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Serotonin Function Following Remission from Bulimia Nervosa

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Abnormal serotonergic regulation in bulimia nervosa is thought to contribute to recurrent binge eating, depressed mood, and impulsivity. To follow-up on previous studies showing decreased neuroendocrine responses in symptomatic patients, this study assessed serotonin-mediated prolactin responses in individuals who had remitted from bulimia nervosa. Subjects included 21 women with a history of bulimia nervosa and 21 healthy female controls, as well as an additional comparison group of 19 women with current bulimia nervosa. Placebo-controlled neuroendocrine response studies utilized a single oral dose (60 mg) of the indirect serotonin agonist d,l-fenfluramine. For the bulimia nervosa remitted group, the fenfluramine-stimulated elevation in serum prolactin concentration was not significantly different from the response in healthy controls, but was significantly larger than the response in patients with current bulimia nervosa ($p < .01$). These findings suggest that diminished serotonergic neuroendocrine responsiveness in bulimia nervosa reflects a state-related abnormality. The results are discussed in relationship to recent reports indicating that some alterations in central nervous system serotonin regulation may persist in symptomatically recovered individuals.
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KEY WORDS: *Serotonin; Bulimia nervosa; Eating disorders; Neuroendocrine*

Impaired serotonergic responsiveness may play a physiological role in symptoms of bulimia nervosa. Thus, it is thought that diminished post-ingestive satiety creates a predisposition to large binge meals in this disorder (Mitchell and Laine 1985; LaChaussee et al. 1992; Kissileff et al. 1996). Studies in laboratory animals and in human volunteers have demonstrated that reduction in central nervous system (CNS) serotonergic function results in increased meal size (Blundell and Hill 1987; Goodall and Silverstone 1988; Leibowitz et al. 1990; Tecott et al. 1995). Patterns of mood lability, depression and impulsivity observed in bulimia nervosa (Jimerson et al. 1990; Wolfe et al. 1994a) may also reflect CNS serotonergic dysregulation (Cowen 1993; Coccaro et al. 1997). Conversely, the efficacy of antidepressant medications in decreasing frequency of binge eating episodes in bulimia nervosa (Jimerson et al. 1996) may reflect enhanced efficiency of signal transduction at serotonergic synapses (Blier and de Montigny 1994).

Psychobiological investigations comparing patients with bulimia nervosa with healthy control subjects have demonstrated diminished CNS serotonergic activity, as manifested by blunted neuroendocrine responses to single dose administration of a serotonergic agonist (Brewerton et al. 1992; Halmi et al. 1993; Goldbloom et

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al. 1996; Jimerson et al. 1997; Levitan et al. 1997; Monteleone et al. 1998). Additionally, previous studies have shown an inverse correlation between symptom severity, as reflected in frequency of binge eating episodes, and measures of serotonergic responsiveness (Jimerson et al. 1992, 1997). These observations are consistent with the hypothesis that diminished responsiveness in CNS serotonergic pathways contributes to the symptoms of this disorder.

The goal of the current study was to test the related hypothesis that individuals who have recovered from bulimia nervosa have increased CNS serotonergic responsiveness in comparison to currently symptomatic individuals. The primary outcome measure for this assessment was the increase in serum prolactin concentration following placebo-controlled, single-dose administration of the indirect serotonin agonist d,l-fenfluramine.

SUBJECTS AND METHOD

Subjects

Subjects were recruited through media advertisements and from local outpatient eating disorder programs. Research diagnostic assessments were made by a trained interviewer (BEW) using the Schedule for Affective Disorders and Schizophrenia-Life Version (SADS-L) (Endicott and Spitzer 1978) and Research Diagnostic Criteria (Spitzer et al. 1978), modified to include criteria for bulimia nervosa based on the Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised (DSM-III-R) (American Psychiatric Association 1987).

The syndrome-remitted group ($BN_{remitted}$) included 21 women who had previously met criteria for bulimia nervosa based on DSM-III-R, with the additional requirement of a history of binge eating and purging (by self-induced vomiting or laxative use) on average twice per week or more frequently over six months. Additional inclusion criteria for the $BN_{remitted}$ group required that participants had experienced less than one binge / purge episode per month for the previous three months and had regular menstrual cycles. Of the 21 remitted subjects, 16 reported complete abstinence from binge eating for three months or longer prior to study.

The control group included 21 healthy female volunteers. A second comparison group included 19 non-hospitalized, medication-free patients with current symptoms of DSM-III-R bulimia nervosa (BN_{active}), with the additional criteria of binge eating and purging (by self-induced vomiting or laxative use) on average at least twice per week over the previous six months. The BN_{active} group included one patient with secondary amenorrhea. Neuroendocrine data for a subset of the BN_{active} and control groups has been previously reported (Jimerson et al. 1997).

Based on diagnostic assessment using the SADS-L, the patient groups were free of major depression, alcoholism, and substance abuse for at least six months prior to study, and controls were free of current and past history of an eating disorder or other major psychiatric disorder. Individuals in the patient groups had not been in treatment with psychotropic medications for at least eight weeks prior to study. Subjects were within a normal body weight range adjusted for height (body mass index between 18 and 26 kg/m^2) (Society of Actuaries and Association of Life Insurance Medical Directors of America 1980), were free of concurrent medical illness, and were abstinent from alcohol for at least one week prior to study. Subjects had not taken oral contraceptives and had not been pregnant during the six months prior to study. All subjects received a complete description of study procedures and gave written informed consent.

Procedures

Studies were conducted after overnight fast and bed rest on a General Clinical Research Center inpatient unit in a single-blind, placebo-first, fixed order design during the follicular phase of subjects' menstrual cycle.

Blood samples for measurement of prolactin concentration were obtained at baseline and at five hourly intervals following oral administration of d,l-fenfluramine (60 mg) or matched placebo at 9:00 a.m. Plasma total fenfluramine (fenfluramine plus norfenfluramine) concentrations were measured at five hourly time points following drug administration. To assess menstrual cycle and metabolic status, baseline blood samples were collected for estradiol, progesterone, cortisol, thyroid hormone and amino acid measurements. Percent lean body mass was calculated based on skin fold measurements (Durnin and Womersley 1974; Lohman et al. 1988).

Baseline behavioral measures included self-ratings on the Eating Attitudes Test (Garner et al. 1982), Beck Depression Inventory (Beck and Steer 1987), as well as the Spielberger State-Trait Anxiety Inventory (Spielberger 1983), and investigator ratings (BEW, EDM) on the 17-item Hamilton Depression Rating Scale (Hamilton 1960). Side effects including "tiredness," "nausea," "stomachache," "headache," and "decreased appetite" were assessed on a five point self-rated Likert scale at baseline and two hours and five hours following drug / placebo administration.

Hormone and Amino Acid Assays

Serum prolactin levels were measured by fluoroimmunoassay (DELFIA kit; Wallac Inc., Gaithersberg, MD). Plasma concentrations of fenfluramine and norfenfluramine were measured by gas chromatography (Krebs et al. 1984). Serum estradiol, progesterone, cortisol and

thyroid hormone levels were measured by radioimmunoassay. Plasma tryptophan was measured by a fluorometric assay (Denckla and Dewey 1967) and large neutral amino acids (LNAA) (valine, methionine, leucine, isoleucine, tyrosine, and phenylalanine) were measured by high pressure liquid chromatography.

Data Analysis

Average prolactin response was calculated as the mean increase in prolactin concentration over baseline levels at the 2, 3, 4, and 5 hour post-fenfluramine time points. Prolactin peak response was calculated as the maximal increase in hormone levels over baseline. For these calculations, the prolactin concentration at each post-drug time point on the active study day was adjusted for the percent change from baseline at the comparable time on the placebo day. Plasma average fenfluramine levels were calculated as the sum of fenfluramine plus norfenfluramine concentrations averaged over five hourly measurements.

Group data are summarized as mean ± standard deviation (SD). Statistical significance was defined as $p < .05$ based on two-sided significance levels. Baseline data for the three study groups were compared by analysis of variance. Variables not normally distributed (Kolmogorov-Smirnov test) were square root- or log-transformed, or else were analyzed by Kruskal-Wallis test. Neuroendocrine responses were compared across groups by analysis of covariance, adjusting for plasma average fenfluramine concentration when the covariate term reached significance. For pre-planned contrasts comparing the $BN_{remitted}$ group with the control and BN_{active} groups, statistical significance was set at $p < .025$.

Relationships between baseline measures and prolactin response were assessed by correlational analysis. Baseline serum prolactin and cortisol levels for paired active and placebo days were compared by repeated measures analysis of variance. Side effect ratings for the two study days, calculated as change from baseline, were compared by Wilcoxon matched-pairs signed-ranks test. For multiple comparisons, Bonferroni-adjusted significance levels were used. Statistical calculations were made using SPSS® 9.0 (1999).

RESULTS

Subject Characteristics

Individuals in the $BN_{remitted}$ group had most recently met full DSM-III-R criteria for the disorder 40 ± 29 months prior to study (range 4 to 126 months). For the BN_{active} group, average frequencies of binge eating and self-induced vomiting over the four weeks prior to study were 6.6 ± 3.7 and 7.0± 4.9 episodes per week, respectively. Season of study did not differ across subject groups ($X^2 = 4.91$, df = 6, p = ns).

For descriptive and behavioral variables, there was a significant group effect for the Eating Attitudes Test, Hamilton Depression Rating, Beck Depression Inventory, and Spielberger State and Trait Anxiety Inventories (Table 1). One or more previous episodes of major depression were identified in seven individuals (33%) in the $BN_{remitted}$ group and six patients (32%) in the BN_{active} group. A history of anorexia nervosa was present in six (29%) individuals in the $BN_{remitted}$ group and 10 patients (53%) in the BN_{active} group. Based on SADS-L data, one $BN_{remitted}$ individual met criteria for current phobic disorder and two met criteria for previous generalized anxiety disorder. One BN_{active} individual met criteria for current generalized anxiety disorder. No subjects met criteria for current or past panic disorder or obsessive compulsive disorder.

Table 1. Descriptive Characteristics and Baseline Behavioral Ratings for Study Subjects

	$BN_{remitted}$ (n = 21)		Control (n = 21)		BN_{active} (n = 19)	
	Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*
Age #	24.9	4.1	22.9	3.4	23.6	3.8
Weight (kg)	58.9	7.8	58.1	7.0	59.9	6.8
Lean body mass (%)	71.9	4.0	72.5	5.0	73.6	5.7
% Expected body weight§	99.4	9.5	98.8	8.8	99.9	9.5
Body mass index	21.8	2.0	21.5	2.0	21.7	2.2
Menstrual cycle day§	8.0	2.0	8.0	3.0	9.0	3.0†
Eating attitudes test§	8.5	6.9a***,b***	3.2	3.3	34.7	6.7c***
Hamilton depression rating#	2.4	2.8a**	0.4	0.6	4.2	4.2c***
Beck Depression Inventory#	2.8	4.3a**	0.2	0.5	5.3	4.7c***
Spielberger State Anxiety Inventory	30.0	8.1b*	25.4	4.6	36.1	9.2c***
Spielberger Trait Anxiety Inventory	36.9	9.7a***,b**	26.5	4.2	45.2	11.8c***

Contrasts: a = $BN_{remitted}$ vs. Control; b = $BN_{remitted}$ vs. BN_{active}; c = BN_{active} vs. Control.
§ Variable transformed prior to ANOVA; # Kruskal-Wallis test; † n = 18, one patient amenorrheic.
* $p < .025$; ** $p < .01$; *** $p < .001$.

Serum Prolactin Response to Fenfluramine Challenge

Baseline serum prolactin concentrations for the $BN_{remitted}$ group were not significantly different from levels for the comparison groups (Table 2). At the four hour time point on the placebo day (corresponding to the time of maximal hormone response on the active study day), the diurnal decrease in prolactin level was not significantly different for the $BN_{remitted}$ group (19 ± 25%), the healthy controls (20 ± 50%), and the BN_{active} group (21 ± 36%).

Plasma fenfluramine mean concentration for the $BN_{remitted}$ group (344 ± 97 nmol/L) was not significantly different from values for the controls (361 ± 75 nmol/L) or the BN_{active} group (309 ± 107 nmol/L). For the combined groups, prolactin average response was correlated with plasma fenfluramine concentration ($r = 0.338$, $df = 59$, $p = .008$), with a trend for an association between prolactin peak response and drug concentration ($p = .07$).

For prolactin average response, analysis of covariance demonstrated a significant main effect for study group ($p = .019$), as well as for the fenfluramine concentration covariate term ($p = .030$). The prolactin average response for the $BN_{remitted}$ group was significantly greater than for currently symptomatic patients, and not significantly different from responses for healthy controls (Figure 1A). Similarly, for the 16 $BN_{remitted}$ individuals who had maintained complete abstinence from binge eating and purging episodes for at least three months prior to study, the prolactin response was significantly greater than for BN_{active} individuals ($p = .004$), and not significantly different from that for controls.

For prolactin peak response, the analysis of covariance found a significant main effect for study group ($p = .004$). The prolactin peak response for the $BN_{remitted}$ group was significantly greater than for currently symptomatic patients (Figure 1B). Similar results were obtained for the subgroup of binge-abstinent individuals. Consistent with previous results, the prolactin response for the BN_{active} group was blunted in comparison to the control group's response (Figures 1A and 1B).

Baseline Blood Hormone Levels

For baseline hormone measurements, analysis of variance showed a significant group effect for serum prolactin, cortisol, and free thyroxine (Table 2). Repeated measures analysis of variance did not demonstrate significant differences in baseline serum prolactin or cortisol concentrations between the active and placebo study days. One individual in each group had estradiol levels more than two standard deviations greater than the group mean, and one individual in the $BN_{remitted}$ and control groups had similarly elevated progesterone levels. When analyses were repeated excluding these individuals, differences in prolactin response between study groups remained similar to those presented above. Fenfluramine-stimulated prolactin response was not significantly correlated with age or with any of the baseline biological measurements.

Behavioral Ratings

Duration of remission for the $BN_{remitted}$ group was significantly correlated with age ($r = 0.49$, $df = 19$, $p = .032$). Prolactin response for the $BN_{remitted}$ group was not significantly correlated with duration of remission, controlling for age, nor with any of the behavioral ratings. Within the $BN_{remitted}$ and BN_{active} groups, prolactin response did not differ significantly for the subgroups with and without a history of anorexia nervosa.

Fenfluramine administration significantly decreased appetite ratings at the five hour time point for the combined sample ($z = 3.11$, $p = .002$), and for the $BN_{remitted}$ group taken separately ($z = 3.02$, $p = .002$). Ratings for other side effects were not significantly different between the two study days.

Table 2. Baseline Blood Hormone and Amino Acid Levels on Active Study Day

	$BN_{remitted}$ ($n = 21$)		Control ($n = 21$)		BN_{active} ($n = 19$)	
	Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*
Prolactin (μg/L)	6.6	1.9	7.5	2.3	5.4	1.8[c**]
Estradiol (pg/mL) [§]	68.4	46.8[†]	50.0	29.2[†]	42.5	35.0[†]
Progesterone (ng/mL) [§]	0.62	0.60[†]	0.49	0.22[†]	0.56	0.31
Cortisol (μg/dL)[§]	13.7	4.1[b**]	15.4	4.5	18.1	5.5
Triiodothyronine (ng/dL)	79.8	14.9	89.4	20.4	76.2	16.5
Free thyroxine (ng/dL)	0.76	0.18[a**]	0.93	0.18	0.70	0.19[c***]
Thyrotropin (μU/mL)	1.31	0.65	1.22	0.49	0.92	0.40
Total tryptophan (nmol/mL)	45.7	6.6	47.8	7.3	46.0	8.3
TRP / ΣLNAA ratio	0.091	0.016	0.091	0.013	0.090	0.015

Contrasts: a = $BN_{remitted}$ vs. Control; b = $BN_{remitted}$ vs. BN_{active}; c = BN_{active} vs. Control.
[§] Variable transformed prior to ANOVA; [†] Mean values exclude one outlier value in designated subject groups.
** $p < .01$; *** $p < .001$.

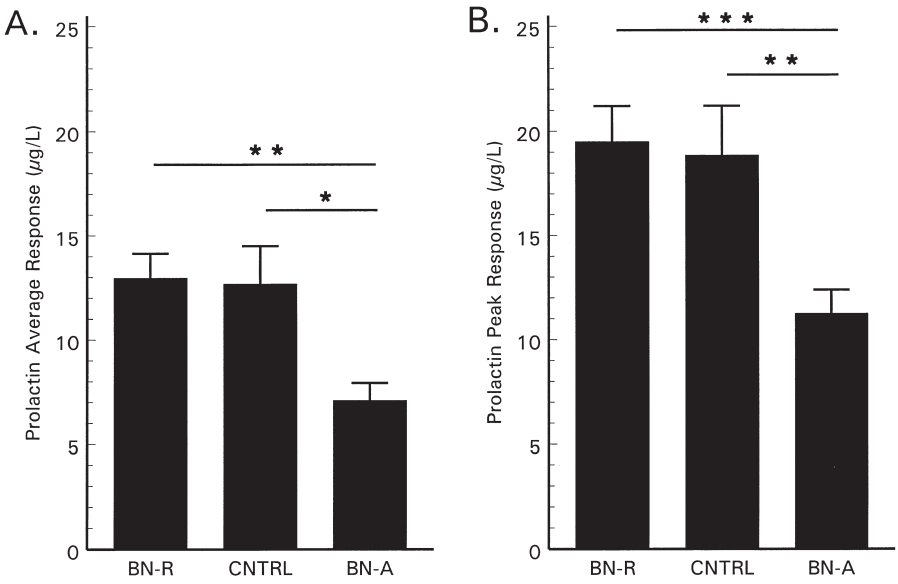

Figure 1. Placebo-adjusted serum prolactin response following administration of d,l-fenfluramine in 21 individuals recovered from bulimia nervosa (BN-R), 21 healthy controls (CNTRL), and 19 subjects with current bulimia nervosa (BN-A). Prolactin response (mean ± SEM) is shown as average increase over baseline **(A)** and peak increase over baseline **(B)**. Statistical significance: $*p < .025$; $**p < .01$; $***p < .005$.

DISCUSSION

Results of this study show that individuals who have recovered from bulimia nervosa have significantly increased serotonergic neuroendocrine responsiveness in comparison to patients with current symptoms of the disorder. Given the behavioral effects of serotonin noted in the Introduction, restoration of CNS serotonergic responsiveness may play a role in recovery from the disorder. This possibility is supported by a recent report that individuals recovered from bulimia nervosa experienced a transient return of eating disorder related symptoms when CNS serotonin function was diminished by administration of a tryptophan-deficient amino acid mixture (Smith et al. 1999).

For the $BN_{remitted}$ group, neuroendocrine responses were not significantly different from results for healthy controls, in agreement with preliminary findings (Wolfe et al. 1994b). These results are consistent with a recent report indicating that neuroendocrine responses to the serotonin agonist m-chlorophenylpiperazine (mCPP) were not significantly different for patients recovered from bulimia nervosa and healthy controls (Kaye et al. 1998).

In evaluating these neuroendocrine results, it is important to note that the prolactin response to d,l-fenfluramine provides an index of localized synaptic throughput in hypothalamic serotonergic pathways, reflecting the drug's enhancement of pre-synaptic transmitter release, blockade of pre-synaptic re-uptake, and possibly stimulation of post-synaptic receptors (Garattini et al. 1986). In contrast, several recent studies have reported differences in other measures of CNS serotonin function in individuals recovered from bulimia nervosa in comparison to healthy controls. Thus, recovered individuals had significantly elevated serotonin metabolite concentrations in cerebrospinal fluid in comparison to controls, and increased sensitivity to several behavioral effects of mCPP, including feelings of anxiety and "difficulty functioning" (Kaye et al. 1998). Additionally, following administration of a tryptophan-deficient amino acid mixture, individuals who had recovered from bulimia nervosa showed increased sensitivity to eating disorder-related behavioral effects in comparison to controls (Smith et al. 1999). Based on these studies, it is possible that normal function is restored in hypothalamic serotonergic pathways following recovery from bulimia nervosa, while dysregulation persists in other CNS serotonergic pathways.

A second possibility is that restoration of hypothalamic-pituitary neuroendocrine responsiveness in the recovered individuals is reflective of compensatory adaptations occurring more widely in CNS serotonergic pathways. For example, increased pre-synaptic serotonin release could compensate for impaired post-synaptic receptor responsiveness. In this case, persisting abnormalities in serotonin function may become apparent only when the systems are challenged, as in the case of dieting (Anderson et al. 1989) or the administration of a tryptophan-deficient amino acid mixture (Weltzin et al. 1995; Smith et al. 1999). Further studies are needed to clarify the regulation of serotonergic pathways involved in the modulation of satiety, mood, anxiety and related behavioral dimensions following recovery from bulimia nervosa.

Measurement of baseline serum hormone levels revealed several differences across study groups. Free thyroxine levels for the $BN_{remitted}$ were significantly lower than control levels. The finding of significantly reduced free thyroxine and baseline prolactin levels in the BN_{active} group is consistent with previous reports (Pirke et al. 1985; Levy et al. 1988; Obarzanek et al. 1991;

Weltzin et al. 1991; Brewerton et al. 1992; Jimerson et al. 1997). It is possible that nutritional factors may have contributed to reductions in thyroid hormone levels, even though study groups were matched for body weight. These observations merit further study, given that decreased thyroid function has been associated with diminished responsiveness in CNS serotonergic pathways (Cleare et al. 1995). The reduction in baseline cortisol levels in the remitted individuals in comparison to the active bulimia nervosa group may also play a role in differential serotonergic responses, given that variations in glucocorticoid levels can influence CNS serotonin receptor function (Fernandes et al. 1997). The finding that blood tryptophan levels and the ratio of tryptophan to other large neutral amino acids were not significantly different across study groups is consistent with previous reports (Wolfe et al. 1997; Kaye et al. 1998; Smith et al. 1999).

A potential limitation of the present study is that criteria for remission from bulimia nervosa were based primarily on recovery from binge eating and purging behaviors. The $BN_{remitted}$ group had ratings on the Eating Attitudes Test that were comparable to scores for female university students (9.9 $\pm$ 9.2) (Garner et al. 1982) and were significantly lower than for symptomatic patients, although they were statistically elevated in comparison to the control group. Self-ratings of depression and anxiety for the $BN_{remitted}$ group, also elevated in comparison to control values, were similar to or slightly lower than ratings for recovered individuals described in previous studies (Kaye et al. 1998; Smith et al. 1999). As noted by others, dieting and other patterns of abnormal eating, associated with modest elevations on ratings of eating disorder symptomatology, tend to persist after binge eating and purging have remitted (Oldman et al. 1995; Kaye et al. 1998). Thus, it is possible that individuals in the $BN_{remitted}$ group had persistent abnormalities in dietary patterns which may have influenced neuroendocrine response patterns.

Another potential limitation of the current study was the cross-sectional design, which did not incorporate repeated neuroendocrine testing in individual subjects followed longitudinally from illness to recovery. Previous symptom patterns for the remitted individuals appeared to resemble clinical characteristics of the currently symptomatic patients, who did show diminished prolactin responses. It would be of interest in future studies to assess whether restoration of serotonergic neuroendocrine responsiveness parallels the decreased risk for relapse observed six months following clinical remission (Olmsted et al. 1994).

In summary, results of this study indicate that recovery from bulimia nervosa is associated with restoration of normal responsiveness in neuroendocrine-related serotonergic pathways. Additional studies are needed to evaluate these results in relationship to other evidence for CNS serotonergic dysregulation in symptomatically recovered individuals.

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