Role of Altered CCK Response in Bulimia Nervosa

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ROLE OF ALTERED CCK RESPONSE IN BULIMIA NERVOSA

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ABSTRACT

Role of Altered CCK Response in Bulimia Nervosa

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The core defining features of bulimia nervosa (BN) are repeated binge eating episodes and compensatory purging behavior. The biobehavioral aspects of binge eating are complex and not fully understood. One area of recent interest is the role of the satiety-signaling peptide cholecystokinin (CCK). Previous research observed a blunted postprandial plasma CCK response in those with BN, therefore suggesting this may be a cause, consequence, or maintenance factor in binge eating. It is unknown whether this altered response is due to a state versus trait phenomenon, thus having implications in 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 biobehavioral study utilized a comparative design to prospectively evaluate the biological CCK response and the corresponding behavioral ratings of satiety and other eating-related sensations in individuals with BN (n=10), RBN (n =14), and healthy controls (CON, n=13). CCK and behavioral ratings were assessed at baseline, +15, +30, and +60 minutes following the ingestion of a standardized liquid test meal.

The BN group's CCK response was blunted and approached significance (p =.052) when compared to the RBN and CON groups. As predicted the RBN and CON groups' CCK response did not significantly differ. This finding supports the premise that

CCK may normalize following abstinence from binge and purge (vomit) episodes and that this is a state versus trait related phenomenon.

A significant positive relationship between CCK response and ratings of satiety occurred in the RBN group only (r=.59, p<.05). A new and unanticipated finding in the BN group was a significant relationship (r=.86, p < .01, two-tailed) between their CCK response and urge to vomit. A greater urge to vomit was reported by those individuals who had increased CCK response. Therefore, it is unknown whether the normalization of CCK functioning is a protective or liability factor in the stabilization and recovery process. Replication studies utilizing a larger sample size are needed to understand the role of CCK in recovery and the subsequent development of novel treatment strategies for those suffering with BN.

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CHAPTER 1

INTRODUCTION

Statement of the Problem

Bulimia Nervosa (BN) is a chronic and debilitating eating disorder characterized by repeated binge eating episodes followed by purging behavior. Research suggests that BN is at least three times more common in young women than men (Hudson, Hiripi, Pope, & Kessler, 2006), culturally-bound (Keel & Klump, 2003), and genetically linked (Bulik et al., 2003) with an estimated range of 1%- 4.2% life-time prevalence (Garfinkel et al., 1995; Hoek & Van Hoeken, 2003; Hudson et al., 2006; Kendler et al., 1991). Onset of the disorder is typically during late adolescence or young adulthood, with an often chronic course of illness (Fairburn, Cooper, Doll, Norman, & O'Connor, 2000; Herzog et al., 1999; Keel, Mitchell, Miller, Davis, & Crow, 1999), and a substantial economic burden (Simon, Schmidt, & Pilling, 2005). Less than half of affected individuals seek treatment (Fairburn et al., 2000; Hoek, 2003), typically for concerns pertaining to symptoms of a co-morbid psychiatric diagnosis (Hudson et al., 2006). The most common comorbid psychiatric conditions include: depression (Johnson, Spitzer, & Williams, 2001) anxiety (Garfinkel et al., 1995; Kaye, Bulik, Thornton, Barbarich, & Masters, 2004) and substance use disorders (Bulik et al., 2004; Herzog et al., 2006). Psychosocial functioning is poor for those individuals diagnosed with persistent BN (Keller, Herzog, Lavori, Bradburn, & Mahoney, 1992) and comorbid Axis II disorders are commonly associated with a slower recovery rate (Herzog, Keller, Lavori, Kenney, & Sachs, 1992). The most studied and widely accepted form of treatment, Cognitive Behavioral Therapy

(CBT), results in less than fifty percent of individuals achieving a full and lasting response (Fairburn, 2002). Overall, long term outcome, recovery, and relapse studies have shown that at least one-third of individuals who had previously recovered were likely to relapse and/or maintain eating disorder symptoms of clinical severity (Fairburn et al., 2000; Herzog et al., 1999).

During active illness, this disorder is marked by repeated binge eating and compensatory behaviors to prevent weight gain. The underlying pathophysiologic mechanisms that may contribute to this aberrant behavior are complex and poorly understood. Individuals with BN report altered perceptions in hunger, fullness, and satiety (Halmi, Sunday, Puglisi, & Marchi, 1989). Laboratory studies have shown that cholecystokinin (CCK), a satiety producing hormone, is blunted in individuals with active BN following a meal when compared to matched healthy controls (Devlin et al., 1997; Geracioti & Liddle, 1988; Pirke, Kellner, Friess, Krieg, & Fichter, 1994). Decreased CCK functioning may contribute to impaired satiety and lead to binge eating episodes in this patient population.

Purpose of the Study

To help evaluate the extent to which postprandial (after a meal) CCK responses are normalized following remission of BN, this project examined CCK responses following a test-meal in persons with active BN, remitted BN (RBN), and healthy controls (CON). This study provides a further understanding of the possible state-related role of CCK to impaired satiety in this patient population. Future studies in these lines of inquiry will

help elucidate effective treatment strategies aimed at obtaining and maintaining full recovery from BN.

Definition of Terms

Satiety: is "the inhibition over hunger and further eating that arises as a consequence of food ingestion"(Blundell & Hill, 1993).

Satiation: is depicted as the process that brings an episode of eating to an end, thus influencing the size of meals and snacks (Blundell, 2002). The individual receives signals from the brain leading to a feeling of *satiety* (fullness and satisfaction) which leads to the termination of the meal or *satiation.*

CCK: is a short-term satiety gut neuropeptide that endogenously signals the brain processes (through alimentary pathways) that enough food has been eaten. Because CCK-8 is the predominant form used by investigators (Chandra & Liddle, 2007) and CCK- receptors in the alimentary pathway only bind to sulfated form (Rehfeld, 2004), peripheral plasma concentrations of CCK-8S were measured using a radioimmunoassay (RIA) in this study. This is consistent with previous studies of CCK and satiety and will allow for comparison across studies.

Bulimia Nervosa: as defined by the fourth edition text-revised of the *Diagnostic Statistical Manual of Mental Disorders Fourth Edition-Text Revision* (DSM-IV-TR) criteria for BN, purging subtype (American Psychiatric Association, 2000). The criteria

identify recurrent binge eating episodes that are characterized by eating (within a 2-hour period) an excessive amount of food that is definitely larger than most people would eat under similar circumstances. Additionally, during this binge eating episode, individuals report a lack of control over eating. Directly following this episode, individuals engage in recurrent inappropriate compensatory behavior to prevent weight gain including: self-induced vomiting; misuse of laxatives, diuretics, enemas, or other medications; fasting; or excessive exercise. Because self-induced vomiting (purging) is the most prevalent compensatory behavior (Reba et al., 2005), only those people who engage in this particular behavior will be included in this study. The DSM-IV-TR criteria further states that these aberrant behaviors must occur a minimum of 2 times per week and be present for a minimum of 3 months. Lastly, individuals' self-evaluation is disproportionately based on their current body shape and weight.

Individuals are further characterized by either purging or nonpurging sub-types. Purging type includes those who engage in regular self-induced vomiting or the misuse of laxative, diuretics, or enemas. The nonpurging subtype includes those people who may either fast or engage in excessive exercise but do not engage in the aforementioned purging subtype behaviors. For the purpose of this study, *purging* behavior connotes a person diagnosed with BN who engages in self-induced vomiting.

Remitted Bulimia Nervosa: individuals have a history of BN (purging subtype) and no history of binge eating, purging behavior, or recurrent inappropriate non-purging compensatory behavior during six months prior to study. These individuals are a major

focus of this study and are important in the assessment of whether CCK responsivity normalizes following remission from this illness. If CCK does normalize, this suggests a state (acquired) response to binge purge behavior. If CCK does not normalize in this subject group, this suggests a trait (genetic or innate) phenomenon.

Assumptions

1. BN individuals consume excessive amounts of food (during a binge episode) in a short amount of time, report altered satiety, and subsequently purge consumed food.
2. CCK is a hormone that endogenously signals the brain processes to indicate that enough food has been eaten.
3. CCK functioning in those individuals diagnosed with BN is diminished in comparison to matched healthy CON.
4. CCK is accurately measured as CCK-8S using RIA.

Research Question

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

Hypotheses

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

H2. Postprandial plasma CCK response will be significantly positively correlated with postprandial visual analog measures of satiety in the RBN and CON groups.

Significance of Project

Findings of the project provide new information about the integrity of the postprandial CCK satiety-signaling in BN. A central question of this study was whether abnormal postprandial CCK response, demonstrated in previous studies of BN, was also observed following remission and whether RBN subjects significantly differ from CON subjects. To date, studies have not examined CCK function following remission of BN. This study provided an opportunity for the assessment of the extent to which clinical remission from BN is associated with normalization of postprandial CCK response. A stable trait related phenomenon could increase the risk and vulnerability of occurrence, perturbation, and relapse of this disorder. However, if CCK responsivity is a state phenomenon, this finding points to future intervention and treatment strategies for this often chronic, treatment resistant or unresponsive disorder. In summary, this determination of post-prandial CCK response in relation to satiety measures will be informative to the direction of future research on intervention and treatment strategies for BN.

CHAPTER 2

Conceptual Framework[1]

The biobehavioral aspects of BN are multi-faceted and poorly understood. Therefore, a comprehensive theory that encompasses a biobehavioral understanding of this debilitating illness is essential in determining appropriate research initiates and practice implications. The Roy Adaptation Model (RAM) has been successfully utilized in research, practice, and knowledge development. According to the RAM, nursing's biobehavioral knowledge "balances understanding of the persons as both physiological beings in a physical world and as thinking and feeling beings with human experience in a cosmic world" (Roy & Andrews, 1999, p. 100). The person affected by BN is viewed from a holistic, expanded and integrated perspective. This thinking and feeling person is considered to possess interrelated parts that comprise a unified whole. Further, this person is considered to possess an adaptive system of control (coping) processes referred to as the "regulator" and "cognator" subsystems respectively. While these coping processes serve to maintain adaptation in four critical modes: (a) physiological, (b) self-concept, (c) role-function, and (d) interdependence, the physiological mode will be the major focus of this research.

From a simple systems explanation the RAM considers stimuli (inputs) to activate control (coping) mechanisms resulting in subsequent behavior (output).

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[1] The following section was originally developed by this author and the final definitive version was published as "Knowledge Development: The Roy Adaptation Model and Bulimia Nervosa" in the *Nursing Science Quarterly*, Vol. 21, No. 2, 126-132 (2008)/

INPUT → COPING MECHANISM = OUTPUT

The success of the human system to effectively *adapt* to stimuli depends on the person's adaptation level, demands of the particular situation, and the condition of the pre-existing life processes. These processes are conceptualized by three levels of functioning: integrated, compensatory, and compromised (Roy & Andrews, 1999). Further explication of these specific levels (as related to BN) are depicted in Figure 1.

The Human as an Adaptive System

Stimuli

Roy depicts three important stimuli (focal, contextual and residual) that subsequently activate the coping mechanisms of the human adaptive system. The *focal* stimulus calls for the immediate and focused attention of the individual. The person with BN is intently focused on and struggles with the thoughts, feelings and behaviors related to the focal stimulus, food. As this struggle persists and the individual attempts to gain control, a pattern of binge and purge behavior becomes ingrained. *Contextual* stimuli include other factors that are currently influencing the person's ability to respond to the focal stimuli. These can include biological vulnerabilities, including altered CCK responsivity and impaired satiety. All other related stimuli that are not evident in the initial assessment can be considered *residual.* According to the RAM, all stimuli are constantly shifting in response to the individual's environment. For example, if an individual is suddenly confronted with a derogatory comment concerning his or her weight and shape, this once residual stimulus can become *focal* and demand immediate attention.

Coping Processes

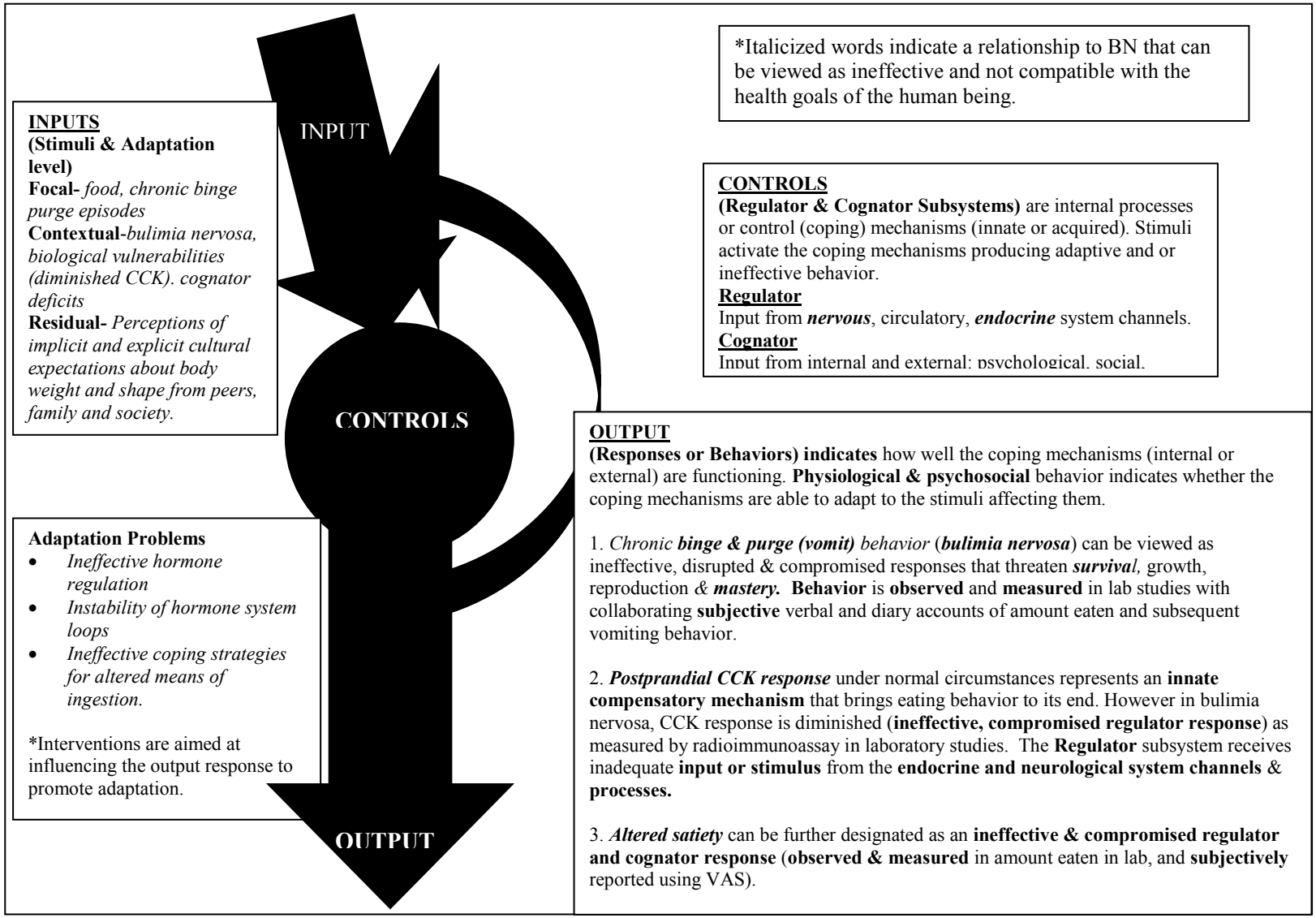
The Roy Adaptation Model (1999) describes the coping processes as those internal "innate or acquired ways of interacting with (responding to and influencing) the changing environment" (p. 46). Those processes considered *innate* are genetically pre-determined and occur without human intervention (Roy & Andrews, 1999). This directly relates to the central question of this research initiative that investigated whether a diminished CCK response to a meal in those with active BN is a genetic trait or a state (acquired) phenomenon. An *acquired* response to stimuli refers to a learned response through repetition. For instance, purging directly following an episode of binge eating effectively rids unwanted calories, food, and abdominal pressure.

Additionally, the RAM characterizes the above responses into two subsystems called the regulator and cognator subsystems. The regulator receives automatic innate signals from the neural, chemical, and endocrine system channels (see Figure 1). The cognator subsystem "responds through four cognitive emotive channels: perceptual and informational processing, learning, judgment, and emotion. Perceptual and informational processing includes activities such as selective attention, coding and memory" (Roy & Andrews, 1999, p. 46). In relation to those affected by BN, binge eating and purging behaviors become a potent way to manage internal emotional states, resolve challenges to personal control, and endure cravings and urge.

Behavior

The subsequent behavioral *response* of a person depends on whether the coping (control) mechanism is either *adaptive* or *ineffective.* Responses also act as feedback and additional input to the overall system. In BN, recurrent binge and purge behaviors are seen as ineffective and compromise the "goals, survival, growth, reproduction and mastery of the human being"(Roy & Andrews, 1991, p. 31). Additional examples and multiple linkages between the conceptual model and BN are described in Figure 1. In view of these multiple linkages, it is clear that the RAM is a comprehensive conceptual model that may serve as a basis for knowledge and research development in relation to BN.

Figure 1. The Roy Adaptation Model



Review of the Literature[2]

A review of the literature begins over 25 years ago when BN was first described by Russell (1979) as an "ominous variant" of anorexia nervosa (AN). In his initial account, he describes this "bulimic" group as having core eating disordered beliefs about weight similar to that of AN. However, unlike those with AN, who severely restrict food consumption, persons with BN have striking and distinct symptom patterns including an irresistible urge to overeat followed by self-induced vomiting (Russell, 1979). Since that time, BN has received increased research and clinical attention due to the severe and chronic nature of this disorder (Keller et al., 1992).

Symptom Patterns and Clinical Characteristics of BN

The DSM-IV-TR identifies the cardinal feature of BN as binge eating, characterized by a "loss of control" during repeated episodes of eating excessively large amounts of food. This is followed by inappropriate purging or nonpurging compensatory behaviors (American Psychiatric Association, 2000). Purging behaviors include self-induced vomiting, laxative abuse, diuretic abuse, and misuse of enemas. Nonpurging behaviors include fasting, strict dieting, and / or excessive exercising in an effort to maintain or lose weight. To meet diagnostic criteria, binge eating and purging behaviors must occur at a minimum frequency of two times per week over the course of three months.

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[2] The following section was originally developed by this author and the final definitive version was published as "Regulating Satiety in Bulimia Nervosa: The Role of Cholecystokinin" in *Perspectives in Psychiatric Care*. 2011 doi: 10.1111/j.1744-6163.2011.00304.x

A pervasive devalued self-worth, including loathing of body weight and body shape, is characteristic of BN. Common premorbid characteristics of impulsivity (Wolfe, Jimerson, & Levine, 1994), dysregulated emotions, anxiety, depression (Brewerton et al., 1995; Kaye et al., 2004), low self-esteem, early menarche, dieting and critical comments about eating (Fairburn, Welch, Doll, Davies, & O'Connor, 1997) may contribute to the vulnerability and expression of this disorder. Individual risk factors include genetic and familial (Kassett et al., 1989) vulnerabilities to dieting, obesity, psychiatric disorders and substance misuse disorders (Fairburn & Harrison, 2003). Individuals affected by this disorder are likely to maintain a normal weight despite fluctuations and a decreased metabolic rate (Birketvedt et al., 2006; Obarzanek, Lesem, Goldstein, & Jimerson, 1991). Food restriction and dieting generally precede episodes of binge eating (Beumont, 2002; Pyle, Mitchell, & Eckert, 1981; White, 2000) and are regularly attempted but interrupted by repeated gorges.

Comorbid medical conditions ensue with persistent illness. Tooth enamel can become eroded secondary to the direct repeated exposure to gastric acids following a vomiting episode (Milosevic, 1999). The most frequent compensatory behavior, self-induced vomiting (Reba et al., 2005), can further compromise electrolyte status, requiring careful monitoring of specific laboratory values to avert complications (Wolfe, Metzger, Levine, & Jimerson, 2001). Surprisingly, even when individuals affected by BN present for routine and/ or related medical care, this illness often goes undetected (Johnson et al., 2001) as patients may under report symptoms secondary to shame, guilt and / or a desire to retain this aberrant eating behavior.

Bulimia Nervosa and Binge Eating

For over twenty years, laboratory studies have been a reliable and valid method to measure eating behavior in BN (Gosnell et al., 2001; Kissileff, Walsh, Kral, & Cassidy, 1986; Mitchell, Crow, Peterson, Wonderlich, & Crosby, 1998). Studies have effectively established dependable paradigmatic protocols within a controlled environment to objectively understand factors contributing to the termination of eating once it has begun (Kissileff, 1992). Initial reports from patients with BN indicate an inability to discern fullness at the end of a normal meal and eating patterns that alternate between severe restriction and binge eating (Mitchell, Hatsukami, Eckert, & Pyle, 1985; Pyle et al., 1981). While self-reports of food consumption by those with BN appeared dramatic (Mitchell & Laine, 1985), studies show a direct correlation between subjective accounts and laboratory measurement of food intake (Walsh, Kissileff, Cassidy, & Dantzic, 1989). Clinical laboratory studies, using both a multi-item and single-item test meal, show that patients with BN consume a significantly larger amount of food compared to controls (Guss, Kissilef, Walsh, & Devlin, 1994; LaChaussée, Kissileff, Walsh, & Hadigan, 1992; Walsh, Kissileff, & Hadigan, 1989). In sharp contrast to healthy controls, despite eating quantifiably larger amounts of food, patients with BN reported less fullness and displayed increased motivation to eat as the meal progressed (Kissileff et al., 1996). These studies demonstrate a clear aberration that may serve to perpetuate this incapacitating disorder.

The macronutrient composition of meal choice by BN subjects has generally remained comparable to controls. However, a trend towards dessert and snack foods has been described (Rosen, Leitenberg, Fisher, & Khazam, 1986). A carbohydrate craving

has been suggested as a driving force in the perpetuation of binge eating; however, this hypothesis remains inconclusive (Hadigan, Kissileff, & Walsh, 1989). In laboratory studies of eating behavior, BN subjects consumed far fewer calories when instructed not to binge in comparison to controls (Hadigan et al., 1989), underscoring that persons with BN may regularly restrict when not engaged in a binge eating episode. One plausible explanation is that due to a lack of inhibitory controls in BN, patients artificially terminate meals in contrast to allowing the naturally occurring mechanisms of satiety to affect both meal size and duration (Walsh, Kissileff, & Hadigan, 1989).

Binge Eating and Satiety

Satiety refers to "the inhibition over hunger and further eating that arises as a consequence of food ingestion" (Blundell & Hill, 1993). Satiation is a term typically used to describe "the process that brings a period of eating to an end and thus influences the size of meals and snacks" (Blundell, 2002). A functional satiety system (see Figure 2) can be best described as a complex integrative central and peripheral signaling network of positive and negative feedback mechanisms that work to maintain energy homeostasis (Smith & Geary, 2002). Positive feedback signals are initiated by feeding behavior. In response, a supposed symmetrical inhibitory or negative feedback signal, requiring greater potency, terminates the episode of eating (Smith & Gibbs, 2002b). If there is a dysregulation in the relative potency of the negative feedback signaling mechanism, meal size and duration can be increased. Thus, binge eating may reflect a relative dysregulation in the negative feedback mechanism of the satiety system (Jarosz & Metzger, 2002).

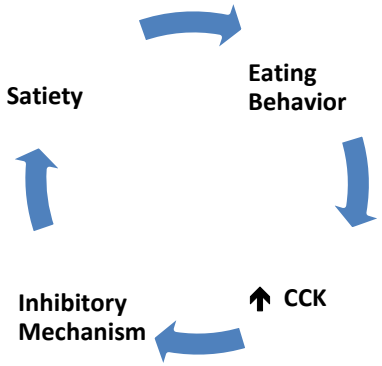


Figure 2. **Normal eating behavior**

Overview of CCK

One key inhibitory component of eating behavior is the gastrointestinal hormone cholecystokinin (Smith, 2002). CCK was originally discovered in 1928 (Ivy & Oldberg) for its ability to contract the gallbladder, and later found to stimulate pancreatic exocrine secretion (Harper & Raper, 1943). Additional physiological actions include regulation of gastric emptying and induction of satiety. In a highly synchronized manner, CCK regulates the intake, digestion, and absorption of nutrients (Liddle, 1997).

CCK is produced by the enteroendocrine cells located in the proximal mucosa of the small intestine (Liddle, 1997). CCK producing cells can be found in the small intestine, vagal afferent nerve fibers, and brain (Moran, 2000). CCK-1 receptors (previously identified as A-alimentary) are primarily located in the gastrointestinal system whereas CCK-2 receptors (previously known as B-brain) are located in the central nervous system (CNS) (Moran, Robinson, Goldrich, & McHugh, 1986). It is the interactions of the

CCK-1 receptors that are thought to contribute to satiety signaling (Moran, Ameglio, Schwartz, & McHugh, 1992). The original bioactive form was isolated as CCK-33 from the small intestine, while other molecular forms were identified in the brain and plasma across species (Rehfeld, 2004). In mammals, CCK molecules range in bioactive forms from CCK-8 to 58. However, it is predominately CCK-58, 33, 22, and 8 that are released into plasma (Rehfeld, 1998)

The signal pathway (see Figure 3) that is involved with satiety, and central to this study, begins with a robust and predictable CCK post-ingestive response to nutrients (Smith & Geary, 2002). After chyme enters the proximal duodenum through relaxation of the pyloric sphincter, CCK is released from the lumen mucosa into the peripheral bloodstream (Smith & Gibbs, 2002a). It then interacts with CCK receptor-1 along the vagus nerve projecting onto the nucleus tractus solitarius (NTS) of the hindbrain (Blundell & Hill, 1993; Moran, Norgren, Crosby, & McHugh, 1990). Further influence extends to the arcuate nucleus of the hypothalamus and the paraventricular nucleus (PVN) (Blundell, 2006; Rehfeld, 2004). This higher order integration evaluates inhibitory signals and metabolic state to determine energy storage needs for regulation, whereas the NTS primarily controls the amount of food eaten (Havel, Larsen, Cameron, Conn, & Freeman, 2000; Hellstrom et al., 2004). Therefore, if this pathway is altered due to a diminished CCK response, it follows that individuals with BN would consume excessive amounts of food.

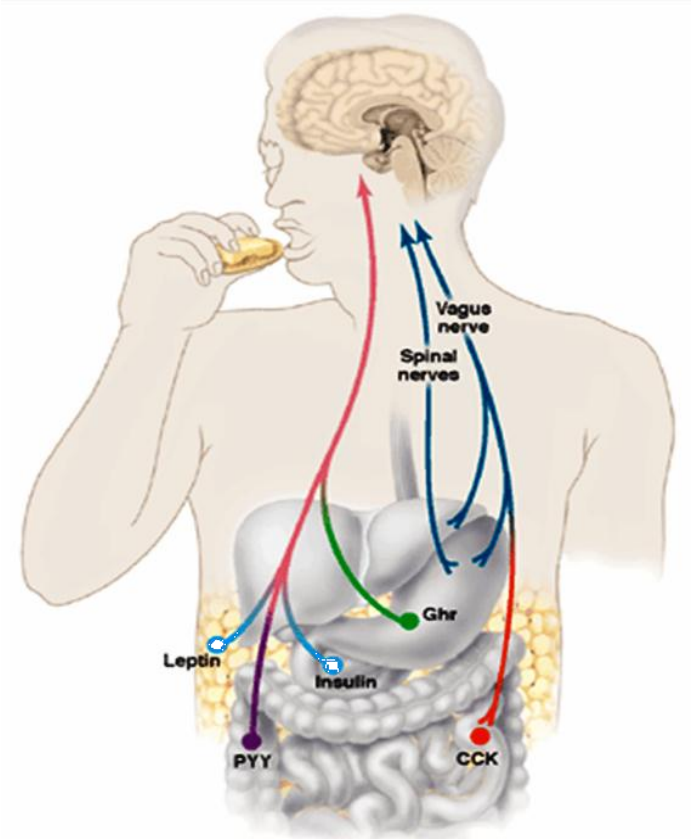


Figure 3. CCK signal pathway[3]

CCK and Satiety: Preclinical Studies

Pre-clinical studies have been essential in demonstrating CCK as an integral component of the satiety system. These studies have shown that intravenous administration of CCK induced satiety in canine (Sjodan, 1972) and rats (Gibbs, Young, & Smith, 1973). Additionally, intraperitoneal injection of CCK during sham feeding in the rat not only stopped feeding but elicited the complete behavioral sequence of satiety

[3] From "Cellular Warriors at the Battle of the Bulge," by J. Marx, 2003, *Science, 299,* p. 846-849. Reprinted with permission of the author.

(Antin, Gibbs, Holt , Young, & Smith, 1975). A total abdominal vagotomy in the rat blocked the satiety effects of exogenous CCK administration (Smith, Jerome, Cushin, Eterno, & Simansky, 1981), confirming that the abdominal vagal afferent nerve fibers mediate the inhibitory signals to the hindbrain. In summary, CCK interacts with the vagus nerve, which sends a robust signal to the hindbrain for the termination of a meal. Again, it is evident that a reduction in CCK results in a weak signal that fails to discontinue a meal, contributing to increased quantity of food intake.

CCK and Satiety: Clinical Studies

In humans, intravenously infused administration of CCK versus saline in a double blind experimental design, yielded a decreased appetite in young normal weight men (n=8) and women (n=8) (Stacher, Bauer, & Steinringer, 1979) and an earlier termination of the meal, without changes in the rate of eating or complaints of side effects in twelve healthy lean (Kissileff, Pi-Sunyer, Hornton, & Smith, 1981) and eight obese (Pi-Sunyer, Kissileff, Thornton, & Smith, 1982) men. Additionally, postprandial visual analog satiety ratings were positively correlated with CCK responses in seven healthy males (Holt, Brand, Soveny, & Hansky, 1992). While initial studies showed administration of CCK reduces meal size and duration, studies using a CCK receptor-1 antagonist showed an increase in caloric intake and feelings of hunger (Beglinger, Degen, Matzinger, D'Amato, & Drewe, 2001). In a preliminary report, (Nolan, Guss, Liddle, Pi-Sunyer, & Kissileff, 2003) a liquid test meal was shown to significantly stimulate CCK release, with subsequent decreased hunger ratings and increased fullness ratings in healthy males and

females. The above evidence establishes CCK as a satiety agent (Smith, 1998) and provides verification that it can be adequately stimulated by a liquid meal in a controlled laboratory setting.

CCK and Satiety: BN

Individuals affected by BN consistently exhibit altered perceptions of hunger, fullness, and satiety (Halmi et al., 1989). A dysregulated satiety system fails to signal and subsequently inhibit intake of food (Devlin et al., 1997). CCK's post prandial plasma measurement, compared to controls, shows a blunted response in individuals with BN (Devlin et al., 1997; Geracioti & Liddle, 1988; Pirke et al., 1994). It has been postulated that patients with BN have a compilation of gastrointestinal dysfunctions (see Figure 4) that serve to diminish the responsiveness of post-ingestive CCK release (Hadley & Walsh, 2003; Walsh, Zimmerli, Devlin, Guss, & Kissileff, 2003). Subjects with BN have been found to have an enlarged gastric capacity, decreased accommodation reflex, diminished sensitivity to distension, and slowed gastric emptying as compared to matched healthy controls (Zimmerli, Walsh, Guss, Devlin, & Kissileff, 2006). An enlarged gastric capacity (secondary to repeated binges) (Geliebter & Hashim, 2001), may take longer to fill, thereby delaying entry into the proximal small intestine. This slowed gastric emptying (Geliebter et al., 1992) could confound a robust release of CCK into the periphery (Devlin et al., 1997).

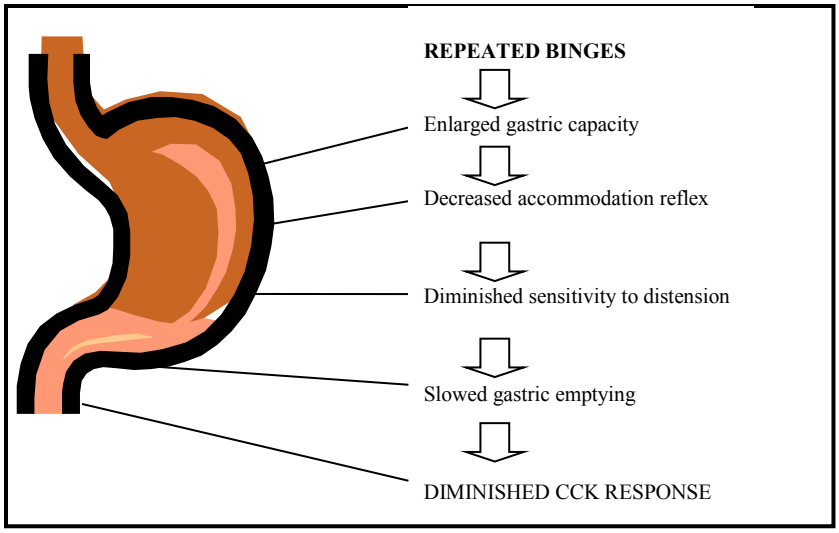


***Figure 4*. Compilation of gastrointestinal dysfunctions in BN**

In review, individuals afflicted with BN and altered satiety are largely defined indirectly by their comparison to matched healthy controls and thus viewed to maintain the following attributes:

1. Feel out of control while repeatedly consuming a significantly greater amount of food.
2. Rate and desire to binge eat accelerates instead of decelerates as the meal progresses.
3. Report feeling less, rather than more, satiated, after eating excessively large amounts of food.
4. Exhibit altered perceptions of hunger and fullness.
5. Feel more anxious, depressed, sick and less relaxed during an episode of binge eating.
6. Exhibit a compilation of gastrointestinal dysfunctions.
7. Demonstrate diminished CCK post-prandially.

Influencing CCK

In a preliminary exploration of five individuals with BN (studied before and after starting a tricyclic antidepressant) an initial improvement in CCK response was shown following a liquid test meal (Geracioti et al., 1989). While the mechanism of this finding is not fully understood, as it may be related to a number of interacting influences, including the limitations of a small sample size, the study points to the importance of examining the underlying mechanism of CCK responsivity in a larger group of carefully characterized medication-free RBN individuals.

Importance of the Knowledge to be Gained

Bulimia nervosa is a serious psychiatric disorder often associated with a chronic course of illness, significant psychosocial distress, and potentially severe medical consequences. Although the etiology remains elusive, previous findings suggest that altered regulation of CCK function may contribute to abnormal eating patterns and meal size in persons affected by this disorder. Results of this project evaluate the extent to which postprandial CCK responses are normalized following remission of BN, contributing an increased understanding of the possible state-related role of CCK in relation to satiety in this disorder. Further understanding of this role has the potential for informing future interventions that may target CCK function, enhance satiety signaling, and decrease the binge eating episodes in BN.

CHAPTER 3

METHODOLOGY

Study Design

This clinical research study used a comparative design to prospectively assess the integrity of the CCK-mediated satiety signaling in persons with RBN, BN and healthy controls (CON).

Subjects

This project included a convenience sample of women with RBN (n=14), BN (n=10), and healthy female volunteers (n=13). A control group (CON) was included to allow for replication of previously reported findings. This latter group of individuals was carefully screened to rule out a diagnosis of a current or past DSM-IV-TR Axis I diagnosis, including eating disorders. Subject group inclusion criteria are as follows:

RBN: 1) History of BN, purging (vomiting) subtype, as defined by the DSM-IV-TR (American Psychiatric Association, 2000). 2) No history of binge eating, purging behavior, or recurrent inappropriate non-purging compensatory behavior during six months prior to study (consistent with previous research).

BN: 1) DSM-IV-TR criteria for BN, purging subtype (full definition, page 3). Patient groups were free of all medications (except birth control), supplements, probiotics for at least eight weeks prior to study.

CON: 1) Free of current or past history of DSM-IV-TR eating disorder; 2) not actively engaged in dieting behavior for the purpose of weight loss as measured by a score of $\leq$ 16 on the Restraint Scale (Polivy, Herman, & Howard, 1988).

All Subjects: 1) age 18-45 years; 2) body mass index (BMI) between 19 - 26 kg/m^2 (considered normal weight); 3) gender, female; 4) in good medical health, free of known medical conditions or medication treatment (except for birth control) or any supplements or probiotics that may have an effect on gastrointestinal function ; 5) not pregnant or nursing an infant in past six months; and, 6) free of alcohol use for 72 hours prior to study. This set of inclusion criteria is similar to those used in previous investigations of CCK functioning (Devlin et al., 1997; Keel, Wolfe, Liddle, De Young, & Jimerson, 2007) thus allowing comparison with previous findings.

Setting

Subjects who met initial participant inclusion criteria (determined by telephone screening) were scheduled for a screening visit conducted by the principal investigator (PI). Screening visits occurred in a private interview room designated in the School of Nursing at Boston College or an outpatient interview room at the NIH funded Clinical Research Center (CRC) at Beth Israel Deaconess Medical Center (BIDMC). This hospital is an academic and clinically research driven environment.

A second study visit was conducted in an outpatient room at the CRC at BIDMC. The CRC is a fully staffed unit providing inpatient and outpatient services. This study utilized CRC outpatient and core lab facilities. A range of research trained staff

including nursing personnel, dieticians, lab technicians and administrative staff supported the operations of this study. Directly following blood sample collection, specimens were centrifuged (spun at 1500xg for 15 min. at 4˚C) and clear plasma was transferred by the PI, lab personnel or nursing staff into the appropriate polypropylene tubes and stored in a freezer at -70˚c at BIDMC until time of assay.

Procedures

Recruitment and screening. RBN subjects, BN subjects, and healthy controls were recruited using study flyers and postings strategically positioned at approved community and university communication sites (e.g., college postings, community centers) and in accordance with the IRB protocol. Additionally, this study was posted in select university magazines, newspapers and internet sites (e.g. Craig's list, Facebook). In addition to basic inclusion criteria, advertisements indicated that each subject would receive thirty- dollars ($30) at the completion of the screening visit and seventy ($70) at the completion of the study visit. The PI conducted 108 pre-screening telephone interviews and subsequently scheduled 68 qualified subjects for a screening visit at Boston College or the BIDMC CRC. Including both the screening and the study visits the PI completed a total of 106 in person visits.

Screening visit. During this visit, subjects received a detailed explanation of study procedures from the PI and read the informed consent document (Appendix B). Directly following, the subjects explained their understanding of the study to the both the PI and the witness per protocol. Throughout this process the subjects had the opportunity to ask questions prior to signing the informed consent document. The initial interviews

proceeded only after written informed consent was obtained. Screening assessment procedures involved the administration of the Structured Clinical Interview for DSM-IV Axis I Disorders (First, Spitzer, Gibbon, & Williams, 2010). Subjects were asked to complete the following self-rated scales: Eating Disorder Examination- Questionnaire (EDE-Q 6.0; Mond, Hay, Rodger, Owen, & Beumont, 2004) , the Restraint Scale (Polivy et al., 1988) to determine the level of current dieting behavior, he Beck Depression Inventory – II (BDI-II; Beck, Steer, & Brown, 1996) was utilized to assess level of depression and need for clinical referral. Interviews were conducted by the PI and assessment materials were evaluated at time of completion in the event there was a need for referral. Additional data collected included fluctuations in body weight, dietary patterns, and medical history. An initial assessment of height and body weight was obtained. Following the screening assessments, subjects were asked to consume the standardized liquid test meal (described below) in order to allow them to acclimate to the study procedure, as well as to assess the acceptability and taste-preference (Peryam & Pilgrim, 1957).

Outpatient study visit. Following the screening visit, the PI scheduled eligible subjects for an outpatient study visit at the BIDMC CRC. Subjects were scheduled during the morning hours and were asked to arrive following an overnight fast. After review of informed consent, subjects received a brief updated assessment of psychiatric and medical symptoms by the PI. Nursing personnel, using an anthropometric station and calibrated metabolic scale, obtained a measurement of height and weight (reported in Table 3) while the subject wore two hospital gowns. Based on these results, the PI

calculated the subject's BMI using http://www.nhlbisupport.com/bmi/. The study visit proceeded only if the subject met BMI inclusion parameters of 19-26kg/m^2. In addition, orthostatic vital signs and a urine sample for a pregnancy screen were conducted. At the suggestion of an NIH reviewer, baseline measure of aggression (Aggression Questionnaire; Buss & Perry, 1992) was collected to obtain descriptive characteristics relative to anger and hostility.

Following placement of an intravenous catheter (in the forearm) by CRC nursing personnel, subjects had a 15 minute stabilization period after which a baseline blood sample was drawn for measurement of plasma CCK. Approximately 5 minutes following the blood draw, subjects were asked to consume a standardized liquid test meal in the course of the next five minutes. 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 in this patient population (Devlin et al., 1997; Keel et al., 2007). The use of the standardized liquid test meal (600ml) was selected based on previous research showing that ingestion of 600 ml had a larger effect (Cohen's $d = 1.47$) on differences in plasma CCK response in patients with BN (n=8) in comparison to controls (n=10) (Devlin et al., 1997). Data collection time points were consistent with those used in previous studies (Devlin et al., 1997) to enable cross comparisons. Subjects were asked to complete a set of 100mm visual analog scales (VAS) that assessed feelings of hunger, satiety, fullness, anxiety, depression, desire to binge, and desire to purge at the time of blood sample collection. Additionally, subjects received a side effect checklist (SEC) at the same time points of the VAS ratings. This

allowed for the monitoring of symptoms before and after the test meal (Figure 5.). The study visit lasted up to two hours.

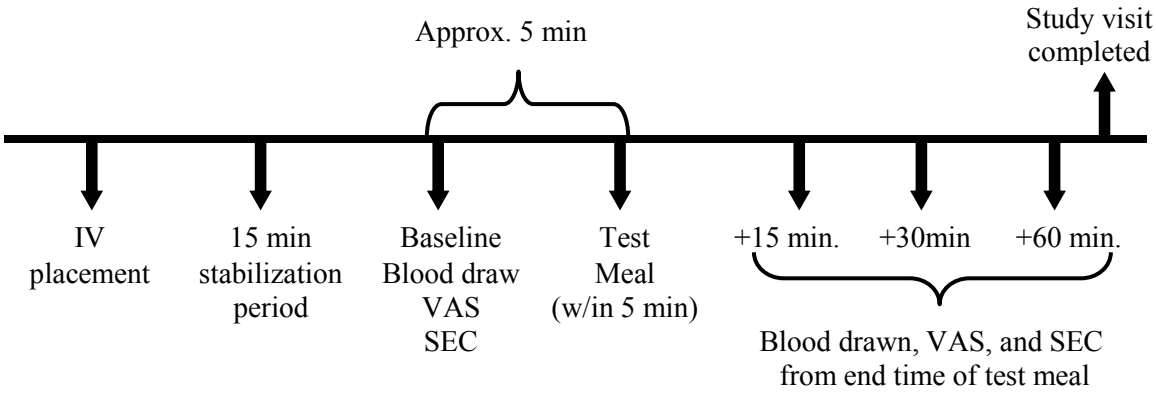


Figure 5. Timeline for pre and post ingestion of standardized test meal.

Blood samples were kept on ice for 5 minutes in tubes prepared with ethylenediaminetetraacetic acid (EDTA) and aprotinin (Trasyol) before cold centrifugation (1500xg) for 15 minutes. The plasma was pipetted into cryo-microtubes and stored at -70ºC until batch assayed. Prior to analyses samples were packed in dry ice according to BIDMC required shipping and handling procedures and sent overnight to KMI, incorporated diagnostics laboratory testing center in Minneapolis, MN. Laboratory analyses were performed (in duplicate in the same assay, along with standardized controls) on coded samples by technicians blind to diagnosis and other clinical information on individual subjects. Plasma CCK concentrations (CCK-8S) were measured using a radioimmunoassay (RIA) kit lot: NS2323US from EuroDiagnostica. The RIA method developed by Rehfeld (1998) was chosen due to its' high degree of accuracy, sensitivity, specificity, in the plasma measurement of CCK, and its' wide use

and acceptance by investigators. This procedure is consistent with previous studies of CCK and satiety (Geliebter, Yahav, Gluck, & Hashim, 2004; Pirke et al., 1994). For this kit, CCK intra-assay coefficient of variation (CV) is 4.4 pmol/L (5.5%) and inter-assay coefficient of variation is 4.2 pmol/L (13.7%). Normal fasting level of CCK is ≤1.12 pmol/L. Assay sensitivity is (LDC) = 0.3 pmol/L. The CCK values supplied by KMI were the mean values of the duplicate RIA analyses.

Instruments

Instruments used in this study are listed in Table 1. Specific psychometric properties for each are described below.

Table 1. List of Instruments

SCREENING VISIT
❑ Structured Clinical Interview for DSM-IV Axis I Disorder, Research Version, Version 2.0 Patient Edition (SCID-I/P)
❑ Eating Disorder Examination- Questionnaire (EDE-Q 6.0)
❑ Beck Depression Inventory-II (BDI-II).
❑ Restraint Scale, Revised
STUDY VISIT
❑ Beck Depression Inventory-II (BDI-II).
❑ The Aggression Questionnaire
❑ Hunger, Satiety, Pleasantness of Foods Visual Analog Scales fullness, anxiety, depression, desire to binge, and desire to purge
❑ Side Effect Checklist

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 (First et al., 2010) is a structured interview administered by a clinician for the purpose of making a DSM-IV Axis I diagnosis. During this study, the PI conducted each interview at the screening visit. Modules of this version include psychotic disorders, mood disorders, substance use disorders, anxiety disorders, somatoform disorders, eating disorders, and adjustment disorder. Language is targeted to an 8th grade education. Kappa values vary among diagnoses, but are reported to be generally comparable to other diagnostic measurements including the Schedule for Affective Disorders and Schizophrenia (SADS; Endicott & Spitzer, 1978) and the National Institute of Mental Health (NIMH) Diagnostic Interview Schedule (DIS) (First, Spitzer, Gibbon, & Williams, 2002; Robins, Helzer, Croughan, & Ratcliff, 1981).

Eating Disorder Examination Questionnaire,(EDE-Q 6.0). The EDE-Q 6.0 is a self-report version (© 2008 by Christopher G. Fairburn and Sarah Beglin) of the Eating Disorder Examination (EDE) (Mond et al., 2004). The EDE is a well-established semi-structured interview designed to assess eating disorder psychopathology primarily occurring over the preceding four weeks (Fairburn & Cooper, 1993). 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. Two studies, both of which included over 100 patients with eating disorders, report the following range of alpha coefficients as a measure of subscale internal consistency: Restraint (.75-.78),

Eating Concern (.68-.78), Shape Concern (.70-.82), and Weight Concern (.68-.70) (Beumont, Kopec-Schrader, Talbot, & Touyz, 1993; Fairburn & Cooper, 1993). Preliminary norms for BN and CON groups from initial studies are published and available for comparison (Fairburn & Cooper, 1993). Correlations between the EDE-Q and EDE subscales ranged from .68 for Eating Concern to .78 for Shape Concern. Scores on the EDE-Q were significantly higher than those on the EDE for all subscales, with the mean difference ranging from .25 for Restraint to .85 for Shape Concern (Mond et al., 2004). 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 (Cronbach α) reliabilities for the EDE-Q subscales were as follows: restraint, 0.83; eating concerns, 0.71; weight concern, 0.94; and shape concern, 0.97.

Restraint Scale, Revised. The Restraint Scale, Revised (Polivy et al., 1988) 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 (Heatherton, Herman, Polivy, King, & McGree, 1988). The revised scale is based on improvements made to the original version, with psychometric properties established following analysis of results from 166 male and 348 female college students (Polivy et al., 1988). The scale demonstrates good internal reliability as determined by item-item and item-total correlations, and is unidimensional as confirmed by principal component analysis. Orthogonal varimax rotation identified factors of the scale that demonstrate a reliable two-factor solution (Polivy et al., 1988) Test-retest reliability coefficients are as high as .93 when re-tested one week later. The median score for

female college students is 15-16. Thus, individuals above this cut-off are likely to display more chronic restraint eating behavior than the other half of the population scoring below this threshold. For this study, control subjects were included if their score ≤ 16 on the Restraint Scale during the screening visit. In the current sample, internal reliability was .93

Beck Depression Inventory®-II (Second Edition) (BDI-II). The BDI -II is a 21-item self-administered rating scale designed to measure depressive symptoms. Each item is rated on a four-point scale (Beck, Steer, & Brown, 1996). 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 internal consistency alpha coefficient is .92 for outpatients and .93 for college students (Beck et al., 1996). The BDI-II was utilized at the screening and study visits to assess for level of depression and the need for clinical referral. The BDI-II was copyright © in 1996 by Aaron T. Beck and all rights are reserved. The PI purchased each scale from Pearson Assessments http://www.pearsonassessments.com at an individual cost of $2.08 per scale. In the current sample, internal (Cronbach α) reliability was 0.91.

The Aggression Questionnaire. The Aggression Questionnaire (Buss & Perry, 1992) is a 29-item self-administered rating designed to measure four factors: physical aggression, verbal aggression, anger, and hostility (resentment and suspicion). The Aggression Questionnaire was constructed from the Buss-Durkee Hostility Inventory (Buss & Durkee, 1957) to measure components of aggression and improve the

psychometric properties of the earlier scale. Psychometric properties are reported in three student cohorts totaling 1,253 individuals (Buss & Perry, 1992). Good internal consistency for the total scale is indicated by an alpha coefficient of .89. Acceptable internal consistency of the subscales is suggested by the following alpha coefficients: .85, physical aggression; .72, verbal aggression; .83, anger; and .77, hostility. Confirmatory factor analysis yielding similar coefficients was obtained in a sample of 306 college students (Harris, 1995). Following a nine-week interval, test-retest correlations in 372 students was .80 for the total scale and .72-.80 for subscales suggesting a relatively stable measure over time (Buss & Perry, 1992). Self-report and peer nomination methods present strong evidence for construct validity of the physical aggression scale, while support for the construct validity of the other three subscales using this method appears modest (Buss & Perry, 1992). As previously stated, a baseline measure of aggression, utilizing the Aggression Questionnaire (Buss & Perry, 1992), was collected to obtain preliminary descriptive characteristics relative to anger and hostility. Cronbach α was 0.89 in this sample. A copy of the tool is available at: http://www.centralquestion.com/aggression/test.html

Hunger, Satiety, Pleasantness of Foods Visual Analog Scales. 100mm visual analog scales (VAS) were used to assess subjective eating-related behavior. The visual analog scale is easily administered and sensitive to incremental changes (Maxwell, 1978). Predictive validity of the hunger and satiety VAS is supported by observations of the predicted changes over time in response to food intake (Geracioti & Liddle, 1988; Hetherington & Rolls, 1987; Keel et al., 2007). In addition, changes in satiety are

associated with changes in plasma CCK (Keel, et al., 2007). However, changes in hunger have not been shown to be correlated with changes in plasma CCK—supporting the discriminant validity of the two measures for assessing different subjective experiences that have been linked to different physiological mechanisms (e.g., satiety to CCK and hunger to ghrelin) (Keel et al., 2007). Thus, these findings support construct validity of the concepts of hunger versus satiety. Because these measures are single-item assessments, which by definition will be less reliable than a multi-item assessment, internal consistency reliability was not examined. The use of the pleasantness VAS was for the purpose of assessing acceptability of the test meal during acclimation procedures at the screening visit. In preliminary data on the pleasantness VAS at a single point following acclimation procedures to a test meal (on two different occasions), test-retest reliability was $r(87)=.649$, $p<.001$ (one-tailed) suggesting acceptable test-re-test reliability for the VAS for collecting subjective rating of a test meal [personal communication: Dr. Pamela Keel 7/24/07], Visual analogue scales have been validated and successfully applied to studies of eating behavior (Hetherington & Rolls, 1987). VAS ratings were obtained before and after the standardized liquid test meal.

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." The Side Effect Checklist has been used in previous studies (Wolfe, Metzger, & Jimerson, 1995; Wolfe et al., 2000).

This questionnaire was used before and after the standardized liquid test meal for monitoring of subjectively experienced side effects only. While not an outcome measure per se, a side effect checklist was included to monitor for any unanticipated effects and will be used for descriptive purposes.

Study Procedure Considerations

The age range of 18-45 years old was chosen to reflect those individuals at greatest risk for and recurrence of the disorder. The selected BMI range was chosen to reflect normal-weight states in order to minimize other potential physiologic confounders. BN subjects were limited to those with purging (vomiting) subtype of BN, based on previous research (Devlin et al., 1997; Geracioti & Liddle, 1988; Phillipp, Pirke, Kellner, & Krieg, 1991; Pirke et al., 1994) and high prevalence (Reba et al., 2005) allowing for comparison across studies.

While gastric size and emptying may play a role in CCK secretion, this project focused on first assessing the postprandial CCK response in persons with BN in remission for several reasons. In the context of the hypotheses, it is important to first establish the functionality of CCK in persons with RBN. Based on the intactness of the CCK responsivity to a test meal, several lines of inquiry resulted. For example, there are several competing hypotheses regarding the possible etiology of altered CCK function in active BN including increased gastric capacity, reduced gastric relaxation, decreased gastric emptying, decreased CCK release, and other enteric autonomic function anomalies (Hadley & Walsh, 2003). Thus, to assess a single aspect of gastric functioning may pose significant limitations in the interpretation of findings. To adequately address

these potential etiologic factors, a more comprehensive examination of gastric functioning would be needed and thus involve greater resources (e.g. radiology, gastroenterology) and invasive procedures. However, this may be a potentially important follow-up study to the project.

Protection of Human Subjects

Prior to the onset of this study, approval was obtained with an inter-institutional agreement between Boston College's Institutional Review Board (IRB) and by the Beth Israel Deaconess Medical Center Committee on Clinical Investigations (CCI) - consent approval date 11/17/2010, protocol number 2009-000261. This study also received "Protocol Approval" from BIDMC CRC Scientific Advisory Committee on 3/3/2010. To protect confidentiality, study data were coded with a research subject number. The code chart linking subject identification and number were stored separately in a locked file.

Study procedures were explained in depth, allowing subjects the time and opportunity to ask questions prior to signing the informed consent form. Individuals with psychiatric disorders that might interfere with informed consent procedures (e.g., psychotic disorders) were not included in this study. Subjects were monitored for symptoms of depression including active suicidal ideation. Referral to a mental healthcare provider would have been made if appropriate. No such instances occurred during this study.

There was minimal risk of serious psychological harm from this study; however, individuals may have found the data collection forms and interviewing procedures to be tedious or stressful. These methods to gather data involved disclosure of sensitive and

personal information that may have been uncomfortable. Individuals who experienced the study procedures as stressful were allowed to withdraw. Three such instances occurred. One individual was advised by her therapist not to participate. Two individuals were concerned that they may become increasingly preoccupied by eating disordered behavior.

Subjects may have found the taste of the standardized liquid test meal unpleasant; however, all individual rated the VAS for pleasantness (during the acclimation procedure) at or above the 50 percentile. While individuals may have been uncomfortable when consuming the drink over the requested five minute interval, none expressed discomfort. Other rare side effects could have occurred (e.g., an allergic reaction to the standardized test meal drink). All subjects were asked about any history of allergic reactions, including allergic reactions to foods, no reactions occurred. Blood drawing and placement of intravenous catheter in the arm could have caused localized discomfort, bruising or syncope. No individuals experienced related syncope or localized infections. The total volume of blood drawn did not exceed 50 mL. Safety measures included careful diagnostic assessment, measurement of vital signs and side effect monitoring. No adverse events occurred during this study.

Informed Consent

During the screening visit, study procedures were carefully explained to the subjects. Questions were answered by the PI. If a subject agreed to participate in the study, the consent form was signed by the subject, the investigator, and a witness. The subject was given a copy of the informed consent form. Consent was reviewed again with the subjects at the start of their study visit on the CRC, prior to the initiation of any study

procedures. Additionally, the PI completed the "Responsible Conduct of Research" (see Appendix A) requirement by completing the CITI Program for Biomedical Research Investigators.

Data Analyses and Sample Size

H1. Subjects with BN will have a significantly blunted postprandial plasma CCK response compared to the RBN and CON groups. 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 liquid test meal procedure. 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. A one- tailed test was used because the a-priori hypothesis was directional, positing that the BN group's response would be significantly blunted (decreased). Additionally, the trapezoidal rule was utilized for all other AUC measurements. Sample size was based on the calculations described below.

H2. Postprandial plasma CCK response will be significantly positively correlated with postprandial VAS measures of satiety in the RBN and CON groups. To test this hypothesis, the relationship between postprandial CCK response (AUC) and visual analog ratings of satiety was assessed by using Pearson's correlation coefficient. Data not normally distributed were log transformed.

Sample size calculations were based on the results reported by Devlin et al. (1997) for mean and standard error for CCK AUC response in patients with BN and controls (effect size d =1.45). Based on these data a comparison of three groups with a planned sample size of 12 per group with alpha set at p=.05, two-tailed, results in a power of .8.

CHAPTER 4
RESULTS

All data were entered into a computerized data base and analyzed using the Statistical Package for Social Sciences (SPSS; version 19.0 for Windows; Chicago, IL). Descriptive statistics were calculated for all variables. Frequency and distribution plots were examined to assess the normality distribution (skewness and kurtosis) and identification of outliers. Data not normally distributed were log transformed prior to analysis.

The primary outcome measure, CCK response, was calculated by the area-under-the-curve (AUC) utilizing the trapezoidal rule. A one-way ANOVA utilizing a-priori contrasts (one-tailed) was used to test for differences in AUC between the three study groups. Additionally, an ANOVA was utilized to compare groups prior to (baseline) and following ingestion (+15min.) of the standardized liquid test meal.

The relationship between postprandial CCK response (AUC) and visual analog ratings of satiety (AUC) was assessed by using Pearson's correlation coefficient. Additionally, AUC was calculated for the following VASs: satiety, fullness, hunger, and urge to binge and vomit. The anchors for the satiety, fullness and hunger where represented as "not all" to "extremely". The anchors for binge and vomit ranged from "no urge" to "extreme urge." These data were utilized to assess for significant relationships and comparisons across groups for descriptive purposes. Group values were reported as mean ± standard deviation (SD). A one-way ANOVA was used with an alpha

level of 0.05, two tailed to determine the probability for significant differences in groups descriptive (Table 2) and clinical characteristics (Table 3).

Fifty- six female volunteers were enrolled and met initial inclusion criteria for the study. Subsequently, 41 subjects completed all study procedures. From those 41, four were excluded for the following reasons: two subjects were excluded due to significant outlier status (absolute z-score greater than 3.29); one disclosed she was taking an antibiotic after study procedures were completed; and nursing personnel reported (following the completion of study procedure) that one subject was administered 300ml versus 600ml of the standardized liquid test meal. Fifteen subjects who initially met inclusion criterion and completed the screening did not complete the study due to the following reasons: BMI < or > 19 – 26 kg/m^2; fear of blood draw; unable to obtain blood sample; scheduling difficulties; and the three subjects that opted to drop out of study as previously stated in the *Protection of Human Subjects Section*.

Data from 37 subjects were included in the final analysis. There were no significant differences between subject groups age, weight, height, and BMI (*p*=ns; see Table 3). Overall sample mean ± SD age was 22.5±5.0 years and BMI 22.5±2.2 kg/m^2. The racial/ethnic composition of the sample participants 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 racial/ethnic composition of these sample participants are consistent with the targeted/planned enrollment for this study and within the of the Boston area.

Table 2. Descriptive Characteristics-*Comparison by Group*

	Mean±SD			
Measures	**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

Note. There were no significant differences among groups for age, weight, height, and BMI.

The average binge/purge frequency among the BN group was 19.7±10.9 per month and 4.9±2.7 per week, respectively. For the RBN group, the average binge/purge frequency during active illness was 6.8 ± 4.6 per week. There was no significant difference (t= -1.1, p=.81) in the average binge/purge frequency between the BN and the RBN groups during active illness. The average illness duration in the BN group was 4.3±3.9 years. In the RBN group the average illness duration was 3.9±4.7 years and length of remission 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. The control group had no current or history of any Axis I diagnosis including eating disorders.

Table 3 presents comparisons on clinical questionnaires assessed at either the screening (EDE-Q and Herman & Polivy Restraint) or study visit (BDI-II and Aggression Scale). The BN group scored significantly higher on the BDI-II scale, indicating

increased level of depression, in comparison to the RBN and CON groups. The BN group also rated significantly higher on measures of eating pathology in comparison to the RBN and CON groups. For instance, the BN group scored significantly higher on global eating disorder severity, dietary restraint, and eating, weight, and shape concerns compared to the RBN and CON groups. Additionally, the RBN group scored significantly higher in comparison to the CON group on ratings of global eating disorder severity, weight and shape concerns and the total restraint scale. There were no significant differences among groups in overall Aggression Scale ratings. There was no significant correlation between aggression scores and CCK response within groups.

Table 3. Clinical Characteristics - *Comparison by Group*

	Mean± SD			
Measures	**Control**	**RBN**	**BN**	**$F_{2, 34}$**
EDE-Q	n=13	n=13	n=10	
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& 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.

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

CCK response, as measured by AUC, tended to be lower in the BN group (M=1.77± .60) compared to the RBN group (M= 2.01± .41) and the CON group (M= 3.13±.47). The assumption of homogeneity of variance was met (p =.35). Planned contrasts revealed a significant linear trend, $F_{2,34} = 3.07$, $p < .05$ (one-tailed), indicating that CCK response increased from the BN, RBN and CON groups respectively. Planned contrasts revealed that the BN group's CCK response approached a significant difference, t (34) = 1.67 (p=.052, one-tailed, f = .30) in comparison to the RBN and CON. Therefore, this hypothesis was not supported, although a trend was observed. The second planned comparison revealed no significant difference, t (34) = 1.67 (p=.27, one-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 after (+15min.) the ingestion of the standardized liquid test meal.

Table 4. CCK Response by Group Mean

	Mean ± SD			
	Baseline	**+15min**	**+30**	**+60**
Control	0.145	4.24 ± 2.9	3.29±3.6	4.44±4.1
RBN	0.145	2.59 ± 2.7	2.68±2.5	2.98±2.1
BN	0.145	2.33 ± 2.7	2.15±3.1	1.78±1.2

Mean CCK concentrations and standard errors of estimates across time points for all groups are depicted in Figure 6.

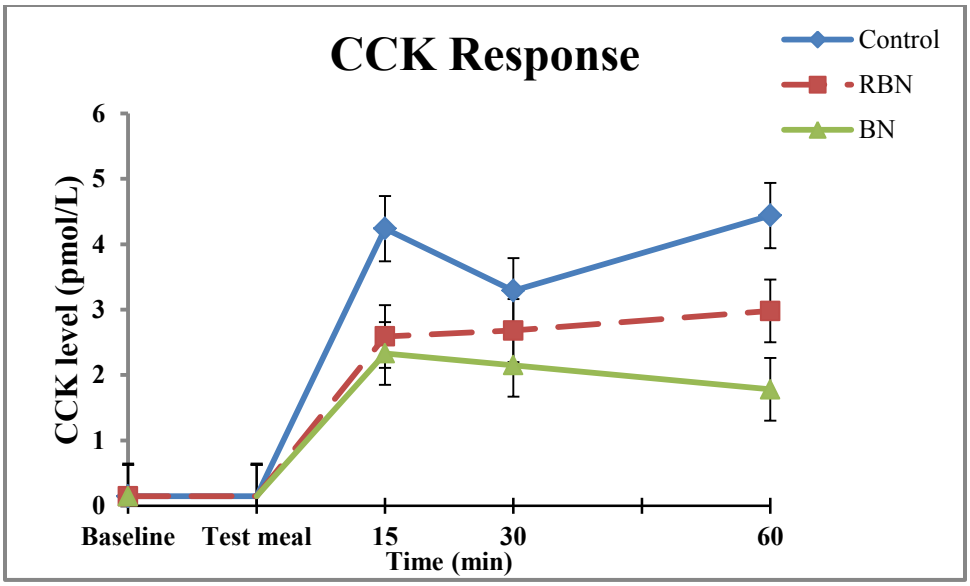


Figure 6. Group mean values of CCK concentrations at each time point before and after the standardized liquid test meal**.** The mean standard error of estimates at each time point is presented.

H2. Postprandial plasma CCK response will be significantly positively correlated with postprandial VAS measures of satiety in the RBN and CON groups.

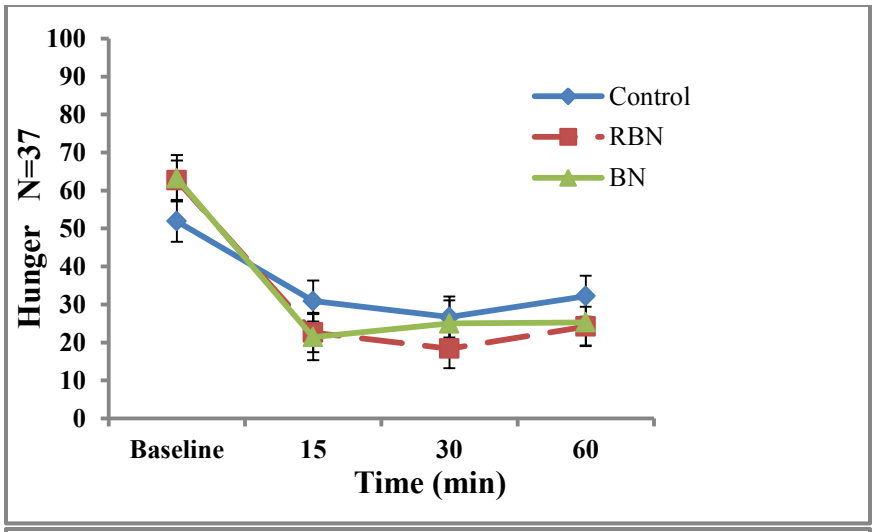
Satiety was measured on 100mm VAS that ranged from "not at all satiated" to "extremely satiated." A significant positive relationship exists between CCK (AUC) response and ratings of satiety (AUC) in the RBN group only. Those subjects in the RBN group that had a more robust CCK response rated higher levels of satiety (r = .58, p < .05).

Additionally, a significant positive relationship exists between CCK (AUC) concentrations and the RBN group ratings of fullness (r = .54, p <.05). Fullness (AUC) and satiety VASs were significantly correlated in the BN (r = .74, p <0.05), RBN (r = .73, p <0.01), and CON (r = .71, p <0.01) groups. Thus, in all groups, as ratings of satiety

increased, subjective ratings of fullness also increased. Increased CCK (AUC) response in the BN group was significantly correlated (r=.86, $p < .01$, two-tailed) with urge to vomit. In the BN group, those who had increased CCK responses reported a greater urge to vomit.

There was a significant difference between the BN and CON (AUC) groups in "urge to binge" ($F_{2,34} = 6.26$, $p < .01$), and "urge to vomit" ($F_{2,34} = 6.47$, $p < .01$), after log transformation and Bonferroni correction (Figure 6) but not in the RBN (AUC). The BN group reported the greatest urge to binge (M=2.8±.76) compared to the RBN (M=2.2±.85) and the group that reported the least was as expected the CON (M=1.6±.72). Similarly, the BN group reported the greatest urge to vomit (M=2.9±.96) compared to the RBN (M=2.4±.85). Again the CON group reported the least (M=1.6±.89) as expected. Figure 7 shows that the BN group's ratings for "urge to binge" did not change or respond differently from before to after the test meal. In contrast, the RBN and CON groups had decreased "urge to binge" following the ingestion of the test meal.

After the ingestion of the test meal both the RBN and the CON groups responded with a modest elevation in "urge to vomit" and steadily declined afterwards. The BN group had an initial sharp increase in "urge to vomit" following ingestion of the test meal and then plateaued for the remaining time points (Figure 7).


Hunger N=37
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Time (min)
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RBN
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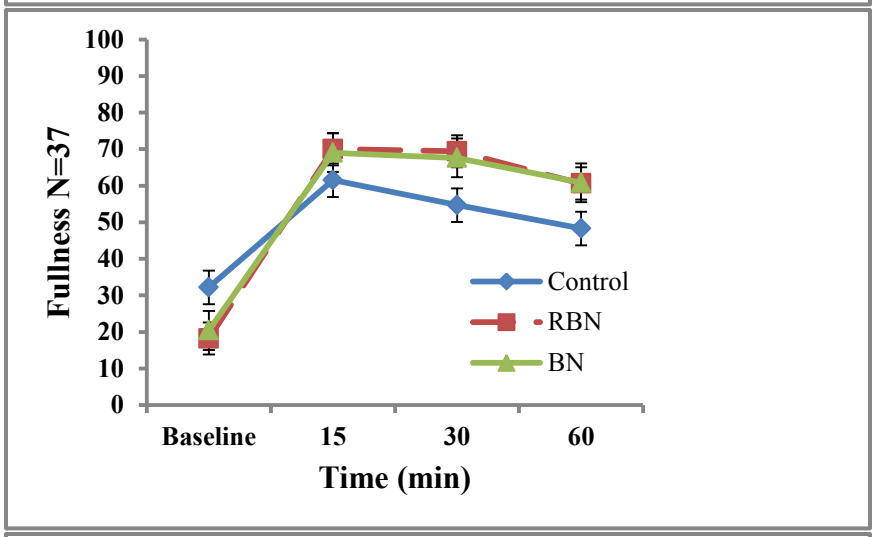
Fullness N=37
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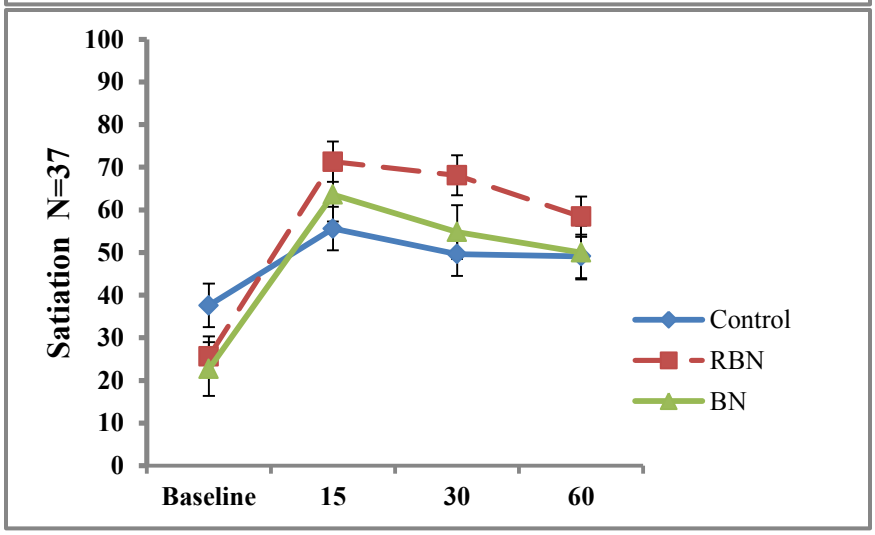
Satiation N=37
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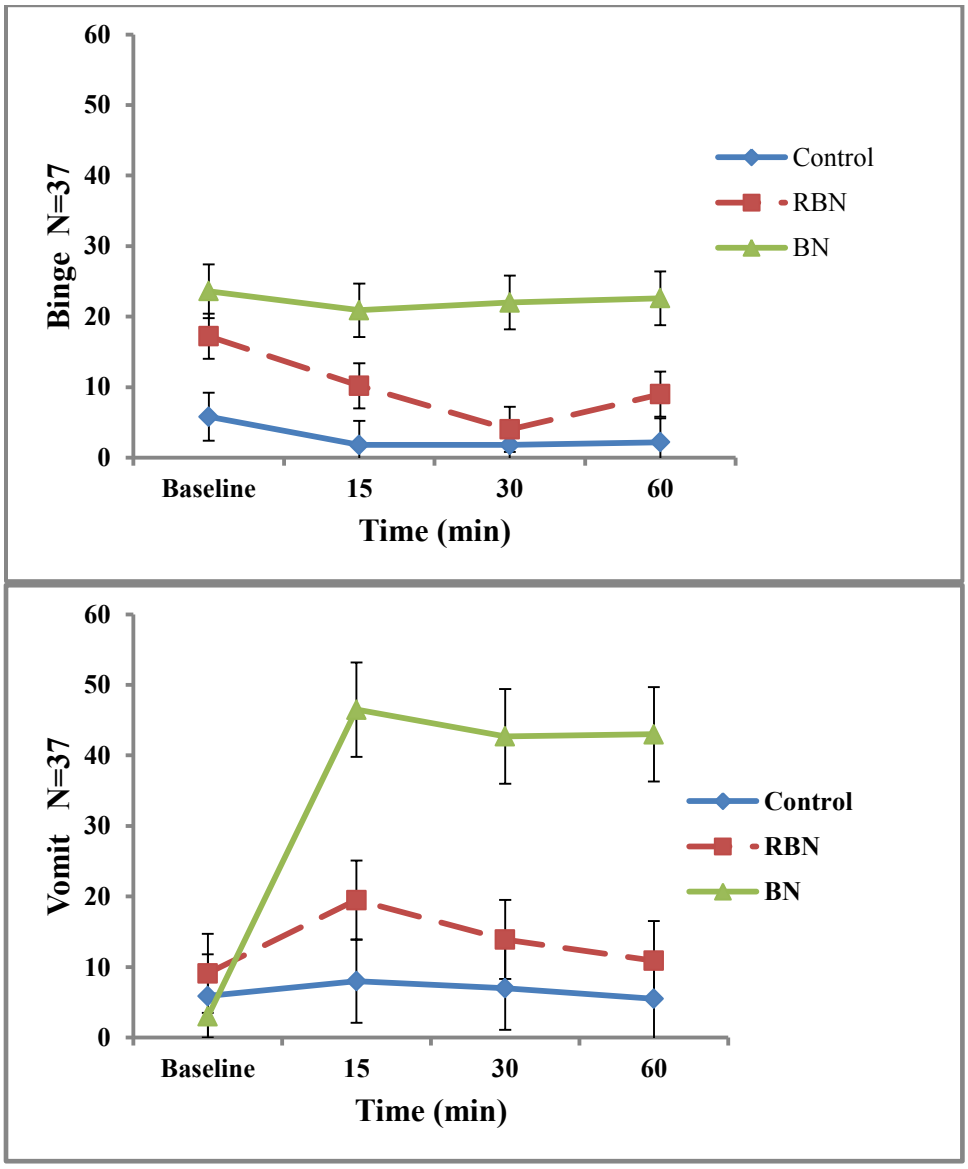

Figure 7. The mean group comparison of subjective eating related responses (VAS measured as 100mm) to the standardized test meal.

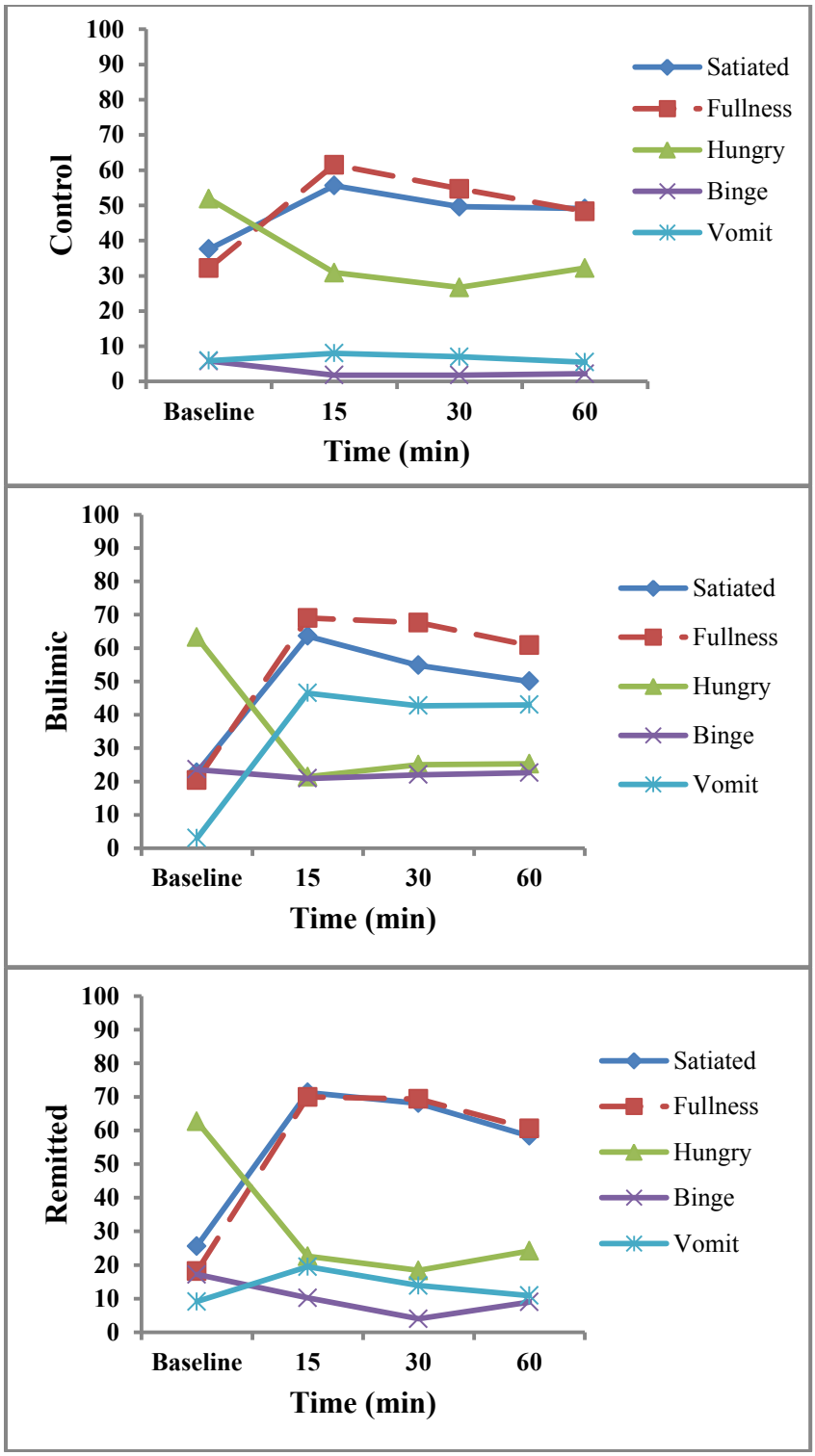

Figure 8. The mean within-group comparison of subjective eating related responses (VAS measured as 100mm) to the standardized test meal.

CHAPTER 5

DISCUSSION

To this investigator's knowledge, this is the first study to compare postprandial 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 controls (CON). Previous studies found that CCK, a satiety producing hormone, is decreased in BN in comparison to healthy CON (Devlin et al., 1997; Keel et al., 2007). These previous results inferred that a decreased CCK response may be a possible cause, consequence, and or maintenance factor for binge eating in individuals suffering from BN. Therefore, it was unknown whether CCK response returns to normal after individuals recover from this illness. This gap in knowledge hinders our understanding and ability to develop effective treatment strategies.

The purpose of this study was to assess whether postprandial CCK response normalizes following remission from BN and if CCK responsivity correlates with subjective ratings of satiety in the RBN and CON groups. Based on theoretical grounds, the assumption was that the binge and / or purge processes and the subsequent compilation of gastrointestinal dysfunctions may disrupt the endogenous signal pathway to the hindbrain and alter the potency of the negative feedback system. When there is a dysregulation in the potency of this feedback system, meal size and duration can be increased.

Postprandial CCK Response

In this study, the BN group's postprandial CCK level was lower (approached significance at p =.052) than both the RBN and CON groups. As anticipated, the RBN and the CON groups' CCK response did not significantly differ from each other. This finding was expected and supports the premise that CCK response may normalize following abstinence from binge and purge episodes. 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 when CCK response begins to normalize, it does indicate that previous findings of a blunted response in the BN population may be a state versus trait related phenomenon.

While the BN group's CCK response approached significance, it was not statistically significantly different from CON as observed in previous studies (Devlin et al., 1997; Keel et al., 2007). In comparison to the Devlin (1997) study, this discrepancy may be accounted for by differences in the BN subjects' characteristics. For example, in the Devlin (1997) study BN subjects reported two times as many (10.3 ± 4.3) binge/purge episodes per week in comparison to that observed in the current study (4.9 ± 2.7). Participants in the Devlin (1997) study reported an average duration of illness of 9.8 ± 1.9 years and their BN group was recruited from inpatient or outpatient treatment settings. In this study, the BN subjects reported their average duration of illness to be half that amount (4.3± 3.9) and none endorsed being in treatment or intending to engage

in treatment. Therefore, in this study, these BN subjects may be healthier sub-group that does not suffer the degree of physiological dysregulation.

In this study, in comparison to the Keel (2007) study, the clinical characteristics of the BN groups' were similar in BMI, on binge/purge frequency, EDE and BDI-II scores. Illness duration was not indicated in the Keel (2007) report. However, in the Keel (2007) study the BN group (n=34) was much larger than this study (n=10). Thus, a larger BN group may have revealed a significant physiological difference between study groups. To replicate this study in the future and ensure an adequate sample size, calculations conducted using G-Power © 1992-2010 (Faul, Erdfelder, Lang, & Buchner, 2007) found that using the current medium effect size (*f*=.30) with an alpha set at p=.05, power of .80, one tailed, that an adequate number of study participants is N=89 or approximately a BN group of n=30.

Biobehavioral Responses to Test Meal

This is the first study to examine the relationship of the biological CCK responsivity to behavioral ratings of satiety and other eating related sensations in those who have remitted from BN. Previous biobehavioral studies have found postprandial visual analog satiety ratings to be positively correlated with CCK responses in healthy males (Holt et al., 1992). Another investigator showed that using a liquid test meal significantly stimulated CCK release and correlated with increased fullness ratings in healthy males and females (Nolan et al., 2003). Yet, another eating disorder study found a positive relationship when examining CCK and satiety responses (Keel et al., 2007).

In this study, only the RBN group had a significant positive relationship between the postprandial CCK (AUC) response with satiety and fullness ratings. In contrast, the BN and CON groups' CCK response did not correlate with satiety ratings. This latter finding does replicate other previous studies (Devlin et al., 1997).

However, overall there is conflicting evidence whether those with BN are able or unable to accurately detect eating related sensations (including satiety) postprandially. In an effort to better understand eating related sensations, a recent study measured and compared the satiety responses to a fixed one-item liquid test meal in those with BN and healthy controls (Zimmerli, Devlin, Kissileff, & Walsh, 2010). This study found no differences in ratings of fullness or hunger at the beginning, end or over the course of the meal between the BN and CON groups (Zimmerli et al., 2010). While these investigators were surprised by these findings, they concluded that when BN subjects are given a fixed meal they tend to report the same subjective findings of satiety and related sensations than controls (Zimmerli et al., 2010). These investigators further noted that previous studies, (Kissileff et al., 1996) using ad-libitum versus fixed meals were able to detect differences in satiety and other eating related sensations between BN and CON groups.

In previous studies, BN subjects report feeling less, rather than more, satiated, after eating excessively large amounts of food. In sharp contrast to healthy controls, despite eating quantifiably larger amounts of food, patients with BN reported less fullness and displayed increased motivation to eat as the meal progressed (Kissileff et.al, 1996). When those with BN are given an unlimited amount of a liquid test meal to consume (more accurately depicting a binge episode) their sensations of satiety are disturbed

(Kissileff et al., 1996). In this study, participants were allowed to drink 900 kcal in an effort to compare across groups and previous studies. However, this fixed meal approach may be a limiting factor in accurately measuring eating related sensations in those with BN.

In the present study, the RBN group had the largest mean satiety ratings in comparison to the BN and CON groups. There is also a significant positive relationship between the biological CCK response and the behavioral satiety and fullness ratings in this group. 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.

In the RBN group, perhaps CCK receptors on the vagus nerve up-regulate and allow for more opportunities for signal transmission to the hindbrain. This up-regulation might occur when higher order signals, while interpreting metabolic status, detect a deficiency in signal transmission (Faris et al., 2008). In an attempt to maintain homeostasis, a mechanism in the hypothalamus may modulate a shift in lower order signaling, resulting in an improvement in the potency of the negative feedback system (Dockray, 2009). In the BN group, an alternative explanation may be that this homeostatic process is ignored (desensitized) by the hypothalamus and the hind brain. This may occur due to the abnormally increased activity of the vagus nerve (chronic and repetitive binge and vomit behavior) resulting in abnormal transmission (Faris et al., 2008).

Interestingly, a new finding from this current study was the positive correlation between the BN groups' CCK response and urge to vomit following the ingestion of the standardized liquid test meal. In the BN group, those with larger CCK responses reported the greatest urge to vomit. 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 (Faris et al., 2008). 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), individuals 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 (Keel, 2007). 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.

Another interesting association to the Keel (2007) study is the VAS of eating related sensations pre and post ingestion of the standardized liquid test meal. The ratings from both studies are similar for fullness, hunger, urge to binge, and vomit in the BN and the CON groups respectively. This suggests reliability in the manner in which these constructs are measured (VAS) and the validity of doing so within these populations.

In the present study, besides scoring significantly higher than CON on global eating disorder severity, the RBN continued to report both urge to binge and vomit without engaging in those behaviors. The RBN group reported fewer urges than that of the BN groups but greater than the CON groups across all time points. These ongoing and persistent urges are cause for concern as they may increase the vulnerability of these individuals to relapse.

Implications for Theory, Research, and Practice

The current study supports the theory that CCK responsivity normalizes when individuals have remitted from this illness. Therefore, in concert with the model presented in chapter two, there may be an adaptive response that recalibrates and begins to effectively regulate and control the input of neuronal and hormonal signals to the hind brain. As a result, homeostasis and the stability of the hormone system loops are restored. The resulting output responses are the absence of these debilitating behaviors (binge/vomit). What is unclear is which adaptive mechanism(s) must be present and properly functioning for CCK responsivity to return to normal and for this behavior to remit. Understanding what biological or behavioral adaptations must occur before remission and how these can 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 the normalization of 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 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, PYY) or orexgenic (e.g. ghrelin) peptides (Monteleone, Martiadis, Fabrazzo, Serritella, & Maj, 2003; Munsch, Biedert, Meyer, Herpertz, & Beglinger, 2009) and eating related pathways (Broft, Berner, Martinez, & Walsh, 2011). Emphasis should be focused on research that explores pharmacotherapeutic agents that may have an effect on increasing CCK levels (e.g. SSRI's, antibiotics, probiotics, and prebiotics). 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.

A previous double blind placebo controlled study reported a significant decrease in binge/vomit behavior in a BN group when administered ondansetron (anti-emetic) compared to placebo (Faris et al., 2006). These investigators contend that the stabilization of the vagus nerve is the rationale for efficacy. Initially this treatment was not considered a viable option in part due to the multiple daily doses of this costly medication, lack of FDA approval for this indication, and thus insurance companies denied to cover its cost (Faris et al., 2008). However, currently this medication is available in generic form and may become a feasible treatment option and future line of investigation.

Further practice implications include a clinician's careful assessment of the frequency of binge and vomit episodes, factors that may perpetuate or maintain this behavior, duration of illness, current motivation, and commitment to treatment and the recovery process. The practicing clinician should provide psycho-education concerning the current etiology, pathophysiology (e.g. dysregulated neuroendrine responses), vulnerability factors for relapse or obstacles to recovery. Those who have remitted from this illness should be aware of current urge to binge/vomit, personal triggers, residual eating disordered thinking and abnormal eating patterns. Clinicians should discuss potential neuroendrocrine protective (e.g. CCK) responses and liability (e.g., residual eating disordered behaviors) factors that may increase patients' vulnerability to relapse or strengthen their road to a fully functional recovery.

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. Study participants may not have fully understood the term satiety in reference to the VAS. Also because the subjects answered identical VAS and SEC at 4 time points during the study visit, their responses may have been affected due to this factor. 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 eating related sensations in those with BN and RBN.

Summary and Conclusions

Results extend the understanding of the postprandial CCK response in those who have remitted from BN. The implications of this study are that CCK responsivity normalizes in those who remit from binge and vomit behavior. While this study does not offer particular guidance concerning when CCK response begins to normalize, 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, will the normalization of CCK functioning prove to be 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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APPENDIX A

Beth Israel Deaconess Medical Center

FOR CCI USE ONLY
Approved by the Beth Israel Deaconess Medical Center Committee on Clinical Investigations:

Administrator: Astrid Joseph / DD

Consent Approval Date: 11/17/10

Protocol Number: 2009P-000261

Study Approval Expiration Date: 11/4/11

BETH ISRAEL DEACONESS MEDICAL CENTER
APPROVED BY THE COMMITTEE ON CLINICAL INVESTIGATIONS
11/04/2011
APPROVAL EXPIRATION DATE

INFORMED CONSENT FORM TO TAKE PART IN A RESEARCH STUDY

SUBJECT'S NAME:
TITLE OF RESEARCH PROTOCOL: Role of Altered CCK Response in Bulimia Nervosa
PRINCIPAL INVESTIGATOR: Sandy Hannon-Engel, PhD(c), APRN
CO-INVESTIGATORS: Barbara Wolfe, PhD, APRN, FAAN & Evgeniy Filin, MD
PROTOCOL NUMBER: 2009P-000261

INTRODUCTION:
You are invited to take part in a research study designed to increase our understanding of bulimia nervosa. You are being asked to take part in this study because you have been diagnosed with bulimia nervosa, have recovered from bulimia nervosa or are a healthy volunteer. Research studies include only those people who choose to take part. Please read this consent form carefully and ask the investigators or study staff to explain any words or information that you do not clearly understand. We encourage you to talk with your family and friends before you decide to take part in this research study.

- Your participation is voluntary;
- You may or may not benefit from participating in the study. However, your participation may help others in the future as a result of knowledge gained from the research;
- You may leave the study at any time;
- If you choose not to take part, or if you leave the study, your decision will in no way affect your care with Beth Israel Deaconess Medical Center.

Once you read this consent form and understand what your participation in this study will involve, you will be asked to sign this form if you wish to take part. You will be given a signed copy of the form to keep for your records.

DISCLOSURE OF SPECIAL INTERESTS OF BIDMC AND INVESTIGATORS
This study is being conducted by Sandy Hannon-Engel, PhD(c), RN,CS, a doctoral candidate at the Boston College School of Nursing, and is funded by the National Institute of Nursing Research (NINR) from the National Institute of Health (NIH). The funding agency in this study NIH is paying Boston College and Sandy Hannon-Engel to perform this research. BIDMC, Boston College, and Sandy Hannon-Engel have no additional interests in this research project.

WHY THIS STUDY IS BEING DONE

This study is designed to increase our understanding of bulimia nervosa. Individuals with this syndrome often binge eat and then purge their food. While emotional problems appear to be key in understanding this disorder, some changes in the natural hormones that influence meal patterns may play a role in these conditions. This study involves standard interviews, questionnaires and blood hormone measurements in women who currently have bulimia nervosa, recovered from bulimia nervosa, and in healthy female volunteers with normal eating patterns. An overall goal of the study is to help assess whether changes in the blood levels of the naturally occurring hormone cholecystokinin (CCK) adds to the continuation of this eating disorder.

WHO WILL PARTICIPATE IN THE STUDY

Approximately 45 people will take part in this study at Beth Israel Deaconess Medical Center. You are invited to participate in this research study as an individual with bulimia nervosa, someone who has recovered from bulimia nervosa, or as a healthy volunteer. Your participation is completely voluntary; you are free to withdraw from the study at any time.

WHAT WILL HAPPEN DURING THE STUDY

If you agree to be in this study, you will be asked to read and sign this consent form. After you sign the consent form, the following things will happen:

1. Screening Procedures: Screening procedures are tests and procedures that will be done to determine if you are eligible to take part in the research study. For this research study, the screening procedures include the following:
   - During the screening visit (to occur at Boston College or BIDMC), you will receive a detailed explanation of study procedures, indicate that you understand the nature of these procedures, are willing to participate, and have the opportunity to ask questions prior to signing this consent form.
   - You will be asked to participate in an interview and complete questionnaires regarding your usual eating patterns and any past or current emotional problems.
   - During this visit, if you qualify, you will learn about the details of the second part of the study to occur at BIDMC. This involves the measurement of blood hormone levels after you drink a nutritional shake (test meal drink).
   - You will be able to sample the shake used during the screening visit.

2. Research Procedures: If you qualify to take part in this research study, you will undergo these research procedures:
   - The study visit (which may last approximately two hours) is usually scheduled within two weeks of the screening visit and takes place in the General Clinical Research Center (GCRC) at Beth Israel Deaconess Medical Center.

- Prior to the visit to the GCRC, you will have been asked not to eat or drink anything from 11 PM the previous evening until you arrive for the study visit the next morning.
- After review of this consent form, you will have your height, weight, blood pressure, pulse and temperature measured. You will also be asked questions about any past or current medical problems.
- You will have a small plastic tube (catheter) placed in a vein in your forearm with a needle. The tube will be taped in place and will remain there until the study visit is over.
- You will be asked to complete a side effect checklist and questionnaires that ask you questions related to your mood, appetite, and any symptoms you may be feeling. You will be asked to drink a nutritional shake (approximately 600ml/900 calories) over a five minute period.
- Blood samples will be collected before you drink the shake, and +15 , +30, and +60 minutes after you drink the shake.

POSSIBLE RISKS, SIDE EFFECTS, AND DISCOMFORTS

RISKS OF THE RESEARCH STUDY

As a result of your participation in this study, you are at risk for side effects listed in this section. You should discuss these with the investigator and with your regular health care provider if you choose.

The total amount of blood drawn for this study will be approximately 50 ml, which is slightly less than two ounces. The risks and discomforts of blood drawing from a vein include the possibility of pain or bruising at the site of the blood draw; occasional feeling of lightheadedness; and rarely, infection at the site of the blood draw. You may find that the nutritional shake does not taste pleasant, or that it may be uncomfortable to consume the drink over the requested five minutes.

LOSS OF CONFIDENTIALITY

There is the potential for loss of confidentiality by participating in this study. Every effort will be made to protect the confidentiality of your identifiable information. All information will be coded by a research number and will be stored in secure filing cabinet and office space in the Center for Nursing Research at Boston College. However, if your participation becomes known, it could create a problem or hardship for you depending upon the type of information disclosed.

PSYCHOLOGICAL STRESS:

Some of the questions we will ask you as part of this study may make you feel uncomfortable. You will be asked to complete and participate in sometimes long and personal questionnaires and interviews in a total of two visits. You may refuse to answer

any of the questions and you may take a break at any time during the study. You may stop your participation in the study at any time.

POSSIBLE BENEFITS
There is no direct benefit to you from being in this study. However, your participation may help others in the future as a result of knowledge gained from the research.

OTHER AVAILABLE OPTIONS
Taking part in this study is voluntary. Your alternative is to not participate in the study. You should not consider participation in this study as a substitute for mental health therapy or treatment. You will be provided with care to help you feel more comfortable and information regarding mental health clinics or professionals can be provided to you if you wish. We recommend that you discuss these and other options with the investigator and your regular healthcare provider so that you can make a well-informed decision about participating in this study.

IF YOU DECIDE NOT TO TAKE PART IN THE STUDY
Participation in this study is voluntary. You have the right to decide not to take part in this study. If you choose to participate, you have the right to leave the study at any time. However, please be aware that there may be risks to leaving the study before it has been completed. If you decide not to participate in the study or decide to leave the study early, your decision will not affect your relationship with your health care provider or with Beth Israel Deaconess Medical Center.

The investigators have the right to end your participation in this study if they determine that you no longer qualify to take part, or if it would be dangerous for you to continue, or if you do not follow study procedures as directed by the investigators. Beth Israel Deaconess Medical Center or the funding source may stop the study at any time.

INVESTIGATORS RIGHT TO STOP THE STUDY
The investigators have the right to end your participation in this study if they determine that you no longer qualify to take part, or if it would be dangerous for you to continue, or if you do not follow study procedures as directed by the investigators. Beth Israel Deaconess Medical Center or the funding source may stop the study at any time.

COSTS AND/OR PAYMENTS TO YOU
You will be paid a total of $100 over the study period. You will receive thirty- dollars ($30) at the completion of the screening visit and seventy ($70) at the completion of the study visit. You will also be given parking vouchers for each visit.

COSTS COVERED BY STUDY
You will not be charged for any tests or procedures that are part of this research study.

PAYMENTS TO YOU:
Any payments made to you may be taxable income to you. This does not include any payments you may receive to reimburse (pay you back) you for certain expenses like parking fees or travel. We are required to obtain your name and social security number for preparation and submission of Internal Revenue Service (IRS) Form 1099-Misc. You may receive an Internal Revenue Service Form 1099 from BIDMC if you receive more than $600 or more in one calendar year for taking part in one or more research studies at BIDMC. Questions about your own tax status should be referred to your personal tax advisor.

COST OF RESEARCH RELATED INJURY:
If you are injured as a direct result of your participation in this study, you should contact the Investigator at the number provided under the section "Who to Call if You Have Questions" in this form. You will be offered the necessary care to treat your injury. We reserve the right to bill your insurance company or the sponsor, if appropriate, for the care you get for the injury. We will try to get these costs paid for, but you may be responsible for some of them. You may be responsible for all co-payments and deductibles required under your insurance. At this time there is no plan to reimburse you for items such as lost wages or lost time from work. By signing this consent form you have not given up any legal rights.

CONFIDENTIALITY
Information learned from your participation in this study and from your medical record may be reviewed and photocopied by the Food and Drug Administration (FDA) and/or other federal and state regulatory agencies, accreditation agencies, the Committee on Clinical Investigations and the Human Subjects Protection Office of the Beth Israel Deaconess Medical Center with protection of confidentiality so far as permitted by applicable law. Information resulting from this study and from your medical record may be used for research purposes and may be published; however, you will not be identified by name in such publications.

AUTHORIZATION FOR USE AND DISCLOSURE OF YOUR PROTECTED HEALTH INFORMATION
As part of this study, we will be collecting and sharing information about you with others. Please review this section carefully as it contains information about the federal privacy rules and the use of your information.

PROTECTED HEALTH INFORMATION [PHI]
By signing this informed consent document, you are allowing the investigators and other authorized personnel to use [internally at BIDMC] and disclose [to people and organizations outside the BIDMC workforce identified in this consent] health information about you. This may include new information generated as part of this study through questionnaires, tests, procedures we may ask you to undergo. This is your Protected Health Information.

PEOPLE/GROUPS AT BIDMC WHO WILL USE YOUR PROTECTED HEALTH INFORMATION

Your Protected Health Information may be shared with investigators listed on this consent form as well as the supporting research team [i.e. research assistants, statisticians, data managers, laboratory personnel, administrative assistants]. Your Protected Health Information may also be shared with the Committee on Clinical Investigations of Beth Israel Deaconess Medical Center as it is responsible for reviewing studies for the protection of the research subjects.

PEOPLE/GROUPS OUTSIDE OF BIDMC WITH WHOM YOUR PROTECTED HEALTH INFORMATION WILL BE SHARED

We will take care to maintain confidentiality and privacy about you and your Protected Health Information. We may share your Protected Health Information with the following groups so that they may carry out their duties related to this study:

- The funding source of this study NINR and NIH and their clinical research organizations
- Research collaborators from the William F. Connell School of Nursing at Boston College
- The Food and Drug Administration [FDA], the Department of Health and Human Services [DHHS], and the Office for Human Research Protections [OHRP]
- Hospital and Clinical Research Accrediting Agencies

Those who receive your Protected Health Information may make further disclosures to others. If they do, your information may no longer be covered by the federal privacy regulations.

WHY WE ARE USING AND SHARING YOUR PROTECTED HEALTH INFORMATION

The main reason for using and sharing your Protected Health Information is to conduct and oversee the research as described in this Informed Consent Document. We also shall use and share your Protected Health Information to ensure that the research meets legal, institutional and accreditation requirements and to conduct public health activities.

NO EXPIRATION DATE – RIGHT TO WITHDRAW AUTHORIZATION

Your authorization for the use and disclosure of your Protected Health Information in this Study shall never expire. However, you may withdraw your authorization for the use and disclosure of your Protected Health Information at any time provided you notify the Principal Investigator in writing. If you would like to take back your authorization so that your Protected Health Information can no longer be used in this study, please send a letter notifying the Principal Investigator of your withdrawal of your authorization to Sandy Hannon-Engel at 140 Commonwealth Ave, Chestnut Hill, MA 02467. Please be aware that the investigators in this study will not be required to destroy or retrieve any of

your Protected Health Information that has already been used or disclosed before the Principal Investigator receives your letter.

REFUSAL TO SIGN
If you choose not to sign this informed consent document and authorization for the use and disclosure of your Protected Health Information, you will not be allowed to take part in the research study.

RIGHT TO ACCESS AND COPY YOUR PHI
If you wish to review or copy your Protected Health Information as it is made part of your medical record, you may do so after the completion or termination of the study by sending a letter to the Principal Investigator requesting a copy of your Protected Health Information. You may not be allowed to inspect or copy your Protected Health Information until this study is completed or terminated.

NOTICE OF PRIVACY PRACTICES
In addition to signing this document, you may also be asked to sign a BIDMC General Agreement form acknowledging that you have received the BIDMC Notice of Privacy Practices.

WHOM TO CALL IF YOU HAVE QUESTIONS OR PROBLEMS
If you have any questions about this research or experience any problems, you should contact Sandra Hannon-Engel at [508] 274-0671. You may contact the Human Subjects Protection Office at [617] 667-0469 in the event that you would like to obtain information or to offer input about the research study. This office is independent of the investigator or investigator's research staff and can also assist with questions relating to your rights as a participant in research, which may include questions, concerns or complaints about your participation in the study.

THE FOLLOWING PARAGRAPHS CONTAIN SOME STANDARD INFORMATION WHICH GENERALLY APPLIES TO INDIVIDUALS PARTICIPATING IN A RESEARCH STUDY.

CONSENT FORM FOR CLINICAL RESEARCH

I have read the previous page[s] of the consent form and the investigator has explained the details of the study. I understand that I am free to ask additional questions.

If I wish additional information regarding this research and my rights as a research subject, or if I believe I have been harmed by this study, I may contact the Human Subjects Protection Office (HSPO) at [617]667-0469

I am aware that this is a research project and that unforeseen side effects may occur.

I understand that the Beth Israel Deaconess Medical Center has no formal program for compensating patients for medical injuries arising from this research. Medical treatment will be provided for injuries at the usual charge to me or to my insurer unless payment is otherwise provided from this consent form.

I understand that participation in this study is voluntary and I may refuse to participate or may discontinue participation at any time without penalty, loss of benefits, or prejudice to the quality of care which I will receive.

I acknowledge that no guarantees have been made to me regarding the results of the treatment involved in this study, and I consent to participate in the study and have been given a copy of this form.

_____ _____

WITNESS DATE STUDY SUBJECT DATE

_____

PARENT /OR LEGAL GUARDIAN DATE

[If subject is a minor, or subject is unable to give consent)

The subject has been given the opportunity to read this consent form and to ask questions before signing, and has been given a copy.

_____

SIGNATURE OF INVESTIGATOR/Co-Investigator DATE

_____

PRINT INVESTIGATOR'S/CO-Investigator

APPENDIX B

Research Study on **BULIMIA NERVOSA**

* **FEMALE VOLUNTEERS** who are currently bulimic, or have recovered from past symptoms of bulimia nervosa, age 18-45, in stable medical health, and not taking medications (with the exception of oral contraceptives), are sought for a study of behavioral ratings and blood hormone levels.
* Eligible participants will receive ***$100 for 2 outpatient visits at or*** 1) Boston College 2) Beth Israel Deaconess Medical Center. (Clinical Research Unit)

FOR MORE INFORMATION CONTACT
Sandy Hannon-Engel , PhD (c) RN,CS
at 508-274-0671 or CCK@bc.edu

Behavioral Research Study
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Behavioral Research Study

* ***HEALTHY FEMALE VOLUNTEERS*** are needed for a study of behavioral rating scales and hormone levels. Eligible participants will receive up to **$100** for a total of 2 outpatient visits at or 1) Boston College 2) Clinical Research Unit at Beth Israel Deaconess Medical Center.

*Volunteers should be between ages 18-45 years old, in stable medical health, BMI between 19-26, not taking medications (with the exception of oral contraceptives), not pregnant, free of alcohol and drug abuse and without current or past history of major psychiatric illness including eating disorders.

FOR MORE INFORMATION CONTACT
Sandy Hannon-Engel , PhD©, RN,CS at
Boston College 508-274-0671 or CCK@bc.edu

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