ORIGINAL ARTICLE

Alterations in Serotonin Activity and Psychiatric Symptoms After Recovery From Bulimia Nervosa

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Background: Women with bulimia nervosa (BN) have disturbances of mood and behavior and alterations of monoamine activity when they are bingeing and purging. It is not known whether these alterations are secondary to pathological eating behavior or traits that could contribute to the pathogenesis of BN.

Methods: To avoid the confounding effects of pathological eating behavior, we studied 30 women after long-term recovery (>1 year with no bingeing or purging, normal weight, and regular menstrual cycles) from BN. Subjects were compared with 31 healthy volunteer women. We assessed psychiatric diagnoses and symptoms to determine whether there was any persistent disturbance of behavior after recovery. We measured cerebrospinal fluid (CSF) levels of the major metabolites of serotonin (5-hydroxyindoleacetic acid [5-HIAA]), dopamine (homovanillic acid [HVA]), and norepinephrine (3-methoxy-4-hydroxyphenylglycol [MHPG]) as well as hormonal and behavioral response to *m*-chlorophenylpiperazine (*m*-CPP), a serotonin-specific agent.

Results: Women who were recovered from BN had mild to moderate negative moods and obsessions with perfectionism and exactness and exaggerated core eating disorder symptoms compared with healthy volunteer women. Recovered BN women had increased levels of CSF 5-HIAA compared with control women (117 ± 33 vs 73 ± 15 pmol/mL; $P \leq .001$) but normal CSF HVA and MHPG concentrations. Recovered BN women had an anxious and disorganized behavioral response to *m*-CPP but a normal hormonal response.

Conclusions: Persistent serotonergic and behavioral abnormalities after recovery raise the possibility that these psychobiological alterations might be trait-related and contribute to the pathogenesis of BN.

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BULIMIA NERVOSA (BN) is a disorder of unknown origin that most commonly occurs in women who are of normal body weight.[1] Bulimia nervosa usually has its onset in adolescence and is characterized by bingeing and purging. Women with BN often have a distorted body image, neuroendocrine abnormalities,[2] and comorbid[3] depression, anxiety, obsessive-compulsive disorder, and alcohol and other substance abuse.

Many animal and human studies suggest that altered central nervous system monoamine neurotransmitter activity[4] could contribute to the appetitive, neuroendocrine, and behavioral alterations found in BN. In fact, disturbances of brain serotonin and noradrenergic activity have been described in BN. Examples of such disturbances include a blunting of prolactin response after the administration of drugs with serotonin actions,[5-8] and increased caloric intake and irritability after depletion of tryptophan, the precursor of serotonin.[9] While one study[10] found that subjects with BN had normal levels of the cerebrospinal fluid (CSF) metabolite of serotonin, 5-hydroxyindoleacetic acid (5-HIAA), another study[11] found that levels of this metabolite were low in subjects who binged more than twice daily. In addition, most studies have found abnormalities of peripheral and central noradrenergic[12] activity, such as reduced concentrations of norepinephrine in body fluids. Importantly, numerous double-blind placebo-controlled studies have found that a wide range of antidepressant medications were effective in reducing bingeing and purging frequency.[13,14] Antidepressants, which act on brain noradrenergic and serotonergic pathways, could correct a disturbance of monoaminergic function in BN.

SUBJECTS AND METHODS

SUBJECTS

Thirty women were recruited who had previously met *DSM-III-R* criteria for BN. No subjects had a history of anorexia nervosa (AN), as they must have maintained a body weight of greater than 85% of average body weight (ABW)[16] since development of an eating disorder. Subjects were previously treated in the eating disorders treatment program at Western Psychiatric Institute and Clinic, Pittsburgh, Pa, or were recruited through advertisements. To be considered "recovered," for the previous year subjects had to (1) maintain a weight above 90% ABW; (2) have regular menstrual cycles; (3) have not binged, purged, or engaged in restrictive eating patterns; (4) not used psychoactive medication such as antidepressants; and (5) not met criteria for alcohol or drug abuse or dependence. Thirty-one healthy control women (CW) were recruited through local advertisements. The CW had no history of an eating disorder or any psychiatric, medical, or neurologic illness. They had no first-degree relatives with an eating disorder. They had normal menstrual cycles and had been within a normal weight range since menarche. All subjects gave written informed consent. They completed a 7-day diary at home in which they listed individual food items consumed, portion sizes, and exercise frequency. This information was used to confirm the presence of relatively normal dietary intake. Biological studies were only done during the first 10 days of the follicular phase for all subjects.

Subjects were admitted to a research laboratory in the eating disorders unit of Western Psychiatric Institute and Clinic at 9 AM of the day prior to the lumbar puncture (LP) for adaptation to the laboratory and for psychological assessments. The LP was done the next day. In 10 subjects (3 CW, 7 BN) the double-blind, placebo-controlled *m*-CPP study was done after the LP. Because of the difficulty in timing the LP and *m*-CPP studies within the space of 1 menstrual cycle, 9 of the CW and 14 of the BN women had the 2 studies within 1 or 2 months of each other, with the rest of the subjects having a longer interval between studies. Subjects were readmitted the night before the *m*-CPP study. There was at least 1 full interval day between administration of drug and placebo. All subjects were served the same standardized, monoamine-controlled diets during their stay in the laboratory.

BEHAVIORAL ASSESSMENTS

The Schedule for Affective Disorders and Schizophrenia–Lifetime Version (SADS-L)[17] was used to assess subjects for lifetime Axis I *DSM-III-R* diagnoses. The SADS-L was administered by a trained master's- or doctoral-level clinical interviewer and blindly reviewed by a psychiatrist who validated final *DSM-III-R* Axis I diagnoses. Current psychopathological symptoms were assessed with a battery of standardized instruments and by self-report. Not all assessments were completed on each subject. Depression was assessed with the Hamilton Rating Scale for Depression[18] and the Beck Depression Inventory.[19] Anxiety was assessed with the Spielberger State-Trait Anxiety Inventory.[20] Obsessions and compulsions were assessed with the Yale-Brown Obsessive Compulsive Scale (Y-BOCS).[21,22] Obsessive concerns with body image, weight or caloric intake, or compulsive behaviors such as exercise and weighing oneself were excluded from the Y-BOCS. Such obsessive and compulsive eating disorder symptoms were assessed by the Y-BOCS Eating Disorders Scale (Y-BOCS-ED), which is similar to another instrument that has been validated for use in eating disorder patients.[23] Cognitive and behavioral dimensions of eating disorders were also assessed by the Eating Disorder Inventory (EDI).[24] Perfectionism was assessed with the Frost Multidimensional Perfectionism Scale (MPS).[25]

LUMBAR PUNCTURE

Eighteen of the CW and 23 of the BN women agreed to undergo LP. Subjects fasted from midnight until the procedure was completed between 8 AM and 10 AM on the next day. The LP was performed at the L3-4 interspace with subjects in a left lateral position. The first 12 mL of spinal fluid was placed into a single aliquot that was stored on wet ice during the LP procedure and then divided by pipette into 1-mL and 0.5-mL aliquots, which were immediately frozen on dry ice and stored at –70°C. The aliquots for monoamine assay were preserved in ascorbic acid.

Cerebrospinal fluid monoamine activity may be influenced by several factors, such as dieting or weight loss.[26] Plasma and CSF large neutral amino acids were measured because ingestion of tryptophan in the diet (and its ratio to other neutral amino acids) is necessary for the synthesis of serotonin.[27] In addition, plasma hydroxybutyric acid (β-HBA), a ketone body, was assessed as an index of starvation. Other factors were characterized, such as body weight, height,[28] and seasonality,[29] that might contribute

It is not known whether behavioral or monoamine disturbances are a consequence of bulimic symptoms or dietary abnormalities, or premorbid traits that contribute to a vulnerability to develop BN. The studies cited earlier were conducted near in time to when subjects with BN were actively bingeing and purging. Determining whether abnormalities are a consequence or a potential antecedent of pathological eating behavior is a major question in the study of eating disorders. It is impractical to study BN prospectively, owing to the young age of onset and difficulty in premorbid identification of people who will develop BN. Therefore, we decided to study women who had been recovered from BN for more than 1 year. Any persistent psychobiological abnormalities might be trait-related and potentially contribute to the pathogenesis of this disorder.

Central nervous system monoamine neurotransmitter status was assessed in recovered BN subjects by measuring CSF levels of the major metabolites of serotonin (5-HIAA), dopamine (homovanillic acid [HVA]), and norepinephrine (3-methoxy-4-hydroxyphenylglycol [MHPG]). Serotonin functional activity was also assessed by the use of *m*-chlorophenylpiperazine (*m*-CPP), a relatively specific serotonin agonist.[15] The *m*-CPP induced changes in plasma hormones such as prolactin, and behavioral symptoms served as indices of serotonin activity.

to monoamine activity. Because menstrual state may influence serotonin activity,[30] the LP was performed during the first 10 days of the follicular phase. Many women in the recovered BN group were found to be taking birth control pills. To recruit a large enough sample of recovered BN subjects, we studied BN women who were taking birth control pills and BN women who were not taking birth control pills. To control for the effects of birth control pills in recovered BN women, we also recruited CW who were and were not taking birth control pills.

m-CPP STUDY

Subjects fasted from midnight until the studies were completed. At 7:30 AM, an intravenous catheter was inserted in an antecubital vein and kept open with a heparinized 5% dextrose solution. After 1 hour of adaptation, blood samples were obtained at –30 minutes, –15 minutes, and 0 minutes. Then the subject ingested capsules containing 0.5-mg/kg *m*-CPP or placebo. Blood samples were then obtained at 15 minutes, 30 minutes, 60 minutes, 90 minutes, 120 minutes, 150 minutes, 180 minutes, and 240 minutes for measures of plasma prolactin and cortisol. Subjects were given *m*-CPP and placebo in random order.

To determine whether there were differences in the effects of *m*-CPP on mood between BN and control subjects, psychological state was assessed at baseline (7:30 AM on the morning prior to administration of *m*-CPP or placebo) and at intervals after the administration of *m*-CPP or placebo. Two methods were used. Mood and behavior were blindly and objectively assessed by a structured interview administered by psychiatrists (T.E.W. and W.H.K.) at baseline and at 90 and 180 minutes after administration of *m*-CPP or placebo. These structured interview assessments of anxiety, depression, disorganization, and obsessionality ratings were adapted from assessments previously described in the literature.[21,22,31] These scales were choosen to assess changes in mood and obsessionality as well as cognitive function. Subjects self-rated anxiety, depression, and difficulty functioning using a subset of items from the National Institutes of Mental Health Global Rating Scale[32] at baseline and at 30-minute intervals for 2 hours after receiving *m*-CPP or placebo. Peak changes were determined by taking the largest deviation from baseline at either 90 or 180 minutes after ingestion of *m*-CPP or placebo and subtracting the baseline.

ASSAYS

All assays were done by laboratory staff blinded to the clinical data. High-performance liquid chromatography[33] was used to assay the major CSF serotonin metabolite (5-HIAA), the dopamine metabolite (HVA), and the norepinephrine metabolite (MHPG). The within-run and between-run coefficient of variation (CV) of each monoamine assay was less than 10%. The level of sensitivity of the assay for 5-HIAA was 0.5 pmol per injection. Radioimmunoassays were used to measure estradiol (Diagnostic Product Corporation, Los Angeles, Calif) and progesterone (Ciba-Corning, Medfield, Mass). Levels of β-HBA were measured by the enzymatic method of Williamson et al.[34] There was a 4% CV. Total tryptophan levels in plasma were quantitated fluorometrically.[35] The plasma levels of the other large neutral amino acids were measured using an amino acid analyzer as previously described.[36] Not all CSF measures were completed on all subjects owing to laboratory error. Methods used to measure plasma cortisol[37] and prolactin[38] levels have been previously described. The sensitivity and interassay CV for cortisol were .03 and .07 µmol/L, respectively; and for prolactin, 1 and 2.86 µg/L, respectively. Plasma *m*-CPP[39] concentrations were measured by high-performance liquid chromatography. For *m*-CPP the intra-assay CV was 6.8% at 3 ng/mL and 3.5% at 50 ng/mL. The interassay CV was 6.8% at 25 ng/mL.

STATISTICS

The BMDP statistical software package[40] was used for data analysis. Between-group comparisons were made using 2-tailed group *t* tests or 1-way analysis of covariance (ANCOVA). When the assumption of homogeneity of variance was met according to the Levine test, pooled *t* tests are reported. When the assumption was not met, separate *t* tests are reported. Factors that were considered possible confounds of CSF monoamine concentrations were explored with a series of 2-factor ANCOVAs with 1 grouping factor (group: BN vs CW). For example, CSF 5-HIAA was predicted using age as a potential confounding factor. Correlations were examined with linear regression analysis. Data related to the *m*-CPP study were reduced for analysis. The 3 baseline hormonal measurements were averaged to form 1 baseline number for each subject. Differences between groups were then tested using 2 (group: BN vs CW) × 9 (time) × 2 (drug: *m*-CPP vs placebo) ANOVAs with time and drug serving as within-subject factors. Psychological data were reduced to baseline measurement and the peak response to each measure for each subject. Psychological response variables were analyzed using 2 (group: BN vs CW) × 2 (time: baseline vs peak response) ANOVAs with time serving as a within-subject factor. Values are expressed as mean ± SD.

RESULTS

DEMOGRAPHICS

Women who were recovered from BN had the onset of BN at 16 ± 3 years of age and had been recovered for 36 ± 24 months at the time of this study. At their worst, when ill with BN, they binged 28 ± 40 (range, 2-210) and vomited 33 ± 43 (range, 0-210) times per week. Fourteen of the BN women had been laxative abusers who used, at their worst, 58 ± 182 laxatives per week. Compared with the CW, the recovered BN women (**Table 1**) were significantly older, although both groups had a mean age in their 20s. The recovered BN women had a higher percent ABW than the CW. The 2 groups of subjects had been at similar low percentage ABW since menarche, but the long-term recovered BN subjects weighed significantly more than the CW in the past.

LIFETIME AXIS I PSYCHIATRIC DIAGNOSES

For the recovered BN subjects, 68% had a lifetime history of major depressive disorder, 25% of obsessive-compulsive disorder, and 11% of generalized anxiety disorder. In addition, 32% had a lifetime history of alcohol dependence and 21% of other substance dependence.

CURRENT PSYCHIATRIC SYMPTOMS

At the time of this study, the recovered BN women had significantly higher scores on standardized assessments of depression, anxiety, perfectionism, and obsessionality compared with CW (**Table 2**). In addition, recovered BN women showed significant elevations on most subscales of the EDI. The most common target symptoms endorsed on the Y-BOCS by women who had recovered from BN were the need for symmetry (56% of BN subjects) and ordering/arranging (56% of BN subjects). There were no significant differences between BN women (or CW) who did both the LP and the *m*-CPP studies compared with those who only did the *m*-CPP study.

Table 1. Comparison of Control Women (CW) and Women Who Recovered From Bulimia Nervosa (BN)*

	CW	BN	*t*†	*P*
No. of subjects	31	30		
Age, y	22±4	26±6	3.06	.003
Height, cm	165±5	162±6	2.09	.04
Weight, kg	58.8±6.0	61.4±7.0	1.55	.13
BMI	21.6±1.9	23.3±2.2	3.34	.001
% ABW	104±9	112±11	3.38	.001
% Low lifetime ABW	95±8	95±8	0.21	.83
% High lifetime ABW	108±9	125±13	5.69	>.001

**All data are presented as mean±SD unless otherwise indicated. BMI indicates body mass index (calculated by weight in kilograms divided by the square of the height in meters); ABW, average body weight.*

†df *was 59 for all comparisons.*

CSF MONOAMINE CONCENTRATIONS

Recovered BN subjects had significantly higher CSF 5-HIAA concentrations ($P<.001$) than CW (**Table 3** and **Figure 1**). In comparison, CSF HVA and MHPG concentrations were similar for both groups. In terms of factors that might affect CSF monoamine activity, recovered BN women and CW were studied on similar days of their menstrual cycle (Table 3) and had similar values, on the day of the LP, for plasma estradiol and progesterone. Birth control pills did not interact with 5-

Table 2. Scores on Assessments of Current Psychiatric Symptoms for Control Women (CW) and Women Who Recovered From Bulimia Nervosa (BN)*

	CW	BN	*df*	*t*	*P*
Hamilton Rating Scale for Depression	2 ± 3 (22)	6 ± 6 (24)	44	3.27	.003
Beck Depression Inventory	2 ± 2 (20)	7 ± 7 (22)	40	2.74	.01
Spielberger State Anxiety	31 ± 8 (20)	36 ± 10 (22)	40	1.99	.05
Spielberger Trait Anxiety	33 ± 9 (20)	40 ± 9 (22)	40	2.43	.02
Frost Multidimensional Perfectionism Scale	63 ± 9 (9)	74 ± 19 (18)	25	2.12	.04
EDI Drive for Thinness	1.1 ± 2.0 (20)	4.3 ± 5.1 (22)	40	2.75	.01
EDI Bulimia	0.3 ± 0.8	1.8 ± 2.5	40	2.60	.02
EDI Body Dissatisfaction	3.9 ± 4.8	12.6 ± 7.5	40	4.46	<.001
EDI Ineffectiveness	0.7 ± 1.5	2.3 ± 3.1	40	2.15	.04
EDI Perfectionism	3.1 ± 3.3	5.1 ± 3.6	40	1.91	.06
EDI Interpersonal Distrust	0.8 ± 1.3	2.0 ± 2.3	40	2.12	.04
EDI Interoceptive Awareness	0.6 ± 1.0	3.2 ± 4.3	40	2.77	.01
EDI Maturity Fears	1.6 ± 2.2	2.0 ± 2.9	40	0.44	.66
Y-BOCS	3 ± 4 (22)	8 ± 8 (24)	44	3.33	.002
Y-BOCS ED	2 ± 2 (21)	8 ± 8 (24)	43	5.02	<.001

**All data are given as mean ± SD (number of subjects) unless otherwise indicated. EDI indicates Eating Disorder Inventory; Y-BOCS, Yale-Brown Obsessive Compulsive Scale; and Y-BOCS ED, Y-BOCS Eating Disorders Scale.*

Table 3. Comparison Between Control Women (CW) and Women Who Recovered From Bulimia Nervosa (BN) for Cerebrospinal Fluid (CSF) Monoamine Concentrations and Relevant Factors That Contribute to Monoamine Activity Variables on the Day of the CSF Study*

	CW	BN	*df*	*t*	*P*
CSF 5-HIAA, pmol/mL	73 ± 15 (18)	117 ± 33 (23)	39	5.72	<.001
CSF HVA, pmol/mL	202 ± 57 (18)	216 ± 73 (19)	35	0.66	.51
CSF MHPG, pmol/mL	42 ± 13 (18)	37 ± 13 (21)	37	1.21	.23
Day of menstrual cycle	4 ± 5 (17)	6 ± 5 (26)	41	1.13	.26
Plasma estradiol, pmol/L	132.1 ± 128.4 (17)	124.8 ± 198.2 (23)	38	0.16	.88
Plasma progesterone, nmol/mL	1.8 ± 0.6 (14)	3.9 ± 5.8 (20)	32	1.60	.13
Plasma tryptophan, µmol/L	54 ± 9 (13)	53 ± 8 (20)	31	0.36	.73
CSF tryptophan, nmol/mL	1.9 ± 0.6 (15)	1.9 ± 0.5 (23)	36	0.25	.8
Plasma tryptophan/neutral amino acid ratio	0.109 ± 0.021 (13)	0.108 ± 0.014 (20)	31	0.21	.82
Plasma β-HBA, µmol/L	119 ± 89 (17)	127 ± 149 (23)	38	0.2	.84

**All data are presented as mean ± SD (number of subjects) unless otherwise indicated. CSF indicates cerebrospinal fluid; 5-HIAA, 5-hydroxyindoleacetic acid; HVA, homovanillic acid; MHPG, 3-methoxy-4-hydroxyphenylglycol; and β-HBA, hydroxybutyric acid.*

HIAA levels. That is, there were similar CSF 5-HIAA concentrations in BN women who were taking birth control pills (n = 10, 130 ± 25 pmol/mL) and BN women not taking birth control pills (n = 13, 107 ± 35 pmol/mL; $t_{21} = 1.71$, $P = .10$). There were also similar CSF 5-HIAA concentrations in CW who were taking birth control pills (n = 3, 85 ± 16 pmol/mL) and CW not taking birth control pills (n = 15, 71 ± 14 pmol/mL; $t_{16} = 1.54$, $P = .14$). Subjects had similar values (Table 3) for plasma and CSF tryptophan and plasma ratios of tryptophan to large neutral amino acids, perhaps the most important index of tryptophan contribution to serotonin synthesis.[41] Subjects had similar values for plasma β-HBA, a measure of plasma ketones. Control women showed a relationship between CSF 5-HIAA and age ($r = -0.463$, $P = .05$, n = 18) but not CSF 5-HIAA and percent ABW ($r = -0.145$, $P = .57$). Recovered BN showed a relationship between CSF 5-HIAA and percent ABW ($r = 0.431$, $P = .04$) but not between CSF 5-HIAA and age ($r = 0.043$, $P = .85$). However, a series of ANCOVAs showed no significant effect of age or percent ABW or any of the variables in Table 1 on CSF monoamine concentration. We found a significant relationship between CSF 5-HIAA and CSF HVA levels in the BN women ($r = 0.62$, $P = .005$) and a trend in the CW ($r = 0.44$, $P = .07$). Monoamine values for recovered BN subjects and CW were not significantly different by 1-way ANOVA for the season of study. Subgroups of BN subjects had similar CSF monoamine values after being segregated by the lifetime Axis I psychiatric diagnosis described earlier. For recovered BN women, no significant relationship was found between any monoamine value and current psychiatric symptoms.

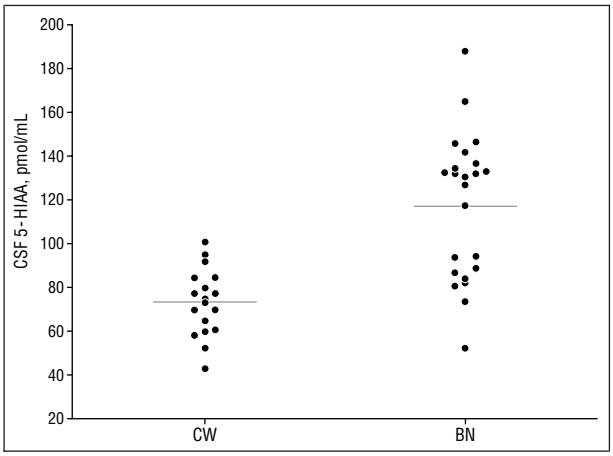

Figure 1. *Comparison of significant (P≤.001) differences in cerebrospinal fluid (CSF) 5-hydroxyindoleacetic acid (5-HIAA) concentrations between control women (CW) and women who were recovered from bulimia nervosa (BN).*

RESPONSE TO *m*-CPP

Recovered BN subjects and CW had similar prolactin and cortisol responses to *m*-CPP either calculated as net area under the curve (the difference between the response to *m*-CPP and the placebo response) (**Table 4**) or by repeated-measures ANOVA (drug × time × group for prolactin, $F_{8,464} = 0.81$, $P = .59$; for cortisol, $F_{8,432} = 1.37$, $P = .21$). Subjects had similar values for plasma β-HBA and plasma estradiol and were studied on similar days of their menstrual cycle. Plasma *m*-CPP levels were measured at 30, 60, 90, and 120 minutes after administration of *m*-CPP. Recovered BN subjects and CW showed no difference in plasma *m*-CPP levels for group ($F_{1,41} = 1.40$, $P = .24$) or time × drug interaction ($F_{3,123} = .07$, $P = .98$). When groups were stratified by presence or absence of lifetime major depression, there was no difference in net area under the curve for prolactin (844 ± 583 µg/L vs 583 ± 557 µg/L, $t_{26} = 1.12$, $P = .27$) or cortisol (21.8 ± 23.7 µmol/L vs 25.0 ± 18.1 µol/L, $t_{26} = 0.32$, $P = .75$). Hormone values were similar when the BN women were segregated by presence or absence of any Axis I psychiatric disorders or current psychopathological symptoms.

Two types of assessments of mood and behavior were conducted during the *m*-CPP study. First, subjects were assessed by trained interviewers who were blinded to group and condition (**Figure 2**). Recovered BN women (n = 27) had significantly higher mean baseline ratings of depression and obsessionality than did CW (n = 29), but similar baseline values for anxiety and disorganization. After *m*-CPP administration, recovered BN women had higher peak ratings of anxiety and disorganization compared with themselves while receiving placebo or with CW after *m*-CPP administration. Second, subjects

Table 4. Comparison Between Control Women (CW) and Women Who Recovered From Bulimia Nervosa (BN) for Hormonal Concentrations and Relevant Variables on the Days of the *m*-CPP Studies*

	CW	BN	*df*	*t*	*P*
Baseline prolactin, µg/L	8.5 ± 3.1 (30)	8.6 ± 4.1 (29)	57	0.08	.94
AUC prolactin	961 ± 998 (30)	772 ± 571 (29)	57	0.89	.38
Baseline cortisol, µmol/L	0.5 ± 0.2 (29)	0.6 ± 0.2 (26)	53	1.37	.18
AUC cortisol	21.4 ± 25.2 (29)	23.6 ± 22.0 (26)	53	0.35	.73
β-HBA, µmol/L (*m*-CPP day)	109 ± 88 (30)	89 ± 137 (29)	57	0.66	.51
β-HBA, µmol/L (placebo day)	91 ± 63 (30)	72 ± 77 (29)	57	1.04	.30
Estradiol, pmol/L (*m*-CPP day)	176.2 ± 190.8 (27)	135.8 ± 172.5 (20)	45	0.78	.44
Estradiol, pmol/L (placebo day)	143.1 ± 172.5 (27)	124.8 ± 209.2 (21)	46	0.37	.71
Day of menstrual cycle, *m*-CPP day	6 ± 3 (26)	6 ± 3 (28)	52	0.0	.96
Day of menstrual cycle, placebo day	5 ± 3 (26)	5 ± 3 (28)	52	0.92	.36

**All data are presented as mean ± SD (number of subjects) unless otherwise indicated. m-CPP indicates m-chlorophenylpiperazine; AUC, area under the curve; and β-HBA, hydroxybutyric acid.*

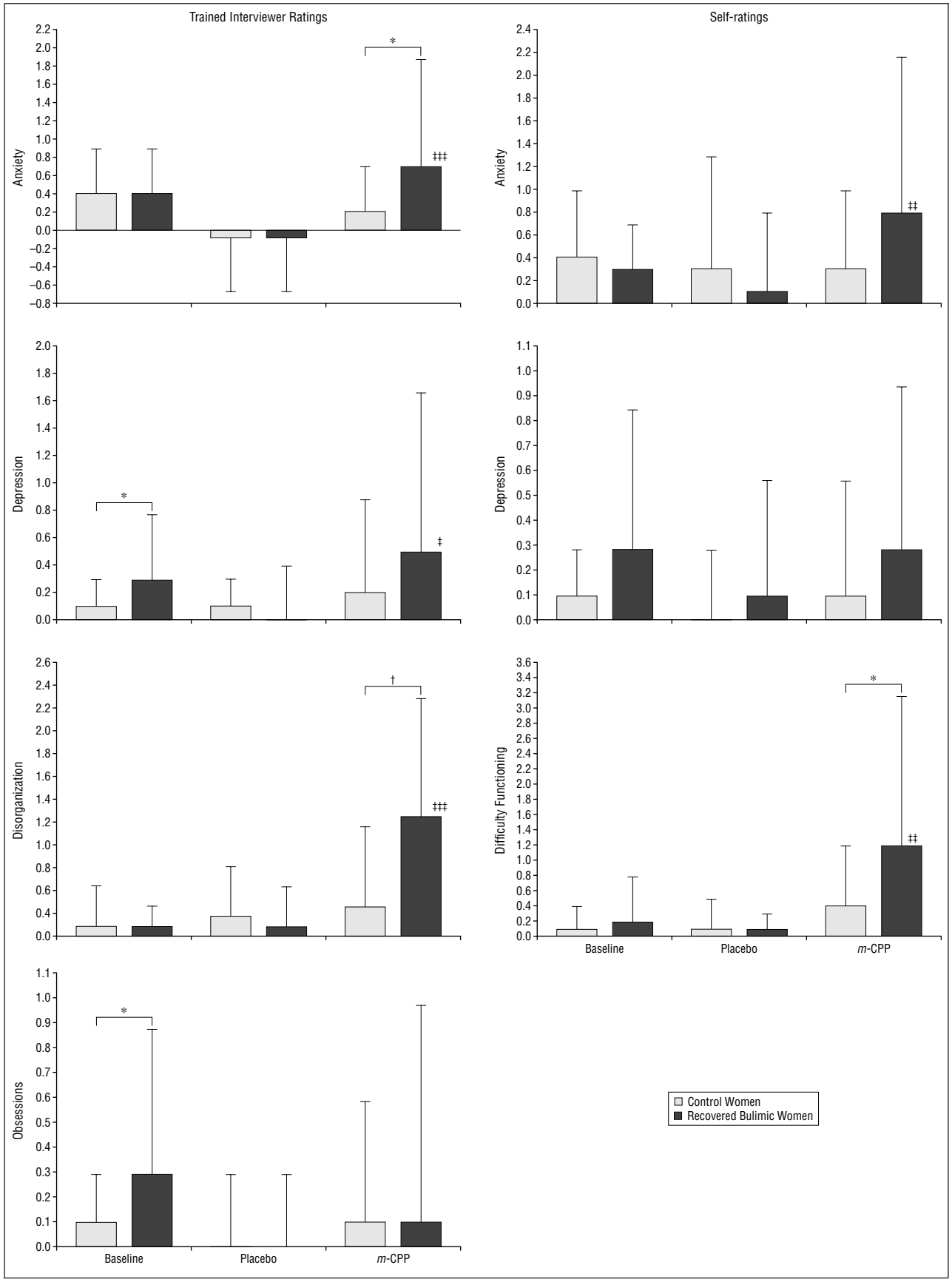

Figure 2. *Baseline and peak changes in ratings of mood and behavior during* m*-chlorophenylpiperazine (*m*-CPP) or placebo administration. Peak changes during* m*-CPP or placebo are the scores remaining after baseline values were subtracted. Between-subject comparison, group* t *test (controls vs bulimic women): asterisk indicates* P<*.05; dagger,* P<*.01. Within-subject comparison, paired* t *test (placebo vs* m*-CPP): double dagger indicates* P<*.05; section mark,* P<*.01; and parallel mark,* P<*.001.*

self-assessed their mood and behavior using the National Institutes of Mental Health Global Rating Scale (Figure 2). Recovered BN women (n = 30) and CW (n = 29) had similar mean baseline values for anxiety, depression, and difficulty functioning prior to the start of the studies. After *m*-CPP administration, recovered BN women reported that they had significantly greater anxiety and more difficulty functioning than did CW after *m*-CPP administration. No relationship was found for recovered BN women between hormonal and behavioral responses to *m*-CPP and lifetime Axis I psychiatric diagnosis or current psychiatric symptoms.

COMMENT

Recovered BN women had elevated CSF 5-HIAA concentrations, an anxious and disorganized response to *m*-CPP, and persistent dysphoric mood, obsessionality, perfectionism, and cognitive and behavioral dimensions of eating disorder symptoms. These data suggest that a disturbance of serotonin neuronal function and behavioral symptoms persist after recovery from BN. Whether altered serotonin activity is related to such behavioral symptoms or is a marker for a biological vulnerability that contributes to the pathogenesis of BN remains to be determined.

PSYCHIATRIC SYMPTOMS IN RECOVERED BN WOMEN

While 30% to 60% of people recover from BN,[42] little is known about persistent behavioral symptoms. We found, as have others, that recovered BN subjects continue to be overly concerned with body shape and weight,[43] a small proportion weigh above 120% of a matched population mean weight,[44-46] and some have depressive symptoms.[43,47] The recovered BN women in this study resembled ill BN women in terms of their lifetime rates of alcohol and substance dependence, major depression, obsessive-compulsive disorder, and generalized anxiety diagnoses.[3] This study is the first to report that recovered BN women have persistent elevations of a range of other behavioral symptoms, including perfectionism, obsessions (particularly with symmetry and exactness), and mild to moderate anxiety.

CSF 5-HIAA

Cerebrospinal fluid monoamine concentrations in recovered BN subjects are distinctly different from findings in ill BN women. Levels of CSF 5-HIAA are elevated in recovered BN women and low to normal in the ill state.[10,11] In addition, catecholamine levels, which tend to be low in the ill state, normalize after recovery.[10-12] Elevated CSF 5-HIAA concentrations after recovery could reflect a "rebound" following cessation of bulimic behaviors. However, persistent behavioral symptoms found in recovered BN women are consistent with a trait-related disturbance of serotonin activity. Moreover, family and twin studies support a role for genetic factors in BN.[48-50] Serotonin dysregulation could be a genetically determined risk factor.[51]

Could increased CSF 5-HIAA levels reflect a premorbid trait-related disturbance of serotonin neuronal function in BN women that reappears after recovery? If so, then pathological eating and/or malnutrition may explain why ill BN subjects have relatively lower CSF 5-HIAA levels.[10,11] In healthy women, dieting significantly lowers levels of plasma tryptophan, the precursor of serotonin.[52] This results in a decreased plasma ratio of tryptophan to neutral amino acids, which in turn reduces the availability of tryptophan to the brain and is thought to result in reduced brain serotonin synthesis.[41] In fact, CSF 5-HIAA values in ill BN patients are inversely related to frequency of bingeing and purging.[11] Importantly, women with AN, who have a more extreme degree of malnutrition and weight loss when ill, have reduced plasma tryptophan availability[53] and reduced CSF 5-HIAA levels[54] in comparison with the recovered AN state. Thus, malnutrition could contribute to low or normal CSF 5-HIAA values in symptomatic BN subjects. Alternatively, low estrogen values during the ill state may affect serotonin activity by effects on gene expression for serotonin receptors[55] or the serotonin transporter.[56] Nutritional factors could also contribute to low catecholamine values in symptomatic BN subjects.[10,11]

RESPONSE TO *m*-CPP

Administration of *m*-CPP was associated with increased anxiety and disorganized thinking in women who were recovered from BN but had little or no effect on depression and obsessionality. Identifying the loci in the serotonin system responsible for an anxious and disorganized response is conjectural because *m*-CPP has multiple sites of action. As Hollander et al[57] noted, *m*-CPP is predominantly serotonergic, affects multiple serotonin receptors, and has both agonist and antagonist activity, but is not exclusive to serotonin sites. Still, the *m*-CPP challenge study provides supportive evidence of an alteration of brain serotonin transmission in recovered BN women.

This and another study[58] found that recovered BN women had a normal prolactin and cortisol response to serotonin agents. In comparison, ill BN women had a blunted prolactin response to serotonin agents as well as blunting of cortisol response and decreased anxiety after *m*-CPP administration.[5-8] These data are further support for physiological differences between ill and recovered BN. Is it reasonable that recovered subjects had elevated CSF 5-HIAA values but a normal prolactin response to *m*-CPP? Prolactin and cortisol secretion contribute to fat, protein, and carbohydrate metabolism as a component in the regulatory mechanism for the disposition of metabolic fuels.[59] Thus, hormonal secretion, which may be affected by abnormal diet[52,60] or even by reduced gonadal steroids,[61] may normalize when diet and gonadal function has normalized. Moreover, anatomical differences are likely to exist beween hormonal and behavioral serotonin pathways.

STUDY LIMITATIONS

Studies of CSF neurotransmitters invariably raise the question of the physiological relevance of such measurements. Still, CSF levels have been found to reflect mono-

amine function in the brains of humans.[62,63] Factors known to affect brain serotonin activity, such as age, percent of ABW, seasonality, or gonadal steroid state, did not seem to explain elevated CSF 5-HIAA findings in this study. Recovered BN women had normal plasma levels of nutritional indices, which is presumptive evidence of a relatively normal dietary intake. It is speculative whether these findings reflect premorbid traits because of the inherent limitation of a cross-sectional design in identifying vulnerability factors compared with a longitudinal, prospective study.[64] However, the relatively low incidence of eating disorders makes a longitudinal design problematic. Thus, the use of a recovered sample is a reasonable proxy for a premorbid state.

RELATIONSHIP OF PSYCHOPATHOLOGICAL SYMPTOMS TO ALTERED SEROTONIN ACTIVITY

Many studies have found that low levels of CSF 5-HIAA are associated with impulsive and nonpremeditated aggressive behaviors,[65] which cut across traditional diagnostic boundaries. Behaviors found after recovery from BN, such as negative affect and obsessionality with symmetry, exactness, and perfectionism, tend to be opposite in character to behaviors displayed by people with low 5-HIAA levels. Importantly, recovered AN women also have increased 5-HIAA concentrations[66] and a complex of behaviors[67-69] that are similar to those of recovered BN women. These data support a hypothesis[70] that increased CSF 5-HIAA concentrations may be associated with exaggerated anticipatory overconcern with negative consequences, while the lack of such concerns may explain the impulsive, aggressive acts that are associated with low levels of CSF 5-HIAA.

A possible common serotonin vulnerability for BN and AN may seem puzzling given well-recognized differences in behavior in these disorders. However, evidence supporting a shared etiologic vulnerability includes high comorbidity of BN and AN in twin studies[49] and an aggregation of a range of eating disorders in their families.[71] Moreover, both disorders respond to serotonin-specific medications[13,14,72] and both have high levels of harm avoidance,[73-76] a personality trait hypothesized to be related to increased serotonin activity. This study raises the possibility that a disturbance of serotonin activity may create a vulnerability for the expression of a cluster of symptoms that are common to both AN and BN. Other factors that are independent of a vulnerability for the development of an eating disorder may contribute to the development of eating disorder subgroups.[71] Individuals with this disturbance of serotonin neuronal function may be specifically vulnerable to developing an eating disorder because they may discover that restricting and bingeing serves to modulate their moods. Their extremes of dietary intake affect plasma tryptophan, which in turn modulates their brain serotonin functional activity.

IMPLICATIONS

The development of an eating disorder is often attributed to the effects of our cultural environment, such as mass media, on body image. However, while all women in our society are exposed to cultural mores that value slimness, only a small percentage of women exposed to these messages develop an eating disorder. Thus, it is possible that there may be an underlying biological diathesis that places someone "at risk" for developing BN. Similar shifts in the understanding of the pathophysiology of obesity have been driven by the discovery of potentially new mechanisms of weight regulation. This study raises the possibility that there are biological vulnerabilities that contribute to the pathogenesis of BN.

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