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Ghrelin concentrations and cardiac vagal tone are decreased after pharmacologic and cognitive–behavioral treatment in patients with bulimia nervosa

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Abstract

Patients with bulimia nervosa (BN) have bulimic and depressive symptoms, which have been associated with abnormalities in the neuroendocrine and vagal systems. Subjects included twenty-four female drug-free outpatients with BN that were selected from patients seeking treatment for eating behavior in our hospital along with twenty-five age-matched healthy females who served as controls. We investigated ghrelin and leptin levels, cardiac vagal tone and sympathovagal balance, frequency of sets of binge-eating and vomiting episodes per week and the Profile of Mood States (POMS) depression scale in BN before and after a 16-week administration of the serotonin selective reuptake inhibitor (SSRI) paroxetine combined with cognitive–behavioral therapy. Compared to controls, the BN group had higher ghrelin levels and resting cardiac vagal tone, and lower leptin levels and resting cardiac sympathovagal balance before treatment, although there was a significant difference between the two groups for the body mass index (BMI). The elevated ghrelin levels (301.7 ± 18.9 pmol/l, mean ± SEM vs. 202.8 ± 15.6 pmol/l, $P < 0.01$), cardiac vagal tone (2246.4 ± 335.5 ms^2 vs. 1128.5 ± 193.3 ms^2, $P < 0.01$), frequency of sets of binge-eating and purging episodes and T scores for the POMS depression scale were all significantly decreased after treatment despite similar BMI, percent body fat and leptin levels. In close association with cardiac vagal function and ghrelin recoveries, abnormal eating behavior and depressive symptoms improved, indicating the usefulness of these indexes in the assessment of clinical condition and therapeutic efficacy in BN.

Keywords: Ghrelin; Leptin; Cardiac vagal tone; Bulimia nervosa

Introduction

Ghrelin was originally discovered in the rat and human stomach and stimulates growth hormone secretion (Kojima et al., 1999; Takaya et al., 2000), increases food intake (Tschöp et al., 2000; Asakawa et al., 2001) and enhances appetite (Wren et al., 2001). This is an orexigenic and gastrointestinal peptide that antagonizes leptin action (Inui, 2001) and which has a role in the regulation of eating behavior and energy metabolism in the central nervous system (Shintani et al., 2001; Nakazato et al., 2001) via the vagal system (Masuda et al., 2000; Asakawa et al., 2001; Date et al., 2002). Recent studies have found that fasting ghrelin levels in patients with bulimia nervosa (BN) are increased (Tanaka et al., 2002; Kojima et al., 2005; Fassino et al., 2005). In addition, we have shown that increased ghrelin concentrations may be associated with binge-eating and vomiting behavior (Tanaka et al., 2003a, 2004). A few studies have shown that BN patients have decreased fasting leptin concentrations (Jimerson et al., 2000; Brewerton et al., 2000) and elevated cardiac vagal tone (Kennedy and Heslegrave, 1989; Rissanen et al., 1998), which suggest that BN patients may have neuroendocrine and vagal system abnormalities. In addition, Rissanen et al. (1998) have shown that the use of the serotonin selective reuptake inhibitor (SSRI) fluoxetine combined with self-monitoring that is based on cognitive–behavioral treatment

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normalizes the elevated cardiac vagal tone in BN patients. Furthermore, BN patients have been reported to respond to treatment with the SSRI fluoxetine (Fluoxetine Bulimia Nervosa Collaborative Study Group, 1992; Goldbloom and Olmsted, 1993; Goldstein et al., 1995). The aim of this study was to examine ghrelin and leptin levels and cardiac vagal tone in subjects before and after a pharmacologic treatment program, which administered SSRI paroxetine in combination with cognitive–behavioral therapy.

Methods

Subjects

Twenty-four female BN patients between the ages of 19 and 32 years old (23.6 ± 0.8 years, mean ± SEM) and twenty-five age-matched (23.1 ± 0.6 years) apparently healthy female volunteers (controls) were enrolled as subjects in this study. BN patients were diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), and all subjects were outpatients examined at Kagoshima University Hospital between April 2002 and August 2003. Patients were excluded if they had a history of alcohol and substance abuse or past anorexia nervosa. Two patients were removed from the study due to non-compliance associated with side effects. Previous treatment histories, including medications, were not used as exclusionary criterion. At the time of initial assessment, all patients had been medication-free for at least 3 months and, once enrolled, did not take any prescription medications until commencement of the drug therapy. Bulimia diagnosis was confirmed by a structured clinical interview (First et al., 1995), which was administered at entry. Information about medical history, age at onset (20.5 ± 0.8 years), duration of illness (3.1 ± 0.4 years) and eating behavior was collected. Patients had habitual sets of binge-eating and vomiting at least twice a week over the preceding 3 months and were excluded if only purging behavior without vomiting was present. Control subjects were recruited from the local community and were interviewed about medical history and food intake over the week prior to initiation of the study. All controls had no history of eating and mental disorders and ate normal diets. In all subjects, body weight, height, percent body fat (Bolanowski and Nilsson, 2001), heart rate variability, plasma ghrelin and glucose, serum leptin, GH, amylase and potassium measurements were performed. BMI was calculated as weight (kg)/height squared (m^2). The Institutional Committee of Kagoshima University approved the study, and all subjects provided written informed consent prior to initiation of the study.

For 16 weeks, patients took 20 mg of paroxetine daily prior to going to sleep. Patients were monitored for side effects that occurred over a 2-week period, including nausea, sleepiness, dry mouth, constipation, blood pressure, tachycardia and sweating. In addition to the medical treatment, patients had individual 50 min cognitive–behavioral therapy sessions (Fairburn et al., 1993). Serum total amylase (Metzger et al., 1999) and potassium (Wolfe et al., 2001) concentrations were measured to determine the severity of binge-eating and purging. Both before and after 16 weeks of treatment, Profile of Mood States (POMS) was used to evaluate associated depressive symptoms. After 16 weeks of treatment, BMI, percent body fat, frequency of sets of binge-eating and purging, heart rate variability, plasma ghrelin and glucose, serum leptin, GH, amylase and potassium were measured and used to determine treatment efficacy.

Sampling and analysis

Blood samples from all subjects were collected between 8:00 and 10:00 AM after an overnight fast. Serum leptin concentrations were measured using an enzyme immunoassay (EIA) kit (LINCO Research, Inc., St. Louis, MO, USA). Serum GH concentrations were measured using a radioimmunoassay (RIA), with reagents provided by Daiichi Radioisotope Laboratories, Ltd. (Tokyo, Japan). Plasma glucose was measured by using a glucose autoanalyzer (Hitachi 7170 Autoanalyzer; Hitachi Ltd., Tokyo, Japan). Serum total amylase was measured using an EIA kit by AZ well corporation (Osaka, Japan). Serum potassium was measured using an ion-selective electrode method. Other blood samples were drawn into chilled tubes containing EDTA·2Na (1 mg/ml) and aprotinin (500 U/ml). The C-terminal region of plasma ghrelin was measured using RIA, as described elsewhere (Shiiya et al., 2002).

Before and after completing the 16-week treatment, subjects were placed in a supine position in a quiet room, and after a 10-min rest period, the surface electrocardiogram was continuously monitored for 10 min. Heart rate variability was assessed by the magnitude of individual components of the heart rate power spectral analysis (Akselrod et al., 1981; Hayano et al., 1990). The power spectral density includes a high-frequency (HF) component at the respiratory frequency and a low-frequency (LF) component at 0.03 to 0.15 Hz (Akselrod et al., 1981; Pagani et al., 1986). We calculated the mean amplitudes for the HF (0.20 to 0.30 Hz) and for the LF (0.03–0.15 Hz). The magnitudes of these components respectively provide indexes of cardiac vagal tone (HF) and cardiac sympathovagal balance (LH/HF) (Pagani et al., 1986; Bigger et al., 1995) with vagal modulation.

Statistical analysis

The subject groups (mean ± SEM) were compared using ANOVA and a post hoc Fisher's test because distributions of the data on BMI and percent body fat were examined for normality. Since the rest of the data distributions were skewed, a Kruskal–Wallis one-way ANOVA with a chi-square statistic was used to test for group differences for the other variables.

Table 1
Comparison of physiological data across study groups (mean ± SEM)

	Bulimia nervosa patients		Age-matched control group	Kruskal–Wallis test	*P* value
	Before treatment	After treatment			
Body mass index (kg/m^2)	18.5 ± 0.4*	19.0 ± 0.4*	21.4 ± 0.3	–	–
Percent body fat (%)	20.8 ± 0.7*	21.7 ± 0.8*	25.9 ± 0.7	–	–
Cardiac vagal tone (ms^2)	2246.4 ± 335.5[a,b]	1128.5 ± 193.3[b]	502.8 ± 42.9	24.3	<0.01
Cardiac sympathovagal balance	0.6 ± 0.1[b]	0.8 ± 0.2	0.9 ± 0.1	10.0	<0.01
Fasting plasma ghrelin (pmol/l)	301.7 ± 18.9[a,b]	202.8 ± 15.6[b]	150.3 ± 7.5	34.2	<0.01
Fasting serum GH (μg/l)	3.7 ± 0.6[b]	2.4 ± 0.7[b]	1.2 ± 0.2	17.4	<0.01
Fasting serum leptin (μg/l)	3.6 ± 0.5[b]	5.2 ± 0.7[b]	8.6 ± 0.7	25.6	<0.05
Fasting serum amylase (U/l)	136.2 ± 15.5[a,b]	89.1 ± 5.3	83.7 ± 2.0	17.0	<0.01
Fasting serum potassium (mmol/l)	4.1 ± 0.1	4.2 ± 0.1	4.3 ± 0.1	5.9	0.06
Fasting plasma glucose (pmol/l)	4.5 ± 0.1	4.8 ± 0.1	4.7 ± 0.1	3.6	0.17
Binge-eating and vomiting episodes (times/week)	9.3 ± 0.9[a,b]	2.1 ± 0.4[b]	0.0	51.5	<0.01
T scores of depression scale in POMS	70.5 ± 0.7[a,b]	61.1 ± 2.5[b]	46.9 ± 1.0	36.3	<0.01

* vs. control group, compared using ANOVA and a post hoc Fisher's test ($P < 0.01$).
[a]$P < 0.05$ vs. after treatment, [b]$P < 0.05$ vs. control group, using a chi-square statistic test.