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Neuroendocrinology of reward in anorexia nervosa and bulimia nervosa: Beyond leptin and ghrelin

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Abstract

The pathophysiology of anorexia nervosa (AN) and bulimia nervosa (BN) are still poorly understood, but psychobiological models have proposed a key role for disturbances in the neuroendocrines that signal hunger and satiety and maintain energy homeostasis. Mounting evidence suggests that many neuroendocrines involved in the regulation of homeostasis and body weight also play integral roles in food reward valuation and learning via their interactions with the mesolimbic dopamine system. Neuroimaging data have associated altered brain reward responses in this system with the dietary restriction and binge eating and purging characteristic of AN and BN. Thus, neuroendocrine dysfunction may contribute to or perpetuate eating disorder symptoms via effects on reward circuitry. This narrative review focuses on reward-related neuroendocrines that are altered in eating disorder populations, including peptide YY, insulin, stress and gonadal hormones, and orexins. We provide an overview of the animal and human literature implicating these neuroendocrines in dopaminergic reward processes and discuss their potential relevance to eating disorder symptomatology and treatment.

Keywords

anorexia nervosa; bulimia nervosa; reward; dopamine; neuroendocrinology

1. Introduction

Anorexia nervosa (AN) and bulimia nervosa (BN) are serious psychiatric disorders with often chronic courses, multifactorial etiopathogeneses, and poorly understood biological maintenance factors (American Psychiatric Association, 2013). A large body of research aimed at identifying these factors has focused on potential alterations in the neurobiology of hunger and satiety. This includes neurotransmitters and central and peripheral neuropeptides involved in promoting and inhibiting eating behavior to maintain energy balance and body weight via the hypothalamus (Bailer and Kaye, 2003), and the insula, which merges sensory

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taste experience (Fudge *et al*, 2005; Small, 2010) with interoceptive signaling from the ventral striatum and hypothalamus to guide behavior.

However, eating is a complex process that involves integration of additional homeostatic signals (e.g., for energy balance, reproductive health, stress level) and input from reward circuitry. In humans and rodents, ventral tegmental area (VTA), nucleus accumbens (NAc), ventral caudate and putamen, amygdala, anterior cingulate cortex (ACC), and orbitofrontal cortex (OFC) are involved in the anticipation and processing of rewards (Baker *et al*, 2016; Daniel and Pollmann, 2014; Diekhof *et al*, 2012; Grabenhorst and Rolls, 2011; Izquierdo, 2017). Critical for mediating the rewarding and reinforcing effects of food, in particular, is the mesolimbic dopamine (DA) pathway, which includes projection neurons from VTA to NAc and dopaminergic D1 and D2 receptors that are involved in reward learning and incentive salience (Berridge, 2009; Berridge and Robinson, 1998; Kelley, 2004; Roitman *et al*, 2004; Schultz *et al*, 1997). A large body of evidence from human neuroimaging studies and animal models of eating disorders suggests that the structure and function of reward circuitry is altered in association with binge eating, purging, and dietary restriction in BN and AN, and that some of these alterations are apparent early in illness onset and persist after symptoms remit (for review, see Avena and Bocarsly, 2012; Frank, 2013; Kaye *et al*, 2013; O'Hara *et al*, 2015).

Disturbances in the integration of homeostatic and reward signaling may promote hedonic eating, or food approach and eating past satiety or energy requirements, which likely also plays a critical role in eating disorder onset and/or symptom maintenance (Keating *et al*, 2012). Although decades of research have documented neuroendocrine alterations in individuals with AN and BN relative to controls (for review, see Culbert *et al*, 2016; Tortorella *et al*, 2014), only more recently have these alterations been hypothesized to contribute to the altered neural bases of reward processes in eating disorders. Improved understanding of how neuropeptides influence reward circuitry and food reward specifically has potential for significant clinical impact, as it could inform targeted interventions for eating disorders.

This narrative review focuses on select neuroendocrine signals that show alterations in individuals with AN and BN and interface with reward circuitry--specifically, striatal DA pathways shown to play an integral role in feeding reward behavior (Ferrario *et al*, 2016). Several neuropeptides play a role in peripheral homeostatic regulation of energy balance. Some of these peptides serve as signals for energy stores or cellular metabolism, and, when integrated with reward signals, influence motivated eating behavior (Volkow *et al*, 2011). Alterations in these signals or their integration with DA reward signaling may potentiate eating disorder symptoms. Interactions of gonadal hormones known to regulate food intake and energy metabolism (Xu and López, 2018) with the reward system also may play an important role in disordered eating. Several prior reviews have focused on potential reward-related roles of leptin and ghrelin in eating disorders (Monteleone *et al*, 2018; Monteleone *et al*, 2008; Monteleone and Maj, 2013). In addition, previous reviews have posited a potential reward-related role for insulin alterations in obesity (Murray *et al*, 2014), but not eating disorders. The current review is the first to focus on interactions of DA reward circuitry with

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peptide YY (PYY), insulin, orexins, and stress and gonadal hormones and the resulting potential implications for AN and BN symptoms and treatment.

Studies through June 2018 were identified using the following search terms in Google Scholar, PubMed, and PsycINFO search engines: eating disorders, anorexia nervosa, bulimia nervosa, binge eating, eating, feeding, stress, peptide YY, PYY, insulin, orexin, cortisol, glucocorticoid, HPA axis, estrogen, estradiol, progesterone, testosterone, androgen, reward, dopamine, animal model, rodent, neuroimaging, fMRI. Of note, to maintain a focused scope for this review, we address research related to AN and BN, and we do not address other reward pathways (e.g., opiodergic) that are also likely implicated in altered reward signaling in eating disorders (Berridge, 2009). This narrative review provides updated examples from the literature and does not represent a systematic or complete update to the entire body of work. For each hormone, we review (1) its basic function, (2) animal and human neuroimaging and biological studies that have revealed its interaction with the dopaminergic reward system, (3) case-control comparison studies that have documented altered levels of the hormone in individuals with AN and BN, and (4) studies that have directly evaluated associations of levels of the hormone with eating disorder symptomatology and related implications for novel interventions for AN and BN symptoms.

2. Peptide YY (PYY)

PYY is a 36-amino acid polypeptide anorexigenic hormone that is released in the endocrine L cells of the distal ileum and colon in response to food intake (Adrian *et al*, 1985; Pedersen-Bjergaard *et al*, 1996) resulting in increased satiety. While the peptide exists in two primary forms (PYY1–36 and PYY3–36), this review will focus on PYY3–36, which is the main circulating form of PYY released in fasting and postprandial states. PYY3–36 binds with the greatest affinity to the Y2 receptor (Abbott *et al*, 2005), which signals satiety by inhibiting Neuropeptide Y and stimulating proopiomelanocortin (POMC) neurons in the arcuate nucleus (le Roux and Bloom, 2005). Peripheral PYY also functions as a satiety signal in response to a meal in part by signaling decreased ghrelin production (Batterham and Bloom, 2003a). Translational research supports that PYY3−36 exerts its anorectic effects by acting upon central appetite-regulating circuits, with the hypothalamic arcuate nucleus and brain stem regions identified as key areas (Chandarana and Batterham, 2008; Ghitza *et al*, 2007). PYY levels start to increase approximately 15 minutes after food ingestion, reaching a peak 1–2 hours postprandially and remaining elevated several hours later (Adrian *et al*, 1985).

2.1 Interactions with the Dopaminergic Reward System

2.1.1 Animal Studies.—Animal studies suggest that PYY3–36 inhibits DA and norepinephrine release in the hypothalamus through binding to Y2 receptors (Brunetti *et al*, 2005) but increases the synthesis and release of DA in the rat striatum (Adewale *et al*, 2007). These dopaminergic effects are thought to be indirectly mediated by other neurotransmitter systems that are functionally connected with dopaminergic pathways (Stadlbauer *et al*, 2014).

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Peripheral infusion of PYY3–36 inhibits food intake in a dose-dependent manner in rats (Batterham *et al*, 2002; Chelikani *et al*, 2004) and produces sustained reductions in food intake and weight gain when administered for 7 to 10 days (Batterham *et al*, 2002; Chelikani *et al*, 2006). Additional studies have examined mechanisms of action of PYY3–36 when administered centrally and peripherally. Injection of PYY3–36 directly into the arcuate nucleus of the hypothalamus inhibits food intake by releasing neuropeptide Y and stimulating release of alpha-Melanocyte-stimulating hormone (Batterham *et al*, 2003b; Batterham *et al*, 2002). To mimic peripheral prandial release of PYY, Stadlbauer et al. (Stadlbauer *et al*, 2013) examined the acute effects of brief, intrameal PYY3–36 infusions into the hepatic portal vein in the GI tract on feeding behavior in mice. PYY3−36 infusions reduced meal size in mice compared to vehicle control, and increased the number of c-Fos expressing cells in metabolic regulation and reward regions including: the nucleus of the solitary tract, the hypothalamic arcuate and paraventricular nuclei, the central amygdala, and the NAc.

2.1.2 Human Neuroimaging and Biological Studies.—PYY3–36 plays a similar role in reducing food intake in humans. Batterham et al. (2002) administered a 90-min infusion of PYY3–36 to healthy humans, which resulted in 36% decreased energy intake during an ad libitum meal, compared to saline control. These anorexigenic effects lasted for up to 12 hours following PYY administration. In a subsequent study, comparable decreases in ad libitum buffet food intake were found following exogenous PYY infusion in both normal-weight and obese adults (Batterham *et al*, 2003b).

Additional information on the central mechanism of action of PYY3–36 in humans comes from multiple studies combining PYY3–36 infusion with fMRI. Indeed, PYY3–36 infusion modulates neuronal activity in homeostatic (brainstem parabrachial nucleus and hypothalamus) and reward regions (amygdala, OFC, VTA, ventral striatum, and insula), with the greatest effects on activity in the left caudolateral OFC (Batterham *et al*, 2007). After PYY infusion, mimicking a fed state, changes in OFC activation predicted food intake, while under the saline condition, mimicking a relatively fasted state, hypothalamic activity predicted food intake. During PYY infusion, but not saline, change in OFC activation negatively correlated with meal pleasantness, suggesting that PYY modulates the OFC to decrease the reward value of food. Consistent with these results, De Silva et al. (2011) found attenuated neural activity across brain regions implicated in reward including the OFC, amygdala, insula, caudate, putamen, and NAc in response to food images during administration of PYY3−36 (versus saline). In a combined PET/MRI study, Weise et al. (2011) found that higher postprandial PYY concentrations were associated with greater grey matter volume and lower regional cerebral blood flow in the bilateral caudate nucleus. Postprandial caudate activity was also strongly negatively correlated with blood flow in the right OFC. Thus, pharmacological neuroimaging findings suggest that PYY3–36 exerts its effects on reducing food intake by acting on brain circuits related to both reward and energy homeostasis, with particular emphasis on attenuating activity of the OFC.

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2.2 Case-Control Comparisons: Altered Levels among Individuals with AN and BN Relative to Healthy Controls

Studies examining basal levels of PYY in participants currently meeting diagnostic criteria for AN have demonstrated mixed findings, with some studies reporting lower levels of PYY (Germain *et al*, 2010; Germain *et al*, 2007), some finding higher levels (Misra *et al*, 2006; Nakahara *et al*, 2007), and some finding no differences between individuals with AN and controls (Berrettini *et al*, 1988; Fernández-Aranda *et al*, 2016; Sedlackova *et al*, 2012; Stock *et al*, 2005). After recovery from AN, plasma PYY levels appear to normalize (Gendall *et al*, 1999a). In regard to differences between AN subtypes, Eddy et al., (2015) demonstrated that PYY3–36 levels were lower among individuals currently meeting diagnostic criteria for the binge-eating/purging subtype of AN (AN-BP) versus restricting-type AN. However, after recovery, levels of PYY are comparable across AN subtypes (Gendall *et al*, 1999a). In response to a test meal, individuals with AN have been shown to display either a time-delayed PYY response (Stock *et al*, 2005) or increased PYY response (Nakahara *et al*, 2007) compared to controls. After treatment and acute weight gain, Nakahara et al. (2007) found that plasma PYY3–36 response to eating was improved, but not normalized. Plasma PYY alterations in response to eating also seem to be nutrient specific, as levels reached significantly higher values in AN during a high protein versus high carbohydrate breakfast, to a greater degree than controls (Sedlackova *et al*, 2012). Further, in adolescent AN, greater levels of PYY predicted lower fat intake, lower percentage of calories derived from fat, and higher percentage of calories derived from carbohydrates (Misra *et al*, 2006).

Studies examining plasma levels of PYY among individuals with BN have been similarly mixed, demonstrating either lower plasma PYY levels compared to controls (Germain *et al*, 2010) or no differences between BN groups and controls (Berrettini *et al*, 1988; Gendall *et al*, 1999b; Sedlackova *et al*, 2012). Individuals with BN who had been abstinent from binge eating or purging for 30 days demonstrated significantly higher CSF PYY values compared to normal controls (Berrettini *et al*, 1988; Kaye *et al*, 1990) and relative to their own values when actively engaging in binge eating and purging (Berrettini *et al*, 1988). In contrast, plasma PYY levels appear to normalize after at least one year of recovery from BN (Gendall *et al*, 1999a). Mixed results have also been found in response to a test meal, with some studies demonstrating no significant difference in PYY response (Devlin *et al*, 2012; Keel *et al*, 2018), lower response (Kojima *et al*, 2005b), or higher response (Sedlackova *et al*, 2012) among individuals with BN compared to healthy controls.

2.3 Associations with Eating Disorder Symptoms and Related Implications for Treatment

Results from animal studies and studies of healthy human subjects support that high levels of PYY may play a role in reducing the hedonic value of food, contributing to decreased food consumption. However, findings from case-control studies of individuals with AN and BN may be mixed because of symptom heterogeneity within eating disorder groups or because of altered PYY responses to disordered eating, regardless of basal levels. Mixed findings among individuals with AN and normalization in PYY levels after recovery make it difficult to determine whether alterations in PYY represent a cause or consequence of low weight. In addition, analyses within groups of individuals with BN suggest that mixed case-control findings may be driven by individual differences in responses to eating, and some

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authors have suggested that BN symptoms may represent an effort to normalize an altered PYY response (Berrettini et al 1988). When PYY levels were examined before, during, and immediately after binge-purge episodes, individuals with BN showed slightly higher postprandial peak values of PYY compared to healthy controls (Kaye et al, 1990), but after vomiting, cerebrospinal fluid PYY levels were comparable to control levels (Berrettini et al, 1988; Kaye et al, 1990). The maximum number of participants with eating disorders included in these prior studies was 22 per group; additional research in larger samples is needed to comprehensively examine associations of basal PYY and PYY dynamics with symptom clusters and severity.

Regarding implications for treatment, results from studies testing the effect of PYY infusion suggest that exogenous administration may reduce short-term food intake (over the course of 12 hours) in healthy humans. In addition, intranasal PYY has been investigated for reducing food intake in obesity (Gantz et al, 2007). Intranasal PYY administered during high-risk periods for binge eating could have potential therapeutic value for BN.

3. Insulin

Plasma insulin levels vary with adiposity and serve as a signal of long-term energy stores (Bagdade *et al*, 1967). However, this anorexigenic pancreatic hormone is also secreted immediately after glucose consumption and is central to glucose metabolism. Animal data show that central administration of insulin suppresses food intake (Air *et al*, 2002a) and deletion of insulin receptors potentiates hyperphagia and obesity (Bruning *et al*, 2000). Insulin crosses the blood-brain barrier (Woods *et al*, 2003), and insulin receptors are highest in concentration in the arcuate nucleus of the hypothalamus, hippocampus, and cortex (Hopkins and Williams, 1997). Its key mechanism of action for appetite regulation may involve the inhibition of norepinephrine reuptake (Boyd Jr *et al*, 1985). Like leptin, high-fat diet impairs the action of insulin (Figlewicz and Benoit, 2009b), even after brief exposure to this diet (Figlewicz *et al*, 2009b). In addition, treatment with insulin mimetics attenuates weight gain and adiposity after high-fat diet maintenance in mice (Air *et al*, 2002b).

3.1 Interactions with the Dopaminergic Reward System

3.1.1 Animal Studies.—In addition to its role in homeostatic feeding, insulin plays a complex role in food reward signaling via the mesolimbic DA system, with seemingly differential effects in dorsal and ventral striatum, and NAc shell and core (Caravaggio *et al*, 2015). DA neurons in the VTA are rich in insulin receptors (Figlewicz, 2003), and insulin reduces excitatory inputs into VTA DA neurons (Labouebe *et al*, 2013), increases DA reuptake transporter synthesis in the VTA (Mebel *et al*, 2012), and changes the rate of DA neuron firing (Figlewicz, 2003). However, insulin increases DA release in the NAc, caudate, and putamen to signal reward (Stouffer *et al*, 2015). In animals, data show that insulin may also impact dorsal striatal DA release, which has been associated in humans with food pleasantness ratings (Morris *et al*, 2011; Small *et al*, 2003).

Across several behavioral paradigms, insulin has been demonstrated to modify both acute and learned reward valuation (Figlewicz *et al*, 2009b). Preclinical models show that insulin's reduction of excitatory inputs into VTA DA neurons reduces the motivational salience of

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contextual cues associated with palatable, sweetened and high-fat food, but has no effect on the effort expended to obtain the food (Labouebe *et al*, 2013). Insulin's effects on VTA DA may therefore affect reward-based learning without directly impacting the reward value of palatable food stimuli. In contrast, insulin has been shown to increase DA release in the NAc shell via cholinergic interneurons, and is required for conditioned preference for a flavor that signals glucose, suggesting that insulin in the NAc shell may play a role in food preferences (Stouffer *et al*, 2015). Chronic food restriction in animals promotes hypoinsulinemia and increases the sensitivity of this striatal DA release to insulin, whereas an obesogenic diet promotes hyperinsulinemia and decreases this sensitivity (Stouffer *et al*, 2015). Together, these data support that at some sites, insulin serves as a satiety signal, but at others, it serves as a signal of the rewarding value of the food that was eaten to promote future, similar eating (Stouffer *et al*, 2015). Insulin's action in the NAc, involved in learning about food's rewarding and nutritional properties (Woods *et al*, 2016), could complement insulin's satiety signaling in the hypothalamus and VTA (Schulingkamp *et al*, 2000).

3.1.2 Human Neuroimaging and Biological Studies.—

Data from healthy adults indicate that insulin levels are positively correlated with ventral striatal endogenous DA at D2/3 receptors and that acute DA depletion decreases insulin sensitivity and increases insulin levels (Caravaggio *et al*, 2015). Moreover, human neuroimaging findings indicate that non-insulin-resistant individuals show NAc activation during food valuation, but that non-diabetic, insulin-resistant individuals do not (Tiedemann *et al*, 2017). Moreover, among individuals with no insulin resistance, intranasal insulin reduces self-reported food valuation ratings and neural activation in the NAc and VTA during food valuation, but increases these signals in individuals with insulin resistance (Tiedemann *et al*, 2017). Results of dynamic causal modeling indicate that insulin negatively modulates projections from the VTA to the NAc, but not from the NAc to the VTA, and this negative modulation from the VTA to NAc predicts reduced self-reported valuation ratings of food cues (Tiedemann *et al*, 2017). These findings directly extend animal data (Labouebe *et al*, 2013; Mebel *et al*, 2012) by suggesting that in non-insulin-resistant individuals, insulin suppresses the NAc salience response to food cues via negative modulation from the VTA. In addition, these findings are consistent with prior reports of an inverse association in healthy-weight men between post-meal increases in plasma insulin concentrations and blood oxygen-level dependent (BOLD) signal in salience and reward circuitry (insula and OFC) (Tataranni *et al*, 1999). Intranasal insulin reduces both OFC and hypothalamic activation (as measured by fractional amplitude of low-frequency fluctuations) in healthy-weight adult females (Kullmann *et al*, 2013).

3.2 Case-Control Comparisons: Altered Levels among Individuals with AN and BN Relative to Healthy Controls

Findings regarding insulin levels across eating disorder diagnoses have been mixed. A recent meta-analysis of 13 studies supports increased insulin sensitivity in AN (Iyas *et al*, 2017), although increased, attenuated, and normal postprandial insulin secretion levels have been documented during the underweight, acutely ill state (Misra and Klibanski, 2010; Prince *et al*, 2009). Data seem to consistently suggest that these levels normalize in recovery (Misra *et al*, 2010; Prince *et al*, 2009), but a recently documented positive association between genetic factors for insulin sensitivity (insulin resistance and fasting insulin) and AN (Duncan *et al*,

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2017) may point to a more trait-like, overlapping neurobiological vulnerability in appetitive and reward alterations.

Data are similarly mixed in BN. One study reported normal insulin levels and insulin sensitivity in BN (Raphael *et al*, 1995) and another reported normative insulin response to an intravenous glucose challenge test (Blouin *et al*, 1993), whereas others report an elevated insulin response to a test meal (Schweiger *et al*, 1987), and still others report attenuated fasting insulin concentrations and peak insulin values relative to controls after a non-binge eating episode (Kojima *et al*, 2005a; Naessen *et al*, 2011). Notably, the altered pattern of insulin response in BN may vary widely depending on behavioral symptoms of the disorder. Data collected throughout the process of binge eating and purging suggest that peripheral insulin levels tend to increase during binge episodes but precipitously decline following vomiting (Kaye *et al*, 1988). However, relative to healthy controls who ingest a large meal, individuals with BN show exaggerated insulin release for 3 hours after binge eating and vomiting (Kaye *et al*, 1989). In addition, insulin response to an oral glucose tolerance test was highest in individuals with the least frequent binge eating and vomiting and blunted in individuals with the most frequent binge eating and vomiting and the greatest weight instability (Russell *et al*, 1996). The authors speculate that this may be related to the greater degree of nutritional depletion in this group of patients.

3.3 Associations with Eating Disorder Symptoms and Related Implications for Treatment

Overall, data suggest that insulin levels and/or insulin sensitivity may alter the reward signal from food via modulation of DA pathways. Chronically high insulin levels or increased insulin resistance could affect this modulation (Tiedemann *et al*, 2017). Increased insulin sensitivity among individuals with AN who engage in chronic food restriction could attenuate motivation to eat, or, as has been proposed for altered ghrelin levels in AN (Monteleone *et al*, 2018), promote reward-based learning about restrictive behaviors. Hypoinsulinemia or increased insulin sensitivity could also, via action in the NAc, ultimately promote overeating, explaining the common onset of binge eating and purging symptoms in individuals originally presenting with restricting-type AN (Eddy *et al*, 2008). It has been proposed that since insulin may promote DA neuron growth, chronic starvation and chronically low levels of circulating insulin could more directly impact DA neuronal function and result in anhedonic mood and amotivation, which are commonly observed in AN, even after weight restoration (Boehm *et al*, 2018). However, insulin insensitivity and/or altered postprandial insulin release in individuals with BN, mimicking that seen in obese rats, may reduce reward after food ingestion and promote further consumption of high-glucose foods (Stouffer *et al*, 2015). Intranasal insulin has been shown to reduce appetite and intake in rodents and healthy individuals (Jauch-Chara *et al*, 2012), and could help to normalize reward responsivity to food stimuli in the context of insulin insensitivity in eating disorder populations.

4. HPA Axis Neuroendocrines

The hypothalamic-pituitary-adrenal (HPA) axis constitutes a major neuroendocrine system that regulates stress and influences appetite and eating. The cascading hormonal release by

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the HPA axis in response to a physical or psychological stressor begins with corticotrophin releasing hormone (CRH), released from the paraventricular nucleus of the hypothalamus, which stimulates the release of adrenocorticotropic hormone (ACTH) from the anterior pituitary gland, which in turn induces release of glucocorticoids (GC) from the adrenal cortex. In humans, the primary GC is cortisol (Adam and Epel, 2007; Herman *et al*, 2003; Ulrich-Lai and Herman, 2009). GCs bind to two receptor types in the brain: the glucocorticoid receptor (GR) and the mineralocorticoid receptor (MR; ter Heedge *et al*, 2015). Ultimately this HPA-mediated hormonal cascade serves to mobilize energy reserves to facilitate either reactive or anticipatory adaption to a stressor (Herman *et al*, 2016). Following termination of a stressor, GCs inhibit HPA axis function through negative feedback, with additional inhibitory influences on associated cortical regions including limbic areas and the prefrontal cortex to return to homeostasis (Herman *et al*, 2003; Herman *et al*, 2016; Oitzl *et al*, 2010). Of particular relevance to eating disorders, GCs impact appetite, food intake, and weight in humans (Epel *et al*, 2001; Tataranni *et al*, 1996; Wolkowitz *et al*, 2001), and play a key role in reward-based eating in response to stress (Adam *et al*, 2007).

4.1 Interactions with the Dopaminergic Reward System

The limbic and paralimbic neural circuits regulating stress and food reward have considerable overlap. This circuitry includes the hypothalamus, amygdala, hippocampus, ventral striatum, and insula (Cleck and Blendy, 2008; Monteleone *et al*, 2018). In these regions, densely concentrated receptors (CRF1, CRF2, GR, and MR) for stress hormones modulate both the stress response and appetite (Chalmers *et al*, 1995; Chalmers *et al*, 1996; Lawson *et al*, 2013; McEwen, 1988; McEwen *et al*, 1986; McEwen *et al*, 1969; Struber *et al*, 2014). The primary hormones involved in the HPA axis-mediated stress response (CRH, ACTH, cortisol) have complex and in some cases opposite effects on reward-driven appetite and eating. Typically, during acute stress, CRH is anorexigenic and induces a similarly anorexigenic effect of cortisol. However, during prolonged stress, chronically elevated cortisol promotes inhibition of CRH and ultimately results in increased appetite and food intake (an overall orexigenic effect; Adam *et al*, 2007; Cavagnini *et al*, 2000; Crespo *et al*, 2014; Greeno and Wing, 1994). This shift from acute to chronic effects of stress on appetite is thought to be an important mechanism underlying the association between stress and weight gain (Gluck, 2006; Torres and Nowson, 2007).

4.1.1 Animal Studies.—Emerging evidence from the addiction literature suggests GCs directly interact with the mesolimbic DA system. In rats, GC release appears to directly activate GRs in DA-sensitive neurons in mesolimbic regions, triggering functional changes in this system and sensitizing response to appetitive stimuli (e.g., psychostimulant drugs; Cho and Little, 1999; Hensleigh and Pritchard, 2013). This stress-induced sensitization is thought to result from increased synaptic excitability in VTA DA neurons after activation of GRs (Daftary *et al*, 2009; Graf *et al*, 2013; Saal *et al*, 2003), with recent work suggesting that corticosterone may also decrease DA uptake in the NAc (Wheeler *et al*, 2017).

An expansive animal literature has investigated HPA axis function with regard to feeding behavior, particularly in relation to stress (Adam *et al*, 2007; Gluck, 2006; Guarda *et al*,

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2015; Jahng, 2011; Torres *et al*, 2007; Yau and Potenza, 2013). Evidence indicates that acute increases in GC (e.g., prompted by stressors) may enhance motivation for food intake, particularly when the stressor is mild to moderate in nature and the food is palatable (Bell *et al*, 2000; Bhatnagar *et al*, 2000; Dallman *et al*, 2004; Torres *et al*, 2007). GC administration and corticosterone (the primary GC in rodents) replacement induce hyperphagia, increased fat intake, and weight gain (Bray, 1985; Castonguay, 1991; Dallman *et al*, 1995; Dallman *et al*, 2003; Zakrzewska *et al*, 1999). In contrast, centrally administered CRH decreases feeding behavior and reduces food approach behaviors (Dunn and Berridge, 1990; Glowa and Gold, 1991). Studies of adrenalectomized rats have demonstrated reduced food intake that is reversible via GC administration (Bell *et al*, 2000; Bhatnagar *et al*, 2000; Freedman *et al*, 1986). Notably, food deprivation in rodents is associated with marked increases ACTH and corticosterone, as well as reduced efficacy of the negative feedback of corticosterone on HPA axis activity (Dallman *et al*, 1999; Jahng *et al*, 2005; Kim *et al*, 2005; Makimura *et al*, 2003; Timofeeva *et al*, 2002).

HPA axis function has also been investigated in studies using animal models of eating disorders, such as the activity-based anorexia (ABA) model, dietary restriction models, and models of binge eating behavior (Corwin *et al*, 2011; Klenotich and Dulawa, 2012; Siegfried *et al*, 2003). For example, HPA axis activity and plasma levels of corticosterone have been found to be increased in ABA rodents undergoing weight loss (Broocks *et al*, 1991; de Rijke *et al*, 2005), and evidence suggests that ABA exposure during adolescence has lasting impacts on HPA axis function and anxiety-like behavior even following return to normal body weight (Kinzig and Hargrave, 2010). Altered HPA axis function, such as elevated corticosterone levels, has also been implicated in animal models of binge eating and during withdraw from a highly palatable diet (Artiga *et al*, 2007; Corwin *et al*, 2011; Teegarden and Bale, 2007). Stress hormones may thus promote continuation of binge-like behavior, particularly when highly palatable food is available. Notably, substantial evidence from animal models suggests sex differences in HPA axis functioning, including greater GC secretion in females versus males in response to various behavioral and physiological stressors, as well as well as more rapid increases and prolonged duration of elevated levels (Goel *et al*, 2014). Such differences could in theory confer greater risk of problematic eating patterns in response to stress among females, perhaps contributing to the known sex differences in disordered eating among humans.

4.1.2 Human Neuroimaging and Biological Studies.—

In human studies, higher levels of stress and cortisol have been found to promote selection and intake of more palatable and calorically dense foods with greater fat and sugar content (Born *et al*, 2010b; Epel *et al*, 2001; Newman *et al*, 2007). Additionally, cortisol levels have been found to differentiate appetite-based subgroups (decreased versus increased) in major depressive disorder, with cortisol values also demonstrating a negative correlation with ventral striatal response to food cue exposure (Simmons *et al*, 2018). Together, these studies suggest stress hormones influence food preference and consumption via influences on reward circuitry.

Studies using stress induction tasks during fMRI reveal that the experience of acute stress dampens brain response to food cues in limbic reward circuitry in healthy weight individuals (Born *et al*, 2010a). In contrast, in overweight or obese individuals, acute stress elicits

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greater amygdala response to taste of highly palatable food (milkshake), with a significant association between amygdala response and basal cortisol (Rudenga *et al*, 2013), which may drive appetitive "stress" eating. In BN, activation to food cues in the precuneus, ACC, amygdala, and ventral medial prefrontal cortex is reduced following acute stress (Fischer *et al*, 2017), and this decreased response is associated with increased perceived stress prior to binge eating, linking brain response to clinical symptoms (Collins *et al*, 2017; Fischer *et al*, 2017). Given the precuneus' role in self-referential thought, these findings have been interpreted to support escape theories of binge eating in BN (i.e., the notion that binge eating is triggered by acute stress and is negatively reinforcing as it serves to distract from or reduce self-awareness and negative self-referential thought; Collins *et al*, 2017; Heatherton and Baumeister, 1991).

fMRI studies in AN suggest that HPA axis disturbances may suppress appetitive drive through directly affecting appetite-regulating brain regions (Lawson *et al*, 2013). Independent of BMI, individuals with AN compared to healthy controls show decreased activation in response to food cues in hypothalamus, amygdala, hippocampus, OFC, and insula, and this decreased activation is associated with elevated cortisol levels (Lawson *et al*, 2013). Furthermore, in a recent study of prediction error brain reward response in AN (Frank *et al*, 2018), cortisol levels were positively associated with prediction error response for sweet taste in the right superior frontal gyrus and caudate head among participants with AN. Accordingly, Frank *et al* hypothesize a model of AN maintenance in which elevated stress hormones, promoted by cognitive symptoms of AN, function to both suppress food intake and enhance reward prediction error signaling.

4.2 Case-Control Comparisons: Altered Levels among Individuals with AN and BN Relative to Healthy Controls

Dysregulated HPA axis function, in response to both acute and chronic stress, has been implicated in eating disorder pathophysiology (Lo Sauro *et al*, 2008; Mazurak *et al*, 2011; Monteleone *et al*, 2018; Peschel *et al*, 2016). Basal serum and salivary cortisol levels in individuals with AN and BN indicate HPA axis hyperactivity (Culbert *et al*, 2016). Cortisol awakening response (CAR), or the rapid increase in cortisol approximately 30 minutes after awakening thought to reflect the reactivity capacity of the HPA axis, is also altered in AN. Women with current AN, particularly those with AN-BP, show elevated CAR compared to controls, suggesting a potentially cumulative relationship between chronic starvation and binge-purge behaviors to HPA axis dysfunction in AN (Culbert *et al*, 2016; Monteleone *et al*, 2016a; Monteleone *et al*, 2016b). However, this enhanced salivary cortisol response is not present following weight restoration (Monteleone *et al*, 2016b), and starvation and weight loss have known effects on HPA hyperactivity (Fichter *et al*, 1986). Thus, elevated CAR in AN may be a consequence of the physical stress associated with starvation, or a compensatory response to starvation, rather than psychological symptoms of AN or a biological risk factor for AN development (Monteleone *et al*, 2016b). Consistent with this hypothesis, CAR levels are not altered in normal-weight individuals with BN (Monteleone *et al*, 2014).

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Data on response to acute, laboratory-based physical and/or psychosocial stress exposure in eating disorders are more variable (Culbert *et al*, 2016; Het *et al*, 2014; Vannucci *et al*, 2015). Overall, however, in contrast to evidence of elevated basal cortisol levels in AN and BN, these individuals show a blunted cortisol response to acute stress (Culbert *et al*, 2016; Ginty *et al*, 2012; Het *et al*, 2014; Vannucci *et al*, 2015). This blunted stress reactivity could reflect HPA axis hormone downregulation due to chronic and pervasive stress exposure.

4.3 Associations with Eating Disorder Symptoms and Related Implications for Treatment

Disturbance of HPA axis functioning associated with both acute and chronic stressors in eating disorders is particularly concerning given that dysfunctional and/or protracted activation of the HPA axis is energetically costly and has been proposed as a potent maintaining factor for psychiatric illness (Herman *et al*, 2016). Average nocturnal cortisol levels were positively associated with multiple cognitive measures of eating disorder psychopathology in a sample of women ranging from underweight to obese, controlling for BMI (Lawson *et al*, 2011). Emerging evidence suggests that altered HPA axis function in AN may contribute to the maintenance of behavioral symptoms, such as food restriction, by reducing appetite and the motivation to eat, possibly by altering food reward and motivation circuity (Lawson *et al*, 2013). Indeed, elevated serum cortisol levels are associated with lower fasting homeostatic and hedonic measures of subjective appetite in AN (Lawson *et al*, 2013). Less is known about the role of HPA axis function in BN, although recent imaging findings provide preliminary support for the notion that stress may perpetuate binge episodes by reducing brain reward response to food or food anticipation and reducing brain activation in attention or self-referential networks, thus facilitating distraction from self-awareness consistent with escape theories of binge eating in BN (Collins *et al*, 2017; Fischer *et al*, 2017).

Notably, a potential confound in this research is the role of trauma exposure. HPA axis dysfunction is also strongly implicated in those who have experienced early-life traumas (e.g., abuse or neglect in childhood; Heim and Nemeroff, 2001), and these experiences are associated with greater eating disorder psychopathology (Smolak and Murnen, 2002). It is possible that altered HPA axis activity resulting from childhood trauma exposure could relate to the development of eating disorder psychopathology; however, prospective research will be needed to address this hypothesis.

5. Gonadal Hormones

Estrogen, progesterone, and androgens (testosterone) are steroid hormones that have distinct effects on the central nervous system depending on the developmental timing of their activity. Pre- and perinatal levels have been shown to have “organizational effects” on brain development and anatomical structure and function that are considered permanent, whereas acute levels can temporarily affect behavior and cognition via “activational effects” (Arnold and Breedlove, 1985). In male and female brains, estradiol is produced from testosterone. Given well-documented sex differences in both reward sensitivity (Becker and Chartoff, 2018) and risk for eating disorder development (American Psychiatric Association, 2013), as well as a link between early pubertal onset, when gonadal hormone levels surge, and risk for

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eating pathology across sexes (Ullsperger and Nikolas, 2017), a growing body of research has focused on the notion that these hormones may influence reward circuit alterations that contribute to eating disorders.

5.1 Interactions with the Dopaminergic Reward System

5.1.1 Animal Studies.—Research supports both organizational and activational effects of gonadal hormones on reward circuity implicated in eating behavior. Of the ovarian hormones, estradiol is typically theorized to primarily affect DA release in the dorsal and ventral striatum, but data suggest that progesterone also plays an important role, and that these hormones may have interactive or synergistic effects (Yoest *et al*, 2018). Within minutes, estradiol can enhance striatal DA release, activity of the D1 receptor, and decrease the affinity and number of inhibitory D2 receptors (Yoest *et al*, 2018). In humans, prenatal testosterone exposure is associated with increased reward sensitivity (Lombardo *et al*, 2012) and, in females, increased impulsivity (Lucas and Koff, 2010). In rats, progesterone further potentiates dorsal striatal and NAc DA release and increases striatal DA D2 receptor binding in estradiol-primed females. However, progesterone administration alone decreases D2 receptor binding. Relatively fewer studies have focused on estradiol effects on ventral striatum DA, but estrogen receptors are expressed in the VTA, and specifically on VTA cell bodies that project to the NAc. The exact mechanism of action is unclear, but similar to the dorsal striatum, estradiol seems to increase DA release in the NAc. Notably, animal data suggest that estradiol and progesterone have an inverted U shape effect on DA activity, such that higher doses inhibit DA activity (Yoest *et al*, 2018).

Animal data suggest that testosterone modulates reward sensitivity via interactions with the mesolimbic DA system (Wood, 2008), and male rats, which are exposed perinatally to increased levels of testosterone, begin to show a greater density of DA D1 receptors in the NAc relative to females during puberty (Andersen *et al*, 1997). In addition, testosterone may alter nigrostriatal responsivity to DA by binding to androgen receptors that alter gene expression of DA transporter and D2 and D3 receptors in the substantia nigra and striatum (Purves-Tyson *et al*, 2014). Pubertal changes in all gonadal hormones can have neurodevelopmental effects on the mesolimbic dopamine system (Yoest *et al*, 2018).

Preclinical models have specifically suggested a role for gonadal hormone alterations in food reward and eating behavior. Estrogens have repeatedly been shown to inhibit standard chow consumption in rodents (Drewett, 1973). On days of high estrogen signaling with natural cycle variation in female rats, operant responding for sucrose is lowest, and injection of beta-estradiol, both directly in the VTA and peripherally, reduces operant responding for sucrose with no effect on standard chow intake (Richard *et al*, 2017). However, female rats are more likely to show conditioned place preference for palatable food than male rats, via increased activation of mesolimbic reward circuity (Sinclair *et al*, 2017). In addition, female rats after puberty show increased preference for sweet tastes relative to male rats, and this effect is mediated by both early testosterone exposure and circulating estrogen (Wade, 1976; Wade and Zucker, 1969). These seemingly contradictory findings may be related to the inverted U relationship between estrogen and DA activity, such that when levels are at their highest, food reward behaviors are inhibited. Although data from mouse models of binge-

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like eating suggest that estrogen's action at their receptors stimulate serotonin neurons in the dorsal raphe nucleus, which suppresses binge-like eating of pure fat (Cao *et al*, 2014), additional research is needed to clarify how estrogen effects on DA may attenuate palatable food consumption.

Some data suggest that progesterone in combination with estrogen stimulates food intake, but has little to no effect on intake in the absence of estrogen (Asarian and Geary, 2006). Ovariectomy increases binge-like eating in female rats (Klump *et al*, 2011) and estradiol and progesterone replacement attenuates binge-like eating (Yu *et al*, 2008). In contrast, Yu et al (Yu *et al*, 2011) found that estrogen alone and estrogen plus progesterone *decrease* standard chow intake and binge-like fat consumption, except when the limited access schedule that potentiates these binge-like episodes is novel (Yu *et al*, 2011). This suggests that estrogen and progesterone may have no effect on the size of binge-like eating episodes in "experienced" rats.

Prepubertally, female rodents with neonatal exposure to either testosterone or to additional estradiol made more impulsive choices on a delay-based impulsive choice food task (Bayless *et al*, 2013). Similarly, higher prenatal testosterone in female rats is associated with increased size of eating episodes (Madrid *et al*, 1993; Wade, 1972), but the timing of effects on eating, and whether those effects apply to standard or palatable foods or are apparent in ad libitum- versus limited-access paradigms may be particularly important. For example, neonatal testosterone injections in female rats increases standard chow intake but decreases sucrose consumption only after pubertal onset (Asarian *et al*, 2006). In animal models of binge-like eating using limited access to palatable food paradigms, perinatal testosterone exposure reduces the risk for binge-like eating in female rats to the level of male risk after mid-puberty (Culbert *et al*, 2018). These results suggest that early testosterone exposure may be protective against the development of binge eating after puberty, perhaps via reduced reward value of binge-like consumption. Overall, data indicate that some combination of organizational effects from early hormone exposure and acute effects during puberty and after could contribute to the sexual dimorphism of multiple reward-based behaviors, and specifically eating and binge-like behaviors (Culbert *et al*, 2018; Parylak *et al*, 2008).

5.1.2 Human Neuroimaging and Biological Studies.—To date, only two human imaging studies have experimentally manipulated ovarian hormones to examine effects on reward circuitry in women. One found that administration of goserelin, which decreases estrogen and testosterone, reduces amygdala response to monetary rewards in young women (Macoveanu *et al*, 2016). The other, consistent with preclinical studies, found that 2 months of an estrogen-progesterone combination hormonal treatment in perimenopausal women increased activation in the ventral striatum and the ventromedial prefrontal cortex during monetary reward anticipation and receipt (Thomas *et al*, 2014). These results suggest that estrogen suppression may somewhat reduce reward responsivity, and prolonged exogenous replacement of estrogen and progesterone increases reward responsivity.

In other studies, menstrual cycle has served as a naturalistic proxy of hormonal variation. As in rodents, menstrual cycle phase in humans has a significant impact on neural response to reward, and this may be related to estradiol fluctuations (Dreher *et al*, 2007). Probabilistic

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learning from rewards has been shown to be enhanced during the late follicular phase, when estrogen is high and progesterone is low (Diekhof and Ratnayake, 2016). Data from fMRI studies are somewhat mixed. BOLD response in reward-related areas of the brain to monetary reward anticipation and receipt as well as high-calorie food pictures is greater when levels of estrogen elevated and progesterone is low (the follicular phase) relative to when both estrogen and progesterone levels are high in the luteal phase (Dreher *et al*, 2007; Frank *et al*, 2010). However, overeating and emotional eating increase when both estrogen and progesterone levels are high compared with phases when estrogen is elevated and progesterone is low (Buffenstein *et al*, 1995; Edler *et al*, 2007; Klump *et al*, 2013). Together, these results suggest that decreased reward from food during the luteal phase potentiates continued eating. This could explain why another study found the greatest ventral striatal response to monetary reward anticipation when estrogen and progesterone are both decreasing after reaching a high during the premenstrual phase, perhaps potentiating a downregulation of DA activity that sensitizes the DA system (Ossewaarde *et al*, 2011).

Consistent with animal literature, fMRI data indicate that women acutely administered testosterone show elevated ventral striatal BOLD response to monetary reward anticipation, and this effect is most pronounced among individuals with low self-reported appetitive responses (Hermans *et al*, 2010). Similarly, elevated prenatal testosterone measured via amniotic fluid was found to be prospectively associated with increased behavioral approach tendencies, and this effect was mediated by increased caudate, putamen, and NAc activation in response to positively valenced cues (Lombardo *et al*, 2012). Prenatal testosterone may have organizational effects that impact reward sensitivity and behavior, biasing toward approach-related problems in children, and in adolescence and adulthood, acute rises in testosterone levels may have similar effects. Given that perinatal testosterone exposure was only protective against binge-like eating after puberty in animal models (Culbert *et al*, 2018), a combination of perinatal organizational effects and pubertal activational effects of testosterone may be required to attenuate binge eating risk.

5.2 Case-Control Comparisons: Altered Levels among Individuals with AN and BN Relative to Healthy Controls

Relative to controls, individuals with AN and BN exhibit reduced estrogen concentrations, but only those with AN exhibit reduced testosterone levels (Monteleone *et al*, 2001). Women with BN have been shown to have increased circulating testosterone levels relative to controls (Sundblad *et al*, 1994), and female children of women with a lifetime history of BN show markers of higher prenatal testosterone exposure (Kothari *et al*, 2014). These hormonal differences relative to controls may be sequelae of dramatic weight and fat tissue loss, but nonetheless have consequences for reward processes that maintain AN and BN pathology. Very little research has focused on altered gonadal hormones in males with eating disorders, but existing data from adolescent males with AN are consistent with findings in females and point to reduced testosterone and estradiol levels (Misra *et al*, 2008).

5.3 Associations with Eating Disorder Symptoms and Related Implications for Treatment

The inverted U relationship between estrogen and progesterone with DA activity observed in rodents may also hold true in humans (Diekhof, 2015) and could explain associations over

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time between ovarian hormones and risk for binge eating and emotional eating. Among women with threshold BN—both the lute al phase, when estrogen and progesterone are the highest, and the premenstrual phase, when both estrogen and progesterone are at their lowest, are associated with increased binge eating in BN (Lester *et al*, 2003). This finding is consistent with data from a large community sample indicating an interactive effect between estradiol and progesterone such that when estrogen and progesterone are high, emotional eating risk is highest (Klump *et al*, 2013). Data from women with BN are also consistent with those from women with clinically significant binge eating suggesting the risk for binge eating is greatest when both progesterone and estrogen are low (Klump *et al*, 2014). Perhaps these hormone-specific increases in risk for binge eating are mediated by enhanced reward-based learning about behaviors when DA release is particularly high or particularly low, making these behaviors more likely in the future. As this hypothesis is inconsistent with pilot research in threshold BN suggesting that increased binge eating episode frequency is associated with decreasing estradiol and increasing progesterone (Edler *et al*, 2007), further research is needed to more conclusively establish the potential causal link between changes in ovarian hormones and risk for binge eating. Elevated testosterone levels in adolescent and adult females with BN also may promote binge eating and purging. Chronically high testosterone, like repeated over-consumption of food, could potentiate D2 receptor downregulation and DA desensitization (Décarie-Spain *et al*, 2016), possibly explaining neuroimaging findings of an attenuated food reward response in women with BN (Frank *et al*, 2011). Moreover, initial data suggest that testosterone antagonism improves bulimic behavior (Bergman and Eriksson, 1996).

In AN, although reduced ovarian hormone levels would presumably promote motivated behavior to obtain food rewards, it has been hypothesized that these low levels instead increase anxiety and promote avoidance-related learning that perpetuates restriction in AN (Guarda *et al*, 2015). Estrogen replacement therapy in AN seems to attenuate anxiety but have no impact on BMI or consummatory behaviors (Misra *et al*, 2013), but research in larger samples is needed. Similarly, testosterone replacement therapy for women with AN has beneficial effects on bone formation, depressive symptoms, and spatial cognition (Miller *et al*, 2005). Healthy women acutely administered testosterone show elevated ventral striatal BOLD response to monetary reward anticipation, and this effect is most pronounced among individuals with low scores on a self-report measure of appetitive responses (Hermans *et al*, 2010). Given that individuals with AN score lower than controls on this measure (Harrison *et al*, 2010), testosterone administration could address reward dysfunction in AN and change eating behavior. A current phase II clinical trial is investigating the impact of transdermal testosterone on body weight in individuals with AN (National Institute of Mental Health Massachusetts General Hospital).

6. Orexins

Orexins (also termed hypocretins) are implicated in a broad array of regulatory functions within the central nervous system including feeding, autonomic control, sleep/wakefulness, memory, and reward (de lecea *et al*, 1998; Sakurai *et al*, 1998). Of the neuroendocrines reviewed thus far, orexins have been the least studied in eating disorders and using human neuroimaging. However, preclinical literature supports their potential relevance for reward

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alterations in AN and BN. Orexins stimulate feeding behavior (indeed, orexin stems from the word “appetite” in Greek) and exist in two primary forms: orexin-A (a 33-amino acid peptide) and orexin-B (a 28-amino acid peptide). Both peptides are localized in the lateral hypothalamus, a region strongly associated with feeding behavior, and perifornical and dorsomedial hypothalamic nuclei (de lecea *et al*, 1998; Sakurai *et al*, 1998). The orexins were initially identified as endogenous ligands for two orphan G-protein-coupled receptors, orexin 1 (OX1-R) and orexin 2 (OX2-R). OX1-R have an affinity for orexin-A, while OX2-R have equal affinity for both orexin-A and -B (Sakurai et al., 1998). Orexin-A and OX1-R have been implicated more strongly in the regulation of feeding behavior than orexin-B and OX2-R (Arch, 2000; Dube *et al*, 1999; Haynes *et al*, 2002; Haynes *et al*, 2000). Thus, the present review will focus more strongly on orexin-A. Orexin-A can cross the blood brain barrier (Kastin and Akerstrom, 1999) and plasma levels of orexin-A in humans reflect the peptide released from both the brain and the gut (Arihara *et al*, 2001; Kirchgessner, 2002). Importantly, while orexins increase food intake, they also simultaneously increase energy expenditure, typically resulting in a net effect of decreased body weight (Teske and Mavanji, 2012).

6.1 Interactions with the Dopaminergic Reward System

Orexins interact with reward circuitry in several ways. Anatomical rat research indicates that hypothalamic orexin neurons project to reward-related brain regions, including the NAc and the dopaminergic VTA (Fadel and Deutch, 2002), and orexin neurons receive projections from the VTA, NAc, and lateral septum (Yoshida *et al*, 2006). Additionally, orexin receptors are expressed on the surface of VTA DA neurons (Marcus *et al*, 2001; Narita *et al*, 2006), and orexin administration increases the firing rate of VTA neurons (Korotkova *et al*, 2003). Further supporting the role for orexins in reward seeking, orexins have been implicated in addictive behaviors, drug-related mesolimbic dopaminergic activity (Harris *et al*, 2005a; Narita *et al*, 2006), and preferences for cues associated with drug rewards (Harris *et al*, 2005b).

Orexin’s potential impact on human reward circuitry in healthy individuals or individuals with eating disorders has not been tested using neuroimaging. However, animal research has demonstrated a clear role for orexin in stimulating feeding behavior and reward-related activity. Orexin injections induce feeding behavior in rats and mice (Haynes *et al*, 2002; Haynes *et al*, 2000; Sakurai *et al*, 1998) and central administration of orexins in non-fasted rats stimulates food intake in a dose-dependent fashion (Sakurai *et al*, 1998). Supporting that orexin neurons are associated with consummatory reward, activation of lateral hypothalamus orexin neurons in rodents is strongly linked to preferences for cues associated with food rewards during a conditioned place preference test, and the amount of c-Fos expression, an indirect marker of activity, in these neurons is positively correlated with the intensity of food reward-seeking (Harris *et al*, 2005a). Anticipation of food specifically may activate orexin neurons to regulate reward-based feeding behavior. Consistent with this, rats trained to expect a palatable food show increased activation of orexin neurons when in a food-cued location (Choi *et al*, 2010). Orexin-A may play a role in food reward valuation, as injection of orexin-A significantly increases chow intake and break point response for sucrose pellets

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in a progressive ratio task compared to vehicle-treated controls (Choi *et al*, 2010) and antagonizing OX1-R decreases responding for high fat pellets.

Terrill and colleagues (2016) found that VTA administration of orexin-A increased palatable food intake (energy-dense high fat chow) both in rats that consumed a chow pre-load and in rats given acute daily access to palatable food without a chow preload. Within the same study, administration of orexin-A in the VTA also increased consumption of a sucrose solution, whereas OX1-R antagonism in the VTA decreased sucrose intake. Interestingly, both for the high fat food and sucrose solution, VTA-administered orexin increased consumption only towards the end of the meal. The authors suggest that orexin activity in the VTA may increase palatable food intake by counteracting post-ingestive feedback that would otherwise decrease intake in a homeostatic fashion towards the end of a meal. This might implicate orexin in the sense of "loss of control," or difficulty stopping eating once one has started, that defines binge episodes.

As noted above, although acute orexin administration stimulates food intake, chronic orexin overexpression increases energy expenditure and decreases consumption. Mice bred to overexpress orexin exhibit resistance to high-fat diet-induced obesity and insulin insensitivity (Funato *et al*, 2009). This resistance occurs by orexin overexpression also increasing energy expenditure, an effect that was mediated by OX2-R signaling (Funato *et al*, 2009). Additionally, orexin overexpression increased the anorectic effects of leptin, while orexin overexpression did not have any effect in obese leptin-deficient mice. This suggests that increased OX2-R signaling may reduce risk for diet-induced weight gain, in part by increasing the effect of leptin.

6.2 Case-Control Comparisons: Altered Levels among Individuals with AN and BN Relative to Healthy Controls

Limited research has examined plasma orexin-A levels in individuals with AN, and has yielded mixed findings. Bronsky and colleagues (2011) demonstrated that orexin-A levels were higher in adolescents with AN compared to healthy controls, while Sauchelli et al (2016) found no difference in plasma orexin-A levels in AN relative to controls. Plasma orexin-A levels do appear to decrease over the course of 3- to 6-months of treatment (Janas-Kozik *et al*, 2011) and 8-weeks of refeeding (Bronsky *et al*, 2011). Thus, limited evidence suggests that orexin-A levels may be altered in AN, and normalize as patients recover, however additional research on this topic is needed before drawing definitive conclusions. Further, given the role of orexin in stimulating food intake, additional information on orexin levels in patients with BN is needed.

6.3 Associations with Eating Disorder Symptoms and Related Implications for Treatment

Given the role that the hypothalamus plays in feeding behavior and preclinical research demonstrating that orexin stimulates feeding and particularly hedonic eating, orexins have implications in eating disorder psychopathology and possibly treatment. The simultaneous role that orexin plays in increasing energy expenditure, resulting in an overall net decrease in body weight, also has implications for the complex metabolic reactions and increased energy expenditure observed in AN. Regarding potential implications for treatment, results from an

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animal model of binge eating suggest that there may be a potential role for OX1-R antagonists in reducing binge eating episodes that are preceded by stress and dietary restriction (Piccoli *et al*, 2012). An OX1-R antagonists inhibited increases in binge eating-like consumption of highly palatable foods when exposed to chronic stress and food restriction, while food intake was unaffected in control animals that were neither food restricted nor subjected to stress. However, a more recent study found that although hypothalamic orexin neurons were activated in response to high fat food, blockage of the OX1-R signaling was not successful in blocking hyperphagia in rats given intermittent access to a high fat diet (Valdivia *et al*, 2015). While the initial consumption of a high fat diet requires OX1-R signaling, the neuronal mechanisms that occur in the escalation of eating are independent of the orexin signaling. Alternatively, orexin may play a more nuanced role in escalation of eating behavior under certain conditions (stress, food restriction).

Conclusions and Future Directions

Taken together, data from preclinical and human research suggest that neuroendocrine signals that regulate both homeostatic and hedonic eating may serve as useful novel targets for the treatment of AN and BN. Although many neuroendocrine alterations in eating disorders are illness state-dependent to some degree, evidence suggests they may maintain eating disorder symptoms. Future, longitudinal research in larger samples is necessary to determine whether neuroendocrine alterations may impact the development of dopaminergic reward systems in humans and precipitate the development of AN and BN symptoms. Such studies will be particularly helpful in disentangling the effects of altered gonadal hormones on the risk for and maintenance of eating disorders, and potential sex differences in these effects. In addition, as most research has focused on AN and BN, additional research on neuroendocrine interactions with reward among individuals with binge eating disorder are needed. As more data become available, future meta-analyses will be helpful in evaluating the relative impact of neuroendocrines on eating disorder symptoms.

Further, additional research is needed to clarify the potentially interacting roles of neuroendocrine signals on altered reward circuitry in eating disorder populations. For example, ghrelin has been shown to interact with orexins and leptin to alter food intake (Perello and Dickson, 2015; Perello *et al*, 2010) and orexin-A may mediate the effects of leptin and insulin (Figlewicz and Benoit, 2009a). In addition, estrogen alters sensitivity to the anorexigenic effects of leptin and insulin (Clegg *et al*, 2006) and is thought to be a protective factor against insulin insensitivity (Hong *et al*, 2009). Research with adrenalectomized rodents has supported a role for corticosterone's interactions with insulin function in overeating and obesity (Chavez *et al*, 1997; la Fleur *et al*, 2004). Given the complex interplay of these neuroendocrines, future neuroimaging studies of food reward in eating disorders should be carefully controlled. The preference for and nutritional composition of food stimuli presented, the method of presentation, how recently participants have eaten, and menstrual status, phase, and pubertal age of participants may all impact reward-related findings via neuroendocrine effects. As neuroendocrines affect distinct reward-related processes, future eating disorder imaging studies should measure valuation of food palatability, food reward consumption, other rewarding sensory aspects of eating

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including smell, and effort exerted to obtain food (e.g., Bragulat *et al*, 2010; Fernández-Aranda *et al*, 2016). Studying neuroendocrines in conjunction with fMRI (e.g., via pharmacological neuroimaging) could improve characterization of aspects of reward circuitry that play key roles in eating disorder pathophysiology. As current human imaging technologies cannot distinguish some small, reward-related regions with distinct neuroendocrine-mediated responses (e.g., the NAc shell and core), conducting pharmacological fMRI research in concert with parallel preclinical studies will be particularly valuable.

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Highlights

- Neuroendocrine disturbances may play a key role in anorexia and bulimia nervosa.
- Interactions with dopaminergic reward circuits may promote eating disorder symptoms.
- We review peptide YY, insulin, stress and gonadal hormones, and orexin alterations.