ORIGINAL ARTICLE

Symptomatic Relapse in Bulimia Nervosa Following Acute Tryptophan Depletion

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Background: Preclinical and clinical studies suggest that lowered brain serotonin neurotransmission may contribute to the pathophysiology of bulimia nervosa (BN). The aim of our study was to test this hypothesis by examining the psychological effects of a dietary-induced impairment in serotonin activity in subjects known to be at risk for manifestation of the clinical syndrome of BN.

Methods: An 85.8 g amino acid mixture lacking the serotonin precursor tryptophan and a balanced mixture were administered to 10 clinically recovered, medication-free female subjects with a history of BN in a double-blind, crossover design. Twelve healthy female subjects with no history of psychiatric disorder were studied as a comparison group. Observer and self-rated measures of mood and eating disorder cognitions were made for the 7 hours following administration of each amino acid mixture.

Results: Compared with healthy controls, subjects with a history of BN had significant lowering of mood, increases in ratings of body image concern, and subjective loss of control of eating following the tryptophan-free mixture.

Conclusions: Our results suggest that diminished serotonin activity may trigger some of the cognitive and mood disturbances associated with BN. Our findings support suggestions that chronic depletion of plasma tryptophan may be one of the mechanisms whereby persistent dieting can lead to the development of eating disorders in vulnerable individuals.

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BULIMIA NERVOSA (BN) is an eating disorder characterized by recurrent episodes of binge eating accompanied by extreme weight control behavior and overvalued ideas concerning shape and weight.[1] Body weight is generally unremarkable.[2] There is frequently concomitant major depression.[3] The depression often seems to be secondary to the eating disorder because it generally responds to treatments that enhance control over eating[4]; however, some patients experience distinct episodes of depression prior to the onset of the eating disorder.[5]

While there is growing knowledge about the personal and social antecedents of BN,[5] its neurobiological basis is unclear. Several lines of evidence have implicated abnormalities in serotonin neurotransmission.[6,7] Animal and human studies suggest that serotonin is involved in the control of feeding, and artificially reducing serotonin function leads to impaired satiety and weight gain in animals.[8] More directly, neuroendocrine studies in acutely ill BN subjects have found blunted prolactin responses to the serotonin-releasing agent, d,l-fenfluramine hydrochloride[9] and the serotonin receptor agonist, *m*-chlorophenylpiperazine.[10,11] These findings are consistent with the proposal that BN is associated with lowered brain serotonin function. However, it is difficult to be sure that these abnormalities are causally related to the development of BN rather than a consequence of the disordered eating pattern.

One way of assessing the role of serotonin in the pathophysiology of psychiatric disorders is to study the neuropsychological effects of acutely lowering serotonin neurotransmission in subjects known to be at risk of the disorder concerned. This can be achieved using the technique of tryptophan (TRP) depletion, in which subjects ingest a mixture of amino acids that lacks the serotonin precursor, TRP. This maneuver produces a rapid lowering of plasma TRP with a consequent decrease in brain TRP and brain serotonin synthesis.[12,13]

The effects of TRP depletion are of additional interest in patients at risk of BN

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SUBJECTS AND METHODS

SUBJECT CHARACTERISTICS

Ten female subjects who had recovered from BN (index subjects) were recruited by advertisement in local newspapers. Their individual and group characteristics are summarized in **Table 1** and **Table 2**. Their psychiatric history was assessed using the Structured Clinical Interview for *DSM-III-R*.[21] All had a history of BN and all also had a history of *DSM-III-R* major depression. Five had experienced episodes of major depression distinct from their eating disorder, 5 reported histories of alcohol abuse, and 4 had histories of deliberate self-harm, but none had a history of anorexia nervosa. Their eating disorder status was evaluated using the Eating Disorder Examination interview (EDE).[22,23] None met operational diagnostic criteria for BN or any other *DSM-IV* eating disorder, and 8 had a global EDE score within 1 SD of the local community norm (community norm: mean = 0.8; SD = 0.7; range, 0-3.8; Table 2). No subject had engaged in any behaviors characteristic of BN, such as bingeing or purging, for at least 6 months before entering the study.

Twelve female controls were also recruited by advertisement in local newspapers. None had a history of BN or any other Axis 1 disorder, as assessed by the Structured Clinical Interview for *DSM-III-R*. All subjects had a global EDE score within 1 SD of the community norm (Table 2).

None of the subjects in either group was pregnant and all had been free from psychotropic medication for at least 6 months. Menstrual phase was documented by self-report and all subjects were tested in the follicular phase (days 3-11). Each subject underwent a routine physical examination and laboratory tests including hematology, biochemistry, and electrocardiography. The subjects who had recovered from BN were told that the procedure might cause a temporary reappearance of eating disorder features or depression, or both. The controls were told that the procedure might result in a temporary change in eating pattern or a lowering of mood. All the subjects gave written informed consent to the study, which was approved by the local research ethics committee.

ADMINISTRATION OF AMINO ACID MIXTURES

The subjects were tested on 2 occasions separated by at least 1 week. On one occasion they received a nutritionally balanced amino acid mixture containing TRP (BAL mixture) and on the other, the same mixture from which the TRP had been omitted (TRP-free mixture). The composition of the mixtures was based on that previously used in men[12] but, as described in other studies,[18,19,24] it was reduced by approximately 20% on the basis of the average lower weight in women, providing a weight of 85.8 g for the TRP-free mixture. All the drinks were made up in 200 mL of water flavored with blackcurrant. The subjects followed a low-protein diet (20 g/24 h) for 24 hours prior to each test day and received an identical snack of low TRP-containing foods (33.5 mg TRP total) 3.5 hours following ingestion of the mixture.

TRP DEPLETION PROCEDURE

The amino acid mixtures were administered in a double-blind, placebo-controlled, balanced-order, crossover design. On each test day, subjects attended the research unit at 8:30 AM, having fasted from midnight the night before. After baseline psychological assessments were made (see below), subjects were given the amino acid mixture. They remained in the testing room for the next 7 hours, during which they were allowed to read neutral material. The psychological measures were repeated at the

because moderate dieting can itself cause a modest degree of plasma TRP depletion,[14] and most cases of BN evolve from normal dieting.[15] This makes it possible that BN could arise in part as a consequence of dieting-induced deficits in brain serotonin function in those vulnerable to developing the disorder.[16,17]

The aim of our study was to assess the effect of TRP depletion on subjects with a history of BN who had clinically recovered. We predicted that TRP depletion would result in a temporary return of key symptoms of BN including characteristic thoughts about weight and shape, together with a subjective sense of loss of control over eating. We also expected that TRP depletion would lead to a return of depressive symptoms because in a previous study we found that TRP depletion was associated with a transient depressive relapse and characteristic depressive cognitions in subjects with a history of major depression.[18] Because TRP depletion may cause modest changes in ratings of mood[19] and in eating behavior[20] in healthy subjects, the responses of the BN subjects were compared with those of a healthy control group.

RESULTS

One control and 1 index subject did not return for their second test, which in both cases was to have been the BAL mixture. The missing data were replaced by series means. Statistically significant results obtained with this method of analysis remained significant when these 2 subjects were excluded.

PLASMA TRP MEASURES

Baseline levels of plasma total and free TRP did not differ between the index subjects and controls on either test occasion (data not shown). After ingestion of the TRP-free mixture, the mean ± SEM fall in plasma total TRP was similar in both groups (index subjects, 57.5 ± 5.3 µmol/L vs controls, 47.5 ± 6.3 µmol/L; $P = .27$). Plasma free TRP also fell equivalently in both groups (index subjects, 2.7 ± 0.38 µmol/L vs controls, 2.0 ± 0.31 µmol/L; $P = .17$). Plasma total and free TRP did not change after the BAL mixture (data not shown).

HAM-D SCORES AND EATING DISORDER COGNITIONS

The HAM-D scores were unaffected by the BAL mixture but after the TRP-free mixture they rose in the index group but not in the controls (**Figure 1**). The mean ± SEM HAM-D score difference for the index subjects was significantly greater than that for the controls (7.9 ± 1.90

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end of the 7 hours, because previous research suggests that the maximal behavioral effects of TRP depletion occur around this time,[18,20] and subjects were given a diary to complete (see below).

PSYCHOLOGICAL MEASURES

Prior to ingestion of the amino acid mixture, the 17-item Hamilton Rating Scale for Depression (HAM-D)[25] was completed and repeated 7 hours later, shortly before subjects left the laboratory. These ratings were carried out by K.A.S., who was blind as to which drink the subjects had received. The HAM-D was modified as previously described[18] by removing items (insomnia, genital symptoms, and weight loss) that could not change during the course of the test. (The HAM-D data on 4 of the index subjects have been previously reported.[18])

At the second assessment interview, the subjects were asked specifically about the presence of cognitions regarding shape, weight, and control of eating. These were rated on a 4-point scale (0 = absent, 1 = mild, 2 = moderate, 3 = severe). In addition, prior to mixture ingestion and at hourly intervals thereafter, the subjects completed unipolar 100-mm visual analog scales (VAS) designed to measure features of BN ("feeling fat," "weight concern," "urge to eat," and "fear of losing control over eating"). They also completed 3 VAS designed to assess subjective changes in mood ("sad," "happy," and "anxious"), and a VAS of "nausea," a possible adverse effect of the amino acid mixture. On leaving the laboratory, the subjects were given a diary to record whether they experienced any loss of control over eating during the next 24 hours.

BIOCHEMICAL MEASURES

Blood samples for measurement of total and free TRP were obtained immediately before administration of the mixture and 7 hours later. Plasma TRP levels were determined by high-performance liquid chromatography with amperometric detection.

DATA ANALYSIS

The HAM-D ratings were analyzed by taking the change in HAM-D score between baseline and 7 hours on each of the 2 test days. The 2 change scores were used to generate single difference scores (HAM-D difference) for the index subjects and controls. These were compared by an unpaired *t* test (2 tailed) or a 1-way analysis of variance (ANOVA) with a post hoc Fisher test of least significant difference. The degree to which the 2 amino acid mixtures triggered eating disorder–related cognitions was compared between the 2 subject groups using unpaired *t* tests (2 tailed) to examine the difference in scores at +7 hours on the 2 test days. The diary data were analyzed similarly.

Visual analog scale scores were measured as area under the curve (AUC) by the trapezoid method, with subtraction of baseline extrapolated from time 0. For each subject, the AUC after the BAL mixture was subtracted from the AUC following the TRP-free mixture to yield a measure of AUC difference. Mean baseline scores did not correlate significantly with AUC difference; however, the difference between the baseline scores on the 2 test days was a significant covariate of the AUC difference for all the VAS. This value was therefore used as a covariate in a factorial analysis of covariance. Adjusted means are reported for the AUC analyses. Changes in plasma TRP concentrations following administration of the 2 amino acid mixtures were compared with unpaired *t* tests. Correlations between variables were carried out using the Pearson product moment correlation.

vs 0.4 ± 0.67; P=.001). In a subsequent analysis, the index subjects were separated into 2 groups: those who had suffered from episodes of depression independent of their eating disorder (n=5) and those who had not (n=5) (Table 1). One-way ANOVA of the HAM-D difference between these 2 groups and the controls showed a main effect of group (F=13.1, P<.001). Post hoc Fisher tests showed that the mean HAM-D score difference (11.0 ± 2.7) in the index subjects with independent depressive episodes was significantly greater than that of the other index subjects (4.8 ± 2.7; P=.02) and the healthy controls (0.4 ± 0.7; P<.001). The difference in HAM-D change score between the index subjects with coexisting depression and the controls was also significant (P=.05). The HAM-D difference scores were significantly higher following TRP depletion in subjects with a history of self-harm or overdose (13.2 ± 0.8 vs 4.5 ± 2.0; P=.01).

Seven hours following ingestion of the mixture, 6 of the 10 index subjects reported at least mild eating disorder cognitions after the TRP-free mixture while only 1 of these subjects reported this after the BAL mixture. None of the 12 controls reported these cognitions on either test day. The difference in cognitions in the index group between the 2 test occasions was significantly greater than that of the controls (P=.008) (Table 1). Differences in eating disorder cognitions correlated significantly with difference in HAM-D scores (r=0.78, P=.04). However, mean difference in eating disorder cognitions did not differ between index subjects with a history of independent depressive episodes and those without (1.2 ± 0.37 vs 1.2 ± 0.73; P=1). There was no significant correlation between duration of recovery and HAM-D difference (r=0.32, P=.37) or difference in eating disorder cognitions (r=0.31, P=.38).

VAS MEASURES

As measured by AUC difference, the TRP-free mixture significantly increased VAS ratings of feeling fat and fear of losing control over eating in the index subjects while a trend to an effect was seen with urge to eat (**Table 3** and **Figure 2**). In addition, VAS ratings of happy were significantly lower in index cases (Table 3). To establish how far significant increases in VAS ratings relevant to BN following TRP depletion might be a consequence of subjectively lowered mood, we repeated the factorial analysis of covariance using the change in ratings of feeling happy as an additional covariate. Ratings of feeling happy were used for this purpose because TRP depletion significantly lowered these ratings in the index subjects compared with controls and because changes in VAS ratings of happy in the whole subject group correlated

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Table 1. Individual Characteristics of the Index Subjects and Their Response to Tryptophan Depletion*

Subject No./ Age, y	No. of Depressive Episodes Preceding Eating Disorder	Depressive Episodes During Eating Disorder	History of DSH or OD	Modified HAM-D Difference	Difference in Eating Cognition Scores (Maximum, 3)
1/39	>3	Yes	1 OD 1 DSH	11	1
2/33	2	No	. . .	14	2
3/22	2	No	1 OD	14	1
4/26	1	Yes	. . .	3	0
5†/25	0	Yes	. . .	0	0
6/27	0	Yes	. . .	3	0
7/29	0	Yes	2 OD 1 DSH	15	3
8/41	1	Yes	DSH	13	2
9/22	0	Yes	. . .	2	0
10/39	0	Yes	. . .	5	3

*DSH indicates deliberate self-harm; OD, overdose; HAM-D, Hamilton Rating Scale for Depression[25]; and ellipses, not applicable.
†This subject completed only the tryptophan depletion test day.

Table 2. Characteristics of Index Subjects Compared With Controls*

Characteristic	Index Subjects	Controls
Age, y	30.3 ± 7.2 (22-41)	28.2 ± 5.5 (19-37)
Body mass index, kg/m^2	24.0 ± 2.9 (19-29)	23.5 ± 2.6 (19-29)
Duration of recovery, mo	24.9 ± 16.7 (9-60)	. . .
Beck Depression Inventory score	3.7 ± 3.7 (0-10)	2.5 ± 3.2 (0-9)
Eating Disorder Examination score	1.0 ± 0.6 (0.2-2.2)	0.4 ± 0.1 (0.2-0.6)

*Data are presented as mean ± SD (range). Ellipses indicate not applicable.

significantly with changes in HAM-D score (r= –0.64, P=.001) while changes in ratings of sad did not (r=0.35, P=.11).

In the analysis of covariance for feeling fat, the change in happy rating was not a significant covariate (R= –0.19, P=.75) and the difference between index subjects and controls remained highly significant (F=8.63, P=.009) (power, 0.79). For fear of losing control of eating, the analysis of covariance showed that change in happy rating was a significant covariate (R=–0.37, P=.04). There was still a significant difference between the index subjects and controls, but the F value was reduced (F=4.82, P=.04).

DIARY RATINGS

In the 24 hours after leaving the laboratory following the TRP-free mixture, 6 of the index subjects reported subjective loss of control of eating on at least 1 occasion. None of the index subjects experienced loss of control after the BAL mixture, and none of the controls reported loss of control over eating after either mixture. The change in the ratings of the index subjects between the 2 test occasions was significantly greater than that for the controls (P=.002). None of the subjects in either group reported objective bulimic episodes (true *DSM-IV* binges as defined by the EDE). One index subject had such an episode 48 hours after the TRP-free mixture, following a sustained period of feeling out of control over her eating. Within 72 hours all the index subjects had returned to their baseline state.

COMMENT

Our results indicate that compared with a nutritionally balanced control mixture, ingestion of a TRP-free amino acid mixture by subjects with a history of BN resulted in the transient reappearance of some eating disorder symptoms, namely, feeling fat and fear of losing control over eating. There was also a trend for urges to eat to increase. These findings suggest that lowered brain serotonin function can trigger some of clinical features of BN in individuals vulnerable to the disorder.

Our index subjects also experienced significant relapses in depressive symptoms, raising the important possibility that changes in BN symptoms may be secondary to depressive relapse. In a previous investigation of women recovered from depression and without a history of BN[18] who were tested in an identical protocol to the present study, there was no difference between the controls and subjects in VAS or objective ratings of BN cognitions, despite significant depressive relapses in the latter group (K.A.S., unpublished observations, 1997). This indicates that relapse of depression in the absence of a history of BN is not itself sufficient to lead to the appearance of BN symptoms.

It is of course possible that depressive symptoms are a necessary mediator of BN symptoms following TRP depletion, but the small number of subjects studied does not allow a clear resolution of this question. On the one hand, changes in HAM-D score correlated significantly with objectively assessed eating disorder cognitions, but on the other subjective measures of feeling fat seemed relatively independent of subjective mood change. It is possible that relapses in some, but not all, aspects of BN symptoms after TRP depletion are mediated by depression. In this respect it is of interest that the greatest increases in depression scores were seen in BN subjects with an independent history of major depression, suggesting that this subgroup of subjects may be particularly psy-

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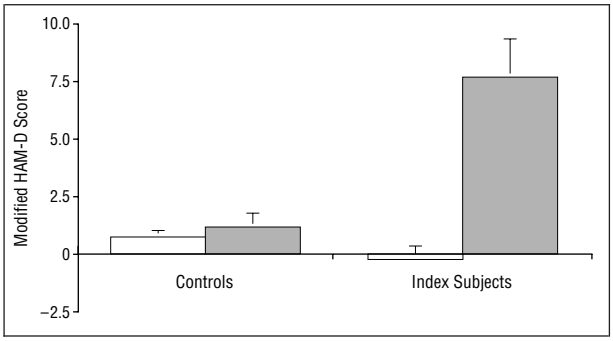

Figure 1. *Mean ± SEM change in ratings on the modified Hamilton Rating Scale for Depression (HAM-D) in controls (n = 12) and index subjects (n = 10). The HAM-D ratings carried out at baseline (open bars) were subtracted from ratings made 7 hours after mixture administration (shaded bars). The difference between balanced and tryptophan-free mixtures is significantly greater in the index subjects than in the controls (*t *= 4.0, P = .001, unpaired* t *test).*

Table 3. Difference in Areas Under the Curve for Visual Analog Ratings Between the 2 Test Days in Index Subjects and Controls*

Rating Scale	Index Subjects	Controls	F	*P*
Feeling fat	42.2 ± 24.9	−27.6 ± 11.8	10.19	.005
Weight concern	38.8 ± 24.3	7.3 ± 22.2	2.06	.17
Fear of loss of control over eating	53.5 ± 46.7	−24.3 ± 10.5	11.12	.003
Urge to eat	98.0 ± 30.9	30.3 ± 40.3	3.63	.07
Happy	−76.4 ± 37.0	−2.3 ± 29.1	5.32	.03
Sad	77.3 ± 46.1	21.4 ± 14.4	2.05	.17
Anxious	44.7 ± 47.7	4.2 ± 27.4	2.35	.14
Nausea	16.7 ± 27.3	−3.0 ± 24.9	0.28	.60

**Visual analog scale scores are presented as mean ± SEM (height in millimeters × hours).*

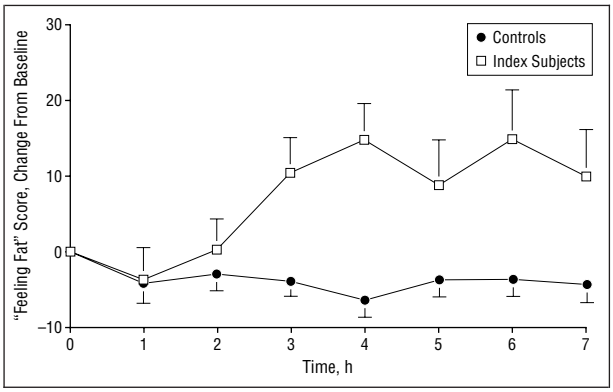

Figure 2. *Mean ± SEM change from baseline rating on the visual analog scale "feeling fat" in controls (n = 12) and index subjects (n = 10). Balanced mixture ratings have been subtracted from tryptophan-free mixture ratings to give a net value. The net area under the curve ratings of feeling fat are significantly greater in the index subjects than in controls (F = 10.19, P = .005, analysis of covariance).*

chologically vulnerable to lowered serotonin neurotransmission.

In a previous study using a 50-g TRP-free amino acid mixture, we failed to find an effect of TRP depletion on BN symptoms or mood[26] in a similar, but less recovered, group of index subjects. In the present study, however, the increased dose of neutral amino acids would be expected to lower brain TRP availability further by elevating competition at the blood-brain barrier. This may have compromised brain serotonin function sufficiently to cause the relapses seen in the index subjects.

A previous study of TRP depletion in acutely ill BN subjects found increases in subjective ratings of fear of fat and depression as well as indecision and fatigue.[27] This suggests that lowering serotonin function can increase the clinical severity of BN in actively ill subjects. Our study suggests that TRP depletion and consequent lowered brain serotonin function may also trigger symptoms of BN in subjects who are known to be vulnerable for the disorder but who are otherwise well. We do not know, however, whether TRP depletion would precipitate BN in subjects who have personal risk factors for the illness but who have not previously experienced clinical symptoms.

The vulnerability of those with a history of BN to TRP depletion assumes particular significance in the light of the effect of dieting on plasma TRP levels. In several studies we have shown that dieting in healthy women leads to a significant decline in plasma TRP which, although small compared with that caused by the TRP-free amino acid mixture, is sufficient to alter brain serotonin neurotransmission as judged by neuroendocrine challenge tests.[14,28,29] Taken together, these findings are compatible with the notion that lowered brain serotonin function may be one aspect of the neurobiological mechanism through which dieting leads to BN in individuals who, by virtue of their genetic endowment and personal experience, are at particular risk of developing the disorder.

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