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CCK response in bulimia nervosa and following remission

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HIGHLIGHTS

- Prior findings in bulimia nervosa indicate an abnormal response of the satiety hormone CCK
- Unknown if altered functioning is cause, consequence or maintenance factor in binge eating
- Implications of study are CCK responsivity may normalize in those who remit from bulimia

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ABSTRACT

The core defining features of bulimia nervosa (BN) are repeated binge eating episodes and inappropriate compensatory (e.g., purging) behavior. Previous studies suggest an abnormal post-prandial response in the satiety-signaling peptide cholecystokinin (CCK) in persons with BN. It is unknown whether this altered response persists following remission or if it may be a potential target for the development of clinical treatment strategies. To examine the nature of this altered response, this study assessed whether CCK normalizes following remission from BN (RBN). This study prospectively evaluated the plasma CCK response and corresponding eating behavior-related ratings (e.g., satiety, fullness, hunger, urge to binge and vomit) in individuals with BN-purging subtype ($n = 10$), RBN-purging subtype ($n = 14$), and healthy controls (CON, $n = 13$) at baseline, +15, +30, and +60 min following the ingestion of a standardized liquid test meal.

Subject groups did not significantly differ in CCK response to the test meal. A significant relationship between CCK response and satiety ratings was observed in the RBN group ($r = .59$, $p < .05$ two-tailed). A new and unanticipated finding in the BN group was a significant relationship between CCK response and ratings of "urge to vomit" ($r = .86$, $p < .01$, two-tailed).

Unlike previous investigations, CCK response did not differ in BN and CON groups. Thus the role of symptom severity remains an area of further investigation. Additionally, findings suggest that in this sample, CCK functioning following remission from BN-purging subtype is not different from controls. It remains unknown whether or not CCK functioning may be a protective or liability factor in the stabilization and recovery process. Replication studies utilizing a larger sample size are needed to further elucidate the role of CCK in recovery from BN and its potential target of related novel treatment strategies.

1. Introduction

Bulimia nervosa (BN) is a chronic and debilitating eating disorder characterized by repeated binge eating episodes followed by inappropriate compensatory (e.g., purging) behavior to prevent weight gain. The underlying pathophysiologic mechanisms that contribute to this aberrant behavior are complex and poorly understood. Individuals with BN report altered perceptions in hunger, fullness, and satiety [1]. Laboratory studies have shown that cholecystokinin (CCK) response, a satiety producing gastric hormone, following a meal is decreased in individuals with active BN when compared to matched healthy controls [2–4].

To date, investigations have not examined CCK function following remission of BN. To help evaluate the extent to which post-prandial (after a meal) CCK normalizes following remission of BN, this study examined CCK responses following a test-meal in persons with active BN, remitted BN (RBN), and healthy controls (CON).

1.1. Research question

Is there a significant difference in post-prandial CCK response and satiety ratings among persons with active BN, RBN, and healthy controls?

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1.2. Hypotheses

H1. Subjects with BN will have a significantly blunted post-prandial plasma CCK response compared to the RBN and CON groups.

H2. Post-prandial plasma CCK response will be significantly positively correlated with post-prandial visual analog measures of satiety in the RBN and CON groups.

2. Materials and methods

2.1. Subjects

Participants included a convenience sample of women with RBN (n = 14), BN (n = 10), and healthy controls (CON; n = 13). Subject group inclusion criteria are as follows:

All subjects: 1) age 18–45 years; 2) body mass index (BMI) between 19 and 26 kg/m^2; 3) gender, female; 4) in good medical health; 5) free of known medical conditions or medication treatment (except for birth control); and 6) free of alcohol use for 72 h prior to study.
BN: 1) Diagnostic and Statistical Manual of Mental Disorders 4th Text — Revised (DSM-IV-TR) [5] criteria for BN, purging subtype. BN subjects were limited to those with purging subtype (vomiting), based on previous research [3,6], allowing for comparison across studies.
RBN: 1) History of BN, purging subtype (vomiting), as defined by the DSM-IV-TR [5]; and 2) no history of binge eating, purging behavior, or recurrent inappropriate non-purging compensatory behavior during six months prior to study.
CON: 1) Free of current or past history of DSM-IV-TR eating disorder; 2) not actively engaged in dieting behavior as measured by a score of ≤16 on the Restraint Scale [7].

Subjects who met initial participant inclusion criteria were scheduled for an outpatient screening visit. Subsequently, eligible participants were then scheduled for an outpatient study visit on the Clinical Research Center (CRC) at Beth Israel Deaconess Medical Center (BIDMC).

2.2. Procedures

2.2.1. Recruitment and screening

Subjects were recruited using study flyers, postings and university communication sites. During the screening visit, subjects received a detailed explanation of study procedures and signed the informed consent document. Screening procedures included the administration of the Structured Clinical Interview for DSM-IV Axis I Disorders [8] to confirm diagnoses. Subjects were asked to complete a battery of rating scales to assess eating-related and psychological behaviors including the Eating Disorder Examination — Questionnaire (EDE-Q 6.0) [10], Restraint Scale [7], and Beck Depression Inventory — II [9].

2.2.2. Outpatient study visit

Eligible subjects were scheduled for an outpatient study visit on the CRC occurring in the morning following an overnight fast. Nursing personnel, using an anthropometric station and calibrated metabolic scale, obtained a measurement of height and weight. Following placement of an intravenous catheter (antecubital), subjects had a 15 min stabilization period after which a baseline blood sample was drawn for measurement of plasma CCK. Approximately 5 min following the blood draw, subjects were asked to consume a standardized liquid test meal in the course of the next 5 min. The standardized liquid test meal consisted of 600 ml of Ensure Plus® (approximately 900 kcal, 30% fat, 15% protein, and 55% carbohydrate) which has been used successfully in previous studies assessing plasma CCK responses in this patient group [3,6]. At the corresponding time of blood sampling, subjects were asked to complete a set of 100 mm visual analog scales (VAS) assessing hunger, satiety, fullness, anxiety, desire to binge, and desire to vomit. Additionally, subjects completed a Side Effect Checklist (SEC) at the same time points.

2.2.3. Specimen processing

Blood samples were kept on ice for 5 min in tubes prepared with ethylenediaminetetraacetic acid (EDTA) and aprotinin (Trasylol) before cold centrifugation (1500 ×*g*) for 15 min. The plasma was pipetted into cryo-microtubes and stored at −70 °C until batch analysis. KMI, incorporated diagnostics laboratory testing center in Minneapolis, MN performed analyses by technicians blind to subject diagnosis and other clinical information. Plasma CCK concentrations (CCK-8S) were measured using a radioimmunoassay (RIA) kit lot: NS2323US from EuroDiagnostica. For this kit, CCK intra-assay coefficient of variation (CV) is 4.4 pmol/l (5.5%) and inter-assay CV is 4.2 pmol/l (13.7%). Normal fasting level of CCK is ≤1.12 pmol/l. Assay sensitivity's lowest detectable concentration (LDC) = 0.3 pmol/l. Because CCK-8 is the predominant form used by investigators [10] and CCK-receptors in the alimentary pathway only bind to sulfated form [11], peripheral plasma concentrations of CCK-8S were measured using a radioimmunoassay (RIA) that also detects the bioactive forms of CCK-58, CCK-33, and CCK-22 [12]. This is consistent with previous studies of CCK and satiety and will allow, in this patient population, for comparison across studies [13].

2.3. Instruments

2.3.1. Structured Clinical Interview for DSM-IV Axis I Disorder, Research Version, Patient Edition (SCID-I/P, 1/2010 revision)© Biometrics Research Department

The SCID-I/P [8] is a structured interview administered by a trained clinician (SHE) during the screening visit for the purpose of making a DSM-IV Axis I diagnosis.

2.3.2. Eating Disorder Examination — Questionnaire (EDE-Q) 6.0

The EDE-Q 6.0 [14] is a self-report version of the Eating Disorder Examination (EDE) [14]. The EDE is a well-established semi-structured interview designed to assess eating disorder psychopathology primarily occurring over the preceding four weeks [15]. Two main areas of assessment include overeating and extreme methods of weight control. The EDE-Q and the EDE are scored in the same fashion by including three types of descriptive data: scores on individual items, subscale scores, and a global score. The EDE-Q 6.0 was used during the screening visit as a diagnostic and descriptive measure of eating psychopathology. For this study, the internal reliabilities (Cronbach α) for the EDE-Q subscales were as follows: restraint, 0.83; eating concerns, 0.71; weight concern, 0.94; and shape concern, 0.97.

2.3.3. Restraint Scale, Revised

The Restraint Scale, Revised [7] is a 10-item self-report multiple-choice questionnaire designed to measure chronic tendencies toward restrained eating. The scale has two factors: Concern for Dieting and Weight Fluctuations [16]. The median score for female college students is 15–16 [7]. Individuals above this cut-off are likely to display more chronic restrained eating behavior. Thus to avoid confounds of dieting in the control group, a cutoff of 16 was used in eligibility criteria. In the current sample, internal reliability (Cronbach α) was .93.

2.3.4. Beck Depression Inventory® — II (Second Edition) (BDI-II)

The BDI-II [9] is a 21-item self-administered rating scale designed to measure depressive symptoms. Each item is rated on a four-point scale. General scoring guidelines include the following categories: nondepressed/minimal depression (score of 0–13), mild depression (14–19), moderate depression (20–28), and severe depression (29–63). Content, construct, and factorial validity have been established. The

BDI-II was utilized at the screening and study visits to assess for level of depression and need for clinical referral. In the current sample, internal reliability (Cronbach α) was 0.91.

2.3.5. Hunger, Satiety, Pleasantness of Foods Visual Analog Scales

100 mm visual analog scales (VAS) were used to assess subjective eating-related behavior (e.g., satiety, fullness, hunger, urge to binge and vomit). The anchors for satiety, fullness and hunger where represented as "not all" to "extremely". The anchors for binge and vomit ranged from "no urge" to "extreme urge." The visual analog scale is easily administered and sensitive to incremental changes [17]. Visual analog scales have been validated and successfully applied to studies of eating behavior sensations [18]. VAS ratings were obtained before and after the test meal.

2.3.6. Side Effect Checklist

The Side Effect Checklist is a brief 22-item descriptive questionnaire in which adjectives are rated on a five point Likert Scale. Subjects are asked to rate the extent to which the listed items are present "now." Examples of items include headache, nausea, and stomach ache. Response anchor points include "not at all," "a little," "moderately," "quite a bit," and "extremely." This questionnaire, used in previous studies [19,20], was administered before and after the test meal to monitor subjectively experienced side effects.

2.4. Data analyses

A one-way ANOVA was used to determine the probability for significant differences in group's clinical characteristics (Table 1). The primary outcome measure, the CCK response, was calculated by the area-under-the-curve (AUC) utilizing the trapezoidal rule. AUC is estimated by the cumulative (concentration versus time) CCK release during the duration of the standardized test meal. A one-way ANOVA with a-priori-contrasts or planned comparisons was used to test for specified differences in the AUC response across the three study groups.

The relationship between post-prandial CCK response (AUC) and VAS ratings of satiety and urge to vomit were assessed by Pearson's correlation coefficient. Data not normally distributed were log transformed. Bonferroni-corrected *P* values were used for post hoc comparison. All analyses were conducted using SPSS 19.0. Group results are presented as mean ± standard deviation (SD) in text and tables and as mean ± standard error (SE) in figures.

Table 1
Clinical characteristics-comparison by group.

Measures	Mean ± SD			
	Control	RBN	BN	$F_{2,34}$
	n = 13	n = 14	n = 10	
Age, yrs	21.0 ± 1.9	22.4 ± 4.1	22.2 ± 3.5	.69
Height, cm	163.5 ± 6.9	165.5 ± 5.5	164.3 ± 6.3	.34
Weight, kg	61.2 ± 10.1	61.6 ± 7.3	60.2 ± 9.5	.07
BMI, kg/m^2	22.7 ± 2.7	22.4 ± 1.8	22.1 ± 2.3	.22
EDE-Q				
Global (subscales below)[a]	.14 ± .39*	1.8 ± 1.8*	3.9 ± 1.2	21.67
Restraint	.48 ± .69*	1.5 ± 1.6*	3.3 ± 1.3	14.60
Eating concern	.14 ± .39*	1.4 ± 1.7*	3.9 ± 2.5	14.22
Weight concern[a]	.38 ± .47*	1.9 ± 1.9*	4.1 ± 1.4	18.52
Shape concern[a]	.63 ± .61*	2.2 ± 2.1*	4.7 ± 1.2	21.82
Binge/purge (last 28 days)	N/A	N/A	19.6 + 9.7	
BDI-II	1.3 ± 1.1*	1.7 ± 2.7*	15.5 ± 11.4	17.65
Herman and Polivy Restraint[a]	5.6 ± 3.3*	14.3 ± 8.5*	21.4 ± 5.5	18.20
Aggression Scale (Total)	49.6 ± 11.7	58.8 ± 19	59.9 ± 13.8	1.67

Note. EDE-Q = Eating Disorder Examination — Questionnaire; BDI-II = Beck Depression Inventory — II.
* Significantly different than BN group: $p < .05$, two-tailed, after Bonferroni adjustment.
[a] The RBN group is also significantly different than CON group: $p < .05$, two-tailed, after Bonferroni adjustment.

3. Results

3.1. Subject characteristics

The overall sample age was 22.5 ± 5.0 years with a BMI of 22.5 ± 2.2 kg/m^2. The racial/ethnic composition of the sample was 71.1% white, 7.9% Black/African American, 18.4% Asian/Pacific Islander, 2.6% American Indian or Alaska Native, and 7.9% Hispanic, Latino or Spanish.

The average binge and purge (vomit) frequency among the BN group was 4.9 ± 2.7 episodes per week. Similarly, the RBN group reported binge and purge frequency during active illness to average 6.8 ± 4.6 episodes per week. There was no significant difference ($t = -1.1, p = .81$) in the average binge and purge frequency between the BN and the RBN groups during active illness. The average illness duration was 4.3 ± 3.9 years in the BN group and 3.9 ± 4.7 years in the RBN group. Length of remission for the RBN group was 2.0 ± 1.4 years. Axis I disorders for the BN group included major depressive disorder (MDD), 10%; history of MDD, 10%; history of anorexia nervosa (AN), 50%; and the remaining 30% endorsed BN only. Those with history of AN were weight restored for a minimum of 2 years. Axis I disorders for the RBN group included history of MDD, 36%; history of AN, 14%; substance use disorder (SUD) 14%; and the remaining 36% endorsed previous diagnosis of BN only. Table 1 presents comparisons on clinical characteristics across subject groups. In comparison to RBN and CON groups, the BN group scored significantly higher on measures of depression and eating pathology.

3.2. Post-prandial CCK response

CCK response (AUC) was not significantly different among subject groups although a trend was observed with lower mean levels in the BN group (1.77 ± .60) in comparison to RBNs (2.01 ± .41) or CONs (3.13 ± .47). Planned contrasts revealed no significant difference in the BN group's CCK response, t (34) = 1.67 ($p = .11$, two-tailed, $f = .22$) in comparison to the RBN and CON. The second planned comparison revealed no significant difference, t (34) = 1.67 ($p = .54$, two-tailed) between the RBN and the CON groups. There was a significant within-subjects effect over time ($F = 19.34$, df = 3, $p = .000$) between all groups, before (baseline) and following ingestion (+15 min.) of the test meal at the peak CCK response time.

Post hoc analysis revealed no significant difference between the combined BN/RBN group in comparison to the CON group (t (34) =

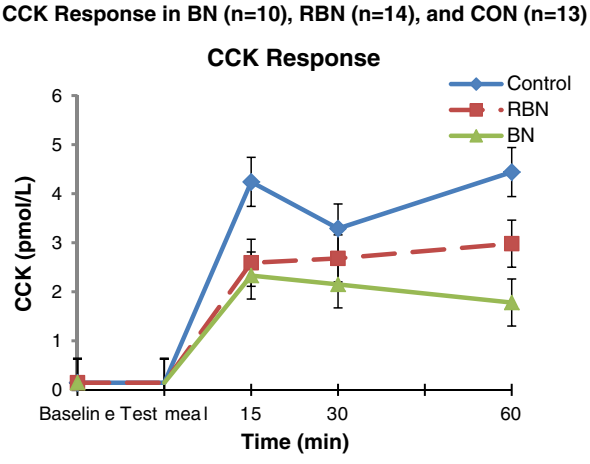

Fig. 1. Group mean (±S.E.) plasma concentrations of CCK at each time point before and after the test meal.

1.41; $p = .17$, two-tailed, $f = .22$). When examining the 15-min mean peak response, as done in a previous report [13], there was no significant difference between the BN (2.33 ± 2.69 pmol/l), RBN (2.59 ± 2.67), or CON (4.23 ± 2.91), ($p = 0.1$), groups respectively (Fig. 1).

3.3. Biobehavioral response to test meal

A significant relationship was observed between CCK response and ratings of satiety in the RBN group only. Thus subjects with a more robust CCK response rated higher levels of satiety ($r = .58$, $p < .05$). Increased CCK response was significantly correlated with urge to vomit in the BN group ($r = .86$, $p < .01$, two-tailed). The BN group reported the greatest urge to vomit (2.9 ± .96) compared to the RBN (2.4 ± .85) and CON group (1.6 ± .89). Consequently, there was a significant difference between the BN and CON groups "urge to vomit" ($F_{2,34} = 6.47$, $p < .01$), but not in the RBN group (Fig. 2).

4. Discussion

This is the first study to compare post-prandial CCK response and subjective ratings of satiety from a group of individuals who have remitted from bulimia nervosa (RBN) to those with the active illness (BN) and healthy (CON). Previous studies found that CCK is abnormal in BN in comparison to healthy CON [21] These former results implied that an altered CCK response may be a possible cause, consequence, and or maintenance factor for binge eating in individuals suffering from BN. To observe the nature of this altered response, this study evaluated whether CCK and other ratings related to eating-behavior normalizes following remission from BN (RBN).

4.1. Post-prandial CCK response

Although not statistically significant, there was a trend for the BN group's post-prandial CCK level to be lower than both the RBN and CON groups. The RBN and the CON groups' CCK response were not statistically significant from each other. In this study, remission from episodes ranged from nine months to six years and there was no significant correlation in this RBN group's CCK response with time since their last binge/purge episode. While these results do not offer particular guidance concerning if and when CCK response normalizes with remission, it does suggest that previous findings of a blunted response in the BN population may be a state versus trait related phenomenon.

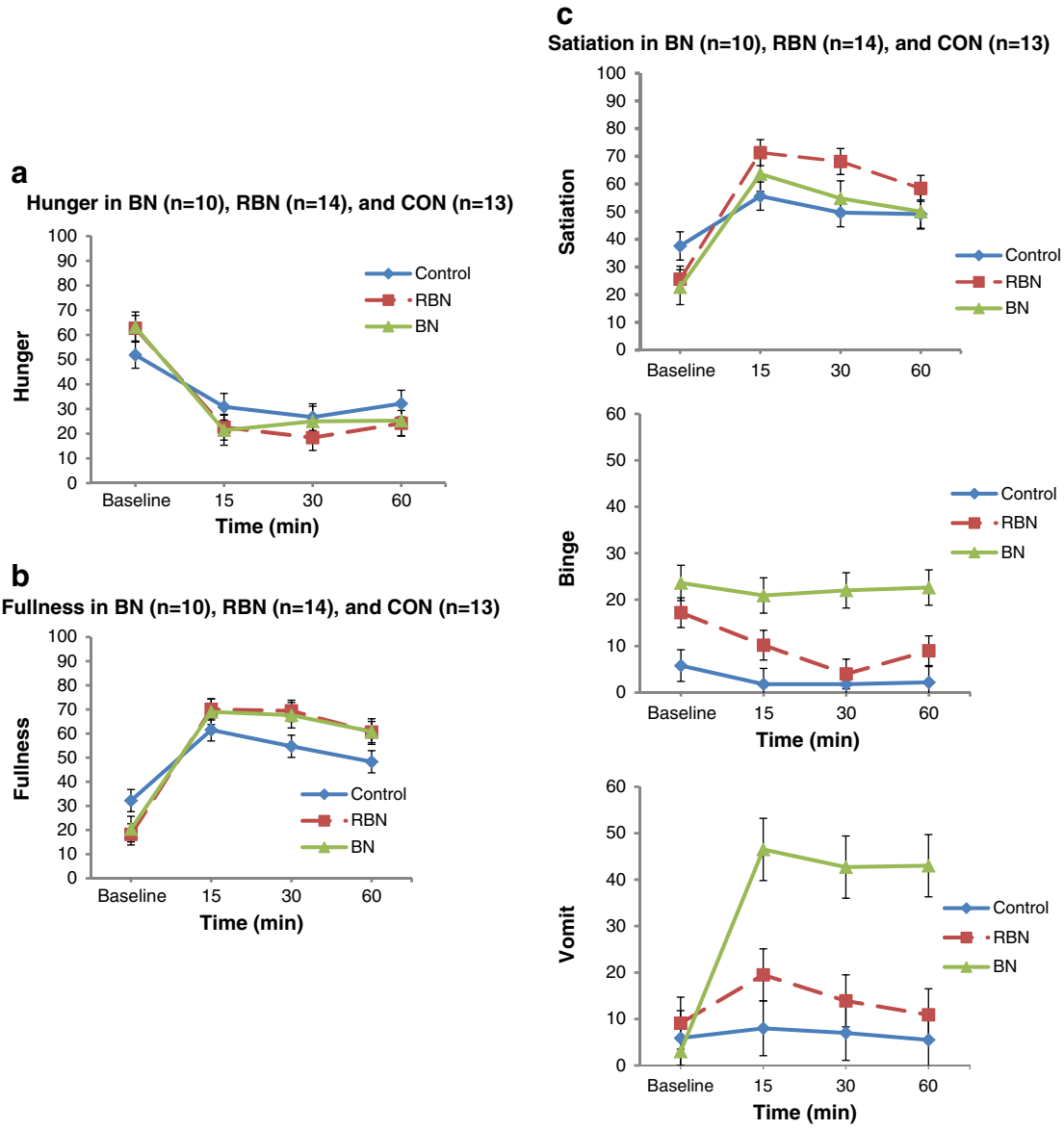

Fig. 2. The mean group comparison of subjective eating related responses (VAS measured as 100 mm) prior to and following to the test meal.

Consistent with a recent study [13] yet divergent from previous studies is the absence of a statistical difference in CCK response between the BN and CON groups. [3,6]. In comparison to the previous study by Devlin et al. (1997), BN subjects reported two times as many (10.3 ± 4.3) binge and purge episodes per week, had a longer duration of illness (9.8 ± 1.9 years), and were recruited from both inpatient and outpatient treatment settings possibly reflecting a more symptomatic group with prolonged physiological dysregulation. In addition, a larger BN group (with an adequate effect size) may have revealed a significant physiological difference between study groups.

4.2. Biobehavioral responses to test meal

Previous biobehavioral studies have found post-prandial satiety ratings to be positively correlated with CCK responses [6,22]. In this study, the RBN group had a significant positive relationship between post-prandial CCK response and satiety. Perhaps this positive relationship decreases the vulnerability and increases the success of this group in abstaining from binge eating behavior. CCK concentrations may become a helpful biomarker of satiety and harbinger of abstinence from these unhealthy behaviors. However, it should be noted that a significant relationship between post-prandial CCK response and satiety was not observed in the CON group, raising the question of the importance of this finding in the RBN group.

A new and unanticipated finding from this current study was the positive correlation between the BN groups' CCK response and urge to vomit following the ingestion of the test meal. Perhaps those in the BN group become sensitive or uncomfortable to the sensations associated with the release of the satiety hormone, triggering an episode of vomiting, and subsequent feeling of relief from this negative experience. There are lines of inquiry that question the afferent vagus nerve in its dual or parallel function of signaling satiety and the vomit (emetic) response [23]. Perhaps due to the abnormal vagal afferent activity of those with BN, these circuits become overloaded resulting in misinformation and vomiting behavior.

In a group of individuals with purging disorder (PD), those who don't engage in typical binge eating behavior but vomit following ingestion of smaller amounts of food, CCK responsivity and urge to vomit were statistically greater than for those with BN [6]. Additionally, the CCK response in the PD group was not significantly different than healthy controls. In comparison to the new results from this current study, perhaps the PD group is also sensitive to elevations in CCK concentrations. Potentially, this proposed sensitivity becomes expressed in vomiting behavior.

4.3. Implications

The current study suggests that CCK responsivity is similar among individuals who have remitted from BN in comparison to controls. Further study is needed to address the possible association between symptom severity and CCK responsivity during active illness that may help to explain discrepant findings between this study and those previously reported in the literature. Understanding what biological or behavioral adaptations must occur before remission and how can these be promoted and maintained is essential to the development of effective treatment strategies, relapse prevention, and merits further investigation.

Replication of the findings from this study using a larger sample size (increasing statistical power) are needed to gain a better understanding of the process and temporal factors associated with CCK responsivity in RBN. For instance, with a larger sample size researchers can examine whether there are relationships among previous frequency of binge/vomit episodes, duration of illness, length of remission, CCK responsivity, and eating and satiety related behavioral responses to test meals. To replicate this study in the future and ensure an adequate sample size, using the current medium effect size ($f = .30$) with an alpha at $p = .05$, power of .80, an adequate number of study participants is $N = 89$ or approximately a BN group of $n = 30$ [24].

To gain a comprehensive understanding of the complex physiological interactions that effect or have an effect on abstinence and relapse prevention, studies are needed to evaluate the relationships between CCK and other dysregulated anorexigenic (e.g., GLP-1 and PYY) or orexgenic (e.g., ghrelin) peptides [25,26] and eating related pathways [27]. Emphasis should be focused on research that explores pharmacotherapeutic agents that may have an effect on increasing CCK levels [13]. It would be informative to evaluate if increased CCK levels would decrease binge/vomit behaviors and or increase urge to vomit in those with BN.

4.4. Limitations

A small sample size may have failed to detect a significant difference between the BN, CON, and RBN groups CCK responsivity to a standardized liquid test meal. Due to the lower frequency of binge/vomit episodes in this study in comparison to others, these findings may not generalize to a more symptomatic population. The inclusion/exclusion criterion limited to purging (vomiting-type) only. Study participants self-reported their frequency of binge/purge behavior; therefore, unable to verify accuracy. In this study, all participants were asked to drink a standardized liquid test meal in an effort to compare across groups and previous studies. However, this may have been a limiting factor in accurately measuring the full extent of eating related sensations in those particularly with BN and RBN [28]. Lastly, the present study utilized independent subjects for BN and RBN groups, whereas a longitudinal within-group design would be stronger.

5. Conclusions

Results extend the understanding of the post-prandial CCK response in those who have remitted from BN. The implications of this study are that CCK responsivity in those who remit from binge and vomit behavior appears similar to controls. While this study does not offer particular guidance concerning possible changes in CCK response that might occur with remission, it does indicate that previous findings of a blunted response in the BN population may be a *state* versus *trait* related phenomenon. The findings from this study also suggest that those with active illness who have increased CCK concentrations experienced greater urges to vomit. Investigators are left to determine if this relationship also exists when pharmacotherapeutic agents are given that may enhance CCK functioning. Therefore, future studies are needed to clarify the extent to which CCK functioning is a protective or liability factor in the stabilization and recovery of BN. Future studies in these lines of inquiry will help elucidate effective treatment strategies aimed at obtaining and maintaining full recovery from BN.

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Sponsor involvement was limited to providing funding for the study.

Disclosure statement

Dr. Hannon-Engel, Dr. Filin, and Dr. Wolfe report no financial, personal, or other relationships with other people or organizations that could inappropriately influence this work.

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