the US adult population was found to be overweight or obese [1],

reaching an epidemic status [2]. Several risk factors have been identified to promote weight gain, including environment and genetic factors [3–6]. Among them, the modern obesogenic environment has been implicated as one of the main drivers in the epidemic of obesity [7, 8], associated with sedentarism [9, 10] and increased consumption of highly palatable and calorie-rich processed foods [8, 11, 12, 13•]. In Western wealthy societies, food became cheaper, widely available, and offered in large portions [4, 14]. Increased consumption of calorie-dense food unopposed by an equal amount of energy expenditure (physical activity) may be playing a major role to the observed progressive increase in the population's body weight.

Food availability and palatability appears to influence food intake, but it cannot solely explain the obesity epidemic. Not all rich Western countries present with this dramatic increase in the prevalence of obesity [3], and in the USA, obesity is more prevalent in lower social economical classes [7]. Therefore, societal, cultural, biological, and genetic factors must be influencing weight gain. During this same period that the prevalence of obesity increased exponentially, major changes in how food is processed and presented for consumption were observed [4, 15, 16•]. Processed foods have been

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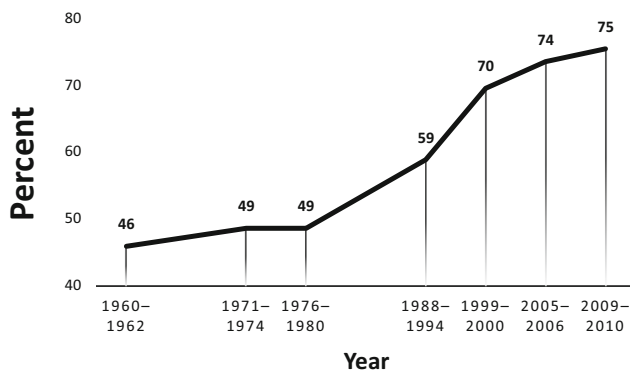
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**Fig. 1** Prevalence of overweight and obesity (BMI > 25), adapted from CDC: “Trends in overweight, obesity, and extreme obesity aged 20–74 years: United States, 1960–1962 through 2009–2010.” Sources: National Center for Health Statistics, National Health Examination Survey, and National Health and Nutrition Examination Survey

precisely tailored to meet the optimal taste and presentation, which is usually achieved by the expenses of adding a significant amount of sugar and fat [16•, 17, 18]. This flavorful and appetizing diet may influence our eating habits by decreasing satiety [19, 20•] and increasing desire and craving for food [21]. In addition, food cues are ubiquitous [22], and they appear to work as a reinforcer for less healthier food choices [16•, 23]. These findings suggest that food cues have significant impact on human physiology.

The obesity epidemic thus suggests that the modern obesogenic environment is overpowering the body’s innate ability to regulate food intake and energy balance in the context of ubiquitous food cues. The current paper will review the physiology of feeding and energy balance and neurophysiology of food cue response and discuss their contributions to obesity.

## Hormone and Energy Balance

### Physiology of Feeding

The feeding process starts even before actual food ingestion. Environmental cues, such as time of the day and food availability, together with homeostatic signals relaying information about the body’s energy status are integrated by the central nervous system (CNS) to regulate eating behavior [24, 25]. Sight and/or smell of a food trigger feeding-related reactions such as increased salivation in preparation for the actual feeding [26, 27]. As food ingestion starts, signals from the oral cavity (food texture and taste) will further influence palatability and desire to eat [28]. Subsequently, mechanical and neural signals from food being swallowed, digested, and absorbed in conjunction with rising circulating levels of nutrients, gastrointestinal peptides, and hormones will be integrated by the brain to help define meal size and when to stop eating (satiety) [29, 30]. These signals can reach the brain both

directly, through receptors in the hindbrain and hypothalamus [31], and indirectly via the afferent vagus nerve [32].

Several hormones have been shown to modulate satiety via peripheral nervous system as well as by direct effects in the CNS in both animal and in humans. (See recent reviews for hormonal regulation of feeding [30, 33, 34••]).

Between meals, the interaction of environmental and homeostatic signals plays an important but underappreciated role in defining when and how much to eat [33]. Prior to and in preparation to receive the next meal, a brain-initiated hormonal release, called pre-meal cephalic hormonal release, was observed in both animals [35, 36] and humans [37, 38]. Animals habituated to eat at a certain time of day demonstrate brain-induced release of insulin, GLP-1, and ghrelin 15 min to an hour before actual meal consumption [39]. This pre-meal hormonal release may work as a signal to control hunger prior to eating and may be a mechanism to help limit food intake [33].

While food is being digested and absorbed, feeding-related hormones are released, influencing satiation and termination of food intake. Among them, insulin is the primary hormone which serves to regulate glucose metabolism [40]. Insulin is secreted in response to a meal [41], in particular to glucose ingestion. This post-prandial rise in insulin levels appears to be a satiety signal [42]. Insulin can cross the blood-brain barrier [43, 44] and insulin receptors can be found throughout the brain [45]. In animal studies, intracerebroventricular injection of insulin inhibits food intake [42, 46–48], and within the brain, the arcuate nucleus of the hypothalamus appears to be the major center regulating feeding behavior and energy balance [34••]. Proopiomelanocortin (POMC) and agouti-related peptide and neuropeptide Y (AgRP/NPY) neurons from the arcuate nucleus can control food intake, energy expenditure, and glucose metabolism [31, 34••]. POMC and AgRP/NPY neurons have insulin receptors [49] and are activated by insulin [50]. In men, but not in women, intranasal insulin decreases food intake [51]. Insulin levels in the periphery correlate with body weight [52] and may work as a peripheral signal informing the brain about the body’s energy status.

Leptin is secreted by the adipose tissue and leptin levels correlate with body weight [53]. Similar to insulin, intracerebroventricular injection of leptin reduces food intake [54], and activation of leptin receptors in POMC and AgRP/NPY neurons modulates food intake and energy expenditure [33, 34••]. In humans, leptin deficiency causes severe obesity [55], confirming a role of leptin as a satiety hormone in both animals and humans. GLP-1 are secreted by L-cells in the intestine in response to a meal [56]. The increase in GLP-1 levels stimulates the pancreas to secrete insulin and to decrease glucagon, and it is important for regulating glucose levels in the post-prandial period [57]. GLP-1 receptors are also found in the brain [58]. In humans, GLP-1 agonist can improve glucose control in patient with type 2 diabetes and

promote weight loss [59]. Ghrelin, on the other hand, is an orexigenic hormone predominantly secreted by the stomach [60]. Ghrelin levels increase prior to a meal and decrease to its baseline levels after eating [61]. Intraperitoneal administration of ghrelin increases food intake and weight gain in mice [62] and increases hunger and food intake in humans [63].

In addition to hormones, nutrients also play a role in brain control of food intake [31, 64]. Among them, glucose [65, 66] and FFA [67] have been shown to affect brain control of food intake. Glucose levels have been described to regulate hunger/satiety and to promote food intake [31, 68, 69]. In the 1950s, Meyer proposed the glucostatic theory where the post-prandial rise in glucose levels could be sensed by the hypothalamus, which would relay the information to other brain regions to regulate food intake [70]. Indeed, a drop in glucose levels has been shown to precede a meal and may be important to initiate feeding [68, 69]. In addition, both centrally [71] or peripherally [72, 73] induced hypoglycemia can increase hunger and promote food intake.

In general, food intake and energy expenditure are very tightly regulated, with the brain playing a central role in integrating homeostatic, environmental, and hedonic signals to modulate food intake and energy expenditure. However, under the current epidemic of obesity, a shift towards increased energy storage has occurred, disrupting the fine-tuning of brain control of energy balance.

### Hormonal Dysregulation in Obesity

Obesity results from an imbalance between food intake and energy expenditure. A sustained positive energy balance promotes energy storage in the form of fat and weight gain. However, it is not exactly known how the body adapts to this new higher body weight status. Indeed, body weight (even in obese individuals) tends to remain constant throughout the years [74]. Therefore, homeostatic control of food intake may adapt to this new increased energy storage level. Obese individuals, in comparison to normal-weight individuals, have elevated insulin [52] and leptin levels [53] and decreased ghrelin levels [75]. Insulin and leptin levels parallel to body weight status [52, 53] and insulin and leptin resistance have been proposed to play an important role in the pathogenesis of obesity [29, 34••]. Insulin and leptin resistance at the level of the arcuate nucleus decreases activation of POMC neurons and increases activation of AgRP/NPY neurons resulting in decreased satiety, increased hunger, and lower energy expenditure. Recent work has pointed out that fatty acid-induced inflammation and increased production of mitochondrial reactive oxygen species in POMC and AgRP/NPY neurons may play a role in the development of central insulin and leptin resistance in obesity (see review [34••]).

### Hormonal Dysregulation in Weight Management

As described above, obese individuals demonstrate a distinct hormonal profile in comparison to lean individuals; which may influence energy balance and help maintain a higher weight. When this energy balance equilibrium is disrupted by diet-induced weight loss, hormonal and metabolic changes occur [76] in order to increase energy intake and decrease energy expenditure to eventually restore the previous energy equilibrium [77]. Weight loss from decreased calorie intake leads to decreased insulin, leptin, and ghrelin levels, and also decreased resting metabolic rate. However, neither weight loss nor long-term weight maintenance can be explained by these hormonal and metabolic changes [76, 78]. In addition, failures to weight management or regaining weight after weight loss are often observed in obese dieters, which suggests the presence of additional mechanisms underlying obesity other than hormonal regulation.

### Food Cue and Feeding Behaviors

In addition to hormone and energy balance mechanisms, food cues in the environment play a crucial role in the development of obesity by altering physiological and brain responses. In modern society with abundant food cues, brain and physiological factors interact with environmental stimuli in modulating feeding behaviors. These environmental factors serve as triggers to arouse food craving and subsequent food intake. Therefore, the neurobiology of obesity and feeding behaviors under food cue exposure is complex. In the face of emotional challenges from abundant food cue environment, vulnerable individuals might have difficulties controlling high food craving and urge for food intake, increasing obesity risk.

#### Food Cue

Food cues include viewing or smelling of food stimuli, advertisements, or any cues or situations associated with food-related memories. These cues serve as conditioned stimuli that elicit food-related responses and subsequent food intake [79]. These cues accompany psychological (e.g., craving, urge) and physiological changes (salivation, hormone secretion) along with brain reactivity [80] that promote subsequent feeding behaviors [81]. These food cue-induced changes mobilize the appetitive system and increase motivation towards food consumption. As a result, highly palatable food cues often facilitate food-seeking even in a state of satiety and are regarded as an important risk factor for obesity. A meta-analysis study reporting the results from 45 studies showed the significant effect of food cue reactivity and craving on feeding behaviors [82•], suggesting that food cue substantially influences eating-related outcomes. To understand food-

related behaviors and obesity risk, relevant neurobiological response to food cues should be clarified in the context of individual differences.

### Food Cue and Obesity

Food or food-associated cues are risk factors for the development of obesity. A study showed that food cues, rather than hunger, are stronger stimulators of unhealthy eating behaviors in overweight individuals [83]. Obese individuals also show greater psychological and physiological responses to food cues. After the viewing and smelling of food cue (pizza), overweight individuals displayed greater salivation and enhanced desire for food compared to lean individuals [84]. Another study found that after repeated exposure to food cues involving gustatory presentation of food, obese women showed delayed decline of salivation response, suggesting their difficulties with the extinction of physiological response to food cues [85]. Furthermore, obese subjects showed increased attention to food images even in a satiated state [86]. Consistent with obese adults, obese adolescents displayed greater food cue responses compared to lean children. Overweight children are more susceptible to food-related triggers and have greater cue-related salivation flow, which was associated with increased food consumption [87]. In addition, children with higher BMI and waist scores demonstrated lower satiety and increased reactivity to food cues, even after controlling for age, sex, and parental education and BMI [88]. These studies point to a strong association between food cue reactivity and obesity risk.

In addition to peripheral responses, neuroimaging studies have provided compelling evidence on the effects of food cues on brain response. A review from 60 studies that were published in 2014 indicates that obese individuals consistently showed increased activation in regions involved in emotion and reward modulation including the insula (emotion/interoception) and orbitofrontal cortex (OFC; emotion/reward regulation) during the viewing of food stimuli [89]. Another study found that increased activity in the neural circuit of reward modulation was elicited in response to high-calorie versus low-calorie food pictures in obese individuals including the medial and lateral OFC, amygdala (emotion), ventral striatum (reward), and insula (interoception), and this difference was larger than lean individuals [90]. Furthermore, women having bulimia nervosa were found to have greater reactivity in reward regions in response to food images including the striatum and insula [91]. Across different studies, researchers have indicated that the food-conditioned responses stimulate the dopamine system in the ventral striatum, which plays a crucial role in the development of obesity, food-related addiction, and failure to weight management after treatment [92, 93].

Multimodal neuroimaging studies reported concurrent changes in both brain and hormone responses during the presentation of food cues. A combined fMRI study with concurrent hormone monitoring compared 25 obese with 15 lean adolescents during the viewing of food-related visual stimuli. The study found increased striatal-limbic response to high-calorie food pictures in obese adolescents, which was also associated with circulating leptin levels. This finding suggests food cue-related impairment in leptin signaling and brain functions in emotion and reward regions in adolescent obesity [94], emphasizing the significant impact of food cues on brain and endocrine functions. This finding is consistent with a study with 21 obese adults and 23 controls, reporting increased activity in the ventral striatum in response to visual food cue, which was associated with plasma leptin levels and BMI [95]. Taken together, neuroendocrine studies indicate altered brain and hormone responses to food cues, especially in obese individuals, suggesting that food cues increase appetitive response and motivation towards high-calorie foods and increase vulnerability to obesity.

### Food Cue, Self-Control, and Weight Management

As food cues, including the smell, taste, and sight of highly palatable foods, arouse strong physiological responses and motivation towards eating behaviors, food cue-elicited responses can serve as a marker of identifying those who are not successful in weight management. It has been suggested that controlling food craving and intake is associated with an ability to control urges to eat in response to food cues [81]. Increased physiological response to food-related reward cues has shown to be a predictor of future weight gain. For example, obese individuals, who failed to lose weight during treatment, displayed increased activity in brain regions of reward modulation including the ventral striatum, insula, and anterior cingulate cortex in response to high-calorie food pictures. Increased activity in the ventral striatum during the presentation of food images was also associated with subsequent weight gain after 6 months follow-up [96]. Another study reported that increased response to food cues in emotion and reward regions (striatum and insula) predicted failure in weight management over a 9-month follow-up period [97].

Likewise, decreased responses to food cues (e.g., reduced salivary response) have predicted successful regulation of food intake and weight control in obese individuals [98]. In a Food Stroop task measuring cognitive control, individuals who were successful in weight loss maintenance showed slower reaction time in response to high-calorie foods, indicating less cognitive interference from food cues compared to normal-weight or obese individuals [99]. In addition, those who were successful in weight management showed decreased activity in reward brain regions and increased activity in regions of inhibitory

control in response to food cues. Consistent with this, individuals who succeeded in weight loss showed greater activity in regions engaged in inhibitory control such as the left superior frontal lobe compared to normal-weight or obese individuals [100]. A literature review of brain imaging studies during visual food images indicated that obese individuals were more reactive to food pictures even during satiety, and brain activity in regulatory regions such as cingulate gyrus and precuneus predicted weight loss [89]. Studies also indicated that successful treatment intervention might be beneficial in assisting weight control by reducing physiological response to food cues. Individuals who received behavioral intervention were successful in weight loss and showed increased brain response to low-calorie food pictures at 6 months later [101]. In addition, decreased brain responses in mesolimbic reward regions to high calorie foods were found in 10 female patients after gastric bypass surgery [102]. Taken together, these studies indicate that food cues have strong impact on human physiology and feeding behaviors, and responses to food cues may serve as a marker of identifying those with increased vulnerability to obesity and be utilized as a predictor of treatment outcomes.

## Homeostasis Overpowered by Food Cues

In the last few decades, significant scientific progress has been made in understanding the hormonal control of energy balance, and the importance of food cues as a contributing factor to weight gain. Food cues can overpower hormonal regulation of food intake in both healthy and obese subjects. In healthy non-obese individuals, an increase in plasma insulin levels via an intravenous insulin infusion (with the use of the hyperinsulinemic-euglycemic clamp technique) in comparison to a saline infusion did not affect brain responses to food pictures, and hunger levels increased in response to high-calorie food images [103•]. This suggests that brain activity and food-related behaviors during food cue exposure were not influenced by hyperinsulinemia or hormonal status. In addition, obese individuals, in comparison to normal weight, appear to be more sensitive to food cues both in the fasted and fed states [104, 105]. Brain responses to taste seem to influence weight gain [106••], and weight loss does not completely reverse brain responses to food cues [107]. These findings point to the significant impact of food cues on psychological and physiological responses. In particular, obesity-induced changes in homeostatic milieu will boost food cue-induced brain responses and elicit higher motivation towards environmental cues, which will promote food intake, help maintain weight at a higher threshold, and also regain weight after diet-induced weight loss.

## Conclusions and Clinical Implications

Taken together, food cues elicit significant changes in brain and physiological functions, trigger feeding behaviors, and influence treatment outcomes. Overweight and obese individuals, in comparison with normal-weight individuals, have greater food cue-elicited responses in the brain and periphery, overpowering hormone and energy balance regulation. This dysregulated brain control or energy homeostasis facilitates continued food intake, resulting in unsuccessful weight management and poor treatment outcomes, which further contribute to obesity epidemic.

Therefore, in the setting of the current obesity epidemic, it is imperative to understand the pathogenesis of obesity in relation to food cues and to develop new ways to prevent and treat weight gain, and to avoid weight regain. In the last decades, anti-obesity drugs have been approved and are available in the market; however, their limited efficacy (~3–7% net weight loss) and side effects prevent their widespread use for the general population [59]. Bariatric surgeries, on the other hand, are more efficacious (21% weight loss 10 years after Roux-en-Y gastric bypass [108•]) but they are only indicated in more severe forms of obesity (BMI  $\geq 40$ , or  $\geq 35$  and one or more severe obesity-related complications) [109].

In order to effectively contain the epidemic obesity, future research studies should consider the multiple factors contributing to weight gain, such as the environment (food cues) and the dysregulated homeostatic milieu, as a whole. Along with conventional treatments, behavioral interventions reducing food cue reactivity, craving and promoting life style for conscious awareness of food cue, and mindful eating might be helpful in reducing obesity. In addition, the current review supports policy-making initiatives for obesity prevention including regulating access to and advertisements of high caloric, unhealthy foods and promoting the public education of healthier diet.

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## Compliance with Ethical Standards

**Conflict of Interest** Renata Belfort-DeAguiar and Dongju Seo declare they have no conflict of interest.

**Human and Animal Rights and Informed Consent** All reported studies/experiments with human subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

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