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The Neurobiology of Binge Eating

A Neurobiologia do Binge Eating

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The Neurobiology of Binge Eating

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Abstract

Binge eating is a recent diagnosis, firstly coded in the fifth edition of the Diagnostic and Statistical Manual of Mental disorders (DSM-5) in 2013. It is characterized by overeating behavior associated to the sense of lack of control, causes marked distress in the individual and has an estimated life-prevalence of 0,85-1,4%. In this article we review the main neurobiological mechanisms underlying this condition. Several studies found associations between binge eating and the dysregulation of the opioidergic and dopaminergic systems. This dysregulation leads to altered hedonic responses to food cues, reward sensitivity changes, and differences in general consumption of food. Orexin, nociceptin/orphanin FQ and oxytocin systems also appear to be involved in the expression of binge eating behavior. Therefore, binge eating behavior might be associated to altered function of mu-opioid receptor in Nucleus Accumbens and disturbances of striatal dopamine receptors D1 and D2. Other neurotransmitters, such as nociceptin/orphanin FQ, orexin and oxytocin have also been implicated. Future binge eating pharmacological therapies might target these neuronal substrates.

Keywords

binge eating; food addiction; reward; dopamine; opioids

Introduction

Although Binge Eating is not new in the context of Eating Disorders, it was only coded as a disorder in the Fifth Edition of Diagnostic and Statistical Manual of Mental Disorders (DSM-5) in 2013 [1]. According to diagnostic criteria A, a binge eating episode is characterized by: 1) eating a portion of food much larger than normal over a defined period; and 2) the episode must be associated to the sense of lack of control. These episodes must occur at least once a week for over a period of three months (Criterion D), cause marked distress (Criterion C), not being associated to compensatory behavior (Criterion E) and being associated with at least three of the following features (Criterion B): eating much more rapidly than normal; eating until feeling uncomfortably full; eating large amounts without hunger; eating alone to avoid embarrassment; and feelings of disgust, depression and guilt towards oneself [2].

Binge Eating Disorder (BED) bears an important epidemiologic burden. Although the greater public and mediatic attention towards other eating disorders such as Bulimia Nervosa (BN) and Anorexia Nervosa (AN), the scarce literature available indicates a higher lifetime prevalence of BED comparing to BN and AN. According to the World Health Organization World Mental Health Surveys, the lifetime prevalence of BED is 1,4% (BN is estimated to be 0.8%), and a recent study estimates the lifetime prevalence of BED in USA to be 0,85% (0,80% in AN, 0,28% in BN) [3,4].

Comorbidities associated with BED are of great clinical importance. BED is associated with obesity and the development of metabolic syndrome[5,6], as well as relevant psychiatric disorders. In fact, recent studies have linked BED to depression, bipolar disorder, panic disorder and obsessive-compulsive disorder[7,8]. In addition to this, when quality of life is compared in an obese population presenting or not binge eating behavior, the BED sample perceives a lower quality of life[9].

Due to all these comorbidities and an age of onset close to the late teens and early 20s[1], BED is a pathology important to understand in order to prevent and treat. Since BED bears significant long-term consequences to the health of individuals, and there is a considerable dispute regarding the best therapeutic approach to BED patients[1,10], it is essential to comprehend the neurobiological mechanisms involved in the expression of the disease.

Considering all, it is our understanding that it is of the most importance to study the neurobiological changes related to BED behavior. In this context, our purpose is to review the literature available, and to identify which mechanisms linked to appetite regulation are relevant in the expression of BED.

Reward Circuitry

Most of the investigation regarding the neurobiology of binge eating focuses on the reward circuitry in the context of addiction. Several mechanisms are involved in the processing of reward stimuli, being the most well studied the dopaminergic projections from de ventral tegmental area (VTA) to nucleus accumbens (NAc), prefrontal cortex (PFC) and basolateral amygdala (BLA); the GABAergic projections from NAc, ventral pallidum (VP) and rostromedial tegmentum (RMTg) to VTA; the GABAergic projections from VP to mediodorsal thalamus (MDT) and subthalamic nucleus (STN); the GABAergic projections from NAc to VP; the glutamatergic projections from the lateraldorsal tegmentum (LDT) and lateral habenula (LHb) to VTA; and the glutamatergic projections from BLA, PFC, ventral hippocampus (vHPC) and MDT to NAc[11]. Most of these studies are based on animal models. Hundreds of studies have been published in the last decades regarding this topic, but some of the most relevant findings are the elicit of reward by modulation of VTA dopaminergic projections to NAc by the glutamatergic neurons from LDT, and the elicit of aversion by modulation of VTA dopaminergic

projections to medial prefrontal cortex (mPFC) by the glutamatergic neuron of LHb[12]; and the role of PFC projections to NAc in the executive control and goal-oriented behavior in the context of drug addiction [13].

The Opioid System

In 2017, Novelle and Diéguez[14] conducted a narrative review of studies from animal models of food addiction and binge eating. The authors found strong evidence in the literature that the endogenous opioid system appears to be involved in the liking and motivational aspects of reward in binge eating, especially through the mu-opioid system present in VTA, PFC and NAc.

It has been shown by Mena and collaborators that ventromedial prefrontal cortex (vmPFC) bilateral injections of DAMGO (a mu-opioid receptor agonist) increased the intake of carbohydrate-enriched foods in male Sprague Dawley rats[15], and by Giuliano and collaborators that intraperitoneal injection of GSK1521498 (a mu-opioid receptor antagonist) diminished hyperphagia and seeking of palatable food in binge-eating rats[16]. Giuliano and Cottone proposed that this phenomenon occurs via activation of GABAergic interneurons in VTA, which diminishes the VTA dopaminergic drive to NAc and hence decreases seeking and motivation for food[17]. These findings are supported by the clinical trial of Ziauddeen and collaborators, where a 4 weeks treatment with GSK1521498 of 63 obese binge eating individuals decreased hedonic responses to sweetened dairy products[18]. However, it is relevant to say that the role of the mu-opioid system in the development of binge-eating behavior might not be exclusively related to hedonic processing, but it might be implicated in high-level cognitive functions as well. In fact, Chamberlain *et al.* observed a decrease of

attentional biases for food cues in obese binge-eating subjects receiving GSK1521498 daily, when compared to placebo[19].

Additionally, Blasio and collaborators studied the role of the opioid system within mPFC in the motivational aspects of binge eating[20]. The authors observed that systemic and NAc injections of Naltrexone (a preferential mu-opioid receptor antagonist) decreased consumption and motivation both in *chow* and palatable-food in male rats; whereas when administered specifically in mPFC, the reduction of consumption and motivation was highly selective for palatable food. This led the authors to hypothesize that NAc plays a general role in the regulation of feeding behavior, whereas mPFC might play a more selective role in the development of binge eating-like behavior.

From the perspective of medical diagnosis, it has been proposed that naltrexone could be relevant in finding a biomarker of hedonic eating. In fact, Daubenmier and collaborators observed that higher emotional and restrained eating behavior correlates positively with higher levels of naltrexone-induced cortisol. According to the authors, this might be due to opioidergic down-regulation, that could induce hedonic eating, or could be caused by chronic hedonic eating[21]. Similar evidence was found by Mason *et al*.[22]

Mu-opioid receptor signaling within vmPFC also modulates feeding behavior and motor activity in dissociable ways: the first by recruitment of glutamatergic neurons projected to lateral-perifornical hypothalamic area (LH-PeF) and the activation of orexin/hypocretin neurons in the zone; the later by recruiting glutamatergic projections to NAc shell[23]. In the conducted experiment, DAMGO injection in vmPFC increased food consumption and motor activity, whereas NMDA blockage in LH-PeF inhibited feeding and AMPA blockage in NAc shell inhibited motor activity.

Regarding the possible role of orexin/hypocretin neurons in the modulation of feeding behavior in binge eating, it is important to note the hypothesis of Alcaraz-Iborra and Cubero[24]. In a narrative review of studies from animal models and human samples regarding the orexin system, the authors emphasize the important role the Orexin system appears to have in the modulation of food reward circuitry in the early and later stages of food addiction, especially through Orexin receptor 1 (OXr1), and hypothesize that impulsivity-driven binge eating might be associated with a positive enhancement OX transmission loop, and the incapacity to adaptively reduce OX transmission might be related to the progressive development from repetitive binge episodes to food addiction. This might be even more relevant considering the previous cited work of Mena *et al.*, where the modulation of feeding behavior by vmPFC was associated with the activation of orexin/hypocretin neurons in LH-PeF area.

Considering all, it is possible to conclude that the opioidergic system has a global function in the regulation of feeding behavior, both at modulating hedonic responses to food cues, and the motivational aspects of eating (assessed mostly by seeking behavior).

The Dopaminergic Pathways

The dopaminergic system seems to be implicated in the motivational and learning processes associated with food reward, especially the dopamine receptor D2 (D2R) expression in striatum, NAc, PFC and VTA[14]. However, when comparing to the opioidergic system, the dopaminergic system appears to have a more selective function, namely the one of regulating motivation. In fact, it was shown that the administration of dopamine antagonists (selective and non-selective) reduced seeking behavior for palatable food in rats, but did not decreased general consumption of food[25].

Johnson and Kenny found that striatal D2Rs were downregulated in obese rats which presented compulsive-like eating behavior, when compared to lean rats[26]. Also, the authors found in the same study that the knockdown of these same D2Rs was associated with the development of compulsive palatable food seeking. These findings suggest that binge eating-like behavior might involve a loop of homeostatic striatal D2Rs downreagulation induced by compulsive eating, and compulsive eating fostered by D2R downregulation. This is supported by Stice *et al*., who found that individuals with the A1 allele of the D2/ANKK1 Taq1 polymorphism (associated to D2R hypofunctioning and attenuated dopamine signalling) are more prone to overeat when compared to individuals with the A2 allele[27]. In this view, activation of the reward cascade to a lesser degree than normal might drive individuals to binge eat in order to achieve satisfaction. However, the association of Taq1 allele A1 with obesity is still matter of controversy and the studies available date at least from a decade ago. If, on one hand, investigators like Blum and collaborators showed that the Taq1 allele A1 increased the risk for obesity and other addictive behaviors[28]; on the other, Benton and Young conducted a meta-analysis concluding no difference was found in the body mass index (BMI) when comparing individuals with the A1 and the A2 alleles. Nevertheless, when comparing Taq1 allele A1 in non-BED obese individuals to BED-obese individuals, Davis *et al*. observed that more individuals from the first group presented Taq1 allele A1 "loss-of-function"[29]. In another study, the A2 genotype was found to be significantly related to BED[30]. According to the authors, this genotype reflects enhanced dopamine transmission.

Putting all this information together, we can say that no specific mechanism was found to clearly associate striatal D2Rs expression changes to BED behavior. On one hand, some data supports a reward deficiency theory, where decreased dopamine transmission leads to compulsive eating or vice-versa (genetically defined D2R downregulation fosters overeating,

or overeating induces homeostatic D2R downregulation, leading to motivational and seeking behavior for palatable food). On the other, compulsive eating might have its cause in hypersensitivity to reward, where enhanced dopamine transmission leads to overeating and motivational behavior towards palatable food. More investigation is needed in order to understand if this is a conceptual problem or if the data is contradictory.

Apart from the motivational aspect of binge eating, the dopaminergic system also appears to be related to learning mechanisms in response to food cues. By learning, following Berridge and collaborators, we mean the prediction of reward induced by specific food cues and the respective induced motivation to obtain the food[31]. Keeping this in mind, Kravitz and collaborators showed that reinforcement and punishment learning are dependent on striatal dopamine signaling. The authors found that D1R striatal stimulation elicits reinforcement, whereas D2R striatal stimulation elicits punishment[32]. This is especially relevant considering that learned food-associated cues can induce cravings and food seeking through the activation of cortico-mesolimbic dopaminergic activation, and that chronic exposure to naturally palatable foods acts as a reinforcement learning mechanism[33]. Also, BED individuals show increased reward sensitivity when exposed to food cues[34]. This way, a neurobiological substrate might be identifiable as a target in the prevention or attenuation of learning-based conditioned responses that result in binge episodes. In fact, Feltmann and collaborators reported that subcutaneous administration of the monoamine stabilizer (–)-OSU6162 (known to modulate dopamine signaling) reduced binge-like eating behavior and reduced palatable food-seeking induced by food cues in male Listen Hooded rats[35].

Other neurotransmitters and hormones

Regarding other neurotransmitters, it is relevant to refer the nociceptin/orphanin FQ (N/OFQ) and the nociceptin opioid peptide (NOP). In spite of having a strong degree of structural homology, N/OFQ does not activate opioid receptors, and NOP is a opioid-like G protein-coupled receptor to which classical opioids have no affinity[36]. According to Polidori and collaborators, lateral ventricular injections of N/OFQ increase food intake in adult male Wistar rats [37], and Olszewski *et al*. observed that lateral ventricular injection of N/OFQ in adult male Sprague-Dawley rats ameliorates conditioned taste aversion (CTA) induced by LiCl[38]. Later, Olszewski and collaborators made their claim stronger by observing that NOP antagonist [Nphe(1)]N/OFQ(1-13)NH(2) injections in the lateral ventricle reduced deprivation-induced food intake and N/OFQ-induced food intake[39]. Additionally, Hardaway *et al.* showed that NOP antagonist SB612111 intraperitoneal injections reduced binge-eating behavior in male and female mice[40]. Therefore, N/OFQ appears to have a role in regulating food intake and aversive responsiveness. This might help to explain the higher physical tolerance to binge episodes and the reduced sensitivity to punishment observed in BED individuals.

Also, it has been shown that N/OFQ reduces the anorexigenic effect of coticotropin-releasing hormone (CRF), suggesting that N/OFQ is a functional antagonist of CRF[41]. Therefore, it is possible that N/OFQ plays a role in regulating stress-induced hypophagia.

Furthermore, Olszewski and collaborators observed that N/OFQ, morphine and butorphanol tartrate (a mixed mu/kappa-opioid agonist) inhibit LiCl-induced activation of oxytocin (OXT) neurons in the hypothalamic paraventricular nuclei (PVN) (these neurons are involved in the mediation of LiCl-induced CTA)[38]. The hypothesis that oxytocin might be involved in the regulatory processes of feeding and, more specifically, in the neurobiology of binge eating was tested in humans by Davis and collaborators[42]. By assessing the association between seven single-nucleotide polymorphisms of oxytocin receptor (OXTR) and reward sensitivity,

punishment sensitivity and food-reward preferences from a sample of 460 adult individuals, the authors concluded that G-T-A-G haplotype was associated with high sugar/fat preferences; A allele carriers at rs2268494 showed higher preferences for fat/sugar food when compared to TT carriers; TT carriers at rs2268493 showed higher overeating when compared with the CC+CT group; GG carriers at rs237885 showed higher reward sensitivity when compared to the other groups; and homozygous C carriers at rs2268498 showed higher reward sensitivity and punishment sensitivity when compared to other groups. These findings are consistent with the view that low levels of OXTR are associated to overeating behavior. The hypothesis that oxytocin is involved in the expression of binge eating behavior is being subjected to intensive study by the scientific community. In fact, we now know that OXT administration generally reduces food intake[43], regulating reward-related food intake and the hypothalamic-pituitary-adrenal axis activity (by reducing snack consumption, and by reducing basal and post-prandial levels of adrenocorticotropin hormone and cortisol)[44]. However, the anorexigenic properties of OXT are conditioned by the social context, as shown by Olszewski *et al.*[45]. Here, the authors observed that dominant mice increased their consumption of sucrose after administration of OXT receptor antagonist L-368,899, regardless of the social context, whereas non-dominant mice only increased consumption of sucrose in the absence of social cues related the dominant animal. These findings may shed some light in the previously unrelated prosocial and anorexigenic effects of OXT.

Conclusion

Several studies found associations between binge eating and the dysregulation of the opioidergic and dopaminergic system. This dysregulation reflects upon the main conceptual components of the reward circuitry: liking, wanting and learning.

In terms of liking and wanting, mu-opioid receptor at NAc appears to have a general role in the regulation of feeding behavior: its modulation alters general consumption and seeking of food. This might happen through VTA GABAergic interneurons that modulate VTA dopaminergic drive to NAc. vmPFC mu-opioid function might be more selective in the development of binge eating. In fact, vmPFC modulates feeding behavior in dissociable ways: on one hand, glutamatergic projections to LH-PeF regulate food consumption; on the other, glutamatergic projections to NAc shell regulate motor activity in the seeking of food. Regarding the role of vmPFC in the regulation of food consumption, it is important to note that binge eating might be associated to the incapacity to adaptatively reduce OX transmission loop in LH-PeF area. The general idea is that mu-opioidergic activation of NAc and vmPFC increase liking and wanting in the context of binge-like behavior.

Comparing to the opioidergic system, the dopaminergic seems to be more implicated in the wanting and learning processes of binge eating. In terms of wanting, two general hypothesis rise from the studies: one, the reward deficiency theory, where genetically-induced striatal D2R downregulation leads to overeating, or a homeostatic downregulation of striatal D2R in response to overeating leads to motivational and seeking behavior for palatable food; the other, the hypersensitivity to reward theory, where enhanced striatal dopamine transmission leads to overeating and motivation behavior towards palatable food. In terms of learning, we know that striatal D2R stimulation elicits punishment, and striatal D1R stimulation elicits reward. Hence, it is possible that the downregulation of striatal D2R implies a punishment sensitivity deficiency, which will be relevant in the reinforcement learning mechanisms of certain food cues.

The dopaminergic and opioidergic mechanisms involved in binge eating are schematically represented in Figure 1.

Other neurotransmitters have been implicated in the development of binge eating behavior, such as nociceptin/orphanin FQ and OXT. The first appears to be implicated in the desensitization of conditioned taste aversion and, by consequence, in the dysregulation of learning mechanisms. The later might also be implicated in reward and punishment sensitivity. In fact, low levels of OXTR relate to overeating. Furthermore, in the context of binge eating, nociceptin/orphanin FQ and OXT might operate in overlaid pathways, once LiCl CTA is PNV OXT activation-dependent, and N/OFQ inhibits it.

Despite all the mechanisms outlined and the potential neurobiological targets in future therapeutics, recent investigation on binge eating lacks an important feature: few studies were developed on human individuals, and the ones who were would require larger samples in order to achieve higher validity. This fact might explained by the use of experimental drugs in the majority of studies. However, several neuroimaging studies are already trying to overcome this gap, and they might reveal more accurate neural mechanisms in binge eating disorder in humans[46-48].

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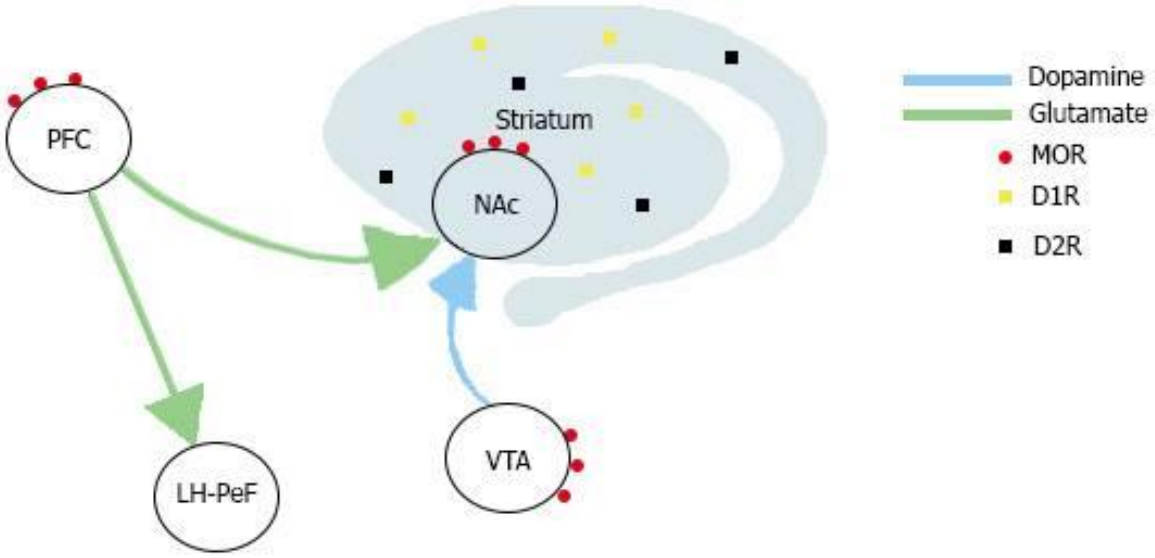
Figure legends

Figure 1: *Representation of the dopaminergic and opioidergic mechanisms involved in binge eating*. Blue arrows represent dopaminergic pathways; green arrows represent glutamatergic pathways; red circles represent mu-opioid receptors; yellow squares represent dopamine receptor D1; black squares represent dopamine receptor D2. Mu-opioid receptor activation in PFC activates glutamatergic pathways to Nac and LH-PeF, that induce motivation and increased food intake respectively. Mu-opioid receptor activation in VTA activates dopaminergic pahtways to Nac, that enhance motivation for food consumption. Mu-opioid receptor activation in NAc induces higher consumption and motivation for food. Striatal D1R and D2R expression is associated to motivational and learning mechanisms in the context of binge eating. D1R – dopamine receptor D1; D2R – dopamine receptor D2; LH-PeF – lateral-perifornical hypothalamic area; MOR – mu-opioid Receptor; NAc – nucleus accumbens; PFC – prefrontal cortex; VTA – ventral tegmental area.

Anexo I – Figure 1: ***Representation of the dopaminergic and opioidergic mechanisms involved in binge eating.***



Anexo I – *Reviews in the Neurosciences* – Instructions to Authors

Reviews in the Neurosciences
Information for Authors

Aims and Scope

Reviews in the Neurosciences (*Rev. Neurosci.*) provides a forum for reviews, critical evaluations and theoretical treatment of selective topics in the neurosciences. The journal is meant to provide an authoritative reference work for those interested in the structure and functions of the nervous system at all levels of analysis, including the genetic, molecular, cellular, behavioral, cognitive and clinical neurosciences. Contributions should contain a critical appraisal of specific areas and not simply a compilation of published articles.

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