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Ghrelin Levels After a Cold Pressor Stress Test in Obese Women With Binge Eating Disorder

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Abstract

Objective: Ghrelin, a peptide hormone secreted mainly by the stomach, increases appetite and food intake. Surprisingly, ghrelin levels are lower in obese individuals with binge eating disorder (BED) than in obese non-BED individuals. Acute psychological stress has been shown to raise ghrelin levels in animals and humans. Our aim was to assess ghrelin levels after a cold pressor test (CPT) in women with BED. We also examined the relationship between the cortisol stress response and changes in ghrelin levels.

Methods: Twenty-one obese (mean [standard deviation] body mass index = 34.9 [5.8] kg/m²) women (10 non-BED, 11 BED) underwent the CPT, hand submerged in ice water for 2 minutes. Blood samples were drawn for 70 minutes and assayed for ghrelin and cortisol.

Results: There were no differences between the groups in ghrelin levels at baseline (–10 minutes). Ghrelin rose significantly after the CPT ($F = 2.4$, $p = .024$) peaking at 19 minutes before declining ($F = 17.9$, $p < .001$), but there were no differences between the BED and non-BED groups. Area under the curve for ghrelin was not related to ratings of pain, stress, hunger, or desire to eat after CPT. In addition, there were no observed relationships between the area under the curves for ghrelin or cortisol after stress.

Conclusions: Although there were no differences between BED groups, there was a significant rise in ghrelin in obese humans after a stressor, consistent with other recent reports suggesting a stress-related role for ghrelin.

Keywords

stress responsivity; stress hormones; appetite; peptide hormones; hunger; eating disorders

INTRODUCTION

Binge eating disorder (BED) is characterized by the ingestion of very large meals with an associated sense of loss of control over eating, but without the purging that occurs in bulimia nervosa (BN) (1). Individuals with BED report significant clinical distress, have high rates of comorbid psychopathology (2), and increased lifetime prevalence of psychiatric diagnoses (3). In addition, BED is associated with (4) and contributes to the development of obesity (5), which has reached epidemic proportions in the United States and globally (6,7). The prevalence of BED in obese clinical samples varies, with estimates ranging from 7.5% to 30% of those who present for treatment (8–11). Obese individuals with BED are more resistant to weight loss treatment, have higher dropout rates, and show greater recidivism after weight loss compared with other people who are obese (1).

Stress is often reported as a primary trigger for binge eating, and self-reported negative mood has been shown to trigger loss of control over eating (12). Perceived stress seems to play a role, as binge eaters tend to judge laboratory and environmental stressors as more stressful than controls (13). Others have shown that restrained (14–16) and disinhibited (15) eating moderate the relationship between self-reported stress and eating behavior. Thus, negative effect arising from stress may increase an individual's sense of loss of control over food intake and precipitate binge eating in BED (12).

However, stress has been associated with both increased and decreased food intake (14,17), and the mechanisms underlying the relationship between stress and eating are poorly understood (18). One previously hypothesized mediator of stress and binge eating is cortisol, a stress hormone involved in regulating caloric consumption (19), which can result in increased food intake (20,21). In a previous study, we observed higher basal cortisol levels in BED and a trend toward greater cortisol after a cold stress test in BED compared with non-BED (22).

Ghrelin, a peptide hormone secreted mainly by the stomach, increases food intake in animals (23) when administered peripherally or centrally and in humans when infused intravenously (24). Surprisingly, fasting ghrelin is lower in obese than in normal-weight individuals (25). In one report, a smaller fall in ghrelin after a meal was observed in obese participants compared with lean participants (26), which might act to maintain hunger. A different result was found in another report (27). The lower fasting ghrelin levels in obesity suggest that ghrelin is down-regulated in response to overeating or excess body weight (25,28). Ghrelin levels have recently been reported in BED, with lower fasting ghrelin (29,30) and a smaller postprandial decline in BED than in non-BED obese individuals (30,31). Ghrelin levels were activated after acute psychological stress in a recent study of rats (32) and in women with and without BN (33) and the night eating syndrome (34), although other reports in humans are inconsistent (35).

Therefore, in this study, we investigated the ghrelin stress response to a cold pressor test (CPT) in obese women with BED. The CPT has been widely used as a stress test (36) and has been shown to produce greater cortisol responses in obese (37) and obese BED individuals (22,38). Our primary aims were to determine whether ghrelin rises in response to

a stressor in humans and whether obese women with BED would exhibit a greater response compared with similarly obese non-BED women. Our secondary aim was to examine the relationship between the cortisol response and the ghrelin response to the stressor.

METHODS

Participants

Overweight women (body mass index [BMI] $>27 \text{ kg/m}^2$) were recruited through local advertisements between July 2000 and December 2004 for an outpatient study at the New York Obesity Research Center of St Luke's/Roosevelt Hospital. During the initial telephone interview, candidates were screened to exclude those with significant health problems (including gastrointestinal, heart, kidney, liver, or Raynaud disease [extreme peripheral sensitivity to cold], cancer, hypertension, or diabetes). Additional exclusion criteria included unstable body weight ($\pm 5\%$) in the past 3 months, current or recent dieting (past 3 months), smoking, use of medications affecting body weight, substance abuse or dependence within the past 6 months, or previous hospitalization for psychiatric illness. Women were also excluded if pregnant or lactating but not if taking oral contraceptives (39–41). At the initial consultation, they signed a consent form that, along with the study protocol, had been approved by the hospital institutional review board. They underwent a physical examination including medical history, electrocardiogram, and blood tests to ensure good health other than obesity.

The participants ($n = 38$) completed the Questionnaire on Eating and Weight Patterns, a validated and widely used self-report instrument to diagnose BED (9,42,43), which was then confirmed by clinical interview. Thirteen were classified as non-BED because they denied episodes of overeating, and 11 met full DSM-IV diagnostic criteria and were classified as BED. The remaining 14 were classified as subthreshold binge eaters, not meeting the full criteria for BED, and were excluded from the analysis. Two non-BED participants dropped out of the study because of their time limitations, leaving 21 women (10 non-BED, 11 BED).

Procedures

Body Composition—Percentage of body fat was assessed by underwater weighing (Precision Biomedical Systems) to obtain water displacement, a classic method to determine body volume and density. The technicians performing the body composition assessments were blind to the participants' binge eating status.

Cold Pressor Test—On a separate day, participants arrived at the hospital after a 12-hour overnight fast, and an intravenous catheter was inserted. Participants were given a fixed meal (600 ml of Boost [complete nutritional liquid meal; Mead Johnson], prepared 1:1 with water, 2.1 J/g) and had periodic blood draws for 120 minutes for an unrelated study and then rested for 2 hours. Participants then underwent the CPT (mean [standard deviation {SD}] = 12:46 [1:14] PM) and immersed their nondominant hand, for a total of 2 minutes, in a rectangularshaped container of 0°C ice water. Blood was drawn at -10 and 0 minutes to assess baseline measures, then at 2 minutes, corresponding to hand withdrawal, and at 5, 15,

30, 45, and 60 minutes relative to initial hand submersion. Digital monitors assessed diastolic and systolic blood pressure (BP) and heart rate (HR). Ratings of stress and pain, as well as hunger and fullness, were made by the participant on a visual analog scale (VAS) from 0 to 100, just before each blood draw.

Hormone Assay

Blood samples for ghrelin were collected in tubes containing EDTA and aprotinin (Trasylol). All tubes were kept on ice and then cold centrifuged for 15 minutes to obtain plasma, which was stored at -70°C until assayed. Total ghrelin was measured by a radioimmunoassay kit from Phoenix (intra-assay coefficient of variation [CV] = 2.7, interassay CV = 3.2). Total plasma cortisol, which may be a better index than free cortisol in assessing adrenal responsiveness (43), was measured by radioimmunoassay kit from Diagnostic System Labs (intra-assay CV = 2.8, interassay CV = 4.8).

Data Analyses

Univariate analyses of variance (ANOVAs) were used to compare group parametric measures. Area under the curve (AUC) by the trapezoidal method was calculated for ghrelin, cortisol, and glucose levels, as well as for BP and HR measures and for VAS ratings. To test for baseline differences between BED and non-BED, we conducted independent t tests, also using averaged baseline values. Pearson correlations (r) were used for continuous dependent variables, and χ^2 for categorical data.

Two-way (BED group, time) ANOVA for repeated measures was performed to reveal effects of “time” (eight levels), “group” (non-BED versus BED), and their interaction on ghrelin, cortisol, and VAS ratings after the CPT. Missing data were obtained by interpolating between adjacent time points or by carrying forward the last value if the final value was missing.

Time to the peak concentration was identified as the time point (2 minutes) with the highest ghrelin concentration for each individual. These values were then averaged to obtain the mean time to peak for each group (BED versus non-BED). Change () from baseline to peak concentration was based on the change from the mean of the two baseline concentrations ($[-10 + 0]/2$) to the peak concentration. Change from peak concentration to the last observation was based on the change from the peak concentration to 60 minutes. Change over the entire blood sampling period was based on the change from the mean of the two baseline concentrations ($[-10 + 0]/2$) to 60 minutes.

Results from the current study are based on the same cohort described previously (22,38). Thus, the primary findings concerning ghrelin will be presented here, but more detailed information about cortisol levels can be found in the prior articles. Results are presented as means (SD), with two-tailed $p < .05$ and $p < .10$ required for statistical significance of repeated-measures analyses. For baseline, change, and AUC comparisons, we set value of $p < .01$ as the α level to control for multiple comparisons. Data were analyzed using the Statistical Package for the Social Sciences (version 17.0, 2009; SPSS, Chicago, IL).

RESULTS

Participant Characteristics

BMI, age, percentage of body fat, contraceptive use, and menstrual phase were similar between BED and non-BED groups and did not change the results when entered as covariates. Because none of these variables differed by BED status, they were not included as covariates in further analyses (Table 1).

Ghrelin

Baseline ghrelin levels at –10 minutes before CPT were not significantly different between BED and non-BED ($F=1.2$, $p=.28$; Fig. 1). Repeated-measures ANOVA revealed that ghrelin levels increased significantly after CPT ($F=2.4$, $p=.024$) but did not differ between BED and non-BED ($F=1.3$, $p=.22$), and there was no significant interaction ($F=1.4$, $p=.20$; Fig. 1). The mean (SD) time to peak ghrelin was 17 (13) minutes (median = 17 minutes [95% confidence interval = 9–26]) in the BED group and 22 (17) minutes (median = 22 minutes [95% confidence interval = 10–34]) in the non-BED group, which did not differ ($F=0.50$, $p=.54$), and there were also no differences in peak ghrelin concentrations between BED (26 [12] pg/ml) and non-BED (33 [15] pg/ml; $F=1.5$, $p=.24$). Ghrelin levels then declined significantly from the peak to 60 minutes ($F=17.9$, $p<.001$), without differing by group (BED = 6.0 [3] pg/ml versus non-BED = 5.0 [2.5] pg/ml; $F=0.17$, $p=.68$). AUC for ghrelin also did not differ between BED (944.3 [376.1] pg/ml) and non-BED (1260.4 [646.6] pg/ml), either before ($F=1.9$, $p=.18$) or after controlling for baseline ghrelin levels ($p=.43$).

Cortisol

After CPT, cortisol levels increased significantly ($F=4.6$, $p<.001$) but did not differ between BED and non-BED ($F=0.39$, $p=.36$; Fig. 1).

Correlations for Ghrelin and Cortisol

AUC for ghrelin was not significantly correlated with AUC for cortisol, and there were no significant correlations between AUC cortisol and ghrelin levels or between ghrelin and cortisol levels at any time point. There were no significant correlations of AUC for ghrelin or changes to peak ghrelin levels with either AUC for BP, HR, or VAS ratings of pain, stress, hunger, or desire to binge eat (all p values $>.05$; Table 2).

DISCUSSION

This study showed a rise in ghrelin levels after a physiological stress in humans. The results are consistent with a report of higher ghrelin in rats after a 60-minute water avoidance stress test (32). It is possible that ghrelin helps organisms deal with stress, although we did not observe a relationship between ghrelin and cortisol responses. It may be that cortisol and ghrelin are acting independently in response to stress (44). Both ghrelin (24,45) and cortisol (20,21) also promote food intake, and both hormones may help replenish fuel stores to deal with a physically demanding and stressful situation.

Our findings differ from those of Zimmerman et al., (46) who failed to observe significant changes in ghrelin in healthy male volunteers after the Trier Social Stress Test (TSST). Results from the present study also differ somewhat from Rouach et al. (35), who observed increased plasma ghrelin levels in humans after the TSST, but only in a subset of cortisol responders. One possible explanation is the choice of stress test used in our study. The CPT is perceived as painful (36) and psychologically stressful to participants (22). It has been shown to reliably produce a cortisol stress response in healthy individuals and in those with depression (36), BED (22), and obesity (34,37) and has been shown to enhance ratings of hunger desire to binge eat in a previous study (22). The water avoidance test used in animal studies is a similarly acute psychological stressor also known to induce robust cortisol and ghrelin responses (32). Thus, it is possible that the CPT may have induced a greater ghrelin response in comparison with the TSST used in previous studies (35,46). Although both the CPT and TSST are considered psychological stressors, we chose the CPT to eliminate the possible confound of conditioned eating in response to social cues that might be elicited during interpersonal social stress tests, such as the TSST. Future studies could directly compare the responses to multiple laboratory stressors to better understand any differing responses.

Ghrelin responses to stress were similar between BED and non-BED in both the present study and the study of Rouach et al. (35). In a recent study, there was a significantly longer and greater salivary ghrelin increase in patients with BN compared with controls after the TSST (33), although it is unclear to what extent salivary ghrelin reflects circulating ghrelin. In the same study, the authors did not observe differences in cortisol levels after TSST in patients with BN compared with controls (33). In a previous study from our group, we found a trend for increased cortisol levels and hunger ratings after CPT in BED compared with non-BED (22). We also observed a relationship between cortisol levels after stress and greater hunger in BED, but we did not observe such a relationship in the present study or between ghrelin and other markers of hunger or stress. The lack of a significant correlation between hunger and ghrelin is somewhat surprising, although we also failed to observe this relationship between hunger ratings and ghrelin levels in a study comparing obese women with and without night eating syndrome (34). Similarly, there are other non-stress-related studies where this has also been found. For example, although hunger ratings increased following a high-dose ghrelin infusion, there were no changes in hunger ratings after a low-dose infusion in lean or obese participants (45). Furthermore, circulating ghrelin concentrations were not significantly related to any satiety marker after a test meal in anorexic, obese, or control female adolescents (47). In one study, obese compared with lean participants ate more during a buffet meal after a low-dose ghrelin infusion (45), but food intake was not assessed in the current study.

It is possible that an increase in stress-induced ghrelin levels does not mediate hunger per se, but instead acts to mediate reward. The affect-regulation model posits that those who binge eat do so to control negative emotions (16) because binge eating alleviates aversive feelings. There is evidence that ghrelin targets key reward circuitry (48,49), increasing motivation for natural rewards such as food (50). In recent studies, both intravenous ghrelin infusions (51) and fasting ghrelin levels (52) were positively correlated with neural responses elicited by pictures of palatable food shown to healthy volunteers during functional magnetic resonance

imaging, particularly in brain regions implicated in areas that control appetitive behavior. These studies support the notion that, in accordance with the affect-regulation model, the ghrelin rise we observed after stress exposure could lead to increased food intake as an attempt to replace negative emotions with the rewarding, positive feelings of pleasure achieved by the ingestion of food (33).

There are several limitations to this study including a relatively small sample size, lack of a nonstress control condition, and lack of a normal-weight control group. Although two appetite-related ratings were obtained, a laboratory measure of food intake was not included. A point for discussion is that the CPT is a physiological stressor rather than a social stressor and might not be as relevant to the type of stress that precipitates eating in BED. Although binge eating is often preceded by psychologically stressful events, our view was that the stress response is similar, whether the stressful event is physical, psychological, social, or physiological as all stress events activate the hypothalamic-pituitary-adrenal axis. Although this physiological stressor does not adequately replicate real-life stress and may not mimic the kind of stress that commonly precipitates binge eating in BED, exposure to a CPT led to elevated ratings of hunger desire to binge eat in our pilot study (22), and thus, we chose a stress test that would reliably produce a physiological stress response. Finally, it is possible that our use of total versus free cortisol may be a factor in the observed results. Saliva-based (free) cortisol measurements might be more accurate in situations where acute changes are present (53), such as the ones examined in the current study, and our results might have differed had we used a free cortisol measurement.

In conclusion, we found increased ghrelin levels in obese women with and without BED after stress, suggesting a possible new stress-related role for ghrelin

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Glossary

AUC	area under the curve
BED	binge eating disorder
CPT	cold pressor test
DST	dexamethasone suppression test
VAS	visual analog scale
BN	bulimia nervosa

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Figure 1.

Ghrelin and cortisol levels before and after cold pressor task in obese women with and without BED. CPT was administered at time 0 and lasted for 2 minutes. There was a significant rise in ghrelin after CPT ($p = .024$), with a mean peak at 19 minutes, without differing between BED and non-BED groups. There was a significant rise in cortisol after CPT ($p < .001$) but no difference between BED and non-BED groups. BED = binge eating

disorder; non-BED = non-binge eating disorder; CPT = cold pressor test; SE = standard error.

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TABLE 1.

Participant Characteristics

	Non-BED	BED	Statistic	<i>p</i>
<i>n</i>	10	11		
Age, y	32.2 (9.3)	29.0 (8.4)	$F = 0.69$	.42
Body weight, kg	92.4 (14.1)	97.8 (18.8)	$F = 0.51$	.49
BMI, kg/m ²	35.5 (5.1)	36.6 (6.2)	$F = 0.20$	.66
P-fat, %	40.6 (4.1)	41.7 (6.4)	$F = 0.21$	.66
Waist-hip ratio	0.88 (0.10)	0.83 (0.05)	$F = 1.9$	.19
Menstrual phase	Menstrual (<i>n</i> = 2)	Menstrual (<i>n</i> = 2)	$\chi^2 = 2.91$	.41
	Follicular (<i>n</i> = 1)	Follicular (<i>n</i> = 3)		
	Luteal (<i>n</i> = 5)	Luteal (<i>n</i> = 4)		
Contraception use	No (<i>n</i> = 9); yes (<i>n</i> = 1)	No (<i>n</i> = 9); yes (<i>n</i> = 2)	$\chi^2 = 0.59$	.54

BED = binge eating disorder; non-BED = non-binge eating disorder; BMI = body mass index; P-fat = percentage of body fat.

Menstrual cycle: 1, follicular/bleeding; 2, follicular/no bleeding; 3, luteal. Values are presented as mean (SD), except for contraceptive use. There were no significant differences between groups in any of these characteristics.

TABLE 2.

Correlation Matrix

	AUC Ghrelin	AUC Cortisol	AUC Desire to Binge	AUC Hunger	AUC Pain	AUC Stress	AUC DBP	AUC SBP	AUC HR	Peak Ghrelin	Peak Cortisol
AUC ghrelin	1	-.077	-.0268	-.305	-.135	-.189	-.316	-.082	-.401	.460*	0.132
AUC cortisol		.74	.23	.18	.56	.41	.20	.74	.07	.036	.57
AUC desire to binge		1	0.242	0.117	0.453*	0.107	-.037	-.0231	0.229	0.307	0.279
AUC hunger			.29	.61	.039	.64	.88	.35	.31	.17	.22
AUC pain			1	0.735**	0.559**	0.664**	0.051	-.0002	-.011	-.0178	0.221
AUC stress				<.001	.008	<.001	.84	.99	.96	.44	.33
AUC DBP				1	0.447*	0.325	0.162	0.206	0.039	-.0142	0.166
AUC SBP					.042	.15	.52	.41	.86	.54	.47
AUC HR					1	0.422	-.020	-.0285	0.185	-.0187	0.180
Peak ghrelin						.057	.94	.25	.42	.42	.43
Peak cortisol						1	0.270	-.0013	0.030	-.0059	0.545*
							.29	.96	.89	.80	.011
							1	0.806**	0.200	-.0351	0.133
								<.001	.42	.15	.60
							1	1	-.0113	-.0400	0.018
								.65	.10	.10	.94
								1	-.0203	-.0224	.33
									.38	1	0.225
											.33
											1

AUC = area under the curve; SBP = systolic blood pressure; DBP = diastolic blood pressure; HR = heart rate.

Binge eating disorder and non-binge eating disorder combined ($n = 21$). Top line represents Pearson correlation coefficient Second line represents p values. Peak ghrelin = change in ghrelin concentration from baseline to peak concentration. Raw AUC values are presented without controlling for baseline levels.* $p < .05$ ** $p < .001$.