Research Report

Bulimia nervosa—a primary defect in the hypothalamic–pituitary–adrenal axis?

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Abstract

Bulimia nervosa has been associated with impaired satiety, decreased resting metabolic rate and abnormal neuroendocrine regulation. The aim of this study was to investigate the diurnal cortisol secretion and the pituitary-adrenal response to corticotropin-releasing hormone (CRH) in subjects suffering from bulimia nervosa. Eight female subjects with remitted bulimia nervosa, ages 24–56, and 8 sex- and weight-matched controls volunteered to participate. After an overnight fast they were admitted to the Clinical Research Center for 24 hour recording of plasma cortisol secretion. Blood were drawn every 2nd hour from 8 AM. After another overnight fast, the subjects performed a 120-min CRH test (100 μg i.v.), drawn for measurements of adrenocorticotropin releasing hormone (ACTH) and cortisol. Compared to the control group (CG), the diurnal cortisol secretions in the bulimic group (BG) decreased at time points 6 AM to 2 PM. In the CRH test, the ACTH response was significantly stronger in the BG than in the CG. Similar observations were found for cortisol, although not at significant levels. Remitted bulimic patients exhibit a neuroendocrine pattern of decreased HPA axis activity with a hyperreactivity to CRH. This may indicate a complex and so far poorly understood neuroendocrine dysregulation of HPA axis associated with the disease.

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Introduction

The eating disorder bulimia nervosa is characterized by recurrent episodes of uncontrolled over-eating, often involving extremely large amounts of high-calorie foods, compensatory behavior to avoid weight gain, and related behavioral and physiological symptoms (Christopher & Harrison, 2003). Although this disorder is of great interest to the public, to clinicians and to researchers, the mechanisms underlying the various symptoms typical of this disease are complex and badly understood. There is a genetic predisposition, and certain specific environmental risk factors have been implicated. Numerous studies have been performed in order to describe the neuroendocrine characteristics of the bulimics, and the eating behavior has been reported as an impaired post-digestive satiety, associated with a diminished responsiveness in satiety-related pathways (Kissileff et al., 1996). Several neurotransmitters have been associated with food intake and satiety (Kaye et al., 1990; Weltzin et al., 1991), and most attention has been focused on the limbic–hypothalamic–pituitary (HPA) axis that plays a crucial role in afferent and efferent signaling of satiety and hunger (Schwartz, Baskin, Kaiyala, & Woods, 1999). Studies have shown either normal (Fichter, Pirke, Pollinger, Wolfram, & Brunner, 1990; Vescovi et al., 1996) or increased (Ferrari et al., 1997; Koo-Loeb, Costello, Light, & Girdler, 2000; Monteleone et al., 2001) circadian secretion of cortisol in bulimics. Therefore, unlike patients with anorexia nervosa who with few exceptions have a hyper reactivity in the HPA axis (Licinio, 1996), the activity in the HPA axis in bulimia nervosa is more heterogeneous. The objective of this study was therefore to investigate the circadian rhythm of cortisol and the HPA axis in female subjects suffering from bulimia nervosa. We studied remitted bulimia patients in order to prevent secondary neuroendocrine disturbances to conditions such as overeating and psychological stress observed in an active phase of the disease.
Methods

Subjects were recruited from University-affiliated eating disorder programs and from advertisement in local newspaper. All the patients met the DSM-III-R criteria for bulimia nervosa (American Psychiatric Association, 1987) with the additional criteria of binge eating and purging, on the average, at least three times per week over the preceding 6 months. Diagnostic evaluation was also based on a modified version of the Schedule for Affective Disorders and Schizophrenia-Life version (Endicott & Spitzer, 1978). The patient group (BG) consisted of eight women (age 22–53 years) (BMI 19.1–38.0 kg/m²) (average duration of illness 5.7 years) without major depression, alcoholism, and substance abuse. None of the subjects had used psychotropic medications for at least 8 weeks before the study (according to self report in diary books and medical cards), no purging and/or overeating had taken place the last 3 weeks before the admittance to the Clinical Research Center. Therefore, at the time of testing, the subjects in the BG were all remitted bulimics with no purging or over-eating according to self-reported documentation. Eight age- (22–53 year) and weight-matched (BMI or over-eating according to self-reported documentation. Eight subjects in the BG were all remitted bulimics with no purging at least 8 weeks before the study (according to self report in diary books and medical cards), no purging and/or overeating had taken place the last 3 weeks before the admittance to the Clinical Research Center. Therefore, at the time of testing, the subjects in the BG were all remitted bulimics with no purging or over-eating according to self-reported documentation. Eight age (22–53 year) and weight-matched (BMI 22–38.3 kg/m²) women volunteered to participate as control subjects in the study. The control group (CG) were recruited among medical students and staff members who responded to advertisement in the local medical bulletin. The control group had no history of eating disorders, alcohol or drug abuse or other major psychiatric disorders. The BG and CG used no medication and were in good medical health as assessed by medical history, physical examination and baseline laboratory studies, including pregnancy and toxicology screening tests.

Protocols of Nutritional Intake. Registrations of all food consumed were recorded in a protocol of nutritional intake for 10 consecutive days prior to a 24 h blood sampling and a CRH test. Patients kept a detailed protocol of their food intake and of relevant events (binge attacks, vomiting, and stressful events). After the patients had been systematically trained to handle this protocol by a nutritional specialist, it was closely monitored. Patients were instructed to use conventional measurements (teaspoon, cup of certain size). Food consumption was calculated using a nutritional computer program (Food in Data, The National Association of Health, Oslo, Norway). The program delivers data for energy and nutrient content of consumed food.

Twenty-four hour blood samplings. Subjects were admitted to the Clinical Research Center at 8 AM after an overnight fast. The 24 h blood samplings were performed as described previously. The subjects remained in the hospital for 24 h, during which time they were free to move about until 11 PM, when they went to bed. Four meals (a total of 2200 kcal) consisting of 55% carbohydrate, 18% protein and 27% fat, were served at 8 AM, 12 PM, 4 PM and 8 PM. The meals were consistent with the average daily consumption of food the last 10 days before the endocrine assessments. No additional meals were allowed, but the subjects had free access to water. After 30 min rest in bed, baseline blood samples were drawn from an indwelling catheter, and blood was drawn every 2 h from 8 AM the first day until 8 AM the next day.

CRH test. The CRH test was performed as previously described (2). In short, after an overnight fast, the subjects were admitted to the Clinical Research Center at 8 AM. After an observation period of 30 min rest in bed, 100 µg CRH (corticorelin human trifluorocacet, Ferring, Kiel, Germany) was injected intravenously. Blood samples were drawn from an indwelling catheter at time points indicated during the 150 min observation period. All the subjects stayed in bed during that time.

Laboratory methods. Blood was collected in pre-cooled glass tubes containing 20 mmol EDTA and 1000 KIU apoproteinin (Trasylol® Bayer, Leverkusen, Germany) per ml blood, and kept on ice until centrifugation at 4 °C and storage at −27 °C. All serum samples were stored at −70 °C until analyzed by radioimmunoassay. Cortisol and ACTH were measured using commercial immunoassay kits (Immulite chemiluminescent immunoassay, DPC, Los Angeles, CA).

Statistical analysis. Group data are presented as the mean ± SD (mean only in figures). The significance of differences between the two groups in caloric intake and the plasma concentrations at a single time point was evaluated by a Wilcoxon sum rank test. The significance of differences between the two groups in the plasma concentrations of cortisol at various time points and the decremental plasma cortisol concentrations from time point 12 AM to 6 PM in the 24-h observation period; and the changes in plasma concentrations (after subtraction from time point at base line, 0 min) during the CRH test were evaluated by repeated-measures multivariate analysis of variance. P <0.05 was considered statistically significant.

Results

Food intake registered by diary card 3 weeks before the 24 h sampling and before the CRH test in the BG and the CG, showed no significant differences in caloric intake. No purging or overeating had taken place. The diary cards showed that the daily caloric intake in the BG equaled the daily caloric intake of the subjects in the CG (data not shown).

During the daytime a gradual decrease in the plasma concentrations of cortisol was found in both groups. The plasma cortisol concentrations were significantly lower in the BG at time point 6 AM to 2 PM (Fig. 1). In both groups, there was a lag in the reductions of cortisol secretion from 12 PM to 6 PM, but significantly more pronounced in the BG from 4 PM to 6 PM (Fig. 1).

Plasma ACTH. The non-rested (−30 min, 9 AM) plasma concentrations of ACTH were 17.7±7.2 (SD) and 13.9±5.6 pg/ml in the BG and CG, respectively (n.s.). After 30 min rest in bed (−30 to 0 min) (9 AM), the plasma concentrations of ACTH were reduced to 10.7±2.5 pg/ml in the BG and 9.9±2.2 pg/ml in the CG (n.s.) (Fig. 2). The plasma concentrations of ACTH increased to an apparent maximal level at 10 min in the BG and 30 min in the CG. At the end of the test (120 min) the values decreased to start level in both
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