

Altered Serotonin 2A Receptor Activity in Women Who Have Recovered From Bulimia Nervosa

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Objective: The authors' goal was to confirm that brain serotonin (5-HT) alterations are present in patients who have recovered from bulimia nervosa. Positron emission tomography imaging with [^{18}F]altanserin was used to characterize binding of

the 5-HT_{2A} receptor, which might contribute to altered feeding, mood, or impulse control.

Method: Nine women who had recovered from bulimia nervosa (they had no episodes of binge eating or purging, were at normal weight, and had regular menstrual cycles for more than 1 year) were compared with 12 female volunteers who had never had bulimia.

Results: The healthy volunteers, but not the women who had recovered from bulimia nervosa, had an age-related decline in 5-HT_{2A} binding. Women who had recovered from bulimia nervosa had a reduction of medial orbital frontal cortex 5-HT_{2A} binding.

Conclusions: The lack of age-related changes in 5-HT activity is further evidence of 5-HT alterations in subjects who have recovered from bulimia nervosa. In addition, vulnerabilities for eating disorders, impulse dyscontrol, and mood disturbances may involve 5-HT and frontal lobe activity.

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Bulimia nervosa usually has an onset in adolescent women who are of normal body weight. It is characterized by restrictive eating alternating with binge eating and purging and body image distortions. Mood disturbances and extremes of impulse control such as impulsive and obsessive behaviors are common (1). Physiological and pharmacological studies support the possibility that altered central nervous system serotonin (5-HT) neurotransmitter activity could contribute to a susceptibility to develop appetitive and behavioral alterations in bulimia nervosa (1). Altered 5-HT activity in bulimia nervosa could be a consequence of pathological dietary behaviors. However, people who have recovered from bulimia nervosa also have 5-HT alterations as well as behavioral symptoms consistent with a dysregulation of 5-HT neuronal pathways (2, 3), raising the possibility that such alterations are trait-related and contribute to the pathogenesis of this disorder.

To further understand 5-HT activity in women who have recovered from bulimia nervosa, we used the radioligand [^{18}F]altanserin, a specific 5-HT_{2A} receptor antagonist, and positron emission tomography (PET) imaging. The 5-HT_{2A} receptor system has been implicated in the modulation of feeding, mood, and anxiety as well as in antidepressant efficacy (4).

Method

Nine women who had previously met DSM-IV criteria for bulimia nervosa were recruited for the study. None of these women had a history of anorexia nervosa, and all had maintained greater

than 85% of average body weight since development of an eating disorder. To be considered recovered, for at least 1 year before the study subjects had to 1) maintain a weight above 90% average body weight, 2) have regular menstrual cycles, 3) have had no episodes of binge eating or purging and not engaged in restrictive eating patterns. Additionally, subjects must not have used psychoactive medication such as antidepressants and not met criteria for alcohol or drug abuse or dependence within 3 months of the study.

Twelve comparison women were recruited through local advertisements. Comparison women had no history of an eating disorder or any other psychiatric, medical, or neurological illness; they also had no first-degree relatives with an eating disorder. They had normal menstrual cycles and a normal weight range since menarche. All subjects gave written informed consent. Methods for recruitment of subjects, assessment of lifetime axis I DSM-III-R diagnoses, and current psychopathology have been described elsewhere (2).

PET imaging was done during the first 10 days of the follicular phase for all subjects. Methods for imaging procedures and data analyses have been described elsewhere (5, 6). In brief, magnetic resonance (spoiled gradient recall acquisition) images were acquired, aligned to the PET images, and used for delineation of regions of interest. PET imaging was done with the 5-HT_{2A} receptor-specific radioligand [^{18}F]altanserin on a Siemens HR+ scanner (Siemens CTI, Knoxville, Tenn.). Repeated arterial blood samples were collected for quantification of plasma radioactivity from [^{18}F]altanserin and metabolite analysis. The Logan graphical analysis (7) was applied to regional specific 5-HT_{2A} binding over 10–90 minutes after tracer injection.

Between-group comparisons were made by using two-tailed group t tests. Levene's test was used to test homogeneity of variance, and pooled or separate variance t tests were reported as appropriate. Correlations were examined with linear regression analysis. Factors that were considered possible confounds of 5-HT_{2A} receptor binding were explored with a series of two-factor

TABLE 1. Cortical Regional 5-HT_{2A} Distribution Volume Ratios for Women Who Never Had Bulimia and Women Who Had Recovered From Bulimia Nervosa^a

Region	Corresponding Brodmann's Area	Distribution Volume Ratio				Correlation Between Distribution Volume Ratio and Age				Multivariate Analysis of Slope of the Correlation Between Receptor Binding and Age	
		Never Bulimic Women (N=12)		Formerly Bulimic Women (N=9)		Never Bulimic Women (N=12)		Formerly Bulimic Women (N=9)		F (df=1, 17)	p
		Mean	SD	Mean	SD	r	p	r	p		
Prefrontal cortex	10	2.44	0.29	2.36	0.17	-0.75	0.005	-0.31	0.42	1.7	0.20
Medial orbital frontal cortex	11	2.58	0.34	2.30 ^b	0.11	-0.71	0.009	0.04	0.91	4.3	0.05
Lateral orbital frontal cortex	47	2.47	0.26	2.33 ^c	0.07	-0.77	0.003	-0.28	0.46	4.5	0.05
Subgenual anterior inferior cingulate	25	2.74	0.31	2.62	0.20	-0.78	0.003	-0.36	0.35	1.5	0.20
Anterior mesial cingulate	24	2.60	0.36	2.55	0.20	-0.71	0.01	-0.17	0.67	2.1	0.20
Anterior cingulate	32	2.49	0.38	2.39	0.12	-0.63	0.03	0.02	0.96	1.5	0.20
Medial temporal cortex (amygdalo-hippocampal complex)		1.72	0.22	1.68	0.13	-0.60	0.04	0.31	0.41	3.9	0.07
Lateral temporal cortex	21	2.58	0.26	2.47	0.12	-0.76	0.004	-0.26	0.51	2.7	0.10
Sensorimotor cortex		2.36	0.36	2.16 ^c	0.10	-0.89	<0.001	0.02	0.95	13.4	0.002
Parietal cortex		2.59	0.36	2.55	0.18	-0.85	<0.001	-0.06	0.88	6.4	0.02
Thalamus		1.32	0.07	1.29	0.05	-0.53	0.08	0.55	0.12	5.4	0.03

^a Regional distribution volume was normalized to the cerebellum (distribution volume ratio) as the specific binding measure.

^b Significant difference between groups ($p < 0.02$).

^c Nonsignificant difference between groups ($p < 0.10$).

analyses of covariance (ANCOVAs) with one grouping factor (women with recovered bulimia nervosa versus women who never had bulimia). Distribution volume ratio values are expressed as means and standard deviations.

Results

Women who had recovered from bulimia nervosa and comparison women were of similar ages (mean=30 years, SD=4, and mean=27, SD=6, respectively) ($t=1.07$, $df=19$, n.s.), current average body weight (mean=110%, SD=14%, and mean=103%, SD=6%) ($t=1.43$, $df=19$, n.s.), and low average body weight in the past (mean=95%, SD=12, and mean=97%, SD=7) ($t=0.62$, $df=19$, n.s.). Women who had recovered from bulimia nervosa had the onset of bulimia nervosa at a mean age of 16 (SD=1, range=14–18) and had been recovered from bulimia nervosa for a mean of 54 months (SD=44, range=12–156) at the time of this study.

In terms of lifetime axis I diagnoses in recovered bulimia nervosa subjects, five of the nine met criteria for major depression, four for alcohol dependence, and three for obsessive-compulsive disorder (OCD). At the time of the study no subject had a current major depressive episode or alcohol dependence.

Compared with the never-bulimic women, the women who had recovered from bulimia nervosa had significantly higher scores on the Eating Disorders Inventory (mean=52, SD=38, and mean=7, SD=5, respectively) ($t=4.18$, $df=7.1$, $p < 0.001$), trait anxiety on the Spielberger State-Trait Anxiety Inventory (mean=41, SD=16, and mean=28, SD=5) ($t=2.62$, $df=8.0$, $p < 0.05$), and depression on the Beck Depression Inventory (mean=8, SD=9, and mean=1, SD=2) ($t=2.18$, $df=7.4$, $p < 0.05$).

The women who never had bulimia had significant negative relationships between [¹⁸F]altanserin binding and age for most cortical regions (Table 1). In contrast,

there were no significant relationships between [¹⁸F]altanserin binding and age in the women who had recovered from bulimia nervosa. The two groups showed a significant difference in slopes for the thalamus, parietal cortex, and sensorimotor cortex and a nonsignificant difference for the medial and lateral orbital frontal cortex and the medial temporal cortex.

Women who had recovered from bulimia nervosa had a significantly lower level of [¹⁸F]altanserin binding for the medial orbital frontal cortex ($t=2.7$, $df=19$, $p=0.02$) than the never bulimic women and a nonsignificantly lower level for the lateral orbital frontal cortex ($t=1.7$, $df=13.8$, $p=0.09$) and sensorimotor cortex ($t=1.8$, $df=13.4$, $p=0.09$). Nonparametric Mann Whitney testing showed a nonsignificant difference for these comparisons. The fraction of unmetabolized [¹⁸F]altanserin in plasma was similar in the two groups over the scanning interval. There was no relationship between binding of any region of interest and lifetime axis I diagnoses or other behavioral measures, weight, duration of illness, or recovery from bulimia nervosa.

Discussion

These data confirm and extend the possibility that a disturbance of 5-HT neuronal activity is present after recovery from bulimia nervosa. The women who never had bulimia had an age-related decline in 5-HT_{2A} binding, but 5-HT_{2A} binding was not associated with age in the women who had recovered from bulimia nervosa. Similarly, in an earlier study (2) our group reported a significant inverse relationship between CSF 5-HIAA concentrations and age for nonbulimic women but not for women who had recovered from bulimia nervosa. The minimal overlap in subjects (N=3) between our two studies provides rela-

tively independent replication of group differences in age/serotonin relationships.

Postmortem human studies and PET imaging with 5-HT ligands show a strong inverse correlation between binding of cortical 5-HT_{2A} receptors and age (5, 8, 9). Bulimia nervosa is a largely gender-specific disorder that invariably begins within a narrow postpubertal age range. Whether 5-HT activity in bulimia nervosa is dissociated from normal age-associated changes is speculative, but the speculation raises the question of whether the 5-HT system becomes free-running and insensitive to normal developmental mechanisms.

To our knowledge, this is the first study to question whether a disturbance of 5-HT_{2A} binding occurs in the orbital frontal cortex in women who have recovered from bulimia nervosa. Many people with bulimia nervosa have unstable, dysphoric mood states and disturbances of self-control, such as impulsive and obsessive behaviors (1). Disturbances of impulsive and compulsive behaviors are associated with prefrontal cortical function in other psychiatric disorders. For example, PET studies using 2-[¹⁸F]fluoro-2-deoxy-D-glucose have found that impulsive aggression disorders have reduced activity of orbital/prefrontal and related areas (10), whereas increased activity has been found in OCD (11). Similarly, serotonergic function has been implicated in behavioral undercontrol and overcontrol, mood, and appetite regulation (12, 13). These disorders may share a common neuronal pathway involving 5-HT and the frontal cortex but have different pathophysiological loci.

Women who have recovered from bulimia nervosa have been found to have elevated CSF 5-HIAA concentrations (2), but it is not known whether this is a consequence of increased extracellular 5-HT. In vitro and animal studies (14) suggest that regionally selective 5-HT_{2A} receptors may be down-regulated in response to increased serotonergic transmission. Thus, altered regional binding of 5-HT_{2A} receptors in recovered bulimia nervosa offers additional support for the hypothesis of increased serotonergic transmission after recovery.

In terms of limitations, the Logan graphical method (7) and similar plasma metabolite concentrations in the two groups argue against group differences in radiometabolites of [¹⁸F]altanserin. A relatively large number of statistical analyses were conducted with small numbers of subjects, potentially leading to type I errors. A priori, we thought that regional 5-HT_{2A} binding differences were likely to be in the frontal cortex or related limbic regions, given the evidence implicating these regions in overcontrol and undercontrol and mood disorders. Multiple brain regions were included to demonstrate consistent group differences between 5-HT_{2A} binding and age. Moreover, the effects of laterality or age or psychiatric comorbidity cannot be adequately investigated in a small study group. These data should be considered preliminary. Replication in larger groups of subjects is needed for confirmation.

A cross-sectional design limited the ability to conclude that reduced [¹⁸F]altanserin binding is a premorbid trait contributing to the development of these disorders. Moreover, it is possible that the persistence of mild abnormal eating behaviors could have contributed to the findings.

In summary, these data add further support to the possibility that biological vulnerabilities contribute to the pathogenesis of bulimia nervosa.

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