Appetite Regulatory Hormones in Women With Anorexia Nervosa: Binge-Eating/Purging Versus Restricting Type

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ABSTRACT

Objective: Anorexia nervosa is a psychiatric illness characterized by low weight, disordered eating, and hallmark neuroendocrine dysfunction. Behavioral phenotypes are defined by predominant restriction or bingeing/purging; binge-eating/purging type anorexia nervosa is associated with poorer outcome. The pathophysiology underlying anorexia nervosa types is unknown, but altered hormones, known to be involved in eating behaviors, may play a role.

Method: To examine the role of anorexigenic hormones in anorexia nervosa subtypes, we examined serum levels of peptide YY (PYY; total and active [3-36] forms), brain-derived neurotrophic factor (BDNF), and leptin as primary outcomes in women with *DSM-5* restricting type anorexia nervosa (n = 50), binge-eating/purging type anorexia nervosa (n = 25), and healthy controls (n = 22). In addition, women completed validated secondary outcome measures of eating disorder psychopathology (Eating Disorder Examination-Questionnaire) and depression and anxiety symptoms (Hamilton Rating Scales for Depression [HDRS] and Anxiety [HARS]). The study samples were collected from May 22, 2004, to February 7, 2012.

Results: Mean PYY 3-36 and leptin levels were lower and BDNF levels higher in binge-eating/purging type anorexia nervosa than in restricting type anorexia nervosa (all P values < .05). After controlling for body mass index, differences in PYY and PYY 3-36 between anorexia nervosa types were significant ($P < .05$) and differences in BDNF were at the trend level ($P < .10$). PYY 3-36 was positively ($r = 0.27$, $P = .02$) and leptin was negatively ($r = -0.51$, $P < .0001$) associated with dietary restraint; BDNF was positively associated with frequency of purging ($r = 0.21$, $P = .04$); and leptin was negatively associated with frequency of bingeing ($r = -0.29$, $P = .007$) and purging ($r = -0.31$, $P = .004$).

Conclusions: Among women with anorexia nervosa, the anorexigenic hormones PYY, BDNF, and leptin are differentially regulated between the restricting and binge/purge types. Whether these hormone pathways play etiologic roles with regard to anorexia nervosa behavioral types or are compensatory merits further study.

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Anorexia nervosa is a psychiatric illness of unknown etiology defined by aberrant eating behaviors, persistent low body weight, body image disturbance, and amenorrhea.[1] Anorexia nervosa is associated with refractoriness to treatment, an often chronic course, and increased mortality risk. The *DSM-5* defines 2 anorexia nervosa subtypes: restricting type, in which weight loss is achieved or maintained primarily through dietary restriction, and binge-eating/purging type, in which restriction is coupled with binge eating and/or purging behaviors. Approximately 50% of patients will experience diagnostic "crossover" from pure restriction to binge/purge behaviors during their illness course.[2,3] Binge-eating/purging type anorexia nervosa is considered to be a more pernicious form of the illness, associated with increased medical morbidity, impulsivity, suicidality, and poor outcome, relative to restricting type anorexia nervosa. However, hormonal mechanisms underlying disordered eating behaviors that characterize anorexia nervosa and the subtypes or predict crossover are unknown, which challenges identification of those with anorexia nervosa who may be at greatest risk.

Neuroendocrine dysfunction is a hallmark of anorexia nervosa, although it is not universally manifested by such patients,[4] and appetite-regulating hormone patterns may be involved in the pathophysiology of the subtypes. Peptide YY (PYY), brain-derived neurotrophic factor (BDNF), and leptin are anorexigenic appetite-regulating hormones, and knock-out rodent models are characterized by hyperphagia,[5–7] suggesting a possible role for these hormones in the development or maintenance of binge/purge or restrictive behaviors.[8] Although these hormones have been found to be dysregulated in anorexia nervosa, whether between-subtype differences exist is not known.

Peptide YY is a 36-amino acid polypeptide hormone released in the ileum and colon in response to food ingestion that modulates appetite by binding with receptors to signal satiety and cue appetite reduction. Peptide YY 3-36 is the main circulating form of the peptide released in both the fasting and postprandial states. Studies report that fasting and postprandial PYY and PYY 3-36 are increased in those with active anorexia nervosa relative to controls.[9–11] Our group previously reported that PYY was positively associated with a drive for thinness and eating concerns in women with anorexia nervosa, lean and obese controls.[9] However, differences between the anorexia nervosa subtypes were not examined.[9] Most studies of PYY demonstrate higher levels in anorexia nervosa than controls, despite the fact that PYY is anorexigenic and therefore would be expected to be suppressed in anorexia nervosa (ie, if it were to function adaptively). However, the literature focuses mostly on restricting type anorexia nervosa. Only 1 study[12] has examined differences in PYY between anorexia nervosa subtypes, finding that PYY was decreased in both anorexia nervosa subtypes, with no differences in PYY between restricting type and binge-eating/purging type. Studies of PYY in normal-weight

Clinical Points

- Appetite-regulating hormones are dysregulated during acute anorexia nervosa, and mean levels differ between the binge-eating/purging and restricting anorexia nervosa subtypes.
- Cross-sectional findings raise the possibility that anorexigenic peptide YY is pathogenic to restriction in anorexia nervosa and that increased brain-derived neurotrophic factor is linked to purging behaviors. Further studies are needed to investigate these relationships.

bulimia nervosa are inconsistent, with some studies reporting decreased levels[12–14] and others reporting an increased response.[15]

Brain-derived neurotrophic factor is also an anorexigenic hormone. Brain-derived neurotrophic factor, a neurotrophic protein and member of the nerve growth factor family, is distributed throughout the central nervous system and is known to exert effects on neuronal growth, differentiation, plasticity (specifically memory and learning), and functions to modulate neurotransmitters. Researchers have postulated a role for BDNF in the regulation of eating behaviors.[16,17] However, the specific nature of the relationship between BDNF and eating behaviors in humans is not understood. A recent meta-analysis[18] found that BDNF levels were lower in active restricting type relative to healthy controls. Further, population genetic studies have raised the possibility that the *BDNF* gene could be an etiopathological factor in the development of restricting-type anorexia nervosa.[19] Published studies in anorexia nervosa have not had sufficient power to examine this possibility. Saito et al[20] demonstrated higher mean serum BDNF levels in a group of normal-weight women with bulimia nervosa compared with women with anorexia nervosa, but the differences between the groups may have been attributable to the differences in weight between the groups. Whether BDNF levels in women with eating disorders are related to restriction, binge eating, and purging behaviors rather than weight has not been previously explored.

Leptin is a fat-derived hormone that signals satiety and is decreased in anorexia nervosa compared to healthy controls[21,22] and increases with weight restoration.[23,24] As it is a fat-derived hormone, it is not clear whether low leptin levels are related to eating disorder psychopathology independent of body weight. Yet, decreased leptin levels have also been found in some women with bulimia nervosa relative to healthy controls and are inversely related to duration of illness and binge/purge frequency.[25] Leptin has not been examined between the anorexia nervosa subtypes.

We chose to examine anorexigenic appetite-regulating hormones in individuals with anorexia nervosa to explore the role of these hormones in relation to the array of eating-related symptoms focusing expressly on anorexia nervosa subtypes; we investigated between-subtype differences in addition to differences between women with anorexia nervosa and healthy control females. We hypothesized that differences in secretion of these hormones in restricting versus binge-eating/purging anorexia nervosa subtypes would reflect the phenotypic differences in eating-related behaviors and possibly also comorbid psychopathology. On the basis of the limited extant literature, we hypothesized that PYY would not differ between the anorexia nervosa subtypes and would be increased in anorexia nervosa relative to controls; that BDNF would be lower in restricting type than in binge-eating/purging type, and lower in both groups relative to controls; and that leptin would be decreased in both anorexia nervosa subtypes relative to controls and explained by differences in body mass index (BMI).

METHOD

The study was approved by the Partners HealthCare Institutional Review Board, Boston, Massachusetts. Written informed consent was obtained from all subjects.

Participants

Participants included 75 women with *DSM-5* anorexia nervosa (50 with restricting type, and 25 with binge-eating/purging type), and 22 lean healthy control females of comparable mean age. Anorexia nervosa participants met *DSM-5*[1] criteria (ie, low weight, intense fear of weight gain, body image disturbance; amenorrhea was not required) and were recruited through a network of referring specialty eating disorders health care providers or through advertising. Healthy control participants were also recruited through advertisements and were defined by an absence of any lifetime eating disorders or significant anxiety and depression, no major medical problems or history of amenorrhea, and a healthy weight (> 90% of ideal body weight, and a body mass index of < 25). Anorexia nervosa subtype assignment was made per *DSM-5* recommendations (ie, on the basis of presence or absence of binge eating and/or purging behaviors in the past 3 months) and thus reflected *current* symptom presentation.

Clinical characteristics and some hormonal data, but not BDNF levels or anorexia nervosa subtype comparisons, were previously reported on small subsets of these subjects.[9,26–29]

Hormone Assays

Serum samples were collected from participants in the morning (fasting not required), and samples were immediately centrifuged and frozen after collection. (Serum samples were not frozen before centrifugation.) The samples were stored at −80°C until assessment. Serum total PYY and PYY 3-36 were measured by radioimmunoassay (Millipore Corp). Serum total PYY had intra-assay coefficients of variation (CV) of 2.8%–4.7%, an interassay CV of 3.3%, and a detection limit of 22 pg/mL. Serum PYY 3-36 had intra-assay CVs of 2.3%–3.3%, an interassay CV of 8.2%, and a detection limit of 44 pg/mL. Note that aprotinin and dipeptidyl peptidase 4 (DPP-IV) were not added per manufacturer's recommendations, which may be a limitation. Serum BDNF was measured by an immunoassay (ELISA, R&D Systems, Inc) with an intra-assay CV of 0.9% and a detection limit of < 1 ng/mL. Serum leptin was measured with an ELISA assay (Millipore Corp.) with an intra-assay CV of 0.3%–2.6%, an interassay CV of 4.7%, and a detection limit of 0.195 ng/mL.

Table 1. Comparison Between Anorexia Nervosa Restricting and Binge-Eating/Purging Subtypes

Variable	Restricting Type Anorexia Nervosa (n = 50)[a]	Binge-Eating/Purging Type Anorexia Nervosa (n = 25)[a]	*P* Value[b]
Clinical characteristic			
Age, y	25.0 ± 0.8	27.5 ± 1.7	.28
BMI (kg/m^2)	17.5 ± 0.1	17.0 ± 0.2	**.01**
Duration of illness, y	6.0 ± 0.7	10.2 ± 1.8	.07*
Oral estrogen or progestin use (yes/no)	11/39	10/15	.11
Psychiatric medication use (yes/no)	26/24	17/8	.22
Selective serotonin reuptake inhibitor use (yes/no)	17/33	8/17	1
Anorexigenic hormones			
Total PYY, pg/mL	116 ± 6	102 ± 7	.10*
PYY 3-36, pg/mL	86 ± 5	68 ± 4	**.01***
BDNF, ng/mL	13.6 ± 0.9	17.2 ± 1.5	**.04****
Leptin, ng/mL	1.6 ± 0.2	1.1 ± 0.2	**.03**
Eating disorder psychopathology			
No. of purging episodes/wk	0.0 ± 0.0	5.6 ± 2.8	**< .0001***
No. of bingeing episodes/wk	0.6 ± 0.4	6.4 ± 3.0	**< .0001***
EDE-Q dietary restraint	2.5 ± 0.2	4.3 ± 0.3	**.0002***
EDE-Q eating concern	2.2 ± 0.2	3.8 ± 0.3	**.0005***
EDE-Q shape concern	3.2 ± 0.3	4.6 ± 0.3	**.003***
EDE-Q weight concern	2.8 ± 0.3	3.8 ± 0.3	**.02****
Associated psychopathology			
Hamilton Anxiety Rating Scale	13.3 ± 1.0	15.7 ± 1.1	**.04**
Hamilton Depression Rating Scale	15.2 ± 1.0	16.2 ± 1.1	.40

[a]Values are reported as mean ± standard error of mean.
[b]Boldface equals significant difference between groups.
*Remains significantly different ($P < .05$) after controlling for BMI.
**Remains a trend ($P < .10$) toward a difference between groups after controlling for BMI (all variables except for BMI were controlled for BMI).
Abbreviations: BDNF = brain-derived neurotrophic factor, BMI = body mass index, EDE-Q = Eating Disorder Examination-Questionnaire, PYY = peptide YY.

All assays were performed in duplicate, and outliers were excluded based on quintiles.

Psychological Assessment

Eating disorder psychopathology was further measured by the Eating Disorder Examination-Questionnaire (EDE-Q),[30] which is a 36-item self-report measure of eating disorder severity indexed along 4 dimensions: dietary restraint, eating concern, shape concern, and weight concern. Frequency of binge eating, purging, and other compensatory behaviors such as excessive exercise is also evaluated. The EDE-Q has demonstrated excellent reliability and validity.[31]

Associated psychopathology was measured via the Hamilton Anxiety Rating Scale (HARS) and the Hamilton Depression Rating Scale (HDRS). Both are semistructured, clinician-administered interviews that are widely used to measure anxiety and depression symptoms and have demonstrated strong psychometric properties.[32,33]

Across the eating disorder and associated psychopathology measures, higher scores indicate increased symptomatology.

Data Collection

All 97 samples included in the data analysis were collected from May 22, 2004–February 7, 2012. The 75 anorexia nervosa samples were collected from May 22, 2004–February 7, 2012 (50 restricting type samples were collected from May 22, 2004–December 19, 2011; 25 binge-eating/purging type samples were collected from May 25, 2004–February 7, 2012). The 22 healthy control samples were collected from March 10, 2006–September 14, 2007.

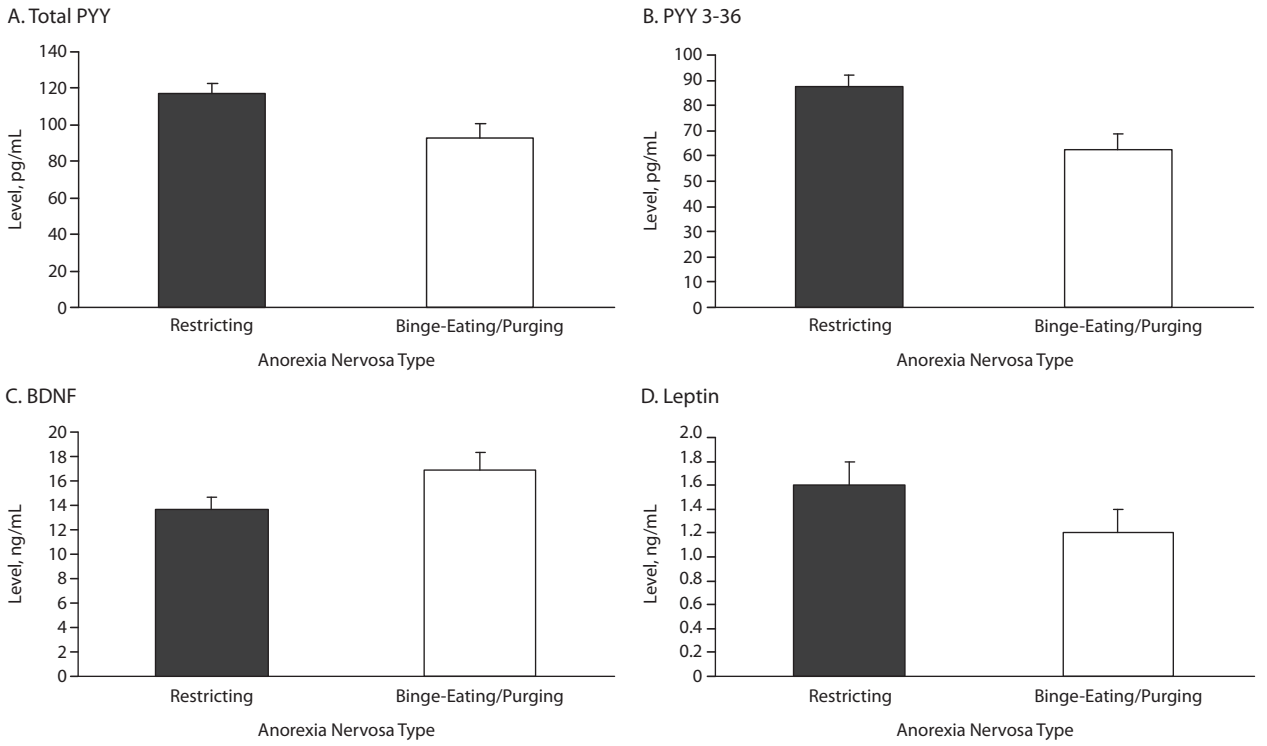
Statistical Analysis

Statistical analyses were performed using JMP Pro (version 10, SAS Institute) software. Between-group comparisons were analyzed in the following manner. Pairwise comparisons were performed using Wilcoxon rank sum test. Categorical variables were compared using the Fisher exact test. Univariate correlational analysis was performed, and Spearman ρ coefficients are reported. Standard least squares analysis was performed to control for BMI; hormone levels and BMI were log transformed before being entered into the models. Two-sided *P* value of < .05 was considered significant.

RESULTS

Clinical characteristics of the anorexia nervosa groups are presented in Table 1. Mean age was comparable and mean BMI slightly lower in restricting type compared to binge-eating/purging type participants. Healthy control women did not differ from the anorexia nervosa groups (restricting type and binge-eating/purging type combined) in age (anorexia nervosa, mean age = 25.8 years [SD = 0.8]; healthy control, mean age = 26.8 years [SD = 1.5]; $P = .47$) but had higher mean BMI by definition (anorexia nervosa, mean BMI = 17.3 [SD = 0.1]; healthy control, mean BMI = 22.4 [SD = 0.4]; $P < .0001$). Given between-group differences in BMI, we controlled for BMI in all between-group analyses.

Figure 1. Mean (SEM) Levels of Total PYY, Active PYY (PYY 3-36), BDNF, and Leptin in Restricting Versus Binge-Eating/Purging Anorexia Nervosa Subtypes After Controlling for BMI[a]



[a]The difference in total PYY levels ($P = .01$) and PYY 3-36 levels were significant ($P = .002$), and the difference in BDNF levels trended toward significance ($P = .06$) after controlling for BMI. The difference in leptin between groups was nonsignificant ($P > .05$) after controlling for BMI.
Abbreviations: BDNF = brain-derived neurotrophic factor, BMI = body mass index, PYY = peptide YY, SEM = standard error of mean.

Mean PYY 3-36 levels were lower in binge-eating/purging type compared to restricting type, and this remained significant after controlling for BMI (Table 1; Figure 1). Mean total PYY was not significantly different between the groups before controlling for BMI, and was significantly different after controlling for BMI (Table 1; Figure 1). Mean BDNF was higher in binge-eating/purging type than restricting type, and this difference was at a trend level after controlling for BMI (Table 1; Figure 1). Mean leptin levels were lower in binge-eating/purging type compared to restricting type but were not significant after controlling for BMI (Table 1; Figure 1). Eating disorder psychopathology and anxiety symptoms but not depressive symptoms were increased in binge-eating/purging type relative to restricting type; differences in eating disorder psychopathology generally withstood controlling for BMI (Table 1). For comparisons between the entire anorexia nervosa group and healthy controls, mean total PYY (anorexia nervosa, mean PYY = 111 [SD = 5]; healthy control, mean PYY = 79 [SD = 6]; $P = .0004$) and mean PYY 3-36 levels were higher (anorexia nervosa, mean PYY 3-36 = 80 [SD = 4]; healthy control, mean PYY 3-36 = 48 [SD = 1]; $P < .0001$), BDNF levels similar (anorexia nervosa, mean BDNF = 14.8 [SD = 0.8]; healthy control, mean BDNF = 14.6 [SD = 1.4]; $P = .88$), and leptin levels lower (anorexia nervosa, mean leptin = 1.4 [SD = 0.1]; healthy control, mean leptin = 6.1 [SD = 0.6]; $P < .0001$) in women with anorexia nervosa compared with healthy controls. Differences in hormone levels between the full anorexia nervosa group and healthy controls were not significant after controlling for BMI ($P > .05$). As expected, eating disorder psychopathology and anxious and depressive symptoms were increased in anorexia nervosa compared to healthy women (all P values $< .0001$). Between-group differences remained significant (EDE-Q eating concern, EDE-Q shape concern, HARS, HDRS; all P values $< .05$) or at the trend level (EDE-Q dietary restraint, EDE-Q weight concern; $P < .10$) after controlling for BMI.

Correlations among all subjects are presented in Table 2. Peptide YY and PYY 3-36 levels were positively associated with EDE-Q subscales including dietary restraint, eating concern, shape concern, and weight concern, and with HARS and HDRS scores. Brain-derived neurotrophic factor was positively associated with purging frequency. Leptin was negatively associated with all 4 EDE-Q subscales, with bingeing and purging, and with depressive and anxiety symptoms. Peptide YY and PYY 3-36 were inversely and leptin positively correlated with BMI in all subjects (PYY with BMI, $\rho = -0.38$, $P = .002$; PYY 3-36 with BMI, $\rho = -0.45$, $P < .001$; leptin with BMI, $\rho = 0.64$, $P < .001$); BDNF did not correlate with BMI.

DISCUSSION

Our data demonstrate differential levels of the anorexigenic hormones PYY, PYY 3-36, BDNF, and leptin between the anorexia nervosa subtypes. Despite the fact that all appetite-regulating hormones studied are anorexigenic

Table 2. Correlations Between Anorexigenic Hormones and Eating Disorder and Associated Psychopathology[a]

Variable	Total PYY, pg/mL	PYY 3-36, pg/mL	BDNF, ng/mL	Leptin, ng/mL
No. of purging episodes/wk				
ρ	−0.005	0.02	**0.21**	**−0.31**
Prob > |ρ|	.96	.9	**.04**	**.004***
No. of bingeing episodes/wk				
ρ	0.10	0.12	0.04	**−0.29**
Prob > |ρ|	.40	.3	0.7	**.007***
EDE-Q dietary restraint				
ρ	0.22	**0.27**	0.08	**−0.51**
Prob > |ρ|	.06	**.02**	.5	**<.0001***
EDE-Q eating concern				
ρ	**0.27**	**0.29**	−0.04	**−0.53**
Prob > |ρ|	**.02**	**.01***	.7	**<.0001***
EDE-Q shape concern				
ρ	**0.27**	**0.34**	−0.01	**−0.40**
Prob > |ρ|	**.02**	**.003***	.9	**.0004***
EDE-Q weight concern				
ρ	**0.25**	**0.36**	−0.04	**−0.44**
Prob > |ρ|	**.04**	**.002***	.7	**<.0001***
Hamilton Anxiety Rating Scale				
ρ	**0.29**	**0.42**	−0.11	**−0.49**
Prob > |ρ|	**.005***	**<.0001***	.3	**<.0001***
Hamilton Depression Rating Scale				
ρ	**0.21**	**0.37**	−0.06	**−0.41**
Prob > |ρ|	**.05**	**.0004***	.5	**<.0001***

[a]Boldface equals significant difference between groups.
*Correlations remain significant after correcting for multiple comparisons.
Abbreviations: BDNF = brain-derived neurotrophic factor, EDE-Q = Eating Disorder Examination-Questionnaire, PYY = peptide YY.

and rodent knock-out models of all 3 hormones result in hyperphagia,[5–7] we found that these appetite-regulating hormones are differentially related to the aberrant eating behaviors that determine the restricting and binge-eating/purging anorexia nervosa subtypes. Specifically, total and active PYY were lower in binge-eating/purging type compared with restricting type, and there was a trend toward higher mean BDNF levels in binge-eating/purging type than in restricting type. Although mean leptin levels were also lower in the binge-eating/purging than restricting subtype, this difference did not withstand correction for BMI. Interestingly, PYY was positively and leptin was negatively associated with dietary restraint, while BDNF was positively and leptin negatively associated with frequency of purging. These data may provide clues to mechanisms responsible for driving or maintaining dietary restraint and bingeing/purging behaviors in anorexia nervosa.

In this report, we show that both PYY and PYY 3-36 are increased in restricting type anorexia nervosa relative to binge-eating/purging type anorexia nervosa independent of BMI, with levels in binge-eating/purging type falling intermediately between those of restricting type and healthy controls. Peptide YY and PYY 3-36 are positively associated with all EDE-Q subscale scores, but not with bingeing or purging. These findings raise the possibility that high PYY and PYY 3-36 levels drive persistent restrictive eating patterns in individuals with anorexia nervosa, above and beyond low weight itself. Although restrictive eating—avoidance of certain foods, limiting of quantity, and fasting—is common to both anorexia nervosa subtypes, those with binge-eating/purging type exhibit restriction punctuated by periods of binge eating and/or purging behaviors. The absolute difference in PYY between subtypes of ~20 pg/mL is comparable to that difference we have observed in our own studies between normal-weight and obese women.[9] Human studies have begun to address the clinical significance of exogenous PYY, finding that caloric intake is reduced and fullness increased following PYY 3-36 administration in those with obesity.[34] It is possible that increased PYY circulating or released in response to eating in anorexia nervosa, contributes to the maintenance of high levels of restrictive eating behavior in these patients. Indeed, PYY may be involved in the pathogenesis of anorexia nervosa rather than an adaptive response to starvation, a hypothesis that fits with the finding that postprandial PYY 3-36 levels are increased in women with restricting type anorexia nervosa following nutritional rehabilitation.[11] Longitudinal studies involving repeated measurements of PYY and eating disorder symptoms are warranted to examine the dynamic relationship between these variables and to test the hypothesis that increased PYY drives persistent restriction.

We report that BDNF levels were elevated in binge-eating/purging type anorexia nervosa compared to restricting type anorexia nervosa, and levels in restricting type were similar to those of healthy women in our sample. Our finding that this anorexigenic hormone was higher in binge-eating/purging type anorexia nervosa in spite of the subjects having lower mean BMI suggests that this hormone may be involved in behaviors or cognition that characterize the anorexia nervosa subtypes and/or contribute to the maintenance of low weight. This suggestion may fit with the findings of one study[35] that demonstrated an increase in BDNF levels with weight restoration. Our findings raise the possibility that this increase in BDNF is related to the change in eating behavior (ie, increase in eating) rather than weight gain per se, although causality cannot be shown. Further, our correlational analyses suggested that BDNF was positively associated with purging frequency but not with any other eating disorder feature measured. This finding may suggest that purging behavior increases BDNF secretion, thereby promoting dietary restraint. In previous reports, BDNF levels are generally decreased in low-weight women with anorexia nervosa, as reported in a meta-analysis.[18] This finding was in contrast to our hypothesis, and the difference between our data and previous reports may be explained by the differences in mean BMI in our anorexia nervosa sample and having a sufficient number of women with both anorexia nervosa subtypes rather than exclusive focus on restricting type, which is generally what has been reported in the literature.[18]

As expected, leptin levels were decreased in anorexia nervosa compared with controls in our study. It is well known that leptin is secreted by adipocytes and that serum leptin levels reflect fat mass. The lower mean leptin levels in binge-eating/purging type compared to restricting type anorexia nervosa were most likely due to the lower mean weight in that group. Of interest, leptin demonstrated moderate negative

associations with all EDE-Q subscale scores and with purging, but was not correlated with bingeing. This finding raises the possibility of a compensatory response of this anorexigenic hormone to the increased eating disorder symptoms.

Added to earlier results, our novel findings suggest that the anorexigenic hormones PYY, BDNF, and leptin are differentially regulated between anorexia nervosa subtypes. Peptide YY may contribute to dietary restraint, while BDNF dysregulation may play a role in purging behaviors. Our study is limited by its cross-sectional design, which precludes determination of causality between hormone dysregulation and eating disorder features. Although many between-group comparisons withstood correction for BMI, whether BMI mediates some of the observed associations between hormones and eating behaviors deserves attention. Further studies are warranted to determine whether these hormone pathways play etiologic roles with regard to anorexia nervosa behavioral subtypes or are compensatory. Likewise, longitudinal research has the potential to inform our understanding of whether observed between-group hormonal differences are state or trait related and may be predictive of or mechanistic in diagnostic crossover between the subtypes. For example, naturalistic studies with frequent follow-up or real-time data collection (eg, ecological momentary assessment) and repeated hormone assays could examine whether changes in hormone levels (and of what magnitude) precede, co-occur with, or follow changes in eating disorder symptoms (restriction, binge eating, purging, and weight). Finally, we had limited power to examine the possible explanatory role of anxiety and depressive symptoms in the relationship between the anorexigenic hormones and anorexia nervosa psychopathology. Given observed hormone-affect associations, future studies designed to investigate nuances of these dynamics are warranted.

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