# 18 The Relationship Between Drugs of Abuse and Palatable Foods: Pre-clinical Evidence Towards a Better Understanding of Addiction-Like Behaviors

Renata B.M. Duarte, Aline Caron Borges, and Marilia Barros

**Abstract**

Food is essential for the survival of all animals, yet ingestive behavior varies significantly between species. In humans, obesity and related pathologies are currently considered a public health issue, having attained global epidemic proportions. Therefore, a better understanding of its etiology may help improve treatment strategies, as well as promote large-scale social changes. In this sense, this chapter discusses mainly "food addiction" within the current framework of eating-related disorders. We first review the two main neurophysiological mechanisms that regulate ingestive behaviors: (i) the homeostatic drive, which, via activation of specific hormones, increases or inhibits food intake according to endogenous energy deposits; and (ii) the hedonic drive, which is related to the subjective pleasurable experiences associated with food and acts independent of the body's energy stores. We then focus on the main concepts and characteristics of "food addiction," with the development of food-related binge-like and craving behaviors that may be induced when the hedonic drive "overrides" the homeostatic system. Several behavioral criteria currently used to define drug addiction can be readily transposed to those related to eating disorders. At the neurobiological level, similar underlying neural pathways are activated and/or altered by compulsive-like drug and food intake. The behavioral and neurobiological overlap is discussed, with an emphasis on pre-clinical evidence, particularly between binge-eating disorders and drug addiction. Different animal models, their advantages and translational limitations to human pathologies are then discussed.

R.B.M. Duarte • M. Barros (✉)
Department of Pharmaceutical Sciences, School of Health Sciences, University of Brasilia, 70910-900, Brasilia, DF, Brazil

Primate Center, Institute of Biology, University of Brasilia, 70910-900, Brasilia, DF, Brazil
e-mail: mbarros@unb.br

A.C. Borges
Department of Pharmaceutical Sciences, School of Health Sciences, University of Brasilia, 70910-900, Brasilia, DF, Brazil



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## Introduction

Feeding is imperative for the survival of all animal species and is influenced by both genetic and environmental factors [1]. Eating patterns, however, may vary significantly among species, with some dedicating most of their time to foraging-related activities, whereas others spend months without ingesting food. Nonetheless, all ingestive behaviors have a common goal — to maintain energy homeostasis and ensure one's survival [2, 3].

However, our current society has generated a very particular problem: pathological eating behaviors. Together with our sedentary lifestyle, modern humans are constantly exposed to an "obesogenic" environment, characterized by a widespread availability of cheap and highly palatable foods with elevated salt, sugar, and/or fat content [4]. The consumption of such items can easily exceed an individual's daily nutritional needs and consequently increase the risk of becoming obese and/or developing other related pathologies, such as type 2 diabetes, cardiovascular diseases, and metabolic syndrome [5]. According to the Centers for Disease Control (2006), since the 1950s there has been a four-fold increase in meal size at American restaurants and a 12-kg increase in adults' average body mass.

People have been characterizing themselves as "food addicts". Chocolate is the item most commonly associated with reports of food craving or "addiction", although other energy-dense foods, such as sweet treats (i.e., cookies) and salty "snacks" (i.e., chips) are highly craved as well [6]. However, the high prevalence of obesity, its known effects on our health [7] and its high healthcare costs [8] have also increased the scientific/medical community's interest on "food addiction" and possible treatment strategies [9].

This new-found perspective and interest on the subject has led different researchers to not only suggest that obesity and some eating-related disorders can be directly related to addiction, but also that studying drug addiction can make significant contributions towards a better understanding of food addiction, obesity, and eating-related disorders [1]. In general terms, the latter are non-adaptive eating patterns that occur when food intake does not correspond to the desire to eat (i.e., food is consumed when satiated or physiological signs of hunger are ignored) [10], inducing a significant energy imbalance [11]. For example, according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) [12], binge-eating disorder (BED) is defined as "recurring episodes of eating significantly more food in a short period of time than most people would eat under similar circumstances, with episodes marked by feelings of lack of control and distress" [12].

The issue of considering overeating as an actual type of addiction has been under debate for some time. Many have argued that foods or their macronutrients have addictive qualities similar to those of drugs of abuse [13–18]. Such view is based on neural circuits, and behavioral and clinical similarities between overeating and addiction.

In this chapter we discuss the relationship between palatable foods and drugs of abuse, based on the view that excessive intake of highly palatable foods and the pattern in which they are ingested may lead to addiction-like behaviors. As previously argued by Davis and Carter [14], the BED phenotype fits the concept of addiction particularly well, as they both refer to loss of control, tolerance, withdrawal, and craving. Within this framework, we first review the two main neurophysiological mechanisms that regulate ingestive behaviors: (i) the homeostatic drive that, via activation of specific hormones, increases or inhibits food intake according to endogenous energy deposits; and (ii) the hedonic drive, which is related to the subjective pleasurable experiences associated with food and acts independent

of the body's energy stores. We then focus on the main concepts and characteristics of "food addiction" and finally discuss different animal models for this type of addiction, including their advantages and translational limitations to human pathologies.

## Neurophysiological Mechanisms Regulating Ingestive Behaviors

As mentioned above, many individuals no longer seem to eat only when physiologically hungry, at least when highly palatable foods are involved. However, eating patterns can generally be divided into two main types. Eating when energy-depleted, and not eating when energy needs have been met, is the main "homeostatic" mode that regulates our energy balance [1]. All other types of food intake may be considered a "non-homeostatic" or "hedonic" eating pattern, as they are not regulated or compensated by metabolic feedback mechanisms.

Therefore, ingestive behaviors are not coordinated by isolated areas of the brain or any one particular system. Complex neural circuits related to executive, reward, and autonomic functions are connected at different levels to the digestive system and circulating homeostatic signals from energy stores in the body [19–22]. These, in turn, respond to various environmental, social, circadian, and contextual factors [23, 24].

The main areas in the central nervous system (CNS) that comprise the appetitive and energy expenditure circuits (i.e., anabolic and catabolic responses to an increase or decrease in fat stores, respectively) include the prefrontal cortex (PFC), anterior cingulate cortex (ACC), insula, ventral striatum, amygdala, hippocampus, *substantia nigra* (SN), ventral tegmental area (VTA) and hypothalamus [22, 25].

In general, the cortical executive circuit exerts a key cognitive control over eating patterns, influencing the decision-making process that induces or represses food ingestion. Adequate executively-mediated self-control over food intake and/or energy expenditure is essential to maintain an overall energy homeostasis [26], particularly in "obesogenic" environments [27]. In fact, self-reported impulsivity in obese individuals has been associated with a higher detection rate of palatable foods [28], while compulsive-like eating patterns are induced by changes in PFC or ACC function, or even impaired connectivity between executive and reward circuits [27], similar to drug addicts [29–32].

### Homeostatic Drive for Ingestive Behavior

The homeostatic control over ingestive behavior is primarily related to maintaining an energy balance. A hunger sensation can be triggered by an interaction between physiological signals from the digestive system and/or endogenous energy deposits, with different environmental, social, emotional, contextual, and circadian factors [23, 24].

The neural control of homeostasis was initially attributed to two nuclei in the hypothalamus. The lateral hypothalamus (LH) seems mainly involved in triggering food intake [2]. When stimulated, its neurons synthesize and release neuropeptide Y (NPY) and agouti-related protein (AgRP), leading to an increase in ingestive behaviors, whereas lesions result in hypophagia [33–35]. The ventromedial hypothalamus (VMH), on the other hand, is related to satiety [2]. Neurons in this nucleus express pro-opio-melanocortin (POMC) and cocaine-and-amphetamine-regulated transcript (CART), which inhibit food intake, and lesions induce hyperphagia [35].

Importantly, the hypothalamus also interacts with several peripheral hormones, such as leptin and ghrelin. The former is released by white adipose tissue, its levels increasing proportionally to fat mass. High levels of leptin can, for example, suppress food intake and stimulate metabolic processes that dissipate excessive energy stores [36]. Ghrelin, on the other hand, is produced in the stomach and its levels increase due to negative energy balance, thus stimulating food intake and energy storage [36]. In humans, high levels of ghrelin precede the initiation of a meal [37],

while in animals, ghrelin content increases during food deprivation and decreases when food passes through the stomach [38].

Although leptin and ghrelin receptors are expressed throughout the body, the arcuate nucleus (Arc) of the hypothalamus has extremely high densities. In this nucleus, leptin-regulated signaling on anorexigenic POMC/CART neurons suppresses feeding and increases metabolic rate. On pro-appetite NPY/AgRP neurons, this hormone normally leads to food intake [2]. As other important mechanisms also take part in the homeostatic system, the reader is also referred to more detailed and recent reviews on this topic [2, 25, 35].

## Hedonic Drive for Ingestive Behavior

Unlike the homeostatic control, the hedonic drive for ingestive behavior is centered on the food's rewarding properties, and may act independent of the body's energy stores. It is important to point out, however, that these two systems do interact at times. For instance, hormones that indicate metabolic states (e.g., leptin, insulin) have been shown to decrease gustatory and olfactory perception and as a result influence the amount and type of food consumed by mice [39].

Berridge and Kringelbach [40] have argued that pleasure was "evolution's boldest trick," as it increases the probability that specific stimuli-related actions will re-occur, thus motivating behaviors that are essential for survival. So, not surprisingly, food and sexual partners have traditionally been viewed as the most prominent natural rewards. Whilst our ancestors seem to have benefited, in particular, from the hedonic aspects of palatable foods [26], in today's "obesogenic" environment with abundant, readily-available, highly palatable foods, the pleasure derived from eating such items may well be a liability leading to maladaptive pursuits [41].

The reward system is mainly located within the brain's mesocorticolimbic pathway [26], in which the VTA, ventral striatum, amygdala, and PFC play a fundamental role [22]. In general, this system — and in particular the shell of the ventral striatum's nucleus *accumbens* (NAc) — integrates the "wanting" and "liking" motivational aspects related to different types of stimuli in our environment, including food [42].

The first aspect is viewed as the incentive salience that is attributed to a specific food item [43], and is mediated mainly by the dopamine (DA) neurotransmitter system [44]. In fact, DA signaling plays a crucial role in translating motivation into action [45]. An increased DA activity within the brain's mesocorticolimbic pathway induces "reward-seeking" behaviors, but does not seem to directly generate the pleasurable experience related to food consumption [46]. This is generally attributed to the "liking" aspect of the reward system, which consists of the pleasure-related sensations induced by the stimulus [43]. These hedonic properties seem to only indirectly interact with the DA system via opioid receptors located on inhibitory GABAergic neurons within the shell of the NAc. Inhibition of these neurons in rodents increased the release of DA in reward-related areas of the brain and consequently the ingestion of high-fat or sugar foods, regardless of being or not in an energy-depleted state [47, 48].

Nonetheless, two main hypotheses have been put forward to explain the participation of DA in ingestive behaviors. The "gluttony hypothesis" posits that overindulgence is based on the positive correlation between DA release and pleasurable sensory experiences [49, 50]. The "reward-deficiency hypothesis," on the other hand, suggests that overindulgence is a self-medication attempt to elevate deficient DA signaling to a "pleasurable" level [17].

Both the "wanting" and "liking" aspects are also linked to the learning-related executive function discussed above [43]. The incentive salience component tends to dominate the initial appetitive phase of ingestive behaviors, the hedonic properties take part mainly in the subsequent consummatory phase, and learning occurs throughout [40]. Also, a rewarding eating experience activates the DA-mediated mesocorticolimbic circuit, which in turn enables food intake-related cues (i.e., flavor, smell, texture) to

become conditioned to the stimulus. Repeated exposure to reward-associated eating leads to a gradual enhancement of the DA response (sensitization) to conditioned stimuli, which in turn reinforces the incentive salience of that particular food item.

## Interaction Between Food and Drug Addiction: General Aspects

The concept of drug addiction and its main characteristics have been under debate for some time and still remain a controversial issue. Whether it is a "lifestyle choice," a pre-set "biological vulnerability" or even both is uncertain, even if drug initiation is essentially a voluntary behavior and its continued use is triggered by inhibition of self-control areas of the brain [51].

Substance-use dependence (SUD), according to the DSM-V [12], comprises a maladaptive pattern of substance use represented by cognitive, behavioral, and physiological symptoms that lead to clinically significant impairment or distress. Its symptomatology includes: (a) tolerance, with increasing amounts being consumed to achieve the same effects or experiencing diminished effects with continued use of the same amount, (b) withdrawal symptoms, when it is no longer consumed, (c) use of larger amounts or over a longer period than intended, (d) a persistent desire or unsuccessful efforts to cut down its use, (e) increased time and effort to obtain or use it, or recover from its effects, (f) decreased social, occupational, and/or recreational activities because of its use, and (g) use despite persistent physical and/or psychological problems caused or exacerbated by the substance [12].

Within this framework, there has been a growing interest in addiction-like behaviors related to putative natural rewards, such as food. Although deemed essential for an individual's survival, they are controlled by both homeostatic and hedonic drives. As the latter is part of the brain's reward system, natural rewards have been shown to induce non-adaptive changes in this neural circuit in a manner similar to that of drugs of abuse [52–54]. However, the homeostatic component (and the evolutionary aspects) related to natural rewards may confound the precise establishment of a pathological state. As such, while the DSM-V recognizes non-substance-related disorders, such as gambling, it still does not include natural reward-related pathologies as a mental disorder [12].

Nonetheless, "food addiction" refers to the notion that specific types of food – particularly highly palatable items — can be overly consumed, regardless of physiological homeostatic needs and in a compulsive-like feeding pattern, but there is as yet no consensual definition. "Food addiction" actually seems to have a compulsive element similar to SUD, while at the same time encompasses symptoms ascribable to both BED and obesity [55]. BED constitutes a diagnostic category of Feeding and Eating Disorders within the DSM-V [12], while others argue that obesity should be viewed as a neuroadaptive disorder [56, 57].

Theron Randolph, in 1956, was possibly the first to use the term [58], and since then sporadic comparisons between drug addiction and pathological eating patterns have been made [59]. Only in the last 20 years has "food addiction" actually received systematic and focal attention. This is clearly demonstrated, for example, by the number of scientific publications per year on this topic as of 2008, compared to 1990–2008, with over 70 articles being published in 2014 [60].

Hoebel et al. [61] carried out in rodents one of the first systematic studies on the similarities between SUD and the behaviors observed towards specific food types. Rats submitted to a feeding schedule consisting of a period of caloric restriction, followed by access to a glucose solution, demonstrated a behavioral response similar to that of drug addicts, i.e., episodes of compulsive-like search and consumption, accompanied by signs of withdrawal when the sugar solution was withheld [13, 62].

Furthermore, the Yale Food Addiction Scale (YFAS) — a questionnaire based on SUD criteria [63] and some additional aspects to clinically assess impairment and/or distress due to overeating — has also provided important clinical

validation for the "diagnosis" of "food addiction" in humans [64]. Based on this instrument, prevalence rates varied between 5–10%, 15–25% and 40–60% in non-clinical, obese, and obese individuals with BED or morbidly obese bariatric patients, respectively [65–75]. Accordingly, "food addiction" symptoms were more commonly observed in a specific subset of obese individuals, having a higher correlation with a binge-type eating pattern than with obesity per se [75].

An overlap in core behavioral symptoms can be seen in terms of pathological overeating, "food addiction" and SUD, as is the case of craving [76] — an intense desire to consume a particular item from which it is exceptionally hard to refrain [77]. While the ingestion of any food item alleviates a hunger sensation, only the specific desired food relieves crave feelings for that item [77]. Food craving is thus unrelated to caloric restriction, dieting, or food deprivation [14], but self-reported craving rates are positively correlated with "food addiction" as measured in the YFAS. Craved foods are usually high in sugar and/or fat content and thus very palatable. Chocolate, pizza, ice cream, and other "junk food" items are typically craved [78], and in the YFAS they comprise the items most likely consumed in an addictive-like manner [79].

Craving sensation is not only a good behavioral example of the similarities between food and substance dependence [77], but a neurobiological one as well. Neuroimaging studies have revealed that both food and drug craving activate the same neural structures of the reward system, such as the PFC [80, 81], insula, NAc, ACC, and amygdala [82]. Self-induced craving also increased hippocampus, caudate, and insula activity [83]. Nonetheless, other neurobiological aspects — particularly those related to DA function in the NAc — also indicate an important interaction between food and drug dependence. For example, prolonged exposure to palatable foods was found to down-regulate D2 receptors in the ventral striatum [17, 32]. The opioid system has also been implicated in withdrawal of both drugs and food [84] and a higher mu-opioid receptor polymorphism is seen in BED patients.

## Interaction Between Food and Drug Addiction: Animal Models and Pre-clinical Data

A considerable number of studies that have demonstrated similarities between drugs and palatable foods are based on animal research. Existing pre-clinical "food addiction" tests typically induce behavioral responses that are also seen in putative drug addition protocols, such as tolerance, continued consumption in spite of an aversive stimulus, withdrawal signs, relapse and cue-induced feeding [reviewed in 12].

While there is a widespread use of non-human primates in the study of drug addiction, there are surprisingly few reports on "food addiction" or binge-like behaviors in this animal model, compared to studies in rodents. This may be partly due to costs and housing difficulties inherently associated with non-human primates.

In 1969, Miller proposed an isolation model for binge eating, where rhesus monkeys isolated from social contact during the first year of life ate and drank approximately twice as much as control animals [85]. Later, in Richard Foltin's laboratory, baboons submitted to an intermittent candy access protocol (see below for more details), after a nine-week period consumed 75% of their total daily caloric intake in candy during their first meal of the day [86]. More recently, in our laboratory, we demonstrated that a highly palatable food (i.e., chocolate) induced a conditioned place preference response in marmoset monkeys, similar to that of drugs of abuse [87, 88].

In the rodent sugar-bingeing model, rats submitted to 12 h of restricted access to a sweet solution (sucrose, glucose, or saccharin) typically developed a binge-like eating pattern [89]. These sugar-bingeing animals repeatedly released DA [90] and had reduced D2 receptor binding in the NAc [91] — a generally accepted neurobiological correlate of drug addiction. In addition, a withdrawal-like state was seen when sucrose availability was interrupted, as indicated by increased levels of anxiety [13] and depression [92]. Administration of the opioid antagonist naloxone increased withdrawal symptoms in rats

that were glucose-fed, similar to rat models of morphine addiction [93].

In addition, satiated rodents with intermittent access to fat gradually escalated their consumption of pure vegetable shortening, resulting in a fat-bingeing eating pattern when this item was available [94–97]. Similarly to animals that are fed a sugar diet, fat-bingeing rats had higher levels of DA in the NAc [52, 53, 98]. Obesity-prone animals, with lower basal DA concentrations, overly consumed fat and increased DA content towards a more "rewarding level" [97, 99]. This may corroborate the "reward-deficiency hypothesis" that was described above [100]. Fat-bingeing rats also demonstrated signs of tolerance and overeating, yet withdrawal symptoms have not been reported so far [56, 101, 102]. Therefore, fat-bingeing may not necessarily fulfill all facets putatively related to addiction [79].

The sweet–fat protocol, on the other hand, may well be the first model to induce obesity, as well as behavioral and neurobiological correlates of addiction. It is based on an intermittent access to a "cafeteria diet" made up of foods with elevated fat and sugar content that are highly processed and commercially available, such as chocolate, cake, cheese and condensed milk [57, 103]. As it resembles more the items of our daily life, it is thought to better mimic the conditions seen in humans [104]. Rats with 2-h access to a cafeteria diet and ad libitum chow binged on these palatable foods [105] and gained significantly more weight compared to other models [13]. Geiger et al. [106] reported a down-regulation in the expression of striatal D2 receptors and a reduced mesolimbic DA transmission in this animal model. Interestingly, diet-induced obesity in rats also down-regulated D2 receptors in the ventral striatum, similar to drug addiction [107].

Based on the models discussed above, a highly relevant feature for inducing a compulsive binge-like eating pattern in animals seems to be the restricted and intermittent manner in which the palatable food is provided [108]. Under such conditions, rats have been shown to escalate food intake [91, 93], present behavioral and neurochemical indicators of withdrawal, and develop cross-sensitization with amphetamine, mimicking behaviors seen in drug-addiction protocols [109].

Under food restriction conditions, preference for palatable foods also seems to increase concurrently to changes in DA function in the NAc. For instance, rats submitted to a restricted-feeding schedule had lower basal extracellular DA levels in the NAc, which increased significantly in response to food or amphetamine [110, 111]. Restricted diets also induced a higher binding of DA to its pre-synaptic reuptake transporter (DAT) in the NAc and VTA, as well as more DAT mRNA in the VTA of rats [112]. Therefore, repeated ingestion of palatable foods under restricted access regimens induces neuroadaptations in the mesoaccumbens DA system, corroborating the notion that similar cellular changes may be involved in restrictive eating disorders and reward bingeing [40].

Lastly, cross-sensitization is another important element that seems to link drugs of abuse to pathological eating patterns. In this behavioral response, repeated exposure to one reward leads to a more robust response of another stimulus. Different studies have demonstrated that exposure to a food reward cross-sensitizes with several types of drugs of abuse. For example, sucrose-bingeing was reported to facilitate cocaine-induced sensitization [113, 114]. On the other hand, cocaine-sensitized rats chose saccharin over cocaine, and maintained this preference even with increasing doses of the drug reward [115, 116]. Sugar-bingeing rats also cross-sensitized with amphetamines and alcohol [117, 118].

## Conclusion

Homeostasis depends on the integration and communication between CNS structures and peripheral mediators. Excessive and easy access to hypercaloric (and consequently palatable) foods, along with habit formation, may induce pathologies such as obesity and compulsive eating, which in turn lead to significant neural adaptations. As these mainly include changes in DA neurotransmission within reward areas of the brain, "food" and

drug addiction may have a similar neurobiological basis.

"Food addiction," binge eating, and obesity may well be maladaptive conditions to our contemporary calorie-rich and "obesogenic" environment. However, contrary to drugs of abuse, it is very difficult to completely remove sugar and fat from our diet. So a better understanding of our eating patterns may lead to more efficient treatments and the prevention of food-related pathologies.

The complex relationship that we have with food — ranging from physiological, environmental, social, emotional, contextual, and circadian aspects — does pose a significant challenge to the study of food-intake-related pathologies, as well as to the development and validation of animal models. In fact, small methodological variations in animal-based studies induce significant differences in results and conclusions. It is therefore essential to take into account both the physiology and natural habits of the animal model under investigation, as well as to approximate the experimental design as much as possible to the conditions seen in humans. For this, non-human primates may provide new and important insights on binge eating and "food addiction" at the molecular, cellular, physiological, and behavioral levels.

Taken together, animal models have contributed to the study of palatable food intake and the development of "food addiction" in humans. Both sugar and sweet-fat protocols induced tolerance, escalation, bingeing, and withdrawal-like symptoms. So far, they underscore the importance of feeding patterns (in particular intermittent access) in habit formation and pathological eating, as much as the palatable food itself. This behavior seems to mimic compulsive eaters, who tend to alternate between self-restriction and binge episodes.

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