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Chapter 26

Eating disorders: anorexia and bulimia nervosa

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INTRODUCTION

Studies have identified anorexia nervosa (AN) to be the third commonest chronic illness of adolescence with the highest mortality of all psychiatric disorders (Nicholls and Viner, 2005). The more secretive and ashaming character of bulimia nervosa (BN) prevents patients from seeking help, with the consequence that treatment is delayed for many years.

DIAGNOSIS, EPIDEMIOLOGY, AND COURSE

Excessive preoccupation with weight and shape and a morbid fear of gaining weight are the core features of both eating disorders. In AN, weight loss is the result of a severe and selective restriction of food often accompanied by excessive exercising. The pursuit of thinness persists in spite of emaciation. The majority of patients experience their symptoms as ego-syntonic, and there is often a denial of the disorder. Restricted interests focusing on weight, food, and shape are followed by social isolation and withdrawal.

In BN, periods of dieting and fasting are interrupted by binge-eating episodes accompanied by a feeling of loss of control, in which a large amount of food is eaten. Bingeing is compensated by self-induced vomiting, laxative, diuretic, or other medication abuse or, more rarely, nonpurging strategies like exercising and dieting (for a review, see Herpertz-Dahlmann, 2009).

DEFINITION AND CLASSIFICATION

According to the *Diagnostic and Statistical Manual of Mental Disorders,* 4th edition (DSM-IV: American Psychiatric Association, 2000; Table 26.1), AN is classified into two subgroups: restricting and binge-eating/purging type. Patients with binge-eating/purging type may engage in bingeing and purging or only purging, i.e., practice self-induced vomiting, laxative abuse, or other extreme forms of weight control. The binge-eating/purging type is associated with a poorer prognosis.

An alternative to the "normal weight" criterion in DSM-IV is a body mass index (BMI: calculated as weight in kilograms/(height in meters)^2) equal to or below 17.5 kg/m^2. BMI centiles must be used to define underweight in children and adolescents, e.g., in Germany a BMI lower than the 10th percentile is considered a threshold for a diagnosis of AN.

BN is also divided into two subgroups, the purging and the nonpurging type (Table 26.1).

COMORBIDITY

Both disorders are characterized by a high psychiatric comorbidity, especially depressive symptoms and anxiety disorders including obsessive-compulsive disorder. Personality disorders comprise anxious-avoidant and obsessive-compulsive disorders in AN and borderline personality disorders in BN. A subgroup of patients, more prominent in BN, practices substance abuse or self-injurious behavior. Emaciation is often accompanied by neuropsychological changes. Such changes as well as depression and obsessive features are often alleviated by weight gain (Herpertz-Dahlmann, 2009).

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Table 26.1

Diagnostic criteria for anorexia nervosa according to DSM-IV (abbreviated form)

Refusal to maintain body weight for age and height (less than 85% of that expected)
Intense fear of gaining weight or becoming fat
Disturbance in the way in which one's body weight or shape is experienced
Amenorrhea
Subtypes: Restricting and binge-eating/purging type
Recurrent episodes of binge eating
Recurrent inappropriate compensatory behavior, e.g., self-induced vomiting, laxative abuse, or fasting
Frequency at least twice a week for 3 months
Self-worth is judged by shape and weight
Bulimic symptoms do not often occur during the context of anorexia nervosa
Subtypes: Purging and nonpurging type

DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders,* fourth edition (American Psychiatric Association, 2000).

EPIDEMIOLOGY

In adolescents and young females most studies found a point prevalence rate for AN between 0.3% and 0.9% (van Hoeken et al., 2003; Hoek, 2006). Lifetime prevalence rates for 20–40-year-old women are estimated between 1.2% and 2.2% (Hoek, 2006).

For BN the point prevalence is calculated as 1–2% (van Hoeken et al., 2003).

Recent incidence rates for AN show an overall stabilization, but report an increase in the adolescent and young adult group; there was an increase in the incidence of BN until the middle of the 1990s and a decrease thereafter (Currin et al., 2005).

For both eating disorders the risk is highest for females aged 15–19 years. The male-to-female ratio is estimated to be 1:10 for AN, and about 1:30 for BN (van Hoeken et al., 2003). According to recent studies there is no appreciable change in this ratio over time.

It has been estimated that up to 50% of AN and even more of BN cases are previously undetected by the healthcare system (Hoek, 2006; Keski-Rahkonen et al., 2007).

COURSE AND OUTCOME

Early studies report frequent seasonal fluctuations in BN, but not in AN. Retrospective self-reports of patients with BN point to a greater likelihood of binge eating and purging during the winter than the summer months (Blouin et al., 1992). Longitudinal analyses of AN suggest a protracted course with several relapses.

In a meta-analysis of 119 studies Steinhausen (2002) concluded that on average less than one-half of patients recover, one-third improve, and 20% remain chronically ill. Mortality is significantly increased with 5–5.9% suffering a premature death. In adolescent AN outcome is better, with two-thirds of patients recovered and a zero mortality rate after 10–18 years (Wentz-Nilsson et al., 1999; Herpertz-Dahlmann et al., 2001). However, many patients suffer from other or additional psychiatric disorders in later life, especially anxiety and affective disorders, obsessive-compulsive disorders, Cluster C personality disorders, and substance abuse.

In BN, follow-up studies of more than 10 years suggest that 50–70% recover, while 10–30% still fulfill all diagnostic criteria (Keel et al., 1999; Fichter and Quadflieg, 2004). Mortality rate is much lower than in AN and estimated at about 2% (Fichter and Quadflieg, 2004).

ETIOLOGY

Multifactorial models

The origin of eating disorders is widely thought to be multifactorial with several risk factors that have to be considered in a complex etiology model. These are a genetic vulnerability, either for the eating disorder itself or, more probably, via personality traits, biological factors associated with starvation and malnutrition, sociocultural factors, family and educational factors, and in some individuals precipitating life events like an experience of separation and loss, physical disease, abuse, or neglect (for a review, see Treasure et al., 2010; Attia, 2010).

Genetics and molecular biology

Many studies confirm the familial nature of eating disorders. Previous results suggest that specific genes may predispose individuals to an unspecific risk for eating disorders, e.g., for AN or BN or partial syndromes. The lifetime risk for first-degree relatives of patients with AN to develop the full syndrome of AN is approximately 10-fold greater than that of healthy individuals. In addition, there is a high prevalence of psychiatric disorders in close relatives, such as anxiety (including obsessive-compulsive disorder) and affective disorders. However, family studies do not allow differentiation between genetic and environmental risk factors.

Twin studies have yielded heritability estimates for AN of between 48% and 76% depending on a narrow or broad definition. For BN heritability rates are estimated to be between 28% and 83%.

In the past decades several molecular genetic studies to identify genes responsible for eating disorders have been undertaken, involving both family-based linkage studies and association studies. However, up to now, they were not able to present unambiguous findings.

Recent linkage analyses managed to discover several regions of interest on chromosomes 1, 2, 4, and 13 for

AN. Fine mapping of these regions led to the identification of genes that might fit into existing theories of the pathophysiology of AN, e.g., of the serotonergic or cannabinoid system. A linkage analysis for BN reported evidence for a susceptibility locus on chromosome 10p, which was already identified in genome scans for obesity.

Association studies have mostly analyzed candidate genes of systems involved in the regulation of hunger and satiety, of body weight and the menstrual cycle. In particular polymorphisms of the serotonergic and dopaminergic system have been extensively investigated. Although there are some promising findings, like those pertaining to the serotonin receptor 1D and the dopamine D_2 receptor gene, all of the previous results warrant replication in independent and adequately powered samples. There are also several studies concerning genes involved in neuropeptides and body weight regulation, like ghrelin, leptin, neuropeptide Y, agouti-related protein, hypocretin receptor 1 gene,. With the exception of the opioid receptor delta-1 polymorphism related to AN, no association was found. The latter also warrants replication.

Probably, systematic genomewide screens could provide significant insight into heritability mechanisms of eating disorders. Collaborative investigations resulting in large sample sizes are critical to identify risk alleles; however, up to now no significant results could be identified (for a review, see Hinney et al., 2004; Bulik et al., 2007b).

Other prenatal and perinatal factors

Besides genetic disposition, the effect of other prenatal factors has to be elucidated. For example, masculinization of the central nervous system by prenatal testosterone exposure may contribute to sex differences in the prevalence of eating disorders. Accordingly, same-sex female twins had a much higher risk of developing disordered eating than opposite-sex twins (Culbert et al., 2008).

Similar to other mental disorders, pregnancy (especially preterm birth) and perinatal complications are associated with an increased risk for AN (Cnattingius et al., 1999).

ENVIRONMENTAL RISK FACTORS

Sociocultural factors

Eating disorders are much more present in western industrialized countries than in other parts of the world. Thus, several studies have analyzed an association between a culturally bound ideal to be thin and the development of eating disorders. This relationship is more pronounced for bulimic eating disorders than for restrictive AN (Ruderman, 1986). However, in a well-designed study on the island of Curaçao, Hoek et al. (2005) demonstrated that the incidence of AN among the majority black population was nil, while the incidence among the minority mixed and white population was similar to that of western societies. Interestingly, most of the cases on Curaçao were subjects who had developed AN after visiting the Netherlands or the USA.

Familial factors

For several decades a model of dysfunctional family interaction style was put forward to explain the development of eating disorders. These interaction styles comprised too close and age-inadequate family structures like overprotection and enmeshment in AN, and indifference, family conflicts, and high criticism in BN.

Empirical studies yielded contradictory results (for a review, see Jacobi et al., 2004). Whereas several studies did not find any difference between family interaction styles in families of eating-disordered patients and those of healthy controls, others found high-concern parenting style in AN and family discord in BN. However, in comparison to psychiatric controls no differences were found. Most of the studies were performed retrospectively. Thus it has to be taken into account that parenting style might change in response to starvation and unhealthy eating behavior in the child.

Other risk factors

Higher rates of sexual abuse have been realized in clinical samples of bulimic patients compared to normal controls, but not in comparison to other psychiatric groups (for a review, see Jacobi et al., 2004).

Only very few studies report on adverse life events preceding the onset of the eating disorder, like loss of a first-degree relative or separation from a close friend. Again, this does not seem to be unique for eating-disordered patients, but is also prominent in individuals with other mental problems.

Further risk factors include chronic physical diseases like diabetes (Herpertz et al., 2000), chronic bowel disease, and other somatic disorders associated with dieting and weight changes.

Neuroimaging and neuropsychological findings

Early lesion studies suggested that pathological eating patterns occur after lesions in the prefrontal, temporal, mesiotemporal cortices, and the thalamus, predominantly on the right-hand side (see Uher and Treasure, 2005, for a review). In addition, postmortem studies of acutely ill AN patients first demonstrated reduced cerebral mass with prominent sulci and small gyri (Neumärker et al. 1997). With the advances of neuroimaging techniques during recent years, more sophisticated analyses have been performed on the brains of AN subjects. Structural brain-imaging studies in acutely ill AN patients have provided

further evidence for reduced cerebral volume along with enlarged ventricles and large cerebrospinal fluid (CSF) volumes (Katzman et al., 1996). The greater the absolute weight loss and the faster the ratio of weight loss, the smaller the total brain volume (Swayze et al., 2003). While some studies found white-matter abnormalities with normal gray-matter volume (Swayze et al., 2003), others showed only gray-matter deficits (mainly in the temporal and parietal lobes) without white-matter abnormalities (Castro-Fornieles et al., 2009). Region-specific gray-matter loss has been reported in the right anterior cingulate cortex (ACC) in underweight AN patients (McCormick et al., 2008). Furthermore, reduced pituitary gland volume (Giordano et al., 2001) and amygdala-hippocampal formation (Connan et al., 2006) reductions have been reported.

Data regarding the reversibility of these abnormalities after weight gain are conflicting. White and gray matter seem to behave differently in this regard. Post-mortem examination of brain tissue after weight gain showed gray-matter deficits in recovered AN patients (Neumärker et al., 1997). Longitudinal neuroimaging research revealed small but persistent changes in gray-matter loss, whilst CSF and white-matter volumes seem to normalize after weight gain (Katzman et al., 1997). For example, Muhlau et al. (2007) reported global gray- (but not white-) matter volume decreases of approximately 1% in recovered patients with AN. In adolescent AN patients, Castro-Fornieles et al. (2009) reported both global and region-specific, i.e., temporal and parietal, gray-matter deficits in the underfed state. Global gray-matter volume was restored, but regionally some parts in the right temporal and both supplementary motor areas were still smaller. One study focused on the volume of the ACC, and demonstrated that right dorsal ACC volume reductions in the acute phase normalized with weight restoration. Furthermore, the degree of right dorsal ACC normalization during treatment was associated with treatment outcome (McCormick et al., 2008). A possible explanation for the conflicting findings in recovered AN patients might be the duration of recovery. In the sample with the longest time in recovery (> 1 year no bingeing, purging, or restricting behaviors, normal weight, and menstrual cycles, not on medication), no abnormalities were found (Wagner et al., 2007), suggesting that brain tissue normalization might lag behind clinical improvement. So far, little is known regarding the mechanism behind structural brain changes and recovery during weight rehabilitation in AN. Data on reversible brain loss suggest that this reflects "pseudoatrophy," resulting from acute metabolic disruption as a consequence of starvation or stress or a combination of both. For example, it has been speculated that the hyperactivity of the hypothalamic–pituitary–adrenal (HPA) axis in eating disorders might contribute to decreased volumes of the amygdala-hippocampal formation in eating disorders (Giordano et al., 2001; Connan et al., 2006) as this area is a main target for glucocorticoid effects during stress. In line with this, Katzman et al. (1996) reported that HPA axis activity was positively associated with CSF volume and negatively with gray-matter volume in adolescents with AN. In addition, the increase in gray matter after weight restoration has been associated with a decrease in cortisol (McCormick et al., 2008). Since white matter is constituted from myelinated axons with myelin consisting of lipids, it could be speculated that reversibility of white-matter loss after weight gain is due to the restoration of the lipid/myelin level in the brain.

In addition, magnetic resonance spectroscopy studies can give information on nerve cell damage by assessing brain metabolites, such as choline, *N*-acetyl aspartate, phosphorus, and myo-inositol. These studies suggest state-dependent changes in brain metabolites that were reversible with weight recovery (Kato et al., 1997). Castro-Fornieles et al. (2007) suggested that improved metabolic findings were also associated with a decrease of cortisol levels (Castro-Fornieles et al., 2007).

The relevance of structural brain abnormalities for brain function and cognitive performance has been hardly addressed. While some studies found a relationship between cognitive impairment and regional-specific brain alterations, others reported that even in the presence of structural abnormalities in the hippocampus no detectable impairment in memory function was found (Connan et al., 2006).

During recent years, functional neuroimaging studies on eating disorders have been conducted, using single-photon emission computed tomography and positron emission tomography (PET) as well as functional magnetic resonance imaging (fMRI) methods. When describing functional imaging data, it is crucial to distinguish between resting-state findings where no specific instruction or task is given to the subject in the scanner, and findings based upon scanning paradigms, including the presentation of a stimulus. The latter is often aimed at provoking symptoms, though other aspects of psychopathology or pathophysiology might be the target as well. First, resting-state studies on eating disorders provided evidence for a reduced global and regional cerebral glucose metabolism with indications of restoration after recovery. Second, functional imaging studies during cognitive tasks have focused primarily on symptom provocation techniques (e.g., by exposure to food stimuli), neural correlates of body image distortion, taste processing and reward mechanisms. An overview of fMRI studies using cognitive and emotional tasks is provided in Table 26.2. These studies suggest dysfunctional brain activation patterns primarily in

Table 26.2

Functional magnetic resonance imaging studies in eating disorders

Reference (year)	Samples	Task	Main findings
Marsh et al. (2009)	20 patients with BN 20 controls	Simon Spatial Incompatibility Task (self-regulation)	Patients with BN responded more impulsively and made more errors on the task than did healthy controls; patients with the most severe symptoms made the most errors. During correct responding on incongruent trials, patients failed to activate frontostriatal circuits to the same degree as healthy controls in the left inferolateral prefrontal cortex (BA 45), bilateral inferior frontal gyrus (BA 44), lenticular and caudate nuclei, and anterior cingulate cortex (BA 24/32). Patients activated the dorsal anterior cingulate cortex (BA 32) more when making errors than when responding correctly. In contrast, healthy participants activated the anterior cingulate cortex more during correct than incorrect responses, and they activated the striatum more when responding incorrectly, likely reflecting an automatic response tendency that, in the absence of concomitant anterior cingulate cortex activity, produced incorrect responses
Redgrave et al. (2008)	6 patients with AN 6 controls	Emotional Stroop tasks with fat, thin, and neutral words compared to letter strings (XXXX)	Contrast: Thin minus XXXX: AN showed increased activity in the left insula, frontal and temporal lobes. Contrast: Fat minus XXXX: AN showed reduced activity in the left DLPFC and right parietal cortex
Sachdev et al. (2008)	10 patients with AN 10 controls	Passive viewing of self and others' body images (matched for age, sex, and BMI)	Self minus nonself: Control subjects had greater activation than AN patients in the middle frontal gyri, insula, precuneus, and occipital regions while the patients did not have greater activation in any region
Wagner et al. (2008)	16 women recovered from restricting-type AN 16 controls	Taste processing and experience of pleasure using a sucrose/water task	Individuals who had recovered from AN showed a significantly lower neural activation of the insula, including the primary cortical taste region, and ventral and dorsal striatum to both sucrose and water. In addition, insular neural activity correlated with pleasantness ratings for sucrose in controls but not in AN subjects
Schienle et al. (2009)	17 overweight patients with BED 17 overweight controls 19 normal-weight controls 14 normal-weight patients with BN purging type	Visual exposure to high-caloric food, to disgust-inducing pictures, and to affectively neutral pictures after an overnight fast	Each of the groups experienced the food pictures as very pleasant. Relative to the neutral pictures, the visual food stimuli provoked increased activation in the orbitofrontal cortex, anterior cingulate cortex, and insula across all participants. The BED patients reported enhanced reward sensitivity and showed stronger medial orbitofrontal cortex responses while viewing food pictures than all other groups. The bulimic patients displayed greater arousal, anterior cingulate cortex activation, and insula activation than the other groups. Neural responses to the disgust-inducing pictures as well as trait disgust did not differ between the groups

Continued

Table 26.2

Continued

Reference (year)	Samples	Task	Main findings
Wagner et al. (2007)	13 recovered patients from AN (≥ 1 year of normal weight, regular menstrual cycles, without binge eating or purging) 13 controls	Monetary reward task (guessing-game paradigm)	Recovered women showed greater hemodynamic activation in the caudate than comparison women. Only the recovered women showed a significant positive relationship between trait anxiety and the percentage change in hemodynamic signal in the caudate during either wins or losses. In contrast, in the anterior ventral striatum, comparison women distinguished positive and negative feedback, whereas recovered women had similar responses to both conditions
Frank et al. (2006)	10 recovered patients from a bulimic-type eating disorder (≥ 1 year) 6 controls	Administration of a solution of glucose or artificial saliva	Individuals who recovered from a bulimic-type eating disorder had significantly lower activation in the right anterior cingulate cortex and in the left cuneus when glucose was compared with artificial saliva
Santel et al. (2006)	13 patients with AN 10 controls	Presentation and rating of visual food and nonfood stimuli for pleasantness in a hungry and a satiated state	When hungry, AN patients displayed weaker activation of the right visual occipital cortex than healthy controls. Food stimuli during satiety compared with hunger were associated with stronger right occipital activation in patients and with stronger activation in left lateral orbitofrontal cortex, the middle portion of the right anterior cingulate, and left middle temporal gyrus in controls
Uher et al. (2005)	9 women with BN, 13 patients with AN 18 controls	Presentation and ratings of line drawings of underweight, normal weight, and overweight female bodies for fear and disgust	In the three groups, the lateral fusiform gyrus, inferior parietal cortex, and lateral prefrontal cortex were activated in response to body shapes compared with the control condition (drawings of houses). The responses in the lateral fusiform gyrus and in the parietal cortex were less strong in patients with eating disorders compared with healthy control subjects. Patients with eating disorders rated the body shapes in all weight categories as more aversive than did healthy women. In the group with eating disorders, the aversion ratings correlated positively with activity in the right medial apical prefrontal cortex
Uher et al. (2005)	10 patients with BN 16 patients with AN 19 controls	Presentation and ratings of food and aversive emotional stimuli	Women with eating disorders identified the food stimuli as threatening and disgusting. In response to these stimuli, women with eating disorders had greater activation in the left medial orbitofrontal and anterior cingulate cortices and less activation in the lateral prefrontal cortex, inferior parietal lobule, and cerebellum, relative to the comparison group. In addition, women with BN had less activation in the lateral and apical prefrontal cortex, relative to the comparison group. Between-group differences in response to nonspecific emotional stimuli were found in the occipital cortex, parietal cortex, and cerebellum

Wagner et al. (2003)	15 patients with AN 11 controls	Confrontation with own digitally distorted body images using a computer-based video-technique	Activation of the attention network as well as of structures involved in visuospatial processing and self-reflection in both groups. Anorectic patients showed a greater activation in the prefrontal cortex (BA 9) and the inferior parietal lobule (BA 40), including the anterior intraparietal sulcus, than did controls. However, an analysis of the BOLD response in the inferior parietal lobule area revealed that anorectic patients showed a specific increase in activation only to their own pictures and not to others, indicating different visuospatial processing, while controls did not differentiate
Uher et al. (2005)	9 recovered patients from restricting AN 8 chronically ill patients with restricting AN 9 controls	Presentation of food and emotional visual stimuli	In response to food stimuli, increased medial prefrontal and anterior cingulate activation, as well as a lack of activity in the inferior parietal lobule, differentiated the recovered group from the healthy control subjects. Increased activation of the right lateral prefrontal, apical prefrontal, and dorsal anterior cingulate cortices differentiated these recovered subjects from chronically ill patients. Group differences were specific to food stimuli, whereas processing of emotional stimuli did not differ between groups
Seeger et al. (2002)	3 patients with AN 3 controls	Digital pictures of own body image, individually distorted by subjects themselves	In anorectic patients, stimulation with their own body image was associated with activation in the right amygdala, the right gyrus fusiformis, and the brainstem region

BN, bulimia nervosa; BA, Brodmann area; AN, anorexia nervosa; DLPFC, dorsolateral prefrontal cortex; BMI, body mass index; BED, binge-eating disorder; BOLD, blood oxygen level-dependent.

frontoparietal as well as in limbic and reward-related neural networks.

As in other domains, BN has been less well studied than AN with neuroimaging techniques. Previous studies suggest that abnormalities in brain anatomy and cortical metabolism during resting state are less pronounced in ill BN individuals compared to patients with AN, although they also have decreased cortical mass during the acute stage of illness (Andreason et al., 1992; Husain et al., 1992; Delvenne et al., 1997). Frank et al. (2007) recruited long-term recovered BN patients and could not demonstrate regional cerebral blood flow (rCBF) abnormalities, suggesting that alterations in rCBF during the acute phase of BN may be a state-related phenomenon that remits with recovery. Interestingly, one study suggested that at least some of the functional abnormalities in BN might be related to mood problems since left lateral prefrontal metabolism correlated negatively with depressive symptoms in BN patients (Andreason et al., 1992).

Using fMRI, Uher et al. (2005) found that, in addition to a medial prefrontal activation, common with AN, BN patients were specifically characterized by lower levels of activation to food cues in the lateral prefrontal cortex (Uher et al., 2005), corresponding to the lack of control over eating. However, more recently, Marsh et al. (2009) demonstrated general abnormal self-regulatory processes in women with BN, associated with a failure to engage frontostriatal circuits appropriately, which may indicate that deficits in neural circuitries underlying self-regulation contribute to binge eating and other impulsive behaviors in women with BN.

Neurotransmitter dysregulation

There has been considerable interest in the role of the monoamine systems, including serotonin (5-hydroxytryptamine, 5-HT) and dopamine (DA), in the etiology of eating disorders. These systems contribute to abnormal appetite regulation, disturbances of impulse control and mood regulation, harm avoidance, as well as obsessionality and anxiety.

However, the majority of investigations have been performed in acutely eating-disordered patients so that state- (starvation, sequelae of bingeing and purging) and trait-related dysfunction cannot be differentiated. Dieting and/or starvation lead to changes of neurotransmitter concentration and to altered receptor sensivity.

During the active state of the illness AN patients have a significant reduction in CSF 5-hydroxyindole acetetic acid (5-HIAA) in comparison to healthy controls, which may be a consequence of diet-related decrease in tryptophan ingestion. In contrast, in BN, CSF levels of 5-HIAA are found to be in the normal range (for a review see Kaye et al. 2009).

To avoid the acute consequences of diet and/or semistarvation, recent studies on the neurobiology of eating disorders have been performed in so-called recovered patients who have attained at least a minimal healthy weight and resumed menses. Note, however, that these former patients on average have a lower weight than those who have never been eating-disordered. In addition, long-term starvation accompanied by hormonal dysfunction probably has deleterious effects on the brain, especially on the developing one. For example, during puberty increase of the size of the hippocampus is related to estrogen levels (Neufang et al., 2009).

In contrast to the ill state, CSF levels of 5-HIAA are elevated in long-term weight-restored AN and in recovered BN subjects. Interestingly, patients with obsessive-compulsive disorder have been shown to display elevated CSF levels of 5-HIAA. More generally, higher CSF 5-HIAA levels may be associated with disorders of behavioral overcontrol, anxiety, and dysphoric mood (for a review see Kaye et al. 2009).

Dieting (especially in the beginning of an eating disorder) and binge–purge cycles tend to improve negative mood states. Thus, Kaye et al. (2009) hypothesize that eating-disordered behavior and restrictive eating are reinforced by an alleviation of mood and obsessionality.

A dysfunction of the serotonergic systems involving 5-HT_{1A}, 5-HT_{1B}, and 5-HT transporter has been confirmed by several brain-imaging studies. However, despite all these findings, medication aimed at the 5-HT system has not proven to be effective (Walsh et al., 2006).

Dopamine is also probably involved in the pathophysiology of eating disorders. AN patients in the ill state have reduced levels of CSF homovanillic acid, a dopamine metabolite, and these reduced levels often persist after recovery. Reduced CSF dopamine metabolites have also been reported in high-frequency binge–purging BN. A PET study demonstrated that recovered subjects with AN had increased striatal D2/D3 binding (Frank et al. 2005). Striatal dopamine dysfunction may contribute to an altered reward response to eating and/or other pleasurable stimuli (for review, see Brewerton and Steiger, 2004; Kaye et al., 2009). Interestingly, genetic studies found several polymorphisms in the dopamine receptor D_2 gene, which were associated with the purging type of AN, although the findings require replication in an independent sample (Bergen et al., 2005).

NEUROENDOCRINE AND NEUROPEPTIDE DYSREGULATION

Neuroendocrinology

AN and, to a lesser extent, BN lead to multiple endocrine and metabolic changes. In general these abnormalities are a consequence of semistarvation or an abnormal

eating behavior with poorly balanced meals (or both) and thus are mostly assigned as adaptive mechanisms to conserve energy and protein. The increase of β-hydroxybutyric acid in both AN and BN subjects indicates the shift from glycogenolysis to lipolysis and ketogenesis. Semistarvation and/or pathological eating behavior may be associated with profound changes in the hypothalamic–pituitary–gonadal axis, the HPA axis, the hypothalamic–pituitary–thyroid axis, and the hypothalamic–growth hormone–insulin-like growth factor axis. A summary of these changes is shown in Table 26.3.

Neuropeptides

The number of studies on changes in neuropeptides in AN and BN is still limited. To date, most studies found neuropeptide alterations, which are apparent during symptomatic states of AN and BN, to be normalized after recovery of the disorder (Table 26.3). This indicates that neuropeptide disturbances are consequences rather than causes of malnutrition. However, with respect to gut-related peptides, there appears to be substantial evidence that eating disorder-related alterations in neuropeptide secretion or functioning may maintain eating disorder pathology. Additional studies will be needed to assess further these mechanisms in symptomatic eating-disordered patients, and to identify stable trait-related abnormalities that persist in individuals who have recovered from an eating disorder.

Recently, autoantibodies directed against melanocortin peptides and other appetite-regulating peptide hormones have been identified in healthy and eating-disordered subjects and classified as important attributors to mechanisms controlling motivation in eating behavior. In AN and BN, serum levels of these autoantibodies correlated with typical psychopathological traits. However, these findings have only been presented by one group and need to be replicated in independent samples of eating-disordered patients (Fetissov et al., 2008).

The following sections provide a brief summary of neuropeptide alterations in AN and BN, focusing on gut-related neuropeptides. An overview of the neuroendocrinological mechanisms involved in the regulation of food intake is given in Fig. 26.1.

Leptin

The anorexigenic adipocyte hormone leptin plays an important role in the hypothalamic regulation of energy homeostasis. Untreated AN patients show significantly reduced serum and CSF leptin levels, primarily reflecting reduced fat mass. During therapeutically induced weight gain leptin levels increase and have been found to be disproportionately high at target weight in comparison to a healthy control group when adjusted for BMI and percentage body fat (Holtkamp et al., 2003). Presumably, both total amount and rate of weight gain are relevant for this upregulation. The relative hyperleptinemia is also found in the central nervous system (Mantzoros et al., 1997). The rapid transition from a state of hypoleptinemia to one of relative hyperleptinemia within several weeks entails an upregulation in energy expenditure adjusted for fat-free mass (Hebebrand et al., 1997; Mantzoros et al., 1997; Haas et al., 2005). Preliminary evidence suggests that hyperleptinemia may be associated with an elevated risk of renewed weight loss (Holtkamp et al., 2004; Haas et al., 2005).

Semistarvation-induced hyperactivity is viewed as an animal model of AN and can be effectively suppressed by the administration of leptin (Exner et al., 2000). Significant correlation between leptin and different measures of physical activity and restlessness implicates hypoleptinemia as an important factor contributing to the behavioral pattern observed in acutely ill patients with AN (Holtkamp et al., 2006). Thus, leptin has been considered as a potential therapeutic agent in acutely ill AN patients severely affected by hyperactivity (Hebebrand et al., 2007), therapeutic agent in acutely ill AN patients severely affected by hyperactivity.

Several studies have shown that the actions of leptin are not restricted to the hypothalamus and the pituitary. Many other brain areas, like the brainstem, cerebellum, amygdala, substantia nigra, and especially the hippocampus, are highly enriched with leptin receptors. Memory impairments are found in leptin-insensitive rodents, and severely underweight AN patients also display memory deficits which are often improved with weight gain (Harvey, 2007).

A subgroup of BN patients has decreased leptin levels despite a normal BMI, whereas normal levels were observed in others (Jimerson et al., 2000; Monteleone et al., 2002, 2003; Calandra et al., 2003). It is still unclear why some subjects exhibit decreased leptin levels after recovery from BN. This alteration could be associated with the tendency to renewed weight gain in bulimic patients.

Ghrelin and obestatin

Ghrelin, an orexigenic peptide of the stomach mucosa, is involved in the hypothalamic regulation of energy intake. Obestatin, a relative of ghrelin derived from preproghrelin, is reported to counteract ghrelin effects on food intake (Monteleone et al., 2008). Fasting ghrelin levels are negatively correlated with BMI and percentage body fat (Tolle et al., 2003). AN patients display significantly increased circulating levels of both ghrelin

Table 26.3

Neuroendocrinological changes in anorexia nervosa (AN) and bulimia nervosa (BN) during the acute illness stage

		AN	BN	Comment
Hypothalamic–pituitary–adrenal axis	Cortisol	↑	n (↑)	Findings indicate a mild to moderate activation of the hypothalamic–pituitary–adrenal axis
	Cortisol CSF	↑	n	
	ACTH	n	n	
	ACTH CSF	↓	n	
	CRH CSF	↑		Intracerebroventricular administration of CRH in rats produces behavioral and physiological changes similar to symptoms of AN
	CRH stimulation (ACTH)	↓		
	Dexamethasone inhibition test	50–90% lacking suppression	20–60% lacking suppresion	Sustained lack of suppression after weight restoration appears to be a poor prognostic factor
Hypothalamic–pituitary–gonadal axis	LH	↓	↓ n	For resumption of menses a sufficient leptin level is a necessary but not sufficient condition
	FSH	↓	↓ n	
	Estradiol	↓	n ↓	
Hypothalamic–pituitary–thyroid axis	fT_3	↓	n ↓	Low fT_3 syndrome (low fT_3, normal fT_4 and TSH) indicates semistarvation; substitution of thyroxine is not indicated
	fT_4	n ↓	n ↓	
	TSH	n	n	
Hypothalamic–growth hormone–IGF-1 axis	GH	↑ n	n ↑	High GH and decreased IGF-1 levels indicate diminished feedback of IGF-1 on GH secretion during starvation/malnutrition
	IGF-1	↓	n ↓	
Systemic peptide hormones	Leptin i.s.	↓	n ↓	During weight restoration an early normalization of serum leptin depends on the amount of weight gain; hyperleptinemia at target weight may be a potential risk factor for renewed weight loss
	Leptin i.s. directly after weight restoration	↑ (relative to BMI) ↓		
	Leptin CSF			
	Ghrelin i.s. fasting	↑	↑	Dysregulation in the acute state of BN may be involved in maintaining binge-eating behavior
	Ghrelin i.s. postprandial	n	↑ (absent decline)	
	Cholecystokinin i.s. postprandial	↑↓	↓	In BN decreased postprandial release may have a role in decreased postingestive satiety
	PYY i.s. fasting	↑ n	n	
	PYY i.s. postprandial	n or ↓ (blunted increase)	↓ (blunted increase)	Continuing postprandial orexigenic stimulation may be involved in maintaining binge-eating behavior
Opioid system	β-endorphin CSF	↓	↓	Pathophysiological relevance of finding remains unclear; decreased central opioid activity might contribute to inhibition of ingestion
	β-endorphin in T lymphocytes	↑ ↓	n	
	Restrictive AN			
	Binge–purging AN			

↑ elevated; ↓ reduced; n, normal; CSF, cerebrospinal fluid; ACTH, adrenocorticotropic hormone; CRH, corticotropin-releasing hormone; LH, luteinizing hormone; FSH, follicle-stimulating hormone; fT_3, free triiodothyronine; fT_4, free thyroxine; TSH, thyroid-stimulating hormone; GH, growth hormone; IGF-1, insulin-like growth factor, type 1; i.s., in serum; BMI, body mass index; PYY, peptide YY.

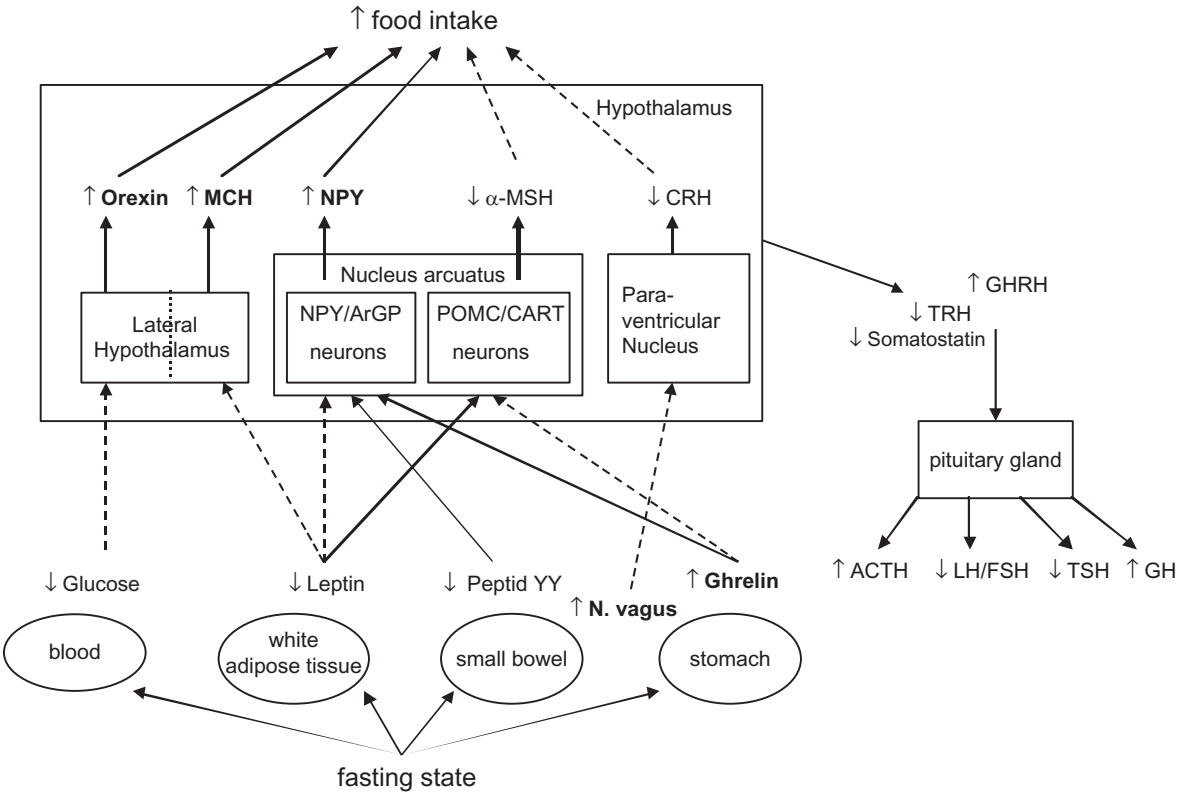

Fig. 26.1. Neuroendocrinological regulation of food intake (dashed lines, inhibition; bold letters, orexigenic effect). MCH, melanin-concentrating hormone; NPY, neuropeptide Y; α-MSH, α-melanocyte-stimulating hormone; CRH, corticotropin-releasing hormone; ArGP, agouti-related protein; POMC, pro-opiomelanocortin; CART, cocaine- and amphetamine-regulated transcript; TRH, thyroid-releasing hormone; GHRH, growth hormone-releasing hormone; ACTH, adrenocorticotropic hormone; LH, luteinizing hormone; FSH, follicle-stimulating hormone; TSH, thyroid-stimulating hormone; GH, growth hormone.

and obestatin (Monteleone et al., 2008). Weight gain decreases to normal elevated fasting ghrelin levels in patients with AN (Otto et al., 2001). The rise of ghrelin levels before food ingestion and the return to baseline levels shortly after meals designate its role in meal initiation. It is not clear whether AN subjects have resistance against ghrelin in the cachectic state. In contrast to normal-weight controls, ghrelin administration seems to have no effect on appetite in acutely ill AN patients (Miljic et al., 2006). On the other hand, Otto et al. (2005) found no differences in postprandial ghrelin decrease during weight gain in AN subjects, indicating that the suppression of ghrelin release is not disturbed by acute changes in energy balance (feeding) and seems to be independent of chronic changes (weight gain).

Preprandial ghrelin serum levels have been found to be normal (Monteleone et al., 2008) or increased (Tanaka et al., 2003, 2006) in symptomatic BN patients. More importantly, BN subjects show a blunted ghrelin response to food ingestion (Kojima et al., 2005), indicating a profound dysregulation of a gut–hypothalamic pathway in the symptomatic state of BN that might be involved in the maintenance of binge-eating behavior.

Obestatin levels in BN are similar to those of normal controls (Monteleone et al., 2008).

Peptide YY

Peptide YY (PYY) is thought to be a short-term appetite regulator belonging to the neuropeptide Y family secreted from endocrine cells of the gut (Adrian et al., 1985). Serum PYY rapidly increases after a meal and then remains elevated for hours, suggesting its possible role as a satiety signal (Batterham and Bloom, 2003). In contrast, injections of PYY into cerebral ventricles of mice potently stimulate feeding (Raposinho et al., 2001). The exact physiological role of PYY is the subject of intensive research. Few studies of PYY in eating disorders have been published so far.

In AN some studies found fasting levels of PYY to be elevated in the acute phase of the disorder (Kaye et al., 1990; Misra et al., 2006; Pfluger et al., 2007), whereas

others reported normal levels of PYY (Otto et al., 2007). Short-term weight recovery was not associated with a normalization of PYY in one study (Pfluger et al., 2007). However, in long-term recovered AN patients another study found normal levels of serum and CSF PYY (Gendall et al., 1999). Postprandial PYY release in AN subjects was blunted in one study (Stock et al., 2005), whereas another study reported a normal reaction of PYY (Otto et al., 2007). While it is theoretically possible that increased levels of PYY may play a role in a subset of patients with AN, further studies are needed to establish a causal relationship.

In BN two studies found normal preprandial PYY levels, but an attenuated PYY response to a test meal (Kojima et al., 2005; Monteleone et al., 2005a). Postprandial changes in circulating PYY were negatively correlated with changes in serum ghrelin levels (Monteleone et al., 2005b). As mentioned above, dysregulation of peripheral mechanisms involved in the short-term regulation of feeding behavior might be involved in the pathophysiology of BN.

Cholecystokinin

Cholecystokinin (CCK) is another satiety-inducing neuropeptide secreted by the gastrointestinal tract. CCK regulates motor functions in the gastrointestinal tract such as gastric emptying and gut motility and is thought to transmit satiety signals via the vagal pathway (Peters et al., 2006).

The results of studies of CCK in AN are inconsistent. Some studies found elevated basal plasma CCK levels and/or increased postmeal secretion of CCK (Harty et al., 1991; Tamai et al., 1993; Tomasik et al., 2004). Other studies found normal or decreased levels of CCK in AN subjects (Brambilla et al., 1995a; Baranowska et al., 2000).

Basal levels of CCK were found to be decreased in BN subjects during the acute stage of the disorder (Lydiard et al., 1993; Brambilla et al., 1995b). Most studies suggest that meal-induced CCK release is diminished in symptomatic BN subjects in comparison to controls (Devlin et al., 1997; Keel et al., 2007) but returns to normal following treatment (Geracioti and Liddle, 1988). It has been suggested that a blunted CCK response to a meal may be one underlying factor for disturbances of postingestive satiety found in bulimic patients.

Neuropsychological findings

Studies investigating neuropsychological functioning of patients with eating disorders have shown inconsistent results. On the one hand differences in methodology and varying stages of illness are regarded as explanations for differing results. On the other hand, only some of the patients seem to be affected by cognitive deficits. Clinical parameters like BMI, severity of the eating disorder, or symptoms of depression do not allow prediction of cognitive deficits (Bayless et al., 2002). In contrast, the presence and extent of neuropsychological deficits do not seem to predict poor prognosis of the eating disorder.

Neuropsychological assessment during the acute stage of AN demonstrates unspecific deficits of psychomotor speed and unspecific attention deficits (Lauer et al., 1999). The most consistent neuropsychological abnormalities that could be found in both acutely ill patients as well as in weight-stabilized subjects with AN affect implicit learning and set-shifting abilities (the ability to change categories: Steinglass et al., 2006; Roberts et al., 2007), indicating a disturbed functioning of frontohippocampal–striatal circuits. Similar dysfunctions are thought to underlie obsessive-compulsive disorders. In addition to multiple clinical similarities of AN and obsessive-compulsive disorder, these corresponding neuropsychological deficits probably suggest a shared biological background.

So far, few studies have been performed looking at neuropsychological deficits in bulimic patients. The results mirror those found in subjects with AN and point to state-dependent impairment of attention during the acute stage of BN (Lauer et al., 1999) as well as persistent deficits in set-shifting abilities after normalization of eating behavior (Roberts et al., 2007).

Treatment strategies

There has been remarkably little empirically supported research on the treatment of AN. This is likely due to the relatively low prevalence of the disorder and a high reluctance of patients to seek help. As a result, most recommendations are based on mainstream clinical opinion with little empirical support. The only controlled trials on behavioral interventions in adolescent AN have been performed in the context of family-based therapy. These studies consistently show that adolescents respond better to this kind of therapy in comparison to individual therapy, regardless of differences in design. However, most of these family-based interventions are performed on an outpatient basis, and patients are required to have a minimum body weight. Thus, these findings may not be transferred to severely emaciated patients.

In adult AN a nonspecific supportive clinical management treatment was more effective than specific treatments like cognitive-behavioral therapy (CBT) or interpersonal therapy (IPT) (McIntosh et al., 2005). In posthospitalization treatment CBT was more effective than nutritional counseling (for a review, see Fairburn, 2005).

A variety of drugs have been investigated in AN, mostly with negative results. Some well-designed studies demonstrated that selective serotonin reuptake inhibitors (SSRIs) are unlikely to provide substantial benefit for patients with AN during acute treatment and prevention. Second-generation antipsychotics are probably helpful for some patients; however, olanzapine is the only atypical neuroleptic that has been studied in more detail with rather positive, but preliminary, results (Bissada et al., 2008). To date, no medication for AN has been approved by the Food and Drug Administration (FDA) (for a review, see Bulik et al., 2007a; Herpertz-Dahlmann and Sahlbach-Andrae, 2009; Herpertz-Dahlmann and Hebebrand, in press).

In BN, CBT is the most frequently applied behavioral intervention, with strong evidence for effectiveness. At the end of treatment 30–40% of patients were symptom-free, and many of these patients maintained their improvement at long-term follow-up. However, in a controlled study at 1-year follow-up, IPT was as effective as CBT (Shapiro et al., 2007; Schmidt, 2009; Herpertz-Dahlmann and Sahlbach, 2009).

In contrast to AN there are several high-quality studies that have investigated psychopharmacological agents in BN. The SSRIs have been most studied in this disorder and are the only pharmacological agents that have been approved by the FDA for the treatment of adult BN. Other classes of medication that have proven helpful in adult BN are topiramate and odansetron, although only in studies with small sample sizes. The side-effect profile of topiramate is quite debilitating, with cognitive impairment and neurological symptoms, so that the usefulness of topiramate in eating disorders has to be questioned.

CONCLUSION

AN and BN are complex psychiatric disorders probably caused by genetic and environmental factors. The dieting and starvation process itself provokes severe neuroendocrinological, neurotransmitter, and neuropsychological alterations that may add to or even maintain eating disorder psychopathology. Although much progress has been made in improving treatment, there is still a rather high proportion of eating-disordered patients who fail to respond to any kind of therapy. Much more research is needed to come up with novel and more effective evidence-based pharmaceutical and psychotherapeutic interventions.

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