

From Pleasure to Pathology: Understanding the Neural Basis of Food Addiction in the Context of Obesity

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Rezumat

De la plăcere la patologie: înțelegerea mecanismelor neurale ale dependenței alimentare în contextul obezității

Pe măsură ce incidența obezității continuă să crească la nivel mondial, sunt necesare eforturi susținute din partea cercetătorilor, medicilor și de politici de sănătate eficiente pentru a identifica mecanismele, a preveni și a trata obezitatea. Este bine cunoscut faptul că obezitatea reduce drastic speranța de viață și calitatea acesteia, devenind una dintre principalele cauze de deces evitabile. Prezentul studiu se axează pe corelația dintre obezitate și dependența alimentară, încercând să elucideze principalele mecanisme neurale, ariile cerebrale, genele, hormonii și neurotransmițătorii implicați, precum și analogiile dintre dependența alimentară și abuzul de substanțe. Definiția obezității se bazează pe indicele de masă corporală (IMC). Un IMC egal sau mai mare de 30 kg/m² este categorisit ca obezitate. Obezitatea nu reprezintă doar consecința alimentației în exces. Are etiologii multiple, ceea ce face prevenirea acesteia deosebit de dificilă. Conceptul de dependență alimentară presupune un apetit exacerb, o lipsă de autocontrol și un consum excesiv, în special al alimentelor cu indice glicemic ridicat. Acest concept este susținut atât de studii clinico-comportamentale, cât și de cercetările neurobiologice. Acestea din urmă evidențiază analogii între episoadele de consum alimentar excesiv și dependența de droguri, manifestate prin poftă, pierderea autocontrolului, consumul excesiv, apariția toleranței și a simptomelor de sevraj. Deși, în general, dependența alimentară este percepută ca fiind distinctă de

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obezitate, majoritatea cercetărilor indică faptul că un procentaj însemnat din persoanele cu dependență alimentară prezintă obezitate. Obiectivul nostru a fost de a evidenția necesitatea unei înțelegeri aprofundate a fundamentului neurologic al obezității și dependenței alimentare, precum și implicațiile acestui concept în domeniul cercetării, terapiei și inițiativelor de sănătate publică.

Cuvinte cheie: obezitate, dependență alimentară, tulburări de alimentație, comportament alimentar, chirurgie bariatrică

Abstract

As rates of severe obesity continue to rise globally, intense efforts are required both from the scientific community, physicians and health policy makers to better understand the mechanisms, prevent and treat obesity in order to stop the upcoming pandemic. Obesity is known to significantly reduce life expectancy and overall quality of life, thus becoming a leading cause of preventable deaths. This article focuses on the relationship between obesity and food addiction, the main neural mechanisms, brain regions, genes, hormones and neurotransmitters involved and on the similarities between food addiction and substance abuse. The definition of obesity is based on the body mass index (BMI). A BMI of 30 or higher is classified as obese. Obesity is not solely a result of overeating, but has multifactorial causes, thus, prevention being extremely difficult. The concept of food addiction implies extreme cravings, lack of self-control, and overeating, especially involving tasty foods. The addiction concept is supported both by clinical-behavioural research and neurobiological research. These studies demonstrate similarities between binge eating and drug addiction, including cravings, loss of control, excessive intake, tolerance, withdrawal, and distress/dysfunction. Although generally food addiction is thought to be distinct from obesity, most studies identify that a significant percentage of individuals with food addiction are obese. Our aim was to emphasize the need to better understand the neurological basis of obesity and addiction, and its implications for research, treatment, and public health initiatives. Understanding the neural mechanisms underlying food addiction can inform future healthcare policies and interventions aimed at addressing the global obesity epidemic.

Key words: obesity, food addiction, eating disorder, behaviour, bariatric surgery

Introduction

Definition of Obesity and Food Addiction

Obesity represents one of the most important health problems of the last decades. It is widely recognized as a chronic and relapsing disease and prevention is difficult due to the multifactorial nature. Overall prevalence is rising globally, across all age and income groups, both in men and in women. While obesity rates plateau at high levels in North America and Europe, they now increase

alarmingly in low to mid income countries. It represents a burden for the economy and the public health systems and also associates considerable rates of morbidity and mortality.

Overweight or obesity is defined as an abnormal or excessive accumulation of body fat which poses a health risk. A body mass index (BMI) of 25 or more indicates overweight, while a BMI of 30 or more indicates obesity. According to the global burden of illness, obesity has exploded into an epidemic with over 4 million deaths in 2017 directly linked to being overweight or obese. Over 1.9

billion adults (over the age of 18) were estimated to be overweight in 2016, according to the most recent WHO data. Of these, over 650 million (or roughly 13% of the population) were obese (1).

Over the past few decades, obesity prevalence has considerably increased, raising serious public health concerns (2). With more than half of their population affected, the Pacific Islands states track the highest rates of obesity. Nearly one third of adults in the United States are obese, with percentages varying from 23% to 38% in different states (3). The global situation has become more serious as a result of the COVID-19 pandemic (4).

Obesity is associated with numerous health threats, including increased risk for certain malignancies, metabolic syndrome, cardiovascular and musculo-skeletal pathologies, and adverse impacts on psychosocial health (5). A body mass index (BMI) of 25 kg/m² or greater was linked to 2.4 million deaths in women and 2.3 million deaths in men, based on the most recent Global Burden of Disease research analysis (6).

The phrase "food addiction" has been used for some time to describe the extreme cravings, lack of self-control, and overeating that certain people exhibit. This happens frequently, especially when it comes to very palatable foods (7). Two different types of studies back up the food addiction concept. The first kind is clinical-behavioural research, which has created a paradigm emphasizing the resemblances between overeating and substance abuse. A scale (8) measuring aspects of food and substance addiction, including cravings, loss of control, excessive intake, tolerance, withdrawal, and distress/dysfunction, has been developed as a result of this concept. The results have been used to better understand the findings of functional neuroimaging and as evidence for the neurobiological nature of food addiction. The second type of research focuses on understanding the neurobiology of substance abuse and addiction, which has led to theories concerning the mesolimbic dopamine system and reward-processing mechanisms. Some studies on

murine models and humans have shown that specific patterns of the availability of desirable food can result in brain alterations similar to addiction, development of eating disorders, and withdrawal symptoms (9).

With a few exceptions, it is generally believed that food addiction is distinct from obesity. However, a study found that 88% of those who fit the criteria for food addiction were obese (10), and food addiction is characterized based on behavioural patterns and experiences associated with eating, not with weight status. Furthermore, food addiction is considered to be separate from established clinical conditions that share similarities, particularly binge eating disorders (7). In contrast to behavioural addictions like gambling disorder, persons who report having a combination of the aforementioned characteristics may identify with food addiction, which is why it is more commonly referred to as a substance addiction. The key suggestion is that food addiction is associated with changes to the mesolimbic dopamine system, which are responsible for the shift from reward-based eating to impulsive and compulsive eating (11).

Overview of the Link between Food Addiction and Obesity

There is a growing consensus that obesity and addiction share a neurological basis, and that research, studies, treatments, and public health initiatives should be aimed in this particular direction. Studies suggest that food dependence, which is comparable to drug addiction in terms of behaviour and underlying neurological processes, is the root cause of obesity. This concept has a significant influence on obesity research and offers strong reasons (although they have not been yet successful) in favour of adding obesity or overeating to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) (12,13).

Despite the fact that this model has clinical validity, neurobiological models that differentiate the clinical condition into

fundamental cognitive processes and their potential neuronal foundations have grown in popularity and, in some ways, have replaced it in the literature on addiction. Therefore, the approach is based on understanding the neurobiology of addiction and might provide new insights into the links between addiction and obesity (14).

Importance of the Topic

Obesity has a major adverse impact on individual and global well-being. It also impacts the healthcare system at pandemic proportions. The primary cause of weight gain is an energy imbalance that results from a complex relationship between biological, environmental and behavioural factors. Understanding how the brain interacts with an obesogenic environment is essential for clinicians, academics, and politicians so that future healthcare policies may be influenced by the outcomes of neuroscience research (15,16).

Food Addiction and its Neural Basis

Brain regions involved in food addiction

Consumption of palatable foods may alter insulin sensitivity, appetite hormones, fat and carbohydrate metabolism, according to emerging research. These changes seem to affect neuronal reward areas that increase the salience and incentive for eating, which would disrupt the energy balance (17). For instance, high levels of peripheral insulin and insulin resistance are frequently present in obese individuals, which may stimulate rather than limit food cravings and food intake. Additionally, dopamine-rich reward regions of the brain like the ventral tegmental area (VTA), nucleus accumbens and dorsal striatum become more active. A similar effect has been observed regarding leptin, a hormone that affects dopaminergic transmission in reward regions of the brain and induces food-seeking behaviour in animals. However, in response to high-fat food images and glucose/fructose intake in adolescents, higher levels of leptin (associated with obesity)

have been linked to decreased activation in the ventromedial prefrontal cortex and rostral anterior cingulate, brain areas involved in the central control of food intake. Additionally, increased activity in the insula and dorsal striatum has been correlated with higher insulin levels, insulin resistance, and food craving when patients are exposed to their favourite foods through imaginative approach. These findings imply that the reward and motivation circuits in the brain and the metabolic system are interconnected adaptations that dynamically influence hunger, food motivation, choice, and subsequent overeating of highly palatable meals (18).

Consuming excessive amounts of highly palatable foods can lead to a reduction in reward thresholds and in an increase in the activity of Corticotrophin Releasing Factor (CRF) in the amygdala and related limbic striatal pathways outside of the hypothalamus. These changes may contribute to food cravings and heightened neural responses to food cues in these brain areas, thereby increasing the risk of overeating tasty foods (19). As a result, extrahypothalamic CRF pathways may change because of exposure to high-fat diets, yo-yo dieting, and withdrawal from such diets, which may affect how stress responses are regulated. Additionally, this disruption may interfere with brain reward and motivation processes, resulting in increased compulsive eating and stress-related desires for appealing foods (20). These findings are consistent with the allostasis model of addiction proposed by Koob et al. (21), which suggests that excessive substance use can result in allostatic load and adaptations in brain reward pathways, ultimately increasing the compulsive pursuit of rewards and intake. Similarly, these effects seem to apply to the overconsumption of both rewarding drugs and highly palatable foods (18).

Neurotransmitters, hormones and genes associated with food addiction

Overeating in obese patients shares characteristics with drug users' loss of volitional control and compulsive behaviour. Although

the mechanism behind these behaviours is not yet fully understood, imaging studies (positron emission tomography) conducted by Wang et al. have found a reduction in D2 dopamine receptors in the striatum in both obese and drug-dependent patients. Moreover, the level of these receptors has been shown to have an inverse proportional relationship with the BMI (22).

Pleasure has been linked to the D2 dopamine receptor, and the DRD(2)A1 allele is referred to as the reward gene. Evidence suggests a triangular relationship between reduced reward sensitivity, predisposition to excess and dopamine receptor deficiency. This connection is supported by individual genetic predisposition, as, for example certain ethnic groups are more predisposed to alcoholism than others (23).

Therefore, dopamine plays an essential role as a neurotransmitter in addiction, acting specifically to control and initiate food intake. To decrease food intake and avoid hyperphagia, which in turn is regulated by leptin, insulin, and other hormones, it acts on the prefrontal area, ventromedial hypothalamus, and arcuate nucleus. Therefore, modifications in dopamine levels, functions, or receptors may make some people more prone to food addiction and obesity than others. It has been shown in animal research that feeding the mother diets high in sugar, fat, and salt during pregnancy and lactation caused the offspring to have a

higher predisposition towards developing a food addiction. As a result, these youngsters have gained weight and had a higher BMI than the control group (24-27).

Similarities between food addiction and drug addiction

Some foods (those high in fat, salt, and sugar) seem to affect neuronal circuits and result in behavioural changes similar to those found in people with substance addiction. This is similar to how addictive chemicals affect the brain. Current theories regarding addiction argue that drugs interfere with the neural pathways that regulate motivation and pleasure. Processed foods are thought to be addictive due to their nutritional profiles, high in sugar and fat, which are not normally found in natural foods (28).

According to an alternative perspective, food addiction is similar to drug addiction as it involves a behavioural phenotype that is common among particular subgroups of the obese population. This opinion is supported by similarities between the excessive eating behaviours and the DSM-IV criteria (*Table 1*) for dependency syndrome (29).

The Yale Food Addiction Scale (YFAS) survey has been developed as a quantitative measurement approach for these traits. Even though the two phenotypes resemble one another, there is only minimal overlap (8).

People with binge eating disorder (BED),

Table 1. Modelling food addiction based on drug addiction

Criteria DSM-IV for drug addiction	Proposed equivalent for food addiction
Tolerance: increasingly larger amounts of drugs are needed to achieve intoxication	Tolerance: increasingly larger amounts of food are needed to achieve satiety
Withdrawal symptoms upon cessation of drug use, dysphoria, sweating, and tremor	Dysphoria during diets
Persistent desire and unsuccessful attempts to reduce drug use	Persistent craving for food and unsuccessful attempts to reduce the amount consumed
Using larger amounts of drugs than intended	Using larger amounts of food than intended
Significant time spent obtaining, using, and recovering from drug use	Significant amount of time spent on food consumption
Giving up important social, occupational, or recreational activities due to substance abuse	Giving up various activities due to the fear of rejection caused by physical appearance
Continuing substance use despite worsening physical and psychological problems caused by drug abuse	Continuing excessive food consumption despite recognizing the physical and psychological adverse effects caused by overeating

which is defined by recurring periods of uncontrolled and rapid ingestion of large amounts of food, even though they are not hungry, exhibit the presence of food addiction phenotype the most. The feelings of remorse and contempt that go along with this conduct would continue despite the physical pain it creates. However, not all obese people who engage in this activity are obese, and not all obese people have this disorder (8,30).

The increased availability of food and a persistent imbalance between energy intake and expenditure appear to be two of the key factors contributing to the rising incidence of obesity in the population. The distribution of BMI within the population can shift in response to even a small, but persistent imbalance. This shows that the majority of overweight people only slightly lose control over their eating, which is essential for the idea that obesity is an addiction. The addiction hypothesis is supported by five essential data elements:

- Clinical overlap between obesity (especially in the case of binge eating disorder) and drug addiction;
- Common vulnerability in both situations;
- Laboratory animals given high-sugar and/or high-fat diets display signs of tolerance, withdrawal, and compulsive feeding;
- Low levels of dopamine receptors in the striatum (similar to drug-dependent patients) in obese patients;
- Modified neural responses to food stimuli in individuals with obesity compared to the control group, as evidenced by functional imaging studies (31).

Behavioural Aspects of Food Addiction

Highly appealing foods, in general, taste better and are enjoyable to eat. These foods are usually sweet and high in sugar and saturated fats and carbohydrates and highly processed, that contribute to savoury flavours, or combinations of foods prepared in ways that are both aesthetically pleasing and enhance taste and appeal. In today's obesogenic

environment, these types of foods are readily available, and their sensory characteristics (both distinct and context-related) and personal associations, such as visual cues, aromas, flavours, the setting in which they are consumed, the company, timing, and other contextual factors, act as conditioned cues. These cues have the potential to increase one's fondness for and preference toward these foods, fuelling a tendency to seek them out, ultimately leading to heightened food cravings and consumption of such foods (18). These highly appetizing and processed foods, along with their associated cues, have a similar effect on the brain's reward and motivation pathways as addictive substances do. Through learning and conditioning processes, they enhance the desire and likelihood of seeking out and consuming them (32).

Significant and positive correlations between high levels of uncontrollable stressful events and chronic stress states and substance addiction, as well as adiposity, BMI, and weight gain, are suggested by both population-based and clinical studies (33). Weight gain and obesity have been connected to stressful situations like job stress, unemployment, family caregiving, marital problems and persistent hardship, including poverty (34, 35). Additionally, studies show that the association is particularly strong in overweight or binge-eating individuals (36). There is also compelling evidence indicating potential negative effects of stress and adversity on eating patterns, such as skipping meals, restricting food intake, and engaging in binge eating. Additionally, stress and adversity have been found to contribute to a preference for fast food, snacks, calorie-dense foods, and highly palatable foods. An increased likelihood of engaging in binge eating behaviours has also been linked to stress. It is worth noting that the impact of stress may differ between lean and obese individuals (37). Stress-induced eating has been observed to be more pronounced in obese women, whereas its effect on food consumption in lean individuals appears to be inconsistent. Furthermore, individuals with a higher BMI demonstrate

stronger connections between psychological stress and future weight gain compared to those with a lower BMI (18,36).

Obesity and its Causes

The discrepancy between energy intake and expenditure is what causes obesity along with being overweight. Food intake and energy expenditure are behaviours; thus, the central nervous system must mediate both of these processes. Although multiple brain regions have been shown to be involved in the regulation of daily intake, several studies have demonstrated that two main regions play a decisive role in the control of feeding and body weight: the lateral hypothalamus (the feeding centre) and the ventromedial hypothalamus (the satiety centre). This is also the location of the arcuate nucleus, which is involved in energy homeostasis. Its neurons receive information from the periphery and express receptors for a multitude of hormones that influence food intake and energy status (leptin, cortisol, oestrogen, progesterone, and growth hormone) (38).

Although the regulation of energy balance has a high degree of precision, it is biased toward a positive caloric balance to attenuate the risk of starvation. This indulgence-oriented toward excessive food consumption has represented a necessary evolutionary strategy to diminish the risk of starvation in times when food availability was low or unpredictable (the "feast or famine" scenario). The system is therefore extremely sensitive to negative energy balance but only moderately tolerant of positive energy balance (39). Fortunately, starvation is not common in the developed world today. Technological advancements and improvements in agriculture, production, storage, preservation, and processing of food over the centuries have resulted in an abundance of affordable, appealing, and nutrient-rich foods that are always available to us. Obesity would not be a concern if energy needs were the main factor influencing hunger and eating habits. It is becoming more and

more clear that the brain's pleasure and reward systems have the power to override the hypothalamic systems that control energy balance, and that the abundance of high-energy, high-fat, and high-sugar foods we consume overstimulates these systems. This condition may cause people to consume more food than they need in order to preserve homeostasis, which suggests a possible cause for the rising prevalence of obesity (40,41).

The satiety cascade, which Blundell and his colleagues described more than 20 years ago, is a conceptual framework that combines the psychological factors that influence food intake with the physiological mechanisms that regulate hunger. Early signs of hunger initiate the feeding process, but when additional information becomes available through eating, the feeding event ultimately comes to an end (41,42).

The signals that are most frequently observed come from the vagus nerve in the stomach and are related to the feeling of fullness in the stomach. Physiological cues like blood glucose levels and ghrelin secretion serve to reinforce these signals. Following a meal, people experience the physiological sensation of satiety, which restricts them from eating more. Sensory and cognitive anticipatory processes and the association with pleasure and reward help define the qualitative and quantitative aspects of meals. The stomach and intestines communicate post-ingestion information regarding the meal volume through signals related to the degree of distension and osmotic load. Intestinal peptide hormones (GLP-1, cholecystokinin and PYY), which are released as the digestive contents pass through the gastrointestinal tract, are involved in the processing of food and have an inhibitory effect on the additional food intake. They also control metabolism and are in charge of medium-term satiety. Long-term satiety in the post-absorptive phase is regulated by insulin, blood glucose, and plasma amino acid content. The brain incorporates signals from each of these processes (43,44).

Treatment and Prevention of Food Addiction and Obesity

Current strategies for treating food addiction

According to obesity treatment guidelines, the most effective approach to weight management involves a multidisciplinary approach that includes lifestyle changes, behavioural therapy, pharmacotherapy and bariatric surgery (45,46).

Different strategies for addressing the rising number of obesity cases have had varying degrees of success. Although bariatric surgery is now the most effective treatment, it is frequently only appropriate in the most serious conditions. It includes a variety of techniques designed to treat severe obesity, which lead to persistent weight loss, an increase in life expectancy and quality of life, and the improvement or remission of several obesity-related comorbidities (47). With the introduction of new techniques and the enhancement of current ones, such as the laparoscopic approach, and the development of new surgical instruments, the field of bariatric surgery has seen a significant transformation since it was founded more than 50 years ago.

Bariatric surgery has also gained ground in Romania, becoming the most effective way to cure obesity significantly and permanently. Bariatric surgical treatments are significantly less invasive than open surgical procedures, which provides benefits in terms of a quicker postoperative recovery, less pain and significantly less complications at the surgical wound site compared to the open approach.

The indications for medication are rather restricted due to various side effects. A considerable segment of the population is overweight rather than obese, but is moving in that direction due to gradual weight gain over time. We require solutions in order to swiftly reverse this rising trend. It is widely accepted that calorie restriction in the form of various diets typically has limited efficacy in helping people in losing weight due to the body's natural response to a negative energy balance (48-52).

Surgical procedures have been proven to be more effective than drug therapy and lifestyle changes in establishing glycaemic control, minimizing the need for chronic medications and reducing cardio-metabolic risk factors, which has long-term improvements on cardiovascular morbidity and mortality. Over 80% of patients maintain good glycaemic control after surgery with little to no hypoglycaemic medication. The remission rate of type 2 diabetes varies depending on the chosen type of surgical procedure, the duration of the illness, and the criteria used to define remission (49,51-56).

Pharmacological interventions

Anti-obesity medications (AOM) are recommended for individuals with a BMI of 30 kg/m² or higher, or for those with a BMI of 27 kg/m² or higher and co-morbidities (57).

Some medications, including orlistat, phentermine/topiramate, naltrexone/bupropion, liraglutide, and semaglutide are approved for rare obesity syndromes. Metreleptin and setmelanotide are approved for non-syndromic obesity. Other incretin-based drugs that operate centrally to reduce hunger and improve satiety as well as secondarily in the gastrointestinal tract to slow gastric emptying are undergoing clinical trials. These drugs have novel modes of action. Despite the fact that all anti-obesity medications have varied degrees of effectiveness and effects on weight and metabolic parameters, there is currently no evidence that suggests an improvement in cardiovascular outcomes. However, it is expected that data will become available soon. When choosing an anti-obesity medication, patient data such as clinical and biochemical profile, co-morbidities, drug interactions and contra-indications, and expected weight loss and improvements in cardio-renal and metabolic risk should be considered (3).

However, the history of AOM has been dominated by the failure of multiple medications as a result of serious side effects, such as cancer, cardiovascular events, suicidality, abuse, and addiction risks. In order to highlight the significance of cardiovascular and central nervous system safety, the Food and

Drug Administration (FDA) and European Medicines Agency (EMA) have changed the regulatory approval criteria for AOM (58).

Conclusions

Obesity is a significant global health problem with high morbidity, mortality, and costs for public health systems. Food addiction is a concept used to describe the strong urges, lack of self-control, and excessive consumption of certain foods. It is supported by clinical and behavioural research and insights into the neurobiology of substance use and addiction.

Obesity and food addiction are related because both have comparable behavioural patterns and neurological underpinnings. Research and therapies should be focused on this approach since obesity can be understood within the same neurological framework as addictions. Regulation and initiation of food intake are influenced by neurotransmitters, hormones, and genes linked to food addiction. Dopamine is particularly involved in reward and pleasure and can influence food intake. In terms of dependence syndrome criteria and patterns of excessive intake, there are similarities between food and drug addiction. Highly palatable foods, with their sensory characteristics and conditioned cues, can increase cravings and consumption. Stress and adversity are also associated with increased food consumption and obesity.

Overall, our aim was to highlight the relationship between food addiction and obesity, the neurobiological basis of food addiction, and the behavioural aspects of food addiction. We tried to emphasize the importance of understanding these factors in addressing the global obesity concern.

Conflicts of Interest and Source of Funding

The authors declared no potential conflicts of interest and no external funding.

Ethical Statement

The study was approved by the Institutional

Ethics Committee of Grigore T. Popa University of Medicine and Pharmacy No. 137/25.01.2022.

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