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HOT TOPIC

Food for Thought: Reward Mechanisms and Hedonic Overeating in Obesity

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Abstract
Purpose of Review This review examines the food addiction model and the role of food hedonic pathways in the pathogenesis and treatment of obesity.
Recent Findings The hedonic pathway interacts with the obesogenic environment to override homeostatic mechanisms to cause increase in body weight. Weight gain sustained over time leads to "upward setting" of defended level of body-fat mass. There are neurobiological and phenotypic similarities and differences between hedonic pathways triggered by food compared with other addictive substances, and the entity of food addiction remains controversial. Treatment for obesity including pharmacotherapy and bariatric surgery impacts on neural pathways governing appetite and hedonic control of food intake. The food addiction model may also have significant impact on public health policy, regulation of certain foods, and weight stigma and bias.
Summary Recent rapid progress in delineation of food hedonic pathways advances our understanding of obesity and facilitates development of effective treatment measures against the disease.

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Introduction

Obesity is a serious chronic relapsing disease that leads to numerous metabolic and mechanical complications including type 2 diabetes, hypertension, hyperlipidemia, cardiovascular disease, non-alcoholic fatty liver disease, obstructive sleep apnea, osteoarthritis, and certain cancers [1]. The considerable social, psychological, and economic burden that obesity places upon the individual and society is also well recognized.

The underlying causes of the obesity epidemic are complex, multifactorial, and have both genetic and environmental influences. On the one hand, twin studies have shown that BMI and adiposity have high heritability rates of 25–50% [2]. On the other hand, most genetic variants identified in genome-wide association studies explain only a small proportion of variance in interindividual BMI [3]. The modern urban environment, with its wide availability and increased intake of palatable, energy-dense food and reduced physical activity, is often cited as a major contributing factor in the obesity epidemic [4]. However, numerous other aspects of our environment also contribute, and assigning proportional blame is problematic [5].

Although food addiction was described more than 60 years ago [6], there has been a surge in interest in the concept of food addiction in recent years by the scientific community and healthcare professionals. The concept of food addiction has also gained traction amongst the lay public as it provides an explanatory narrative for those with difficulty adhering to caloric restriction required for weight loss [7]. In the food addiction model, certain foods, typically energy dense with high

salt, sugar, or fat content, have addictive qualities which lead to overeating, weight gain, and obesity.

In this paper, we aim to review recent literature on the relevance and integration of homeostatic and hedonic systems in the pathogenesis of obesity. We examine the neurobiological and phenotypic similarities and differences between hedonic pathways triggered by food compared with other addictive substances. We explore the effect of pharmacotherapy and bariatric surgery on these neural pathways, and how they interact with gut hormonal changes. We also review the implications of food addiction model on broader public health measures and regulations of certain types of foods. We conclude by examining the way in which the concept of food addiction affects stigma and bias by both healthcare professionals and the lay public towards patients with obesity.

Homeostatic and Hedonic Systems in Obesity

Homeostatic Energy Balance Circuitry

The hypothalamus is the key brain area that controls energy intake and expenditure via two sets of antagonistic neurons: agouti-related peptide (AgRP) neurons to promote feeding and pro-opiomelanocortin (POMC) neurons to decrease feeding [8]. These neurons receive feedback and integrate signals from a complex network of peripheral neuropeptide hormones including leptin, ghrelin, cholecystokinin, peptide YY, insulin, pancreatic polypeptide, and glucagon-like peptide 1 (GLP-1) to regulate energy balance and body weight [4, 9]. The long-term precision of energy balance required to maintain weight stability has led to the hypothesis of "set point" of body weight regulation, with an active feedback mechanism linking adiposity to energy intake and expenditure [10]. This homeostatic feedback mechanism is evident in the physiological neurohormonal changes that occur following weight loss that drive food-seeking behavior to increase energy intake, whilst simultaneously reducing energy expenditure [9]. These physiological adaptations provide ideal conditions for weight regain and explain the limited efficacy of lifestyle interventions in effecting durable weight loss. However, the set-point model does not explain the increase in obesity prevalence over the recent decades, which coincided with significant change in environment and a shift in work and social practices favoring a more sedentary lifestyle.

Hedonic Controls of Appetite and Food Intake

In our modern environment, eating often occurs even in the absence of hunger. This "non-homeostatic" or "hedonic" eating refers to food intake that is not regulated by metabolic feedback and is related to cognitive, reward, and emotional factors [11]. Key components of this hedonic pathway are located in the cortico-limbic areas of the brain and include the nucleus accumbens and caudate nucleus (dopaminergic reward pathways which govern anticipation and motivation); amygdala and hippocampus (learning); anterior insula (sensory processing); and orbitofrontal cortex (reward value appraisal, executive control, and decision-making) [11]. Apart from influencing energy balance, the cortico-limbic circuitry plays many vital roles including memory, learning, and emotional regulation [12]. Weight-loss pharmacotherapy and bariatric surgery which affect the hedonic pathways therefore have potential for unintended neuropsychiatric adverse effects, which are explored later in this review.

Integration of Homeostatic and Hedonic Pathways

The homeostatic and hedonic pathways interact; peripheral hormones involved in energy homeostasis such as leptin, insulin, and ghrelin can modulate the activity of the mesolimbic dopamine system [13]. It has been hypothesized that hypothalamic AgRP and POMC neurons may not directly drive eating, but rather these signals are mediated by the brain reward circuitry in response to food and other cues in the environment [14]. The interaction between homeostatic and hedonic systems, shown in Fig. 1, could at least partially explain the relatively recent obesity epidemic, whereby the ubiquitous marketing of abundant, cheap, nutrient-poor, energy-dense foods overwhelms cognitive restraints and overrides homeostatic mechanisms, leading to weight gain. Subsequently, there is an upward drift of the set point, leading to higher maintained body weight [15]. The food industry expends tremendous effort to manipulate the salt, sugar, fat, and other additives in products to enhance their rewarding properties [16]. However, despite similar environmental conditions, some individuals are more susceptible than others to weight gain, and it has been suggested that the hedonic system may play an important role in influencing food intake and development of obesity [17].

In appetite research, these hedonic processes have been explored using functional magnetic resonance imaging (fMRI) [18]. Greater activation of the hedonic pathways on fMRI in response to food images has been shown to influence satiety and food consumption [18, 19], predict short-term weight loss [20, 21] or weight gain [22], and was associated with successful maintenance of ≥ 13.6 kg (30 lb.) weight loss over 3 years or more [23]. On the other hand, cross-sectional studies involving individuals with obesity or binge-eating disorder have shown inconsistent findings on activation of the different areas of the reward circuitry in response to food-related stimuli [24], which complicates the role of hedonic systems in obesity. Most of these studies had small sample sizes, and there was significant heterogeneity in age, gender, and other baseline characteristics, which may explain the discordant results.

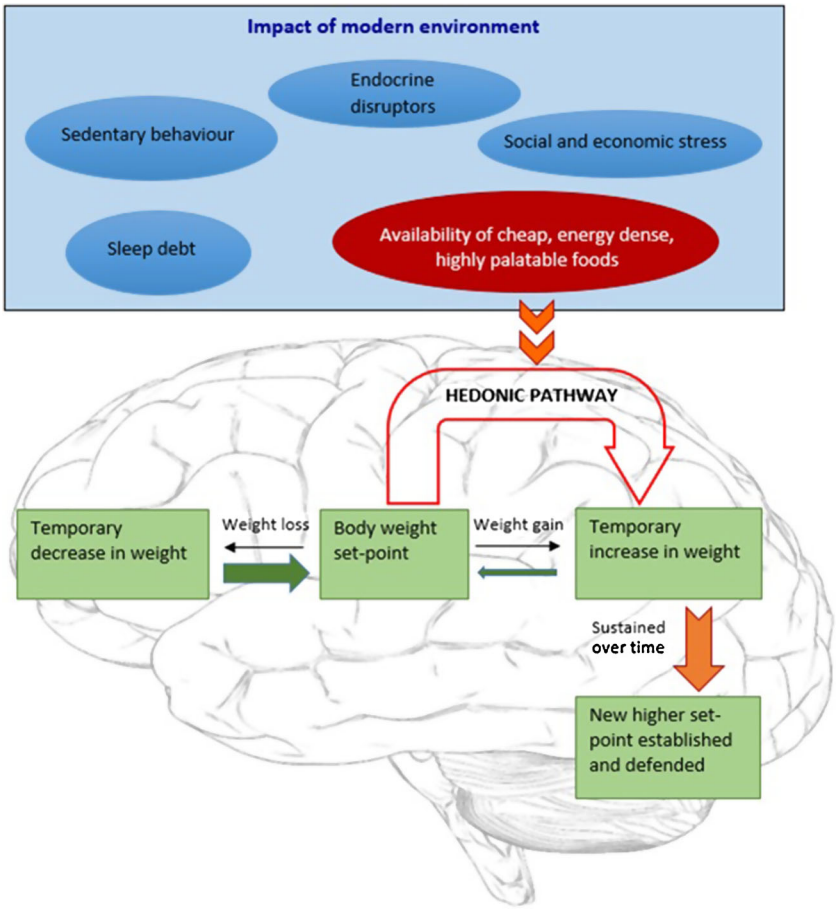

Fig. 1 Interaction between homeostatic and hedonic mechanisms in the regulation of body weight and development of obesity. Green boxes depict the homeostatic circuitry governing energy balance and body weight. The feedback mechanisms to defend body weight in response to weight loss is stronger than to weight gain, as indicated by the size of green arrows. The hedonic pathway interacts with the obesogenic environment to override homeostatic mechanisms to cause increase in body weight. Weight gain sustained over time leads to upward setting of defended level of body-fat mass

Food Addiction: Useful Concept or Damaging Distraction?

The characteristics of addiction can be divided into three stages: binge and intoxication, withdrawal and negative affect, and pre-occupation and anticipation (craving) [25]. There is loss of control and inability to reduce or stop the behavior despite negative physical, emotional, social, or economic consequences. Addiction, often attributed to poor lifestyle choices or character flaws, is increasingly recognized as a brain disease, and repeated drug use leads to progressive neuroadaptations in the brain [26]. Similar to obesity and many other chronic conditions, susceptibility also varies across individuals depending on various genetic, environmental, and social factors.

Addiction is not limited to substances alone. For example, gambling is considered a non-substance-related addictive disorder in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), given that the behavior elicits symptoms similar to substance addictions such as craving, tolerance, and withdrawal [27]. Eating is intrinsically rewarding, and it is intuitive to consider that the ability of food to activate hedonic pathways may mean that there are addictive properties to food. Proponents of the food addiction model point to the neurobiological resemblances between hedonic responses to food and other substances, and similar phenotypic traits of cravings, withdrawal, and loss of control [28]. The increased activation of the reward circuitry in response to food cues and reduced activation of inhibitory regions in response to food intake seen with addictive-like eating behavior on fMRI studies also display neural patterns similar to substance dependence [29].

However, there has been controversy surrounding the concept of food addiction. Critics of the concept point out that much of the data on food addiction were based on animal models, and the regimented experimental conditions do not readily translate to humans [7]. There is also as yet no identified biochemical property of food that has been shown to be addictive, nor any clearly defined phenotype, genetics, or pathophysiology of food addiction [18]. Although it is clear that certain types of food induce changes in the mesolimbic system and activate the endogenous opioid system, that in itself does not imply that excessive consumption of these foods would lead to dependence. Another key difference between drugs and food is that sensitization of the wanting pathways in the brain occurs with drug use, but not with food [30]. It is this neural sensitization in susceptible individuals that is postulated to be the essence of addiction [31].

Yale Food Addiction Scale

In an effort to provide clarity to the definition of food addiction, Gearhardt and colleagues developed the Yale Food Addiction Scale (YFAS), modeled after the criteria for substance dependence in DSM-IV-TR [32•]. The YFAS tool has sparked interest and research into food addiction. Many cross-sectional studies have shown positive association between YFAS scores and BMI [33]. A systematic review estimated that prevalence of YFAS-diagnosed food addiction was almost fivefold higher in overweight or obese samples compared to the general population (33 vs 6.8%) [33]. Nevertheless, the relationship between food addiction and obesity is not straightforward. The majority of persons with obesity do not meet YFAS criteria for food addiction, whilst some with food addiction have normal BMI [34]. YFAS scores have been used in short-term studies to predict response to weight-loss intervention, with mixed results. One study showed that YFAS-diagnosed food addiction has no effect on weight loss or attrition after a weight-loss program [35], whilst in another study, lower YFAS scores after a 7-month cognitive behavioral therapy program for weight loss predicted weight-loss maintenance at 12 and 24 months [36].

Perhaps the condition that more closely resembles food addiction is binge-eating disorder (BED) (Table 1). There are many similarities between BED and substance addiction including behavioral impulsivity and compulsivity, heightened sensitivity to reward, increased neuroticism, and reduced conscientiousness [17, 38]. A recent systematic review estimated that up to 56.8% of those with BED and 83.6–100% of those with bulimia nervosa have YFAS scores consistent with food addiction [34]. Although the development of YFAS has spurred research on food addiction, critics argue that YFAS remains an extrapolation of the constellation of clinical symptoms seen in substance dependence, and further research to explore the underlying etiology and neurobiological underpinnings of food addiction is needed, rather than relying on a diagnosis-by-proxy [9, 17].

Genetic Studies

It has been argued that altered dopamine signaling in the brain could potentially lead to compensatory reward-seeking behavior which predisposes to substance dependence and overeating. Genetic studies have shown that polymorphisms in D2 dopamine receptors, such as Taq1A, are associated with reduced striatal D2 receptors and reduced reward sensitivity [39]. There are allelic associations between Taq1A A1 carriers and cocaine and opioid dependence as well as binge-eating disorder [34]. A meta-analysis has also shown an association between Taq1A polymorphism and alcohol dependence [40, 41]. However, a recent meta-analysis has shown that Taq1A A1 allele was not associated with difference in BMI [42].

Table 1 Criteria for binge-eating disorder [37]

- Recurrent episodes of binge eating
- Binge eating with at least three of the following: eating rapidly; eating until uncomfortably full; eating large amounts when not hungry; eating alone out of embarrassment; or feeling disgusted, depressed, or guilty after eating
- Feeling a lack of control during bingeing
- Marked distress regarding binge eating
- Binge-eating episodes occur on average at least once a week for at least 3 months
- Binge eating that is not associated with purging and does not occur exclusively during a course of bulimia nervosa or anorexia nervosa

Similarly, a large genome-wide association study (GWAS) involving > 300,000 individuals did not detect any relationship between Taq1A polymorphisms and BMI [3]. Another recent GWAS study in a food addiction cohort, using a modified YFAS in the Nurse's Health Study population, has shown limited genetic similarities between food and drug addiction [43•]. Together, these genetic, functional neuroimaging and psychometric studies cast doubt on the entity of food addiction and its relevance in the pathogenesis of obesity.

Targeting Hedonic Pathways in Obesity Management

There has been arguments suggesting that treatment of obesity is guided by specific etiology, whether it is "metabolic" or "hedonic" obesity. This would imply tailoring treatments such as behavioral interventions, and possibly pharmacotherapy for "hedonic" obesity; whilst using pharmacotherapy and bariatric surgery for "metabolic" obesity. But is there a clear distinction?

In this section, we explore the effects of behavioral interventions, weight-loss pharmacotherapy, and bariatric surgery on food reward pathways.

Behavioral Interventions

Central to the addiction model are certain behavioral characteristics including increased impulsivity, compulsivity, and susceptibility to internal and external cues. It has been posited that behavioral interventions may be helpful in those with susceptibility to cue-based eating [44]. A randomized controlled trial (RCT) has shown that mindfulness training, when used in conjunction with diet and exercise, resulted in reduced reward-based eating, decreased consumption of sweets, and better short-term weight loss [45, 46]. Another pilot RCT showed that behavioral intervention over 6 months led to increased activation in the striatum for healthier food cues and decreased activation for unhealthy food cues on fMRI compared with controls [47]. Larger, longer-term studies are

needed to confirm and quantify the effect of behavioral interventions on the hedonic pathway and weight loss.

Pharmacotherapy

With the exception of orlistat, all currently approved pharmacotherapies for weight loss in the USA work primarily via a variety of mechanisms to decrease appetite and food intake. Most of these agents affect neurotransmitters in the brain. Conversely, most antipsychotic medications lead to increased appetite and weight gain, due to their interactions with serotonergic and dopaminergic neurotransmitter systems [48]. Given our understanding of neurobiological responses to food, drugs that target the dopaminergic pathway could potentially alter hedonic responses to energy-dense foods. In 2014, the USFDA approved the combination of naltrexone/bupropion (Contrave) for long-term management of obesity [49]. Bupropion, a dopamine and norepinephrine reuptake inhibitor, appears to activate pro-opiomelanocortin (POMC) neurons, whereas naltrexone, an opioid antagonist, amplifies this effect by blocking autoinhibition of these neurons [50]. In a study involving fMRI, Contrave attenuated hypothalamic reactivity to food cues, but also enhanced activity in brain regions thought to be involved in hedonic control [51], which suggests that the drug may influence hedonic pathways directly. Indeed, Contrave has been marketed as a solution to reduce cravings for food [52], given that it is a combination of two drugs that are used to treat other addictive disorders (naltrexone for alcohol and opioid dependence, and bupropion for smoking cessation).

Liraglutide is a GLP-1 receptor agonist, originally developed as a diabetes drug, but more recently approved for use in weight management. GLP-1 is an incretin hormone released by L cells in the small intestine, with pleiotropic effects throughout the body. GLP-1 receptors are present in areas of the brain involving both homeostatic and hedonic appetite control [17]. A study showed that infusion of GLP-1 led to reduced activation in brain areas associated with reward-driven eating as seen on fMRI in response to visual stimuli [53]. This finding also corresponded to decreased food intake in a meal provided right after scanning [53]. In another RCT, fMRI showed reduced activation in the brain's reward system in response to highly desirable food cues after treatment with liraglutide [54]. Hence, the anorectic effect of GLP-1 receptor agonist could be, at least in part, explained by its effect on the brain's mesolimbic system and reward-seeking behavior.

Phentermine is a sympathomimetic amine that increases norepinephrine in the brain and causes reduced appetite and weight loss. Unlike amphetamine, phentermine does not increase brain dopamine levels, which likely explains its much lower addiction potential [55]. There is currently a lack of evidence on the effect of phentermine or other pharmacotherapies for obesity, including topiramate and lorcaserin, on the hedonic pathway.

Targeting the brain dopamine pathway with ecopipam, a dopamine antagonist originally developed for cocaine addiction, leads to weight loss [56]. Unfortunately, unintended neuropsychiatric adverse events including anxiety, depression, and suicidal ideation were observed [56]. Rimonabant, a cannabinoid-1 receptor blocker, targets the endocannabinoid system in the brain which is thought to link the homeostatic and hedonic systems of energy balance regulation [57]. Rimonabant was withdrawn from the European market following safety concerns of increased risk of suicide [58]. These off-target effects of suicidal ideation and depression have also been seen, albeit rarely, with some other weight-loss pharmacotherapies such as bupropion (increased risk especially in those under 25 years old) and topiramate.

Bariatric Surgery

Bariatric surgery has the ability to alter energy balance set point and circumvent the body's compensatory physiological responses to weight loss. The impact of surgery on these homeostatic mechanisms is not yet fully understood but is thought to be due to changes in key hormones, especially gut hormones, which are related to energy balance and weight loss [59]. Additionally, significant changes in food choice, taste sensitivity, hedonic evaluation, motivation, and self-control have also been observed after bariatric surgery [60]. Remarkably, self-reported questionnaires reveal changes in food preference, with a shift away from highly palatable, energy-dense foods to healthier, less energy-dense foods after laparoscopic adjustable gastric banding (LAGB) and Roux-en-Y gastric bypass (RYGB) [60–62]. A multicenter study of the LAGB has reported improvement in Three-Factor Eating Questionnaire scores which suggest cognitive restraint, and reduced disinhibition and hunger over a 5-year period [63]. Notwithstanding the limitations of YFAS, the prevalence of YFAS-diagnosed food addiction decreased from 57.8% prior to bariatric surgery to 13.7% at 12 months after surgery, although presence of food addiction did not impact on weight loss [64].

Given the above, delineating the potential impact of bariatric surgery on the brain reward pathway via fMRI studies has also garnered significant interest. Patients who had LAGB appeared to have attenuated fasting activity in brain reward areas on fMRI in response to food cues following weight loss. In contrast controls with similar weight loss following behavioural interventions had increase fasting activity in these reward regions indicating a greater interest and attention to the food. The method of weight loss therefore generated different responses to food cues with the reduced food focus in the surgically treated group [65•]. Similar fMRI studies have also shown reduced activation of mesolimbic reward areas after RYGB [62]. However, not all bariatric procedures exert the same effects on brain activation. One study found that visual

food cues trigger lower activation of brain reward areas in patients who had RYGB compared to LAGB [66•]. Correspondingly, there was comparatively lower palatability for energy-dense foods and healthier eating behaviors in the RYGB cohort [66•].

Reasons for the changes in brain reward system after different bariatric procedures are yet to be fully elucidated, but changes in gut hormones including GLP-1, peptide YY, and oxyntomodulin may play an important role [62]. As discussed earlier, GLP-1 modulates the mesolimbic system and is increased after RYGB, but unchanged after LAGB. GLP-1 signaling might also alter taste perception [11], appetite, and changes in food preferences. Post-ingestive unpleasant symptoms (dumping) after RYGB may contribute to conditioned aversion or avoidance of certain sugary or fatty foods [62, 67]. Ghrelin, a gut hormone that acts on the hypothalamus to stimulate appetite, also has important extra-hypothalamic neuronal effects on learning, memory, mood, reward, motivation, and neuroprotection [68]. Animal and human studies have shown that ghrelin activates the mesolimbic dopaminergic system to affect motivation and reward [68]. Ghrelin levels increase following LAGB, decrease following sleeve gastrectomy (SG), and can be variable following RYGB [59]. Recent preliminary data have also shown associations between alterations in gut microbiome with reduced hedonic eating after SG [69], though this would need to be explored further. The notion that surgical alteration of the gut can lead to such powerful changes in energy homeostasis and hedonic evaluation of food underscores the importance of the gut-brain axis as a target in developing future treatments for obesity.

However, the loss of hedonic response to food after RYGB appears to have adverse consequences in a small subset of patients, who may turn to alternative avenues including alcohol or other substance abuse. In this "addiction transfer" hypothesis that has been popularized recently, patients with underlying food addiction prior to surgery would simply trade their food addiction with another form of addiction after surgery. The evidence for this thus far is mixed. Several studies have shown increased alcohol and other drug misuse and dependency after bariatric surgery, particularly RYGB [70•, 71, 72]. In a Mayo Clinic cohort, 17% of post-bariatric surgery patients presenting for alcohol dependency treatment remarkably did not consume any alcohol prior to surgery [73]. Altered metabolism of alcohol after RYGB has been proposed as a possible mechanism [74], but sensitization of the brain reward systems to other addictive substances following loss of hedonic response to food is obviously a concern. In a retrospective analysis, there was also an association between higher pre-surgical YFAS scores and substance use disorder after RYGB [75]. On the other hand, the prospective Longitudinal Assessment of Bariatric Surgery-2 cohort study did not show an association between pre-operative binge-eating disorder (which may be closely linked to food addiction) with alcohol use disorder after surgery [70•]. The observations that off-target neuropsychiatric adverse effects involving risks of suicide and depression can occur after RYGB [76] as well as with certain pharmacotherapies raise the question of the importance of hedonic effects of food for mental well-being.

Changing the Obesogenic Environment: Public Health Measures and Policy

The current obesity epidemic cannot be solved by solely focusing on the treatment of individuals afflicted by the disease, when it is the modern obesogenic environment that has triggered the crisis. Hence, broader public health measures and policies that aim to modify behavior and the environment are paramount to combat obesity and prevent weight gain.

Tobacco and alcohol are two widely available substances that have potential to cause dependence and impaired health. Taxes on alcohol and tobacco have been seen as an attractive lever to both achieve public health goals and raise revenues for public spending in many countries. Advocates of the food addiction model argue that the addictive nature of energy-dense foods warrants regulations similar to that of tobacco and alcohol, and that restrictions on sale and advertising of these foods would be effective to reduce obesity rates. An online survey of the general public in the USA and Australia have shown interesting results; although the majority agreed that some types of foods are addictive, there was very little support for increasing taxes on these obesogenic foods [77]. In another recent US survey, belief in the food addiction model appeared to be significantly associated with greater support for obesity-related initiatives and policies [78].

Regulations and taxes on some of these foods (e.g., sugar-sweetened beverages, saturated fat) have been imposed in several countries such as Mexico, Finland, France, and Hungary. The evidence base for these "health taxes" in changing consumer behavior and producing positive health outcomes is still growing, and current studies suggest the effect to be price-sensitive, with price increases of $\geq 20\%$ being more effective [79]. The appreciation of nicotine as an addictive substance was crucial in garnering public and political support for tobacco control and taxes [34], and similar work to delineate the food addiction model (particularly in children and adolescents) would be important to build the scientific basis and public support for these innovative taxes.

Impact on Weight-Related Stigma and Health Beliefs

Individuals with obesity are often negatively stereotyped as being lazy, unmotivated, and lacking in self-control and discipline [80]. In Western societies, weight-based discrimination and stigma is highly prevalent in various settings (including

employment, healthcare, and education) with consequent adverse physical, emotional, social, and economic outcomes [80]. Much work is still needed to change the public narrative around obesity, in that it is a disease that is influenced by genetic, environmental, and many other factors beyond a person's control, and not simply a matter of personal choice.

Given the above, how does the food addiction model influence stigma associated with obesity? Surveys have shown conflicting results on whether holding the view that obesity is a food addiction influences stigmatization, with some studies suggesting it reduces bias [81], whilst others do not [82]. A recent review suggests that people who believe that they have food addiction may lead to restrained eating in the short term, but that these restrictions could lead to cravings and subsequently more aberrant eating behaviors in the long term [83]. These findings merit further research on the impact of the food addiction message on weight bias and stigma, as well as on health-related behaviors in individuals with obesity.

Conclusions

Over recent years, there has been rapid progress in our understanding of food hedonic systems and changes in neural pathways in response to different types of foods. Insights from bariatric surgery highlight the importance of the gut-brain axis in energy homeostasis, and further research into mechanisms in which alterations in gut hormones affect the brain's food reward systems would advance our understanding of the pathogenesis and treatment of obesity. However, the central nervous system is complex, and we have yet to fully elucidate how the pleasure of food affects our brain and behavior. Moving forward, we need to be wary of potential off-target neuropsychiatric adverse effects in the pursuit of novel therapeutic strategies for obesity. There remains much controversy surrounding the food addiction model. Further research into this area is warranted as validation of the model would have important implications for public health policy and may affect eating behaviors in individuals with obesity, as well as influence attitudes of society towards obesity.

Compliance with Ethical Standards

Conflict of Interest Phong Ching Lee declares that he has no conflict of interest.

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