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Review

Obesity and food addiction: Similarities to drug addiction

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ABSTRACT

The global obesity epidemic suggests that this condition isn't triggered by a lack of motivation for weight loss. These findings lead to the theory that some foods, or substances added to them, can trigger an addiction process by activating in the brain the same reward system generated by drugs, the mesolimbic system via dopamine. It is possible to identify the existence of a cerebral metabolism, mainly controlled by the arcuate nucleus and a "cognitive" brain allowing interactions with the environment that offers the food, including its search and storage. Palatable foods and drugs seem to activate this same circuit of reward and pleasure in the brain, through the release of dopamine. The reviewed studies showed that the same neural basis is involved in the phenomena related to food and drug addiction. Individuals with morbid obesity present a reduction in dopamine D2 receptors and may develop resistance to leptin, leading to compulsive eating. This excessive consumption promotes the increased release of endogenous opiates, increasing the desire for food by determining the weight gain and obesity.

1. Introduction

Obesity is considered a public health problem and is defined as the excessive accumulation of adipose tissue in the body, being a risk factor for several chronic diseases, such as diabetes mellitus type II, cardiovascular diseases, and cancer among others (World Health Organization, 2000).

Conforming to the World Health Organization (WHO), this nutritional condition affects approximately 10% of the adult population, and by 2025 obesity is estimated to reach 300 million people worldwide (World Health Organization, 2000). In Brazil, the prevalence increased continuously over the last 35 years. Between 2008 and 2009, 49% of the adult population was overweight and 14.8% were obese (Instituto Brasileiro de Geografia e Estatística IBGE, 2010).

A strong motivation for weight loss, coupled with the tremendous amount of energy and resources spent on the obesity epidemic, suggests that this problem is not triggered commonly by lack of motivation (Gearhardt et al., 2008). Despite clinical efforts and research, rates of obese individuals continue to increase, resulting in more deaths from obesity-related diseases (Mokdad et al., 2004). Although treatments can help people lose weight in the short term, most recover their weight after a period of time (Wadden et al., 2004).

The causes of increased obesity are not yet fully definite. Obesity is directly related to the decrease in energy expenditure associated with the increase in the consumption of foods with high palatability and energy density (Pinheiro et al., 2004). This latter presents high availability for consumption nowadays which requires the frequent need to inhibit the desire to eat them. However, each person has a more or less ability to inhibit this desire and control how much one eats (Berthoud, 2007). These findings lead to the theory that some foods, or substances added to them, can trigger an addiction process similar to drug addiction (Gearhardt et al., 2008).

Human eating behavior is modulated by two distinct but related mechanisms: homeostatic mechanisms, that include hormonal regulators of hunger, satiety and adiposity levels, such as leptin, ghrelin, and insulin, which act by stimulating or inhibiting appetite, in order to maintain an adequate energy balance; and non-homeostatic or hedonic mechanisms, also known as a reward system (Morton et al., 2006; Lutter and Nestler, 2009; Egecioglu et al., 2011; Saper et al., 2002; Berthoud, 2004, 2006). Both food and drug addictions seem to activate this same reward system in the brain, the mesolimbic system, through activation of dopamine (DA) (Volkow et al., 2008a).

This review aims to present data related to the association between chemical dependence and food, as well as the key mechanisms responsible for the processing of food reward and its implications for food addiction, since this is likely to be a relevant factor, which contributed to the significant increase in obesity in the last three decades.

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2. Neural control of hunger and satisfaction

A sophisticated neural system regulates the food intake and energy expenditure, real integrating systems, receiving afferent signals from the digestive system through the adipose tissue and reaching the central structures (Damiani and Damiani, 2011).

The hypothalamus, especially the arcuate nucleus (ARC), is the place of nutritional integration, responsible for the regulation of food intake and energy expenditure (Williams et al., 2001; Sainsbury et al., 2002). In the digestive tract, chemoreceptors and mechanoreceptors inform about the number of nutrients that are stored temporarily in the gastrointestinal tract. This important communication established between gut-brain acts in the short-term control of food intake (Berthoud and Morrison, 2008).

In response to food intake or by nutrients, the vagal receptors located in the gastric mucosa stimulates the area of satiety and suppress of food intake (Douglas, 2006). Ghrelin, secreted in the gastric fundus when the stomach is empty, exerts a stimulant action of hunger so that the effect produced is a higher food intake (Klok et al., 2007).

In the upper portion of the small intestine, cholecystokinin (CCK) signals satiety via the vagus nerve, mainly due to the presence of lipids and proteins (Geary, 2004). The simple presence of food in the stomach or duodenum causes even greater secretion of insulin and glucagon, factors that, by direct action in the hypothalamus, determine a decrease in the sensation of hunger, reducing the food intake. Also, in the lower portions of the small intestine and colon, the peptide YY (PYY) and the glucagon-like peptide-1 (GLP-1) are secreted through the negative ghrelin feedback. This mechanism can promote the sensation of satiety accompanied by a pleasant sense of well-being (Douglas, 2006).

Leptin and insulin are hormones secreted in proportion to the adipose mass that act in the long-term control of food intake. The hormone leptin informs the brain of the presence of excess fatty tissue, determining the depression of neurons expressing NPY in the arcuate nucleus, thereby suppressing appetite. It also acts as an agent that blocks neuropeptide receptors that reduce hunger: alpha- MSH and CART. When fat stores are low, the decrease in leptin stimulates the production of NPY with increased appetite (Damiani and Damiani, 2011). Insulin acts by increasing glucose uptake, thus dropping glucose is a stimulus for increased appetite (Woods et al., 1998). Insulin also interferes with the secretion of neurohormones such as GLP-1, which works to inhibit gastric emptying and thus promoting a prolonged satiety (Verdich et al., 2001).

Other neural circuits are involved in the control of hunger and satiety, especially in the cognitive and emotional aspects of eating, such as pleasure. These circuits also seem to influence food dependence.

3. Cerebral reward system (limbic system)

It is possible to identify the existence of a metabolic brain, that reports to signals from the stomach, intestine and nutrients, and a "cognitive" brain that allows interacting with the food environment, including its search and storage (Damiani and Damiani, 2011).

The "reward center" is mainly related to the medial prosencephalic bundle in the lateral and ventromedial nuclei of the hypothalamus, with connections to the septum, amygdala, some areas of the thalamus and the basal ganglia (Damasio et al., 1994; Guyton and Hall, 2006). Research in apes demonstrated the participation of the medial pros encephalic bundle in the stimulation of appetite, and it is possible to characterize a certain expectation of pleasure. This bundle and its integrated regions (ventral tegmental area, hypothalamus, nucleus accumbens, anterior cingulate cortex, and prefrontal cortex) form the circuit called mesolimbic system (Barreto and Silva, 2010). The mesolimbic reward system functions as a reward center where several chemical messengers, including serotonin, enkephalin, gamma-aminobutyric acid (GABA), DA, acetylcholine (ACH), among others, work together to provide the release of DA in nucleus accumbens (NAc). This circuit is involved in the pleasure triggered by natural rewards, such as food, and is the neural basis for phenomena related to food addiction (Morton et al., 2006; Adam and Epel, 2007).

Although several brain regions are part of the circuit, the NAc, the ventral tegmental area (VTA) and the dopaminergic neurons appear to be their key zones (Kelley and Berridge, 2002; Wise, 2002). Also, the amygdala, hippocampus, and other specific brainstem structures are essential components of the brain reward circuit and, therefore, are also involved in the feeling of pleasure in eating and the addiction in eating certain foods (Haber and Knutson, 2009).

4. The association between chemical and food dependence

Food intake is controlled by a set of cognitive and emotional factors involving the reward, the same neural pathway that exerts addiction to a particular substance. Once this reward system becomes the target in the complex neural circuitry of appetite control, it is always important to consider the need for therapies that attenuate their activity (Damiani and Damiani, 2011).

This system can modulate the alimentary behavior, only by the desire of some food and not by its metabolic necessity, being able to be stronger than the metabolic regulation processes of the food intake. These subconscious mechanisms exceed satiety and lead these individuals to eat beyond their needs (Sawaya and Filgueiras, 2013).

Palatable foods (such as sugar, salt and fat) and the drugs appear to activate the same reward and pleasure circuit of the brain (via mesolimbic dopaminergic), but in different ways, as shown in Table 1. Food moves this way through fast sensorial stimuli such as palatability, which acts through the activation of endogenous and cannabinoid opioids, as well as increased glycemia and insulinemia, which work by increasing the DA in the mesolimbic system. On the other hand, drugs directly activate the reward circuit through its pharmacological effects, via direct effects on dopaminergic cells or indirectly through neurotransmitters (opioids, nicotine, GABA or cannabinoids) that modulate

Table 1
Comparison between food and drugs as boosters.

	Food	Drugs
Power as a reinforcer *	+ +	Oral + +, inhaled + + +, smoked, injected + + + +
Form of administration	Oral	Oral, inhaled, smoked, injected
Reward mechanism	Somatosensory (palatability), chemistry (glucose)	Chemistry (drugs)
Relevance of kinetics	Not investigated	Faster stimulation
Ingestion regulation	Peripheral and central factors	Mainly central factors
Adaptations	Physiological	Supraphysiological
Physiological role	Necessary for survival	Unnecessary
Learning	Conditional responses	Conditional responses
Role of stress	+ + +	+ + +

* Potency as an incentive is estimated based on the magnitude and duration of dopamine increase induced by diet or drugs in the nucleus accumbens. Adapted from: Volkow and Wise (2005).

these cells (Volkow and Wise, 2005).

The development process of the individual is one of the factors that influence the association between eating behavior and drug use (Volkow and Wise, 2005). Studies show that exposure to drugs during adolescence results in a series of neuroadaptations that will show up in adult behavior (Sowell et al., 2003). Adolescents exposed to nicotine presented significant changes in their receptors, making the individuals more susceptible to drug use (Adriani et al., 2003).

Still, drug use during fetal development increases vulnerability to drug use as an adult. Similarly, exposure to certain types of food during pregnancy or in the neonatal period will influence future food preferences (Buka et al., 2003; Toscheke et al., 2003; Mennella et al., 2004).

Also, frequent and excessive intake of palatable foods and sweet-flavored beverages leads to even deeper modifications, as there is growing evidence of alteration in the formation and production of nerve cells and in gene expression (which controls cellular activity). Ingestion of sugar for weeks can modify gene expression, rearrange the nerve circuits of reward, and pleasure (Spangler et al., 2004).

In research with rat fed with high-fat diets during the growth period, was observed an alteration in the gene expression of a large number of neurohormones that act on the hypothalamus and in control of appetite and food intake (NPY, orexin, galanin, among others), and consequently in the respective neural circuits. These changes occurred early in life were associated with the development of obesity in adult life (Ferreti et al., 2011).

The precise mechanism established in common with food and drug use has the ability to activate the reward circuit through dopamine in the brain (Di Chiara and Imperato, 1998). Drugs blocking the dopamine system attenuate excessive feeding and decrease the reward mechanism (Wise and Rompre, 1989).

Accompanied by intake of foods with high palatability, there is the release of dopamine in the dorsal striatum, in turn, the level of dopamine released relates to the level of pleasure obtained through ingestion (Small et al., 2003). Foods rich in sugar, fat, and salt can maintain their causing effect over a long period through the extended release of dopamine by the hedonic system (Yeomans, 1998).

In general, people are attracted to food because it is rewarding and produces pleasure. The brain recalls not only the taste of food but also the sense of satisfaction itself, as well as the suggestions or behaviors that preceded it. This memory grows stronger as the cycle of prediction, seeking and obtaining pleasure becomes more reliable. In scientific terms, we call this process conditioning. Thanks to the conditioning, neutral stimuli attached to the booster (either a natural booster or by drugs) acquire the ability to increase the release of dopamine in the striatum. The message received when dopamine is released is that you need to act to get the food or the drug (Owesson-White et al., 2009). Dopamine liberation is higher if palatable food is offered in small amounts intermittently, and if the animal can anticipate its offer by some recognizable environmental sign, or if the schedule is maintained every day (Yeomans, 1998).

The adaptations in reward circuits caused by repeated exposure of large amounts of highly palatable foods are similar to those observed in drug use. The two dependency processes have in common the inability to contain the behavior despite the awareness of its adverse effects. Overcoming these impulses only with willpower is extremely difficult (Volkow et al., 2008b) (summarized in Fig. 1).

5. The link between obesity and addiction

The rising increase in obesity and associated comorbidities have stimulated the development of studies that address the factors involved in its genesis, as well as ways to prevent and treat it (Volkow et al., 2008b). Although several factors contribute to this increase in obesity, the greater diversity and access to palatable foods cannot be underestimated, since these factors may contribute to the individual's

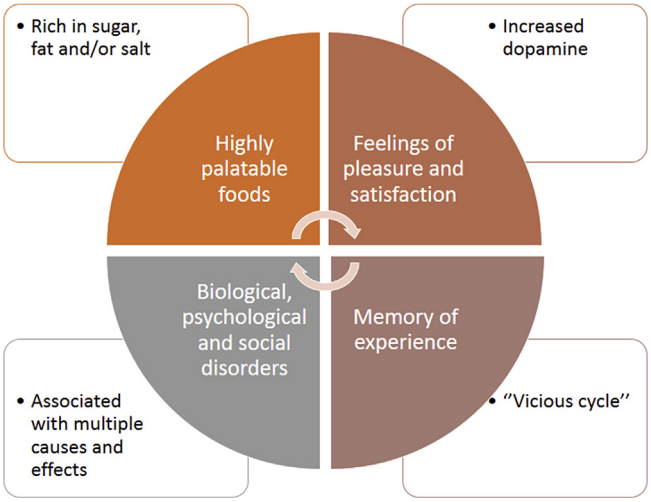

Fig. 1. Schematic figure showing the complex system of variables involved in food addiction.

overeating. Easy access to food requires the frequent need to inhibit the desire to eat it. The ability individuals use to inhibit this desire and control how much they eat is what most likely modulates the risk of overeating in our current palatable food environments (Berthoud, 2007).

Drugs and foods exert their reinforcing effects in part by increased DA in limbic regions, which has generated interest in understanding how drug abuse and/or food dependence are related to obesity.

In healthy and eutrophic individuals (Volkow et al., 2003), the availability of dopamine D2 receptors in the striatum is modulated by behavioral patterns. Specifically, there is a reduction of D2 receptors when the individual is emotionally stressed, presenting a higher probability of eating. However, individuals with morbid obesity (body mass index (BMI) greater than 40 kg/m^2) present lower D2 receptor availability than eutrophic individuals, as well as less activation of the striated DA in response to higher intake of palatability food (Volkow et al., 2008b; Wang et al., 2001; Stice et al., 2008). These results indicate that the low availability of D2 receptors could lead a person to acquire an excessive dietary pattern as a means of compensating for the lower activation of reward circuits that are modulated by dopamine (Berridge and Robinson, 1998).

A research with rats induced to obesity by a diet high in sugar, salt and fat, showed decreased dopaminergic activity in the limbic system in relation to normal weight rats fed with commercial feed. These findings showed that these animals tend to ingest palatable foods in larger amounts so that dopamine levels reach the basal level, similar to the effect described for drug addicts (Sawaya and Filgueiras, 2013). These results were confirmed in humans in a functional magnetic resonance imaging study, in which women who had gained weight in the last six months showed a reduction in dopaminergic response in reply to high palatability food intake compared to women with stable weight (Stice et al., 2008).

A likely contributing factor to the reduction of dopaminergic receptors would be that food can increase the concentration of extracellular DA in the nucleus accumbens (Bassareo and Di Chiara, 1999). Thus, decreases in D2 receptors in obese individuals may represent a way to compensate the increase in DA caused by chronic super-stimulation of overeating (Wang et al., 2001).

Low levels of dopamine D2 receptors have also been reported in drug-dependent individuals, including cocaine and alcohol addiction, suggesting that a reduction in these receptors is associated with compulsive behavior, whether caused by food or drug (Wang et al., 2001).

Initially, it was thought that the classic signs of nutritional feedback, like leptin, acted only in specific areas of the hypothalamus and

Table 2
Diagnostic Criteria for Substance Dependence as stated in DSM-IV-TR.

1. Tolerance:
The need for progressively larger amounts of the substance to acquire the desired intoxication or effect. It has a reduced effect with continued use of the same amount of the substance.
2. Withdrawal, manifested in one of the following ways:
The individual has characteristic abstinence syndrome for the substance. This is consumed to relieve or avoid withdrawal symptoms.
3. Increased dose and frequency of substance use.
4. There is a persistent desire or an unsuccessful effort to reduce or control substance use.
5. Spend a great deal of time on activities necessary to obtain or use the substance or to recover from its effects.
6. Give up social, occupational or recreational activities because of the substance use.
7. Continue to use the substance even knowing the complications arising from its use.

Adapted from: Gearhardt, Corbin & Brownell (2009).

brainstem. Recent studies suggest that this hormone may exert an extensive influence on brain functions (Zheng et al., 2009). According to Figlewicz et al. (Figlewicz et al., 2003), leptin administration has been shown efficient in suppressing the electrical activity of dopaminergic neurons in the ventral tegmental area (VTA); and in releasing DA in the nucleus accumbens (basal and induced by feeding), thus inhibiting the motivation to obtain the reward, consequently promoting the reduction of food intake.

Studies reveal that the obese organism often develops brain resistance to leptin, suggesting a higher sensitivity to the reward (Kenny, 2011). A research of two individuals with leptin deficiency syndrome demonstrated that in seven days, peripheral leptin administration led to a decrease in total caloric intake and a change in reward response to visual stimuli of food (Farooqi et al., 2007).

In addition to DA, opioid peptides and their receptors appear to be involved in the reward properties of palatable food, playing an essential role in the regulation of food intake (Bodnar, 2004; Le Merrer et al., 2009). The opioid system consists of three receptors (μ, k, and σ) that are activated in response to natural reward stimuli and drugs. They are present in most regions of the neural circuit that mediates the sensory, metabolic and integrative processes of eating behavior, seven namely in the nucleus accumbens, VTA, and hypothalamus (Le Merrer et al., 2009).

Consumption of alcohol, sweet foods, and especially high-fat foods can lead to the release of endogenous opioids into the brain (Drewnowski et al., 1995). The increase of opioids in these regions results in a greater desire for food, especially in the intake of foods with a high concentration of sucrose and fat, besides ethanol, creating a vicious circle that can contribute to weight gain and consequent obesity (Pandit et al., 2011; Zhang and Kelley, 2002).

In humans, the use of reversible opioid antagonists selectively reduced the intake of more palatable foods, assessed through a hedonic scale (Yeomans and Gray, 2002). Also, recent genetic studies indicated variations in the gene encoding of the human opioid receptor (OPRM1) associated with the preference of these individuals for high fat foods (Haghighi et al., 2013).

The understanding of these complex systems related to reward and pleasure is an opportunity to develop interventions aimed to correct eating behavior, at least in part, by modulating these reward mechanisms, bringing new hope for the prevention and treatment of obesity (Ribeiro and Santos, 2013).

6. Proposed diagnostic criteria for food dependence

According to Diagnostic and Statistical Manual of Mental Disorders DSM-IV-TR (2000), that defines a dependency on a particular substance as a "set of cognitive, behavioral and physiological symptoms associated with continued use of the substance, despite significant problems related to its use" (American Psychiatric Asso, 2000).

Gold, Frost-Pineda, and Jacobs (Gold et al., 2003) found that most diagnostic criteria for substance dependence are compatible with the requirement needed to achieve a diagnosis of binge eating, such as loss of control over consumption and an inability to stop or to reduce it, despite a desire to do so. The diagnosis of dependence occurs when three or more of the seven criteria are met, resulting in clinically significant impairment or distress (Gearhardt et al., 2009a). Table 2 provides a list of the diagnostic criteria described.

To establish an adequate tool to identify food addiction, the Yale Food Addiction Scale (YFAS) (Gearhardt et al., 2009b) was proposed, composed of 25 items based on the substance dependence criteria of the DSM-IV-TR, and two factors clinically assess whether there are significant impairment and distress from eating. The questions were adapted to evaluate the range of diagnostic criteria related to the consumption of fat/high sugar foods. The diagnosis happens if the participant presents three or more of the seven symptoms and at least one of the two situations "injury or suffering" over the last few months.

7. Conclusions

There is a strong evidence that drugs and foods, especially the most palatable ones, activate the same circuit of reward and pleasure in the brain, indicating that there is a same neural basis involved in the phenomena related to food and drug addiction. The reviewed studies, linking food addiction to obesity, demonstrated that the individuals with morbid obesity as well as chemical dependents present a reduction in dopamine D2 receptors, which can lead to a compulsive eating behavior that seeks to compensate for this lower activation of reward circuits modulated by dopamine.

In this way, understanding the similarity between the mechanisms activated in food and drug addiction and the behavior of dependent individuals is of paramount importance, since in this way, it is possible to seek new therapeutic approaches for both disorders aimed to correct food behavior by modulating these reward mechanisms. To promote effective treatment, it is necessary to adopt a multifaceted strategy to address food addiction.

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Conflicts of interest

The authors declare that they have no conflicts of interest to disclose.

Author contributions

B.C.; P.G.A.B.; A.S.A. and S.C.P.D.L.: drafting of the manuscript and study review. All authors approved the final version of the article.

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