Neuronal Substrate of Eating Disorders

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Abstract

Eating disorders are devastating and life-threatening psychiatric diseases. Although clinical and experimental investigations have significantly progressed in discovering the neuronal causes of eating disorders, the exact neuronal and molecular mechanisms of the development and maintenance of these pathologies are not fully understood. The complexity of the neuronal substrate of eating disorders hampers progress in revealing the precise mechanisms. The present review describes the current knowledge on the implication of the neuronal systems that regulate food intake, stress, emotions, and reward in eating disorders. The current data based on clinical and experimental research strongly suggest that these systems are interconnected and a misbalance in one system leads to altered activity in other food-related regulatory networks.

Keywords: Anorexia Nervosa; Bulimia; Binge Eating; Stress; Food Intake; Reward; Hypothalamus; Limbic System; Striatum; Prefrontal Cortex

Abbreviations:

5-HTTLPR: 5HT-Transporter-Linked Polymorphic Region; ABA: Activity-Based Anorexia; ACTH: Adrenocorticotropic Hormone; Agrp: Agouti-Related Peptide; AN: Anorexia Nervosa; AN-BP: Anorexia Nervosa Binge-Purge Subtype; AN-R: Anorexia Nervosa Restrictive Subtype; ARC: Arcuate Nucleus; BED: Binge Eating Disorder; BDNF: Brain-Derived Neurotrophic Factor; BN: Bulimia Nervosa; CART: Cocaine- And Amphetamine-Regulated Transcript; CB1: Cannabinoid Receptor 1; Cea: Central Amygdala; CRF: Corticotropin-Releasing Factor; CRF1R: Type 1 CRF Receptor; CRF2R: Type 2 CRF Receptor; CSF: Cerebrospinal Fluid; DMH: Dorsomedial Hypothalamic Nucleus; DRD2: Dopamine Receptor D2; DRD4: Dopamine Receptor D4; DSM-5: Fifth Edition Of The Diagnostic And Statistical Manual Of Mental Disorders; FTO: Fat Mass And Obesity Associated Protein; GABA: Gamma Aminobutyric Acid; HPA: Hypothalamic-Pituitary Adrenal Axis; LH: Lateral Hypothalamus; LS: Lateral Septum; MC4R: Melanocortin 4 Receptor; 5-HT: 5-Hydroxytryptamine; MRI: Magnetic Resonance Imaging; Nacb: Nucleus Accumbens; NPY: Neuropeptide Y; PFC: Prefrontal Cortex; POMC: Proopiomelanocortin; PVN: Paraventricular Hypothalamic Nucleus; PVT: Paraventricular Thalamic Nucleus; VMH: Ventromedial Hypothalamic Nucleus; VTA: Ventral Tegmental Area

Introduction

Eating disorders are severe psychiatric illnesses with a high incidence of psychological and physical comorbidities [1]. The modern food supply of the population of the Western world is characterized by an abundance of high-energy foods [2], eating “comfort” food has become an easy way to relieve increased pressure of everyday stress [3-5]. On another hand, there is also strong cultural pressure for thinness, and various dieting strategies have become very popular [6]. Hence, chronic stress and dieting have been identified as strong antecedents and relapse factors in eating disorders [7-16].

Food intake is controlled by complex, redundant, and distributed neural systems to ensure adequate nutrient supply, homeostatic control, and energy balance. The brain neuronal networks that regulate energy homeostasis and reward are the principal determinants of food intake control, known as homeostatic and hedonic signals, respectively. The homeostatic system is based on biological needs to maintain the body’s energy and optimal conditions for biochemical reactions whereas hedonic control is involved in the motivation to eat and is based on pleasure and reward [17-19]. Abnormal changes in the food intake regulatory systems play an important role in triggering and maintaining eating disorders [20], however, the neural substrate underlying these diseases is not yet fully understood.

Clinical and experimental investigations have pointed out the importance of non-homeostatic control of food intake and the neuronal mechanisms that modulate the activity of the brain homeostatic centers in promoting eating in the absence of hunger or inhibiting eating despite hunger in eating disorders. However, the neural substrate underlying these diseases is not yet fully understood. Here we review the physiological, morphological, molecular and genetic abnormalities in the neuronal systems in eating disorders obtained in clinical and experimental research.

General Characteristics of Eating Disorders

Anorexia nervosa (AN), bulimia nervosa (BN), and binge eating disorder (BED) are three formal eating disorders outlined in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) [16]. AN is characterized by self-restriction in energy intake resulting in significant weight loss in concerned individuals. This self-starvation is associated with an important body image disturbance accompanied by an intense fear of gaining weight or of becoming obese. Individuals suffering from AN can be engaged in recurrent
episodes of binge eating and purging behavior (AN binge-purge subtype, AN-BP) or not (AN restrictive subtype, AN-R) [16]. BN is defined by recurrent binge eating episodes followed by either self-inducing vomiting, taking of laxatives, or by some other means to compensate the excess ingested food. As in AN, BN sufferers are characterized by a fear of gaining weight and a distorted body image [16]. BED has more recently been included in the DSM as an eating disorder and is characterized by recurrent episodes of binge eating without compensatory behaviors. Binge eating episodes are characterized by the ingestion of a large amount of food accompanied by a sense of a lack of control over eating [16].

Although AN and BN are relatively rare in the general population, they are more common among adolescent girls and young women. According to large population-based studies, AN and BN affect 0.3% to 0.9% and 0.8% to 1.5% of women (life time prevalence), respectively [21-24]. BN and AN affect women disproportionately more than men, with the female-to-male ratio ranging from 3:1 to 10:1 [21,23,25]. Conversely, BED is more common for both sexes and in older people, affecting between 1.1% and 2.8% of the population [21-24].

The etiopathogenesis of eating disorders is complex and poorly understood, and genetic predisposition and specific environmental factors have been implicated in triggering and maintaining eating disorders [20,26]. The common characteristics of AN, BN, and BED are elevated anxiety and deficit in emotion regulation, which are thought to contribute to the development and maintenance of the disorders [27-30]. Clinical research has provided strong evidence that individuals with eating disorders are inclined to use maladaptive strategies to regulate their emotions and distress [29,31]. Among these strategies, inappropriate ingestive behavior such as bingeing or extreme dietary restriction may be used to alleviate or prevent negative emotion, stress, or anxiety [32-34]. Because several physiological contingencies including eating and metabolism as well as emotions, anxiety, and stress are implicated in the etiopathogenesis of eating disorders, the brain systems related to regulating feeding and stress may be involved in triggering eating disorders.

Role of Stress in Eating Disorders

Life stress events often precede the onset of eating disorders whereas chronic stress is associated with the persistence of these disorders [26,35,36]. Activity of the stress system is usually altered in subjects suffering from eating disorders [37], and these changes may be closely related to the psychopathological, behavioral, and biological abnormalities found in AN, BN, and BED.

The HPA axis and its interaction with feeding regulatory brain system

Stress, a "general adaptation syndrome" [38], quickly mobilizes the neuronal, endocrine, and motor systems, which are essential for survival in threatening situations [39]. The stress reaction is regulated by a complex system involving the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system. The central component of the HPA axis includes the parvocellular neurons of the paraventricular hypothalamic nucleus (PVN) that produce corticotropin-releasing factor (CRF), which, via the anterior pituitary adrenocorticotropic hormone (ACTH) from the anterior pituitary and glucocorticoids (cortisol in humans and corticosterone in rodents) from the adrenal glands (Figure 1). In turn, glucocorticoids signal to the brain to downregulate further activation of the HPA axis [40-42]. The HPA axis is exquisitely sensitive to perturbations in the external environment and glucocorticoids responses can be initiated by activation of the PVN by nociceptive pathways, recruitment of innate defensive systems or sensory stimuli associated with fear [42-44]. Depending on the stressors, sometimes divided into "systemic" (related to homeostatic threats such as hemorrhages or immune response) and "psychogenic" (related to exteroceptive sensory systems signalling the presence of real or potential danger), specific regions of the brainstem or limbic system activate directly or indirectly the parvocellular PVN neurons that trigger rapid general activation of the HPA axis [42,43].

Activation of the HPA axis is mediated by the type 1 CRF receptor (CRF1R) [45]. In basal, non-stressful conditions, the levels of CRF1R are undetectable in the parvocellular PVN. However, during stress, the CRF1R is strongly expressed by the PVN neurons [46,47]. Induction of expression of CRF1R may be triggered in the PVN by CRF [48], and this CRF auto-regulating mechanism may rapidly intensify activation of the PVN neurons and general activation of the HPA axis during stress. Implication of the CRF1R in stress-induced activation of the HPA axis was demonstrated by inhibiting stress-induced rise in the ACTH and corticosterone plasma levels in rats treated with a specific CRF1R antagonist [49].

In addition to activating the HPA axis, CRF produces strong anorectic effects [50-53]. In contrast to the inhibition of CRF corticotrophic effects by specific CRF1R antagonists, the anorectic effects of CRF are blocked by a specific antagonist of type 2 CRF receptor (CRF2R) but not by a specific CRF1R antagonist [49,54]. If expression of CRF1R is largely distributed in the brain, the expression of the CRF2R is mainly confined to the ventromedial hypothalamic nucleus (VMH) and the lateral septum (LS) [55]. Experimental research involving animal models suggested that the CRF2R in the VMH is generally involved in the homeostatic control of food intake and energy metabolism (Figure 1) [56,57]. The levels of CRF2R expression in the VMH are decreased by negative energy balance such as food deprivation [58]. In the LS, activation of the CRF2R mediates stress-induced anxiety and anorexia (Figure 1) [59-61].

The LS is a subcortical brain structure predominantly composed of the inhibitory projection neurons that densely innervate the lateral hypothalamus (LH) and the ventral tegmental area (VTA), brain regions involved in controlling food intake [62-66]. Interestingly, a rat

Figure 1: Corticotropin-releasing factor (CRF) mediates the central effects of stress. In response to stress, CRF activates the hypothalamic-pituitary adrenal (HPA) axis via the CRF type 1 receptor (CRF1R) by increasing the synthesis and release of adrenocorticotropic hormone (ACTH) from the anterior pituitary and glucocorticoids (cortisol in humans and corticosterone in rats) from the adrenal glands. The CRF type 2 receptor (CRF2R) mediates the anorectic effects of CRF in the ventromedial hypothalamic nucleus (VMH) and the lateral septum (LS). In addition, activation of the CRF2R in the VMH activates the energy metabolism, and in the LS increases anxiety. Activity of the VMH is directly related to the homeostatic control of feeding whereas the LS is sensitive to interactive effects of stress and diets.
 binge eating model developed by repeated food restriction and stress, showed lower neuronal activation of the LS [67]. The long-term decrease in the activity of the LS inhibitory neurons in this model may result in disinhibition of the LH and VTA neurons. The LH is an important food intake-regulating hypothalamic region closely related to the brain reward system [68,69]. Activation of the LH neurons significantly increases motivation to eat as well as stimulates appetitive behavior and enhances reward functions [70-73]. Interestingly, LS lesions enhanced lateral hypothalamic reward sensitivity [74], while LS electrical stimulation counteracted the effects of LH stimulation on feeding [75]. Electrical stimulation of the LS also inhibited a population of the VTA neurons [76]. The VTA contains dopaminergic neurons whose activity codes for the hedonic value of food [77-79] while inactivation of the VTA reduces overconsumption of palatable food [80]. Interestingly, LS lesions significantly enhanced the incentive value of positively rewarding events such as water intake in thirsty rats, salt in sodium-deprived rats, and sucrose in all feeding conditions [66,81-83]. For example, an LS lesion significantly increased sucrose intake but not water intake in non-thirsty rats [81]. The increase in sucrose intake in the LS-lesioned rats was not dependent on hunger because food deprivation and stomach preloading did not affect higher sucrose-eating activity in the LS-lesioned rats [81]. Enhanced motivation for food was revealed in LS-lesioned rats by faster performance speed in food-motivated tasks [84,85]. Therefore, the LS is an important modulator of activity of the HPA axis and feeding. Activation of the LS during acute stress may induce anorexia and anxiety, while a decrease in LS activity in binge eating may disinhibit feeding and reward centers in the hypothalamus and midbrain and induce episodes of binge eating.

### Interaction between stress and feeding in eating disorders

Food intake is strongly modulated by stress. Anorectic stress effects are important to stop physiological activities that are not related to stress such as ingestion and digestion, and mobilize all resources for a stress-coping activity (fight or flight). CRF is a potent anorectic peptide involved in stress-induced food intake inhibition [86,87]. Conversely, glucocorticoids promote food intake that helps to restore energy resources depleted during stress response [88,89]. Therefore, anorectic-orexigenic regulation of food intake in response to acute stress is very important for survival and adequate maintenance of energy resources. However, misbalance of the HPA axis activity by chronic stress or by an isolate but very strong traumatic experience may produce devastating effects on eating.

Interestingly, evidence of the hyperactivity of the HPA axis was revealed by a significant increase in the basal cortisol levels in patients with AN [90-96] and BN [97-101] (Table 1). This dysregulation may persist in AN after weight gain [95,96] suggesting that the hyperactivity of the HPA axis may be involved in the pathogenesis of the disease. In BED, the results are contradictory showing higher [102] or normal [103] basal cortisol. Following stress exposure, the patients with BED showed a hyperactive [102] or hypoactive [103] response of the HPA axis. However, it is well-established that stress plays a major role in the initiation of binge eating episodes [33,34,36,104,105] and in the maintenance of BN [97,106]. Therefore, imbalance in the HPA axis may lead to the development of eating disorders and may be involved in the maintenance of the diseases [37].

### Table 1

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plasma levels of glucocorticoids as well as in induction of the brain serotonin levels [112,113]. Therefore, restrictive dietary behavior contributes to dysphoric consequences of eating [32]. Indeed, ingestion of palatable food decreased stress-induced rise in the secretion of glucocorticoids, which increase motivation for food and food suppresses HPA axis activity [129]. Negative affective states and stress are thought to be the primary causes of binge eating episodes [33,34,104,105,142,143]. Binge eating may thus be an attempt to reduce stress and anxiety with hedonic self-medication [128,144], and negative feelings are in effect transiently reduced during binge eating [34,142,145,146] or binge-purging episodes [146-149]. However, large meals ingested during binge-eating episodes promote increased secretion of glucocorticoids [97] that overrun the transient “relief” created by palatable food intake and contribute to the chronic state of stress in individuals suffering from BN and BED. In addition, binge eating or binge-purging episodes are usually followed by feelings of depreciation and guilt in the hours following binge eating [142,146,148,149].

Therefore, in AN, BN, or BED, stress participates in inducing pathological eating behaviors such as starvation or binge eating. These aberrant eating behavior strategies may be considered as the attempts to cope with stress and decrease the negative affective states by providing short-term relief. However, these aberrant eating strategies impact the long-term maintenance of chronic stress, misbalanced HPA axis activity and eating disorders.

### Homeostatic Regulation Of Food Intake In Eating Disorders

Although BN, AN, and BED are considered eating disorders, it remains unknown whether in these disorders there is a primary disturbance of appetitive function or whether disturbed appetite is secondary to other phenomena, such as anxiety, chronic stress, or nutritional changes that accompany eating disorders [150]. It has been suggested, however, that disturbances in the food intake regulating system may contribute to the maintenance or exacerbation of cycles of food restriction, binge-purge, or binge eating in AN, BN, and BED as well as affect the response to therapies in these conditions [150].

### Neuronal substrate of homeostatic regulation of food intake

Energy homeostasis regulation involves a coordinated effort between a number of interconnected brain regions including, but not limited to, the hypothalamus and the brainstem. These central regions are accessible to the sensory signals from the taste and digestive systems and to the circulating hormones signaling short-term nutrient availability and long-term energy storage. The brain integrates these nutritional feedback signals and uses them to modulate food intake.
Numerous signals and, in turn, generates relevant behavioral, autonomic, and endocrine output [18].

The hypothalamus plays a crucial role in homeostatic functions [151]. The ventromedial hypothalamus, which consists of the VMH and the arcuate nucleus (ARC), is a key region that integrates satiety (e.g., cholecystokinin, peptide YY, glucagon-like peptide-1, etc.), hunger (e.g., ghrelin) and adiposity (e.g., leptin) signals from the periphery and transmits signals to the forebrain and brainstem areas involved in satiation, neuroendocrine regulation, learning, memory, and reward [18,19]. The ARC contains two distinct neuronal populations that produce orexigenic and anorexigenic peptides [152,153]. The "anorexigenic" population is located in the lateral sub-division of the ARC and produces anorectic neuropeptides proopiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript (CART) [154,155]. The "orexigenic" population of neurons is located in the medial sub-region of the ARC and produces orexigenic neuropeptides agouti-related peptide (AgRP) and neuropeptide Y (NPY) [156,157]. The major recipients of the ARC are the PVN-producing anorectic neuropeptide CRF [50], and the LH-producing orexigenic neuropeptides orexin and melanin-concentrating hormone [18,158]. The hypothalamic neurons control the activity of the sympathetic and parasympathetic efferents innervating the digestive system via direct innervation of the pre-ganglionic brainstem and spinal cord neurons [159,160].

Dysregulation of appetite hormones and neuropeptides in eating disorders

Changes in the neuroactive peripheral and central peptides regulating appetite in eating disorders have been extensively studied and reviewed [150,161-163]. Some of the food-intake-regulating molecules (peptides, monoamines, etc.) also interfere with other brain functions such as the reward processes, motivated behaviors, cognition, or emotion whose changes have been reported to contribute to the psychopathological core of eating disorders [16]. Therefore, changes in the central and peripheral components of the feeding regulatory system may not only represent homeostatic adaptation to malnutrition but also contribute to the development and maintenance of aberrant non-homeostatic behaviors of eating disorders, such as starvation or binge eating [163] (Table 1).

In patients with AN, starvation and weight loss correlate with changes in feeding regulatory peptides mainly by an increase in orexigenic peptides and a decrease in anorexigenic peptides as a compensatory mechanism to counteract the negative energy balance [150,161-163]. Plasma leptin levels have been consistently reported to be markedly lower than normal, which was correlated with the patients’ body mass index [164-167]. Leptin is an adiposity signal involved in regulating energy balance through stimulating anorexigenic POMC neurons and inhibiting orexigenic NPY/AgRP neurons in the ARC [168]. In AN, general low levels of leptin are accompanied by a disrupted circadian rhythm of leptin [169]. Because leptin generally inhibits HPA axis activity [170], low leptin in AN may contribute to hyperactivity of the HPA axis. Another major abnormality in AN is significantly increased plasma levels of ghrelin at fasting and impaired response to meals [93,161,171-173]. Ghrelin is a stomach hunger hormone that stimulates appetite through activating the NPY neurons in the ARC [174]. The “activity-based anorexia” (ABA) model in rodents [175] reproduces core behavioral correlates of AN like self-restricted food intake in the presence of hunger, hyperactivity, weight loss, and physiological consequences of undernutrition [176]. In this model, it has been shown that mRNA expression of NPY was increased in ARC and that this increase was not correlated with food intake but instead with increased physical activity [177]. In AN, increased CSF NPY was also found [178] and might be involved in the hyperactivity reported in anorectic patients [16]. The ability to maintain restricted eating seems to occur in spite of the physiological hunger signals and hunger feelings [92,179]. The restriction of food intake is voluntary, and non-homeostatic regulation of energy intake seems to override hunger signals at the level of homeostatic control of food intake. Leptin and ghrelin not only act as signals regulating homeostatic feeding driven by metabolic need but also are seemingly involved in modulating the reward system and motivation to obtain food [180]. Leptin suppresses [181,182] and ghrelin activates [183,184] the reward system. In the case of AN, the effects of leptin and ghrelin do not restore the energy balance by increased motivation for food [180], but low leptin and high ghrelin in AN might participate in maintaining starvation as a rewarding behavior [163].

In BN, the role of leptin as a peripheral signal of available energy stores is preserved [163]. Contradictory results exist regarding increased [185] or not [186-188] fasting ghrelin levels in patients with BN. However, postprandial suppression of ghrelin has been reported to be reduced in BN [189-191]. The decrease in plasma ghrelin reflects suppression of hunger signals, and reduced ghrelin suppression after a meal may contribute to the impaired satiety sometimes observed in patients with BN and BED [192,193]. In BED, fasting ghrelin levels are lower than in healthy people [190,194] and plasma ghrelin decreases only slightly after a meal [194,195]. Lower levels of plasma ghrelin may contribute to the dysphoric states the frequently occur in BED.

The reduced levels of brain-derived neurotrophic factor (BDNF) have been found in plasma in AN and BN [196,197]. BDNF is an important neuropeptide regulating neuronal survival, development, and functional plasticity in the brain that is also involved in energy homeostasis. In fact, BDNF and its receptor are highly expressed in the brain regions involved in eating behavior and homeostatic control [198,199] while lacking of BDNF or its receptor was associated with hyperphagia and obesity [200,201]. Similar to leptin, reduction of BDNF in AN might be seen as a homeostatic adaptive phenomenon aiming to promote food intake in condition of chronic starvation. Moreover, decreased expression of BDNF in the mice model of ABA was linked to increased locomotor activity and decreased motivation to eat [202] suggesting that impaired BDNF transmission in AN might sustain hyperactivity and decreased motivation to eat due to modulating the reward system [163]. Eating is co-determined by homeostatic and non-homeostatic neuronal mechanisms. Interaction of these mechanisms seems to play a particularly crucial role in aberrant ingestive behavior in eating disorders [163,203,204].

Cognitive and Hedonic Regulation of Food Intake in Eating Disorders

The reward circuitry and food intake regulation

Food intake is a highly motivated behavior and a source of pleasure [205]. Food cues and their hedonic values are linked through learning association and generate motivation to eat. Food-related sensory information (including visual, olfactory, gustatory, and somatosensory signals) is integrated with metabolic cues at the level of the prefrontal cortex (PFC) (e.g. orbitofrontal cortex, anterior cingulate cortex and insular cortex) [206,207]. These cortical structures work in an intimate
interaction with hippocampal formation and the amygdala nuclei to store, update, and retrieve salient information related to food [18,208,209]. Food-related activation of the PFC is triggered via several pathways including (i) the paraventricular thalamic nucleus (PVT) that relays signals between the visceral and homeostatic centers of the hypothalamus and the brainstem to the limbic system and (ii) the mesolimbic dopaminergic pathways that originate in the dopaminergic neurons of the VTA that project directly to the nucleus accumbens (NAcb) and the PFC [18,210-214]. In addition to dopamine, activation of opioid, endocannabinoid, as well as GABAergic (GABA for gamma aminobutyric acid) neurotransmission have been associated with food-related hedonic response [206,210]. For example, daily binging on sugar repeatedly releases dopamine in the NAcb [215], and activation of the opioid neurotransmission in the PFC and the NAcb is related to binge-like overeating of highly palatable food [216-218].

Activation of the PFC neurons increases during food reward anticipation and consumption [219,220]. Conversely, optogenetic inhibition of the PFC attenuated stress-induced reinstatement of palatable food seeking [221] and neurotoxic PFC lesions produced impairment in food consumption driven by conditioned motivational cues [222]. Food-restricted rats submitted to scheduled feeding displayed strong activation of the regions of the medial hypothalamus such as the PVN and the dorsomedial hypothalamic nucleus (DMH) when the rats anticipated regular food [140]. Adding sucrose to feeding schedules led to a gradual increase in the daily intake of highly palatable sucrose but not regular chow [139]. Surprisingly, the sucrose-anticipating rats did not show neuronal activation in the medial hypothalamus. In contrast, strong neuronal activation has been detected in the PFC, NAcb, and LH during sucrose anticipation [139]. Therefore, anticipation of regular food activates the medial hypothalamic regions involved in homeostatic control of feeding whereas highly palatable food anticipation activates the brain regions of the reward system, but not the medial hypothalamus (Figure 2).

Brain reward system in eating disorders

The brain reward system controls eating behavior in close interaction with the neuronal networks involved in emotions, learning, and memory functions. Rewarding and punishing events and the environmental cues associated with these events are learned and memorized by the interactive mechanisms in this distributed network. Food predictive cues can thus stimulate eating despite satiety while fear cues can inhibit eating despite hunger [73]. In eating disorders, food intake regulation via environmental cues produces abnormally low association with reward in patients with AN and high association with reward in patients with BN and BED [203,223] (Table 1).

Figure 2: Regular foods and highly palatable foods are anticipated by different parts of the brain. Anticipation of regular food by food-restricted rats activates the medial hypothalamic regions involved in the homeostatic regulation of food intake such as the paraventricular hypothalamic nucleus (PVN) and the dorsomedial hypothalamic nucleus (DMH). Anticipation of sucrose activates the brain reward system, which includes the prefrontal cortex (PFC), nucleus accumbens (NAcb), and lateral hypothalamus (LH). The paraventricular thalamic nucleus (PVT) is activated by anticipation of both diets and seemingly provides a relay between the homeostatic and reward systems. Excitatory neurotransmission from the PFC to its projecting areas including the NAcb and LH may be facilitated by a decrease in expression of the PFC cannabinoid CB1 receptor by palatable food.

Patients with AN are characterized by a sustained fear of weight gain, and this fear is consequently associated with food and eating [223]. The fear circuitry includes principally the amygdala but also involves the hippocampus, insular cortex, PFC (including the anterior cingulate cortex), and striatum [224]. A meta-analysis of functional magnetic resonance imaging (fMRI) studies [225] showed that patients with AN display stronger activation of some regions involved in fear circuitry compared to the control subjects in response to visual food cues [223]. These activations were specific to food. Cues that predict danger, i.e., fear cues, inhibit feeding as part of the coordinated threat and stress response [209,226]. The studies of conditioned fear learning in animal models suggested that the central amygdala (CeA) is a critical region for expression of conditioned fear learning [227]. The CeA could exert its action on feeding via direct projections to the brainstem, the LH, and the bed nucleus of the stria terminalis or indirect projections to the PVN [228-231]. Therefore, sustained fear might be an important contributor that facilitates the maintenance of restricted eating in anorexia via the amygdala-hypothalamic network [223,222].

Food is fearful in AN while self-starvation is anxiolytic [107-109] and pathologically rewarding [116,204]. Dysfunctions in the reward system that occur in AN [92,204,233,234] may explain the rewarding properties of aberrant eating behaviors. Dysfunction in the dopamine system has been demonstrated in patients with AN [235-237] as well as in animal models of food restriction and weight loss [238,239]. Furthermore, cues associated with self-starvation (such as underweight body images) increased ventral striatal activity in AN [240]. These data support the hypothesis that dysfunction in the reward system in AN may be related to an altered dopamine striatal system that can increase the drive for self-starvation. Stress might be implicated in the development and maintenance of starvation dependence in AN [241] since stress-related secretion of glucocorticoids is a known modulator of the ventral striatal dopamine system [242-245]. Therefore, in AN, self-starvation may result from avoidance of food linked to fear circuitry together with a rewarding effect of food restriction.

Accumulating evidence suggests that highly palatable food may promote dependence in some individuals. Similar to drugs of abuse, palatable food can activate the brain reward system, thus producing powerful behavioral reinforcement for this type of food [141,210,246]. Activation of the reward system may be triggered by multiple...
mechanisms. Long-term consumption of highly palatable food in rats significantly decreased expression of the cannabinoid receptor CB1 in the PFC [247]. The CB1 receptor is usually located in the axonal terminals, and activation of the CB1 receptor leads to inhibition of neurotransmitter release [248,249]. Since the projecting neurons of the PFC are excitatory glutamatergic neurons, a decrease in CB1 expression in the PFC would facilitate excitatory glutamatergic neurotransmission in the PFC projecting areas which include the NAcb and the LH [250,251]. Activation of the LH neurons expressing orexin may further reinforce feeding motivation via the direct projections to the VTA neurons and activation of the mesolimbic dopamine system [18,210,252,253]. Binge eating of sucrose in the rat model produces recurrent dopamine release to the ventral striatum that produce modifications in the mesolimbic dopamine system [215]. Higher activation of the reward centers would escalate the intake of highly palatable food despite creating metabolic and psychological complications [141]. Therefore, repeated stimulation of the reward pathways with highly palatable food leads to neurobiological adaptations that eventually result in compulsive overeating characterized by the frequent drive to initiate eating [254].

An altered reward system is thought to participate in the development and maintenance of pathological binge eating of palatable food in people suffering from eating disorders [255]. Indeed, perturbations of the reward-related brain areas have been demonstrated in patients with BN [256-261]. Decreased activation in the brain regions involved in hedonic evaluation of food (e.g., NAcb, olfactory, cingulate, and insular cortex) [256-258] have led to a hypothesis of hypo-responsiveness of the reward circuitry in BN that might explain the need to eat a large amount of food to stimulate the reward system [223]. In contrast, in BED, food cues presentation induced great activation of the medial olfactory cortex that suggested heightened anticipatory reward sensitivity [261]. Abnormalities in the mesolimbic dopamine and opioid systems in animal models of binge eating support the dysfunctions observed in the reward system in BED [238,262-268]. According to experimental research, an increase in dopamine release to the dorsal striatum was observed in patients with BED during food stimulation [269]. There is also some evidence of higher sensitivity to opioid effects on feeding in BED. Thus, an opioid antagonist decreased the pleasantness and consumption of sweet and high-fat foods in binge eaters, but not in non-bingers [270].

Binge eating is frequently triggered by negative emotions or stress [33,34,104,105,142,143], and negative affect is known to increase the reward value of food in BN [271]. As mentioned previously, glucocorticoids may trigger the initiation of binge eating mainly through stimulation of the reward system. Glucocorticoids are known modulators of dopaminergic activity in the NAcb [138,272,273]. In addition, glucocorticoids participate in consolidating memory for emotionally arousing experiences [137]. Secretion of opioid and dopamine during stress participates in terminating and attenuating stress response [138,274,275]. Through stimulating the same opioid and dopamine pathways, palatable food may participate in attenuating stress response. This learned association may trigger long-term modifications in the reward system [276]. Therefore, food is naturally rewarding; however, repeated stress and learned association of stress relief and ingestion of palatable food can trigger long-term changes in the brain reward circuitry as well as modulation in reward sensitivity that may lead to pathological binge eating.

Role of Genetic Polymorphisms in Eating Disorders

Twin and family studies revealed a substantial genetic background in the etiology of AN, BN and BED. Thus, impact of heritability ranges from 48% to 74% in AN [277,278], from 28% to 83% in BN [279] and from 39% to 57% in BED [11,280]. As previously highlighted, a number of neurotransmitters, hormones and peptides regulating stress response, food intake and reward brain circuitry plays an important role in the etiopathogenesis and maintenance of eating disorders. Extensive molecular genetics studies have been undertaken over the last decades to identify alterations in DNA sequences and gene expression related to the pathogenesis of eating disorders and their symptoms.

The variants of serotonergic genes have been revealed in AN, BN and BED. Between them, the high levels of polymorphisms of the 5-HT2A receptor and 5HT-transporter-linked polymorphic region (5-HTTLPR) genes were reported for eating disorders. Meta-analyses suggested that polymorphisms of the 5-HT2A [281,282] and 5-HTTLPR [283,284] genes were significantly associated with increased risk for AN, whereas no significant associations between 5-HTTLPR polymorphisms and BN were found [283-285]. However, there is evidence that polymorphism in 5-HTTLPR may contribute to the genetic susceptibility to BED [286].

Several studies focusing on dopaminergic mechanisms have linked polymorphism in the D2 (DRD2) and D4 (DRD4) dopamine receptor genes to eating disorders. In some studies [287,288] but not all [289,290], DRD2 and DRD4 polymorphisms displayed a significant association with AN. Similarly, a potential role of DRD2 polymorphism was found in BED [291]. The brain reward system seems to be altered in eating disorders and increased body of evidence has linked dopamine genes polymorphisms with reward [292-296]. Functional MRI studies in adolescent girls found that polymorphisms of DRD2 and DRD4 were associated with modulated food reward sensitivity [297,298]. In fact, the individuals with high polymorphisms of DRD2 and DRD4 showed weaker responsiveness to food reward and significantly increased risk for unhealthy weight gain [297,298]. Polymorphism of dopamine receptors that renders the reward system less sensitive to dopamine stimulation has been proposed to promote self-stimulatory behavior such as consuming drugs of abuse or binging on foods [299,300]. Furthermore, association between polymorphism of the DRD2 gene and obese patients with BED has been demonstrated [291]. The changed sensitivity to reward in binge eating might thus also be linked to genetic variants of the dopamine system.

An association between gene polymorphism of BDNF and eating disorders has also been demonstrated [301]. Heterogeneity in the BDNF DNA sequences has been found in the restricting type of AN and binging/purging type of BN [301-303]. The fat mass and obesity associated protein (FTO) is a nucleic acid demethylase which is abundantly expressed in all hypothalamic sites regulating feeding behavior [304]. Expression of FTO in the hypothalamic neurons is up-regulated by negative energy balance [305,306] while inactivation of the FTO gene in mice protects from obesity [307]. In children a polymorphism in the FTO gene was associated with loss of eating control and frequent selection of energy-dense palatable foods [308]. A polymorphism in the FTO gene was also detected in BN and AN [309], but contradictory results were reported for AN [310]. Mutation in the gene of melanocortin 4 receptor (MC4R) was also associated with BED [311]. Binge eating has been identified as a major phenotypic characteristic of subjects with a mutation in the MC4R [311,312]. The MC4R is highly expressed in the hypothalamus and mediates the
anorectic effects of α-melanocyte stimulating hormone, a product of enzymatic cleavage of POMC [313].

In addition, the role of genetic variations in a number of other molecules involved in food intake or body weight regulation (e.g. ghrelin, estrogen, cannabinoid receptors) has been confirmed by some but not all studies [314,315]. The small sample sizes and non-identified subtypes of eating disorders are frequently in the origin of the controversial results [314,315]. Uncovering of a variety of potential genetic variants involved in eating disorders or their symptoms helps to understand the variability of treatment responses. The research focusing on the genetic causes of eating disorders is important for development of prevention strategies and pertinent timely treatments of eating disorders.

Conclusions

The neuronal substrate of eating disorders includes interconnecting brain systems that regulate homeostatic energy metabolism, stress response, memory, emotions, and reward. The principal players of the homeostatic system are the medial hypothalamic nuclei integrating the sensory and hormonal signals related to food intake and energy metabolism as well as the specific brainstem nuclei regulating activity of the preganglionic neurons of the autonomic nervous system. Stress response is regulated by the sympathetic nervous system and the HPA axis. The principal hypothalamic nucleus of the HPA axis is the PVN that produces stress-related neurohormone CRF. The anorectic effects of acute stress are mainly mediated by the CRF2R in the ventromedial hypothalamus and the lateral septum. The principal memory storage is the hippocampus that via the lateral septum may affect the activity of the homeostatic and reward systems. Emotions are strongly regulated by the amygdala that by their direct and indirect connections may affect activity of the hypothalamic food-intake-regulating nuclei. The reward system includes the mesolimbic pathway with the VTA, prefrontal cortex, and striatum. In addition, the lateral hypothalamus is closely related to the brain reward system. Animal models helped to uncover mechanisms related to stress- and activity-induced anorexia, or stress-induced eating of palatable food in binge eating models. However, the complexity of the neuronal systems related to eating disorders hampers clear understanding of the molecular and neuronal mechanisms of the development and maintenance of these pathologies. Misbalance in one system leads to altered activity in other food-related regulatory networks. For example, hyperactivity of the stress-regulating system affects via peripheral and central stress hormones the activity of the homeostatic system, memory formation, expression of positive and negative emotions, as well as sensitivity of the reward system. However, the reward system may provide certain “relief” from stress by inhibiting the HPA axis, but at the same time the reward system may “hijack” homeostatic control of feeding and favor episodes of binge eating. Implication of multiple brain systems in eating disorders therefore requires a complex strategy for treatment and recovery. After precise diagnostic by a health professional an eating disorder might be treated with particular medication, but also with psychotherapy sessions, dietary consultations, and physical and psychological activities that balance emotions and help with stress.

References


