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Behavioral Responses to Catecholamine Depletion in Unmedicated, Remitted Subjects with Bulimia Nervosa and Healthy Subjects

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ABSTRACT

BACKGROUND: Bulimia nervosa (BN) has been associated with dysregulation of the central catecholaminergic system. An instructive way to investigate the relationship between catecholaminergic function and psychiatric disorder has involved behavioral responses to experimental catecholamine depletion (CD). The purpose of this study was to examine a possible catecholaminergic dysfunction in the pathogenesis of bulimia nervosa.

METHODS: CD was achieved by oral administration of alpha-methyl-para-tyrosine (AMPT) in 18 remitted female subjects with BN (rBN) and 31 healthy female control subjects. The study design consisted of a randomized, double blind, placebo-controlled crossover, single-site experimental trial. The main outcome measures were bulimic symptoms assessed by the Eating Disorder Examination—Questionnaire. Measures were assessed before and 26, 30, 54, 78, 102 hours after the first AMPT or placebo administration.

RESULTS: In the experimental environment (controlled environment with a low level of food cues) rBN subjects had a greater increase in eating disorder symptoms during CD compared with healthy control subjects (condition $\times$ diagnosis interaction, $p < .05$). In the experimental environment, rBN subjects experienced fewer bulimic symptoms than in the natural environment (uncontrolled environment concerning food cues) 36 hours after the first AMPT intake (environment $\times$ diagnosis interaction, $p < .05$). Serum prolactin levels increased significantly, and to a comparable degree across groups, after AMPT administration.

CONCLUSIONS: This study suggests that rBN is associated with vulnerability for developing eating disorder symptoms in response to reduced catecholamine neurotransmission after CD. The findings support the notion of catecholaminergic dysfunction as a possible trait abnormality in BN.

Keywords: Behavioral effects, Bulimia nervosa, Catecholamine depletion, Dopamine, Norepinephrine, Pathophysiology

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Bulimia nervosa (BN) is a psychiatric disorder characterized by recurrent episodes of binge eating and inappropriate compensatory behavior to prevent weight gain. The pathophysiology of BN is poorly understood; however, there is growing evidence that neurobiological vulnerabilities contribute to the pathogenesis of BN. Bulimia nervosa has been associated with dysregulation of central catecholaminergic system especially with decreased norepinephrine neurotransmission (1,2). Dopamine (DA) has been implicated in the valuation of the rewarding properties of food (3) and in addiction (4), which are likely related to the pathogenesis of BN.

One instructive technique for assessing the relationship between catecholaminergic function and psychiatric disorders has involved the behavioral responses to catecholamine depletion (CD) achieved by oral administration of alpha-methyl-paratyrosine (AMPT) (5–7). AMPT is a competitive inhibitor of the rate-limiting enzyme in catecholamine synthesis, tyrosine hydroxylase (8), and temporarily decreases catecholamine transmission by depleting central dopamine and norepinephrine stores, evidenced by reduced concentrations of catecholamines and their metabolites in plasma, urine, and cerebrospinal fluid (9,10) and decreased occupancy of striatal DA receptors by DA (11).

Most studies using CD have been conducted in affective disorders (7,12–14). In BN, several studies using tryptophan depletion (TD) have demonstrated a relationship between diminished serotonin activity and lowered mood, irritability, body image concerns, and loss of control of eating (15–18). Thus far, no study has used CD to evaluate the roles played by norepinephrine and dopamine in the pathophysiology of BN.

Monoamine depletion may not induce psychiatric symptoms in untreated acutely ill patients (15,19), possibly because of a ceiling effect. The marked depressive responses following CD in subjects in the remitted phase of major depressive disorder who either were medicated with norepinephrine reuptake inhibiting antidepressant drugs (12–14) or were drug free (5,7) raised the possibility that manifesting specific symptoms following catecholamine depletion may constitute a neurobiological trait marker for depression (6).

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The purpose of this study was to identify a potential traitlike hypersensitivity to catecholamine depletion in BN by measuring the CD-induced behavioral responses in remitted subjects with BN (rBN). We hypothesized that CD would induce more eating disorder symptoms in rBN subjects than in healthy control subjects. Given that the risk of BN is associated with the risk of mood and anxiety disorders (20), we also predicted that CD would induce mood and anxiety symptoms in remitted subjects with BN.

METHODS AND MATERIALS

Female subjects aged 19 to 39 years who had previously met DSM-IV criteria for BN and had been in remission from BN for at least 6 months (index subjects; $n = 18$; length of illness, mean = 53.7 months; time in remission, mean = 29.2 months) or had no history of any psychiatric disorder and no major psychiatric condition in first-degree relatives (control subjects; $n = 31$) took part in this study. The screening visit included a diagnostic interview with a psychiatrist, the Structured Clinical Interview for DSM-IV (21), and a physical examination. Both study groups were recruited by advertisements in local newspapers and announcements at the University of Zurich and the Swiss Federal Institute of Technology Zurich. Exclusion criteria for participation were current Axis I psychiatric disorders, a lifetime diagnosis of psychosis, major medical or neurological illness, psychoactive medication exposure within the previous 6 months, lifetime history of substance dependence, pregnancy, suicidal ideation, and a history of suicide attempts. Remitted subjects with a history of BN (rBN) had been in remission for at least 6 months; more precisely they had no recurrent episodes of binge eating and no recurrent inappropriate compensatory behavior to prevent weight gain during the last 6 months (mean time in remission from BN = 29.2 months [SD = 23.6], range: 6–84 months) at the time of study participation.

All subjects gave written, informed consent before participation. The study protocol was approved by the ethics committee of the Canton Zurich. The sample of this study overlaps with the sample of previous published data (22,23). We used a randomized, double-blind, placebo-controlled, crossover design in which each subject underwent two identical sessions separated by at least 7 days in which they received either AMPT or placebo. Each session included 2 days at the Department of Psychiatry and Psychotherapy of the University Hospital of Zurich. On a segregated floor, a one-bed room with separate lavatory was available for all participants. Thus, participants had no contact with other hospitalized subjects. None of the rBN subjects had been hospitalized at the Department of Psychiatry and Psychotherapy before. During hospitalization, participants received regular nonvegetarian meals with standardized amounts of calories (Day 1 at 7 PM 650 kcal; day 2 at 7:30 AM 650 kcal, and at 12 PM 700 kcal).

For the subsequent 3 days after each trial, subjects were contacted daily by telephone for follow-up interviews. To avoid any risk of adverse reaction, a body weight–adjusted AMPT dose of 40 mg/kg body weight orally, to a maximum of 4 g, over 22 hours (on Day 1 at 9 AM, 12 PM, and 7 PM; on Day 2 at 7 AM) was administered. During sham depletion, subjects received inactive placebo on Day 1 at 9 AM and 12 PM and 25 mg diphenhydramine orally on Day 1 at 7 PM and on Day 2 at 7 AM because AMPT frequently induces mild sedation. To prevent the formation of crystalluria during AMPT administration, subjects were instructed to drink at least 2 L of water daily. Possible adverse reactions were assessed regularly (26, 30, 54, 78, 102 hours after the first AMPT or placebo administration) during hospitalization by a medical examination including blood pressure measurement and for subsequent 3 days after each trial within the daily telephone follow-up interview.

In each session, blood samples were drawn 26 hours after the first AMPT dose to measure serum prolactin levels.

Behavioral ratings were conducted immediately before the first AMPT or placebo intake (prechallenge) and 26, 30, 54, 78, 102 hours after the first AMPT or placebo administration.

Bulimic symptoms were assessed using the German Version of the Eating Disorder Examination—Questionnaire (EDE-Q) (24). EDE-Q is a 28-items self-report scale originated from the EDE interview (25,26) designed to measure behavioral and cognitive features of eating disorders. Respondents indicate the value of particular feelings and attitudes toward eating behavior and body concerns over a definite time frame. Six of the 28 items assess the frequencies of eating disorder-related behavior in terms of number of binge-eating episodes and compensatory behavior. These items do not contribute to scale score. An EDE-Q global score and four separate EDE-Q subscales scores for the subscales: 1, “control of eating/drive for thinness”; 2, “urge to eat/fear of binge eating”; 3, “weight concerns”; 4, “feeling fat/body dissatisfaction” can be derived from the instrument. For the purpose of this study, the EDE-Q was adapted to a shorter time frame from past 28 days used in the original version (24) to past 12 hours to measure bulimic symptoms in response to AMPT or placebo. We tested this adapted scale in a pilot study. On the basis of our clinical assessments, we came to the conclusion that it provides valid data. Additional behavioral ratings included the Montgomery-Åsberg Depression Rating Scale (MADRS), Young Mania Rating Scale (YMRS), Beck Anxiety Inventory (BAI), Snaith-Hamilton Pleasure Scale (SHAPS), and Stanford Sleepiness Scale (SSS).

Full factorial linear mixed models with restricted maximum likelihood estimation were applied to determine the effects of condition (cond), diagnosis (dx), and time on each behavioral measure. SPSS subcommand for fixed effects: /FIXED = cond dx time cond*dx cond*time dx*time cond*dx *time | SSTYPE (3). Mixed models effects were computed based on change scores for each behavioral measure. For each condition (AMPT or Placebo), and each participant change scores were calculated by subtracting the baseline (time point 0 hours) from the score of each time point (26, 30, 54, 78, and 102 hours). For all models, a random effect for the subjects was included.

Because of the crossover study design, period was handled as 2*2 (and 5, respectively) repeated measures. SPSS subcommand: /REPEATED = sequence*time♠SUBJECT(id) COVTYPE(covst), where sequence captures the real sequence of AMPT or Placebo administration (randomly assigned to each patient). For each behavioral measure an appropriate covariance structure (covst) for the residuals was chosen