



1 Introduction

Bulimia nervosa (BN) is a severe eating disorder characterized by aberrant patterns of feeding behavior and weight regulation, as well as distorted perceptions and deviant attitudes toward body weight and shape (Kaye, 2004). BN is a complex condition related to a combination of long-standing behavioral, emotional, psychological, biological, interpersonal and social risk factors (Capasso et al., 2009). Several lines of evidence suggest that neurobiological vulnerabilities also contribute to the pathogenesis of BN.

Much research was conducted on the role of serotonin in bulimia nervosa (Jimerson et al., 1992; Kaye et al., 1998; Kaye et al., 2001), but there are also many indications of disturbance of the catecholamine system. Bulimia nervosa has been associated with a dysregulation of central catecholaminergic systems. Norepinephrine (NE) levels were found to be reduced in the cerebrospinal fluid of BN patients relative to controls (Buckholtz et al., 1988; George et al., 1990). Dopamine (DA) is involved in the rewarding properties of food (Fulton, 2010), in addiction (Koob, 2010) and is thought to moderate feeding by inhibiting hunger and reducing protein consumption. Thus, the dopaminergic system is considered a key neurotransmitter system in the pathophysiology of BN (Graybiel et al., 1994; Wang et al., 2002).

One instructive paradigm for directly investigating the relationship between catecholaminergic function and psychiatric condition involves the behavioral response to experimental catecholamine depletion (CD) achieved by oral administration of alpha-methyl-para-tyrosine (AMPT) (Berman et al., 1999; Booij et al., 2003; Hasler et al., 2004; Hasler et al., 2008). AMPT is an inhibitor of tyrosine hydroxylase, the rate-limiting enzyme in catecholamine biosynthesis (Nagatsu et al., 1964). The aim of CD is to lower brain catecholamine by depleting central norepinephrine and dopamine stores.

Most studies using catecholamine depletion were conducted in affective disorders (Delgado et al., 1993; Miller et al., 1996; Bremner et al., 2003; Hasler et al., 2008). While several studies using tryptophan depletion in BN showed a relation-



ship between diminished serotonin activity and lowered mood, irritability, body image concerns and loss of control over eating (Weltzin et al., 1995; Smith et al., 1999; Kaye et al., 2000; Bruce et al., 2009), no study has used CD to evaluate the roles played by norepinephrine and dopamine in the pathophysiology of BN.

The study presented in this Ph.D.-thesis was the first using the paradigm of catecholamine depletion in remitted subjects with bulimia nervosa (rBN).

The goal of the study was to evaluate the role of a possible catecholaminergic dysfunction in the pathogenesis of bulimia nervosa by assessing behavioral effects of catecholamine depletion in unmedicated, remitted female subjects with bulimia nervosa and healthy controls. The study employed a randomized, double blind, placebo-controlled crossover, single-site experimental trial in a psychiatric inpatient unit. Behavioral effects of CD were assessed using rating scales for eating disorder symptoms, depression and anxiety. Findings concerning CD-induced behavioral response are presented in Report 1.

Moreover, specific CD-induced changes of the brain reward system were assessed using a neuropsychological task measuring reward responsiveness. Results regarding dopamine related deficit in reward learning after catecholamine depletion are presented in Report 2.

Our results on the role of catecholamine in the pathophysiology of BN may have important clinical implications for subjects affected by bulimia nervosa and may provide relevant information for future research in BN and other eating-related conditions. The development of neurobiological and behavioral markers represents an important step toward an improvement and individualization of psycho- and pharmacotherapeutic interventions.



2 Theoretical Background

2.1 Bulimia Nervosa

Bulimia nervosa (BN) is a complex eating disorder characterized by recurrent episodes of binge eating and associated compensatory behaviors with the purpose of purging the ingested calories (Brambilla, 2001). Individuals with BN usually exhibit abnormal perceptions and pathological concerns towards body weight and shape (Kaye, 2004).

The onset of BN is often related to a period of food restriction and dieting, which may be associated with weight loss. The loss of control, demonstrated in binge-eating episodes, usually occurs proximate after the onset of dieting behavior.

Various means of compensation, such as self-induced vomiting or excessive exercise, are then adopted to balance the excess food-intake. Such inappropriate compensatory behaviors to prevent weight gain may lead to medical consequences. Most pathophysiological complications are reversible through improved nutritional status or remittance of abnormal eating and purging behaviors. However, some may have later repercussion on health. Some physical consequences as a result of weight change strategies, such as vomiting or misuse of diuretics and laxatives, can result in aspiration pneumonia, gastroesophageal reflux disease, Mallory-Weiss syndrome, electrolyte imbalances (e.g. hypokalemia), acute renal failure, underhydration or dental problems and caries (Treasure et al., 2009). Moreover, clinical consequences such as hypotension, bradycardia and hypothermia may occur due to a dysregulation of various neurotransmitter systems (e.g. noradrenergic system) (Pirke, 1996).

The occurrence of binge episodes, their duration and the quantity of food ingested during any one episode varies among patients. Irregular feeding patterns may also impair satiety in individuals with bulimia nervosa (Kaye et al., 2000).



2.1.1 Definition and Diagnosis

The term *bulimia nervosa* was introduced into medical literature by Russell in 1979 (Russell, 1979). However, BN, characterized by excessive food consumption (binge eating) and by inappropriate compensatory behavior such as self-induced vomiting to avoid weight, was not officially recognized until 1980, when the American Psychiatric Association (APA) provided criteria for its diagnosis (DSM-III, 1980).

In the fourth revision of the Diagnostic and Statistical Manual of Mental Disorders DSM-IV (APA, 1994); the section on eating disorders lists anorexia nervosa, bulimia nervosa and otherwise not specified disorders (EDNOS). Table 1 shows the diagnostic criteria for bulimia nervosa according to the DSM-IV. The criteria focus mainly on eating behavior and body distortions.

Table 1. Diagnostic Criteria for Bulimia Nervosa, DSM-IV.

DSM- IV, Diagnostic Criteria for Bulimia Nervosa	
A	Recurrent episodes of binge eating. An episode is characterized by both of the following: (1) Eating, in a discrete period of time (e.g., within any 2-hour period), an amount of food that is definitely larger than most people would eat during a similar period of time and under similar circumstances. (2) A sense of lack of control over eating during the episode (e.g., a feeling that one cannot stop eating or control what or how much one is eating).
B	Recurrent inappropriate compensatory behavior in order to prevent weight gain, such as self-induced vomiting; misuse of laxatives, diuretics, enemas, or other medications; fasting, or excessive exercise.
C	The binge eating and inappropriate compensatory behaviors both occur, on an average, at least twice a week for 3 months.
D	Self-evaluation is unduly influenced by body shape and weight.
E	The disturbance does not occur exclusively during a period of anorexia nervosa.
Specify type:	
<i>Purging type:</i> during the current episode of bulimia nervosa, the person has regularly engaged in self-induced vomiting or the misuse of laxatives, diuretics, or enemas.	
<i>Non-purging type:</i> during the current episode of bulimia nervosa, the person has used other inappropriate compensatory behaviors, such as fasting or excessive exercise, but has not regularly engaged in self-induced vomiting or the misuse of laxatives, diuretics, or enemas.	



The core features of bulimia nervosa include repeated episodes of binge eating followed by inappropriate compensatory behavior to prevent weight gain, such as self-induced vomiting, misuse of laxatives, excessive exercise, as well as abnormal concern with weight and shape (Kaye et al., 2000). The DSM-IV differentiates between those individuals with BN who apply self-induced vomiting or laxative, diuretic, or enema abuse (purging type) and those who engage in other forms of compensatory action, such as fasting or exercise (non-purging type).

Individuals with BN exhibit normal body weight (BMI=20-25), although they may aspire to ideal weights far below the normal range for their age and height.

2.1.2 Epidemiology and Comorbidities

Bulimia nervosa usually emerges during adolescence and affects 1% to 1.9% of females in the general population (Fairburn & Beglin, 1990; Treasure et al., 2010). BN typically begins during the period from mid-adolescence to the mid-twenties and generally peaks between 18 and 19 years of age (Kaye et al., 2000). The gender ratio between female and male is approximately 11:1 (Jacobi, 2004).

Compared to the normal population, people with BN have higher rates of lifetime diagnoses of anxiety disorders (30%), depressive disorders (50-75%) alcohol and substance abuse (30-37%) and obsessive compulsive disorders (up to 25%) (Jacobi, 2004; Kaye et al., 2004). The incidence for personality disorders account for between 42 and 75% (Jacobi, 2004). The personality characteristics of bulimia nervosa are heterogeneous; some are associated with borderline personality disorder (Cassin & von Ranson, 2005) and include high impulsivity, emotional instability, perfectionism, neuroticism. Other traits, such as harm avoidance, compulsivity, obsession, sensation seeking, extremes of intense emotion, low cooperativeness are also significant and may persist after recovery (Schmidt, 2003).