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Neuroendocrinological factors in binge eating disorder: A narrative review

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ABSTRACT

Neuroendocrine mechanisms play a key role in the regulation of eating behavior. In individuals with binge eating disorder (BED), alterations in these mechanisms signaling hunger and satiety have been observed. It has been investigated that these alterations may underlie the development and maintenance of compulsive overeating in BED. The present narrative review examined the current literature related to the neurobiological processes involved in feeding dysregulation in BED with the aim of updating the most relevant aspects with special attention to neuroendocrine signaling. Studies have shown both central and peripheral endocrine dysfunctions in hormones participating in homeostatic and hedonic pathways in BED. Most studies have been especially focused on orexigenic signals, pointing out the existence of a hyperactivated mechanism promoting hunger. Fewer studies have explored anorexigenic pathways, but the findings so far seem to suggest an abnormal satiety threshold. Despite this, to date, it is unable to identify whether these alterations are typical of the BED pathophysiology or are related to an obesogenic pattern due to most studies included patients with BED and obesity. The identification of endophenotypes in BED may provide a new approach to aberrant eating behavior, favoring the implementation of biological therapeutic targets.

1. Introduction

Binge eating disorder (BED), recognized as an eating disorder (ED) in the last edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) (APA, 2013), is characterized by distressful and frequent episodes of excessive food intake accompanied by a sense of loss of control (i.e., binge episode, BE). Considering BE, individuals with BED and bulimia nervosa (BN) share this diagnostic criterion. However, BED is the most prevalent ED (Guerdjikova et al., 2019; Hilbert, 2019) with an estimated mean prevalence between 0.9% and 2% (Keski-Rahkonen, 2021). A recent review reported a worldwide prevalence between 0.6% and 1.8% in adult women and 0.3–0.7% in men (Giel et al., 2022). Its negative impact on functionality and quality of life (Giel et al., 2022) is usually related to negative health consequences (Wassenaar et al., 2019) and comorbid clinical conditions (Guerdjikova et al., 2019), such as obesity (Agüera et al., 2021; Villarejo et al., 2012) which increases morbidity and mortality rates (Giel et al., 2022). In fact, the lack of control over food intake and increased binge frequency contribute to an 87% prevalence of obesity in individuals with BED (Villarejo et al., 2012).

Considering this epidemiological overlap of both obesity and BED, in the last decades, some studies have investigated the underlying factors of excessive food consumption (Bulik et al., 2003; Haines and Neumark-Sztainer, 2006). Thus, some neurobiological models have described similar alterations in the crosstalk between bottom-up processing initiated by sensory stimuli and top-down cognitive processing driven by the central nervous system in individuals with BED (Avena et al., 2011; Kakoschke et al., 2019; Kung et al., 2022) and obesity (Carnell et al., 2012; Chen et al., 2016; Furlong et al., 2014). On the one hand, it has been described that an attentional bias towards high-calorie foods and high reward sensitivity could trigger excessive food consumption which would end up altering neuroendocrine signaling going

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from peripheral tissues to brain regions (i.e., the bottom-up processing) (Berner et al., 2018; Burger and Berner, 2014; Steward et al., 2019). On the other hand, dysfunctions in brain regions involved in the control of motivated behavior could contribute to override normal hypothalamic signaling (i.e., the top-down processing) (Carnell et al., 2012; Chen et al., 2016; Donnelly et al., 2018; Kakoschke et al., 2019; Kessler et al., 2016; Steward et al., 2018). However, although most studies point in this direction, the results have been unable to establish a consensus that would be useful in identifying potential endophenotypic profiles with therapeutic implications based on pharmacological interventions to ensure recovery or a better response to treatment. Currently evidence-based psychological therapy is recommended as first-line treatment in BED (NICE, 2020) being the cognitive behavioral therapy (CBT) the most effective (Giel et al., 2022).

Psychopharmacological strategies have emerged as a complement to psychological treatment aimed at reducing symptomatology derived from psychiatric comorbidities, impulsivity levels, or contributing to weight control, but are not directly focused on counteracting the eating psychopathology of these patients (Hilbert et al., 2020). For instance, to date, the only drug specifically approved by the US Food and Drug Administration (FDA) for BED is Lisdexanfetamine, addressed to adults with moderate to severe BED (Guerdjikova et al., 2019; Hilbert, 2019), which is hypothesized to reduce BE by normalizing dopaminergic (DA) activity (Schneider et al., 2021).

Bearing all this in mind, the main objective of this work was to provide an updated overview of literature regarding neuroendocrine dysfunctions associated with overeating in BED, expecting to collaborate in the identification of possible biological targets in the treatment of BED psychopathology.

2. Methods

In this narrative review, we have summarized and synthesized the main findings from studies and reviews exploring neuroendocrine alterations in BED considered as potential factors entailed in the pathogeny of BE. The PubMed/MEDLINE database until May 2022 were used to identify relevant articles for inclusion. Search terms included were “binge eating disorder”, “overeating”, “binge episode”, “orexigenic/hunger endocrine signaling” and “anorexigenic/satiety endocrine signaling”. Studies involving endocrinological aspects of overeating without contemplating BED were excluded.

The findings identified to date are presented from the central to the peripheral level. First, this review outlines the main alterations described by studies investigating the functioning of brain regions and neurotransmitters altered in BED, and subsequently, deepens in the alterations in the endocrine signaling of hormones and peptides. In addition, we included a section for genetic alterations regarding these endocrine factors and linked to BED, as well as for their potential implications as biological targets in the treatment of the disorder.

2.1. Neural signaling alterations in BED

It has been widely described that eating behavior is a result of a crosstalk between central nervous system and peripheral tissues. Beyond the metabolic energy-based homeostatic mechanism, there are motivational, emotional, and cognitive processes involved in promoting or suppressing eating behavior. Therefore, problems in weight and feeding disorders have allowed the definition of a complex phenomenon regulated by homeostatic and non-homeostatic (i.e., hedonic) mechanism (Chen et al., 2016; Schwartz et al., 2000).

Focusing on the homeostatic mechanism that regulates the process of feeding in the brain, studies have described the hypothalamus as the main orchestrator of eating behavior that receives neuropeptides signaling from peripheral tissues (Roh et al., 2016). It has been described that lesions in the hypothalamus can induce alterations in eating behavior in individuals who, without having an ED, exhibit food restriction or overeating, similar to BED (Uher and Treasure, 2005). Main subregions in the hypothalamus such as the lateral hypothalamus (LH) and the medial hypothalamus (MH) have been described as responsible for hunger and satiety signaling, respectively (Margules and Olds, 1962). Specifically, the primary hypothalamic receptor of hunger and satiety peripheral signals is the arcuate nucleus (ARC) (Roh et al., 2016). The ARC holds two cell populations: neuropeptide Y (NPY) neurons and pro-opiomelanocortin (POMC) neurons (Hellström et al., 2004) whose crosstalk directly modulates feeding behavior (Cuesto et al., 2017). Both circuits send signals mainly to the periventricular nucleus (PVN): NPY neurons release NPY and Agouti-related peptides (AgRP) stimulating appetite (Hellström et al., 2004), whereas POMC neurons release alpha-melanocyte-stimulating hormone (alpha-MSH) and cocaine and amphetamine-regulated transcript (CART) suppressing appetite (Cuesto et al., 2017). Increased fasting circulating NPY levels have been observed in individuals with obesity, with or without BED, compared to HC (Turan et al., 2021), indicating orexigenic signals could underlie motivation for eating in obesity and BED. In the case of anorexigenic signaling, a study compared circulating fasting alpha-MSH between individuals with BED and other EDs finding no significant differences (Galmiche et al., 2020).

At the central level, it has been hypothesized that the LH could be a potential region involved in overeating problems in BED due to its orexigenic implications (Stuber and Wise, 2016). The LH plays a crucial role in the interplay between homeostatic and non-homeostatic mechanisms communicating with the reward brain system through DA neurotransmission (Castro et al., 2015; Stuber and Wise, 2016). The DA neural pathway mainly projects along the frontostriatal circuit composed of the frontal lobe and basal ganglia orchestrated by the nucleus accumbens (NAcc), which is located at the ventral part of the striatum. The NAcc mediates DA neurotransmission from the ventral tegmental area (VTA) to the prefrontal cortex, the insula, the amygdala, and the LH, promoting or suppressing hunger and satiety signals through emotional and reward value processing (Castro et al., 2015). The DA release can increase the rewarding value of food promoting hedonic mechanisms towards food intake (D’Addario et al., 2014). Consistent with this notion, neuroimaging studies have described more hyperreactivity of the reward brain system to food-related stimuli in individuals with BED compared to HC (Schienle et al., 2009). For this reason, research has focused on investigating whether alterations in the DA circuit may underlie BE along with impulsivity and compulsivity problems observed in patients with BED (Kessler et al., 2016). However, despite there is broad consensus of alterations in the DA circuit in BED, a recent review reported both hyperactivation and hypoactivation of the DA system regarding animal and human studies. Then, the directionality of DA alterations in BED is not fully understood (Yu et al., 2022).

Furthermore, other neuroendocrine systems such as the serotoninergic (5HT) and opioid (POE) ones have shown to be involved in feeding regulation, interacting with different endocrine signals. For instance, 5HT release can induce satiety signals and regulate mood when connecting with striatal limbic regions (Cuesto et al., 2017). In line with this understanding, a neuroimaging study demonstrated deficits in the 5HT system in women with obesity and BED compared with those without BED (Kuikka et al., 2001). Selective 5-HT reuptake inhibitors (i.e., fluoxetine) have demonstrated to reduce eating disorder symptomatology in BED, emerging the 5HT system as an interesting biological target in the treatment of these patients (Tammela et al., 2003). In the case of POE, its release can promote appetite processes influencing food choices because this system reinforces the hedonic properties of food, predominating its rewarding effects (Micioni Di Bonaventura et al., 2021) over its role in homeostatic signaling (Valbrun and Zvonarev, 2020). Studies in BED have shown that the mu-POE receptor (μ-OPR) can promote hedonic eating in BED triggering overeating (Giuliano and Cottone, 2015). In addition, POE actions modulate orexigenic signaling by stimulating the release of NPY, orexins or hypocretins (OX), and endocannabinoids (Valbrun and Zvonarev, 2020). Overall, these

findings may indicate that the POE system is a strong appetite stimulator, and its dysfunction could be potentially involved in BED psychopathology.

Orexins A (OXA) and B (OXB) are peptides released in the LH and the gastrointestinal tract (GI) promoting eating (Cuesto et al., 2017; Micioni Di Bonaventura et al., 2021). While LH-OX projections to the mesostriatal circuit can enhance food reward, a link with the limbic area might be implicated in emotional eating under stressful circumstances (Giardino and de Lecea, 2014). In BED, dysfunctional prefrontal and limbic circuits seem to have an impact on self-control and emotion regulation, increasing the risk of compulsive overeating (Donnelly et al., 2022; Koob and Volkow, 2016). Studies have widely described that a lack of strategies to cope with strong emotional states is a trigger for BE in BED (Dingemans et al., 2017; Eichen et al., 2017). However, studies investigating the role of OX in BED have not provided conclusive results to date. Preclinical findings have demonstrated that an antagonism of the OX receptor type 1 (OX1R) can reduce overeating in mice (Piccoli et al., 2012). In humans, although describing lower fasting circulating OXA levels in obesity (Hellström et al., 2004), no significant differences were reported among individuals with and without BED (Yagin et al., 2020). While a resultant compensatory mechanism to an increased hunger signaling has been hypothesized in obesity (Hellström et al., 2004), it remains unclear whether variations in OX levels in BED are linked to the presence of obesity or may also underlie BED psychopathology.

Similar to OX, the endocannabinoid system (ECS) exerts its orexigenic functions increasing seeking for food, motivation for reward, and food palatability, in an interplay with DA and POE circuits. The ECS is mainly represented by the action of two endogenous ligands, anandamide (AEA) and 2-arachidonoylglycerol (2-AG), and the endocannabinoid receptor type 1 (CB1R), widely distributed throughout brain homeostatic and hedonic pathways, and peripheral tissues (e.g., adipose tissue and GI) (D'Addario et al., 2014). A dysfunctional ECS has been described in EDs and obesity, which is characterized mainly by a hyperactivated ECS (Matias and Di Marzo, 2007; Monteleone et al., 2005b). Different studies have also reported higher circulating AEA levels in fasting among individuals with overweight/obesity and BED, compared with the non-BED group, and HC (Monteleone et al., 2005b; Yagin et al., 2020). Conversely, no differences in plasma 2-AG levels have been found when compared with HC, neither in fasting nor postprandially (Monteleone et al., 2012, 2005b), regardless of the food type (Monteleone et al., 2017). Therefore, it has been hypothesized that increased AEA levels (not 2-AG) in BED may reinforce the hedonic properties of hypercaloric nutrition, favoring the preference for high-calorie food intake and perpetuating BE (Monteleone et al., 2005b).

2.2. Peripheral signaling alterations in BED

There are different sets of peripheral endocrine signals mainly from the GI tract (i.e., gut hormones, such as ghrelin), which have primarily short-term effects on food intake, and those from the white adipose tissue that exert long-term regulatory actions (i.e., adipocytokines, such as leptin) (Geliebter et al., 2008b; Giel et al., 2022). Similar to central endocrine signaling, peripheral signals can be mostly divided into those that promote food intake, increasing in fasting (e.g., ghrelin), and those that inhibit intake, increasing in satiety (e.g., cholecystokinin (CCK), glucagon-like-peptide 1 (GLP-1), the activated form of the peptide YY (PYY 3–36), leptin, insulin) (Yu et al., 2021). These signals could act on central homeostatic and hedonic pathways (Yu et al., 2021) by crossing the blood-brain barrier or connecting with the vagus nerve (X) located in the brain stem, being a gateway of peripheral signals (e.g., ghrelin, CCK, GLP-1, PYY). In the brain, they established a crosstalk with different neuroendocrine systems (e.g., DA, POE, OX, ECS) (Novelle and Diéguez, 2018) and some of them could also regulate mood and cognition (e.g., ghrelin, GLP-1, adipocytokines) (Hellström et al., 2004).

Ghrelin is one of the peripheral endocrine signals that has aroused greater interest in the pathogenesis of BE, being related to increased adiposity and risk for obesity (Micioni Di Bonaventura et al., 2021). In comparison with HC, Monteleone et al. (2005b) described lower circulating ghrelin levels in fasting in obesity with and without BED. These results contrast with other works that reported a lack of significant differences between individuals with obesity, with and without BED, and HC, neither in fasting nor postprandially (Rouach et al., 2007; Troisi et al., 2005). Overall, there are two circulating forms of ghrelin (Hellström et al., 2004): the acylated (AG) form, which has been classically considered an active form, and the des-acylated (DAG) form, of which it has been suggested an antagonist role and therefore, anorexigenic function (Fernandez et al., 2016). Some studies have suggested a negative relationship between AG levels and BE in obesity (Yu et al., 2021; Perna et al., 2022). Studies in overweight and obesity showed that individuals with BED had lower concentrations of AG and total ghrelin during hunger with a smaller AG decrease after feeding when compared to the non-BED group (Geliebter et al., 2008a, 2005, 2004; Hernandez et al., 2019). Interestingly, Hernández et al. (2019) suggested that AG could have a dual function in BED: a compensatory down-regulation mechanism secondary to overeating linked to a lower fasting AG whereas a role in promoting overeating associated with the smaller AG decrease in satiety. On the other hand, this work found no differences in DAG between groups (Hernandez et al., 2019). This lack of differences in DAG concentrations observed between individuals with obesity with and without BED suggests that DAG is rather an indicator of obesity with a lesser involvement in BE (Hernandez et al., 2019). Indeed, a recent study (Perna et al., 2022) hypothesized DAG deficiency could be a potential marker of obesity. Although these findings are considered interesting, further investigation is still needed to resolve some conflicting results. For instance, there are studies that reported no significant differences in total ghrelin levels between individuals with overweight/obesity with and without BED (Monteleone et al., 2005a; Munsch et al., 2009; Rouach et al., 2007). Curiously, among EDs, similarities in plasma total ghrelin, DAG, and AG profile in fasting have been assessed (Galmiche et al., 2020), above all between disorders within the binge spectrum (BSD) (i.e., BN and BED), sharing BE (Monteleone et al., 2005a; Troisi et al., 2005). In this line, the later study found lower plasma ghrelin levels in fasting among BSD than AN (Troisi et al., 2005). After therapeutic intervention within the BED group, inconsistent results have been yielded regarding changes in ghrelin levels (Geliebter et al., 2008a, 2005; Munsch et al., 2009). In sum, the role of ghrelin in BED physiopathology is still unclear. Future studies should focus on standardizing sample collection protocols, as well as considering the role that body mass index (BMI) could be playing in ghrelin signaling.

Fewer studies have assessed anorexigenic gut signals. Most works have shown a lack of significant differences, neither in fasting nor satiety, in circulating CCK, GLP-1, PYY levels in BED compared with other EDs, or individuals with obesity without BED (Galmiche et al., 2020; Geliebter et al., 2008b, 2005, 2004; Hernandez et al., 2019). Only one study reported significantly higher postprandial plasma CCK and PYY levels in BED, followed by a stronger decline in the non-BED group (Munsch et al., 2009). After a therapeutic intervention in BED, results agreed regarding a lack of pre-post changes in CCK and PYY levels, in fasting and satiety, and therefore, these postprandial levels were not related to BE post-intervention (Geliebter et al., 2008a, 2005; Munsch et al., 2009). These aforementioned findings are mostly consistent with the absence of differences in gastric emptying between individuals with obesity, with and without BED (Geliebter et al., 2005, 2004).

On the other hand, the stomach serves as a food reservoir, whose capacity can limit meal intake. Then, the smaller the capacity, the lower the meal intake, being gastric distention a satiety signal in response to the activation of gastric receptors and mechanoreceptors (Hellström et al., 2004). In this line, a higher gastric capacity has been reported in BED than in subthreshold BED nor in the non-BED group with obesity (Geliebter et al., 2005, 2004). This fact could suggest an altered satiety

threshold in individuals with BED favoring a greater meal intake related to BE although gastric emptying does not differ between individuals with obesity with or without BED.

Within adipocytokines, leptin production seems to be proportional to the amount of body fat mass and positively related to BMI, contrary to adiponectin, which is decreased in obese mice and in individuals with obesity (Geliebter et al., 2008b; Hellström et al., 2004; Yu et al., 2021). As leptin has anorexigenic functions, increased circulating levels have been linked to central leptin resistance in obesity. However, whether leptin resistance could be a cause, or a consequence of obesity needs to be further investigated. Studies in BED have explored adipocytokines in fasting and satiety states showing mixed results. In fasting, Monteleone et al. (2002, 2000) assessed plasma leptin levels and soluble leptin-receptor (LeR) among women with EDs and obesity with and without BED. These groups with obesity had significantly higher leptin but decreased LeR levels than HC, after adjusted for age (Monteleone et al., 2002, 2000), suggesting that changes in the synthesis of leptin may inversely influence LeR production. On the other hand, studies have observed higher fasting leptin concentrations only in individuals with obesity and BED but not in obesity without BED (Adami et al., 2002; Yagin et al., 2020) whereas other works described lower leptin concentrations in BED, but higher than in individuals with BN (Messerli--Bürgy et al., 2010; Paraguassu Brandao et al., 2010). Exploring postprandial leptin levels, no significant differences in obesity groups were observed (Monteleone et al., 2002, 2000; Geliebter et al., 2005, 2004; Turan et al., 2021). Opposite to above studies, some research has reported differences between obesity with and without BED with lower plasma leptin levels in individuals with BED (Hernandez et al., 2019; Paraguassu Brandao et al., 2010). It has been hypothesized this lower leptin concentrations could promote overeating due to a deficient satiety signaling (Hernandez et al., 2019). Adiponectin acts on food intake regulation in a glucose-dependent way, with insulin-sensitizing effects (Geliebter et al., 2008b; Hellström et al., 2004). Lower fasting serum levels have been observed in individuals with BED (with overweight/-obesity) compared with HC (Monteleone et al., 2003), similar to obesity (Yu et al., 2021). Carnier et al. (2012) found no significant differences in fasting plasma adiponectin levels in individuals with obesity and an ED (i.e., BN or BED). However, a previous work reported lower plasma adiponectin levels in women with obesity and BED than without BED, in fasting and postprandially (Paraguassu Brandao et al., 2010). Despite studies being mixed, these findings could suggest the existence of leptin resistance and adiponectin disturbances in BED. As all the above-mentioned studies included patients with BED and obesity, it is questionable whether the alterations in leptin levels respond to an obesogenic pattern rather than to a BED pattern. Given the interaction between leptin and adiponectin with BMI, future studies should consider normal-weight samples with BED.

Finally, insulin is a pancreatic hormone with anorexigenic effects based on glucose levels and positively linked to BMI (Hellström et al., 2004). Clinical studies exploring circulating insulin levels in BED have shown inconsistent results. Some studies described higher fasting plasma insulin levels in individuals with obesity and BED compared to those with obesity without BED (Geliebter et al., 2004; Succurro et al., 2015; Yagin et al., 2020). Although these findings suggest that comorbidity between obesity and BED may be associated with a higher insulin resistance, other works reported no differences neither in fasting nor satiety, regardless of the diagnosis of BED (Galmiche et al., 2020; Geliebter et al., 2005; Gluck et al., 2004; Messerli-Bürgy et al., 2010).

2.3. Genetic disruptions related to endocrine signaling in BED

Over the last decades, some studies have focused on the genetic mechanisms involved in the etiology of BED (Manfredi et al., 2021). Family and twin studies reported that BED is a moderately heritable condition, with an estimated range of 41–57% (Kessler et al., 2016). However, the genetic polymorphisms implicated in the pathophysiology of BED are still unclear (Manfredi et al., 2021). So far, candidate gene association studies have mostly explored DA and 5HT genes due to their relationship with the reward system (Manfredi et al., 2021). Although multiple genetic polymorphisms have already been described, genome-wide association (GWAS) and epigenetic studies in BED are needed for a better understanding of the mechanisms involved in the development and maintenance of this disorder.

Genetic polymorphisms at DA receptor type 2 (D2) genes have received considerable attention. A recent review of genetic polymorphisms associated with BED showed that the Taq1A polymorphism of D2/ANKK1 is the genetic variant that showed the most significant association with the disorder (Manfredi et al., 2021). This is consistent with previous research showing that both the ANKK1 and D2 are significantly associated with addiction (Davis, 2015). In addition, Leehr et al. (2016) investigated the Val(108/158)/Met polymorphism of the catechol-O-methyltransferase (COMT) gene, an important regulator of DA neurotransmission. Their findings suggest that Met/Met homozygous individuals with BED might represent a specific group in the BED spectrum, showing higher behavioral impulsivity. However, this association must be interpreted with caution due to the small sample size of the study.

As mentioned above, evidence suggests that genes regulating 5HT neurotransmission in the central nervous system may also play a critical role in the pathogenesis of EDs (Davis, 2015; Monteleone et al., 2006). To date, relatively few studies have focused on investigating the functioning of the 5HT system specifically in BED. The existent works have reported conflicting results. For example, Monteleone et al. (2006) showed that a 5HTTLPR polymorphism in the SLC6A4 gene was significantly more frequent in individuals with obesity with and without BED, suggesting that this may constitute a vulnerability factor for developing BED. However, another study did not find a significant relationship between BED diagnosis and this 5HTTLPR polymorphism (Palmeira et al., 2019).

Within the POE system, the μ-OPR type 1 (μOPR1) gene has been extensively analyzed due to its relationship with hedonism and its role in drug abuse (Valbrun and Zvonarev, 2020). The functional A118G allele has received particular attention and, although the exact mechanism remains unclear, in vivo evidence suggests a "gain-of-function" for those possessing this allele. In previous work, Davis et al. (2009) focused on both DA and POE genetic markers to examine their joint association in brain reward functioning. Authors targeted three functional polymorphisms related to D2 gene, as well as the functional A118G polymorphism of the μOPR1 gene, and found that 80% of participants with BED and obesity had a genotype combination characterized by gain-gain of function genotype (G allele of A118G and A+ of Taq1A). In addition, Pucci et al. (2019) highlighted the potential role of fatty acid amide hydrolase (FAAH) polymorphism in the up-regulation of the ECS in a female rat BED model. Taken together, these results support the idea that the BE propensity may be influenced by greater responsiveness to the hedonic properties of food.

2.4. Therapeutic targets related to endocrine signaling in BED

It is worth noting that findings regarding biological aspects of BED have also provided potential targets for researchers to investigate effective treatments. For instance, the only drug for BED that is approved by the FDA is Lisdexanfetamine, addressed to adults with moderate to severe BED (Guerdjikova et al., 2019; Hilbert, 2019). It is a D-amphetamine prodrug that facilitates DA and noradrenaline neurotransmission, blocking reuptake in presynaptic neurons and increasing the release to inter-synaptic space (Schneider et al., 2021). Therefore, it is hypothesized to reduce BE by normalizing the DA activity. Moreover, amphetamines have been demonstrated to reduce appetite and have weight loss effects (McElroy, 2017).

Noticeably, other drugs have been used as off-label treatments for BED, such as antidepressants (e.g., selective 5HT reuptake inhibitors,

SSRIs), anticonvulsants, and weight-management agents. However, each one has its strengths and limitations, and patients must be carefully assessed in order to select the most suitable treatments. On one side, antidepressant drugs target neurotransmitters that are thought to be disrupted in BED, such as DA. Evidence supports a modest effect of antidepressants on BE but not on weight (McElroy, 2017). On the other side, some anticonvulsant drugs have been used in the management of BED because of their association with weight loss (Heal and Gosden, 2022). More specifically, these drugs are known to affect peptide and neurotransmitter systems involved in appetite, craving, and feeding behavior (McElroy, 2017). Topiramate is the one that has received the most attention in BED and has been found to decrease frequency of BE in clinical studies assessing weight loss (Nourredine et al., 2021). Unfortunately, its use is associated with several adverse effects (e.g., paresthesia, upper respiratory tract infection, somnolence, nausea, dry mouth, pain, etc.).

Regarding drugs for weight management, Orlistat is an approved weight loss medication that has also been used in BED. Orlistat's mechanism of action is different from those aforementioned: it does not act on the central nervous system, but instead, it promotes weight loss by partially inhibiting dietary fat absorption (McElroy, 2017). More specifically, this drug is a peripheral lipase inhibitor that partially prevents the absorption of lipids from the gut. However, contradictory results on its effectiveness have been reported. While some studies showed that Orlistat reduced symptomatology remission rates for BED, other researchers reported that remission rates were similar for placebo/CBT group (Heal and Gosden, 2022).

Another weight management drug that received so much attention has been Rimonabant. This medication is a CB1R inverse agonist that showed to promote significant weight loss in patients with obesity (Reas and Grilo, 2015). Its use has been tested in human studies under the presence of BE (Pataky et al., 2013). However, this drug was quickly withdrawn due to the emergence of significant side effects, such as severe mood disturbances (e.g., anxiety and depressive symptomatology).

Although the recent inclusion of BED as a diagnostic category in the DSM-5 has stimulated additional research, the reality is that the empirical base regarding pharmacotherapy for BED remains unclear. For instance, a scarce investigation is related to the potential utility of the Glut receptor mGlu5 antagonists for the treatment of BED (Bisaga et al., 2008). This study demonstrated that the mGlu5 antagonist MPEP decreased candy consumption in a baboon model of BED, which may be related to a reduction in the rewarding value of reinforcing stimuli. Naltrexone is a nanomolar affinity, partial agonist/antagonist at μ- and δ- OPR, and a κ- partial agonist. In animal models, its use decreased intake of preferred fat and sucrose diets and suppressed palatable food intake (Naleid et al., 2007). So far, this medication is approved to treat alcohol dependence, and no trials have been performed on BED with naltrexone as monotherapy (Heal and Gosden, 2022; Valbrun and Zvonarev, 2020). On the other hand, it has been seen that pharmacological activation of GLP-1 receptor in a model of BED-like in female mice resulted in a decreased BE size (Lutter et al., 2017), as well as the pharmacological disruption of OX signaling decreased cue-induced reinstatement of highly palatable food (Piccoli et al., 2012). In this line, further studies focused on the biological mechanisms involved in the development and maintenance of BED are needed for developing new effective treatment models.

3. Conclusions

The aim of this review was to describe the endocrine mechanisms involved in BE to delineate possible biological targets in the treatment of BED psychopathology. Despite a considerable number of animal and human studies describing neuroendocrine dysfunctions in BED, these have predominantly focused on orexigenic signals rather than anorexigenic mechanisms. In relation to anorexigenic signals such as 5-HT or adiponectin, findings seem to suggest that patients with BED have an even higher satiety threshold than those with obesity without BED, which could be an underlying mechanism for BE. However, studies regarding leptin levels are similar in individuals with obesity with and without BED. Likewise, studies concerning orexigenic signals described a hyperactivation of the orexigenic signal in patients with obesity and BED displaying no significant differences compared to individuals with obesity without BED but did when comparing with HC. This raises the question of whether these neuroendocrine alterations respond to an obesogenic pattern and not to the specific pathophysiology of BED. In that sense, it would be interesting for future studies to consider investigating populations with BED without obesity to answer this unresolved question. Furthermore, given that most of the studies correspond to cross-sectional designs, it is also not possible to infer causality between neuroendocrine alterations and the psychopathology of BED. Taking all this into account, future studies should consider these existing handicaps in the literature and contribute with longitudinal studies to answer these questions.

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CRediT authorship contribution statement

Isabel Baenas: Conceptualization, Investigation, Data curation, Writing – original draft, Visualization. **Romina Miranda-Olivos**: Conceptualization, Investigation, Data curation, Writing – original draft, Visualization. **Neus Solé-Morata**: Data curation, Investigation, Writing – original draft. **Susana Jiménez-Murcia**: Funding acquisition, Supervision, Writing – review & editing. **Fernando Fernández-Aranda**: Conceptualization, Project administration, Funding acquisition, Supervision, Writing – review & editing.

Declaration of Competing Interest

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