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Reduced Density of Platelet-Binding Sites for [3H]Paroxetine in Remitted Bulimic Women

Howard Steiger*[1,2,3], Jodie Richardson[1,2], Mimi Israel[1,2,3], NMK Ng Ying Kin[2,3], Kenneth Bruce[1,2,3], Sandra Mansour[1,2] and Anne Marie Parent[1,2]

[1]Eating Disorders Program, Douglas Hospital, Montreal, Quebec, Canada; [2]Research Center, Douglas Hospital, Montreal, Quebec, Canada; [3]Psychiatry Department, McGill University, Montreal, Quebec, Canada

Findings show brain serotonin (5-hydroxytryptamine (5-HT)) activity to be altered in individuals who have had bulimia nervosa (BN), even after substantial remission of symptoms. Such findings could reflect persistent sequelae due to BN, or a vulnerability 'trait' that exists independently of active eating-disorder manifestations. We compared women with full-blown BN (BN; $n = 22$), BN in remission (BN-R; $n = 11$), and no eating or psychiatric disturbances ($n = 22$) on measures of platelet [^{3}H]paroxetine binding, eating symptoms and psychopathology. The BN-R group showed normal-range scores on eating and psychopathological symptoms, but reductions in density (B_{max}) of binding sites for paroxetine similar to those obtained in the actively ill women. Both BN groups had substantially lower B_{max} than did healthy controls. Our results corroborate other findings indicating recovered BN patients to have anomalous 5-HT functioning. While such effects could represent a lasting 'injury' to the system, reported covariations between personality traits and 5-HT indices in BN encourage us to favor the argument that some alterations of 5-HT activity (in this case, consistent with reduced transporter activity) represent a 'trait' associated with the risk of developing BN and/or associated psychopathology.
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INTRODUCTION

Active bulimia nervosa (BN) sufferers display altered serotonin (5-hydroxytryptamine (5-HT)) system functioning, as evinced by reduced platelet binding of 5-HT uptake inhibitors (Marazziti *et al*, 1988; Steiger *et al*, 2000), reduced central 5-HT transporter availability (Tauscher *et al*, 2001), blunted neuroendocrine responses to 5-HT precursors and agonists (Levitan *et al*, 1997; Steiger *et al*, 2001a, b), and decreased 5-HT metabolites in cerebrospinal fluid (Jimerson *et al*, 1992). As food restriction is known to alter central 5-HT activity in animals (Huether *et al*, 1997; Zhou *et al*, 1996) and in humans (Goodwin *et al*, 1987), abnormal 5-HT function in BN could, reasonably, be a consequence of disordered eating. In keeping with this conceptualization, two studies report neuroendocrine responses after 5-HT agonists to be normal in fully recovered bulimics (Kaye *et al*, 1998; Wolfe *et al*, 2000), as might suggest the resolution of a disturbance seen in the actively bulimic state.

*Correspondence: Dr H Steiger, Eating Disorders Program, Douglas Hospital, 6875 LaSalle Blvd, Verdun, Quebec H4H 1R3, Canada, Tel: +1 514 761 6131 ext. 2895, Fax: +1 514 888 4085,
E-mail: stehow@douglas.mcgill.ca
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In contrast, other studies in recovered BN patients indicate persistent serotonergic abnormalities—and on indices that (arguably) provide a more direct reflection than do endocrine indices of central serotonergic activity: Positron emission tomography reveals abnormally low 5-HT2a receptor activity following one or more years of abstinence from bulimic symptoms in former bulimics (Kaye *et al*, 2001) and binge-purge anorexics (Bailer *et al*, 2004). Likewise, recovered bulimics reportedly show ongoing hypersensitivity to effects of acute tryptophan depletion (Smith *et al*, 1999), and abnormally high cerebrospinal fluid 5-HT metabolites (Kaye *et al*, 1998). Kaye *et al* (2001) proposed that such findings could reflect (a) a lasting 'scar' resulting from having had BN, or (b) a pre-existing, 5-HT-mediated vulnerability 'trait'.

The present study further explored 5-HT status in women showing remission from BN, this time using platelet [^{3}H]paroxetine binding. Platelet binding of 5-HT reuptake inhibitors is believed to model aspects of central 5-HT transporter (reuptake) function (Lesch *et al*, 1993). Previous platelet-binding studies in actively bulimic women have used [^{3}H]imipramine (Marazziti *et al*, 1988) or [^{3}H]paroxetine (Steiger *et al*, 2000, 2001a, b) to show markedly reduced density (B_{max}) of binding sites—findings that are compatible with documented reduction of central transporter availability in BN (Tauscher *et al*, 2001).

METHODS

Participants

All participants in this institutional ethics board approved study provided informed consent, and were free of 5-HT active medications for at least 6 weeks. Women with BN-spectrum disorders were recruited at a specialized eating disorders (ED) program. Healthy women (with neither ED nor psychiatric manifestations) were recruited through university classes or newspaper advertisements (to approximate the student/non-student ratio among bulimics). Remitted BN patients consisted of 11 women, formerly meeting full DSM-IV (American Psychiatric Association, 1994) criteria for BN. When tested, these women had been abstinent from bingeing and purging from 3 to 60 months (mean = 17.09 ± 17.85), and all had normal menstrual function and body mass (body mass index (BMI) of 19 or more). While three of the BN-R cases were abstinent for less than 6 months, visual inspection of the data, and tests for association between duration of abstinence and density of paroxetine-binding sites (see Results, to follow), suggested no obvious effects of shorter 'duration of abstinence' on findings.

From available samples of women with active DSM-IV BN and healthy non-eating disordered women (recruited during the same time frame as were cases in remission), we selected groups of $n = 22$ each, taking care to match as closely as possible for age and BMI (kg/m^2) two actively bulimic (BN) and two healthy control (HC) individuals to each of our remitted bulimic (BN-R) cases. Mean ages for the BN, BN-R, and HC groups, respectively, were 27.77 (±3.70), 28.18 (±8.45), and 25.0 (±5.72). Mean BMIs, respectively, were 22.58 (±2.11), 22.46 (±2.55), and 21.99 (±1.48). Neither of the preceding values yielded significant group effects, according to ANOVA tests. Over the 3 months prior to testing, the mean monthly binging in the BN group was 36.71 (±30.01). Mean monthly episodes of purging, including vomiting, laxative, or diuretic misuse (computed among purgers only) was 45.54 (±49.61), and mean monthly vomiting (computed among vomiters only) was 51.99 (±47.22).

Measures

Well-validated interviews and scales, chosen for psychometric strengths and familiarity, were used to assess eating and generalized symptomatology. Given a bilingual population, French translations of scales were required. Support for the validity of French translations has been provided elsewhere (Steiger *et al*, 2000, 2001a, b).

We assessed ED symptoms using the Eating Disorders Examination (EDE: Fairburn and Cooper 1993), a structured interview evaluating criterion ED symptoms (eg, frequency of binge/purge behaviors, weight preoccupation), the Eating Disorders Inventory-2 (EDI-2: Garner, 1991), and the Eating Attitudes Test (EAT-26; Garner *et al*, 1982). To reflect nutritional status, we computed the BMI. Psychopathological characteristics were assessed using: the Barrat Impulsivity Scale (BIS, version 11: Patton *et al*, 1995), selected subscales from the Dimensional Assessment of Personality Pathology-Basic Questionnaire (DAPP-BQ; Livesley *et al*, 1992) tapping such traits as Compulsivity, Sensation Seeking, and Affective Instability, and the Centre for Epidemiological Studies Depression (CES-D) scale (Weissman *et al*, 1977). To screen for psychiatric comorbidity, we used a computerized version of the Diagnostic Interview Schedule, Version IV (DIS4: Bucholz *et al*, 1991; Robins *et al*, 1981) to guide face-to-face interviews.

Serotonin Measures

Participants were asked to refrain from coffee, cigarettes, exercise, alcohol, or other drugs on the day of testing. Detailed procedures for blood draws, processing, and [^{3}H]paroxetine-binding assays are described elsewhere (Steiger *et al*, 2000, 2001a, b).

RESULTS

Table 1 shows the mean (±SD) scores for BN, BN-R, and HC groups on indices of eating and psychopathological symptoms, and paroxetine-binding density (B_{max}) and affinity (K_d). Isolated missing values appear as variations in NS and df's in the tables. Results of one-way ANOVAs and of Newman–Keuls comparisons among groups are also shown. Group effects on EAT-26, Drive for Thinness, and Interoceptive Awareness scores indicate a progressive reduction, in a statistical sense, in these symptoms across BN, BN-R, and then HC groups. The means indicate full-blown eating symptoms in BN cases, and nonclinical-range scores in the BN-R and HC groups (Garner *et al*, 1982; Garner, 1991). On Bulimia, Interoceptive Awareness, and Body Dissatisfaction, means of BN-R and HC groups did not differ, but were both significantly lower than those in the active BN group. Significant effects obtained on the various psychopathological indices (ie, CES-D, Identity Problems, Affective Instability, Compulsivity, Restricted Expression, and Anxiousness) always showed heightened psychopathology in the BN group, relative to that in either BN-R or HC groups. The latter two groups never differed. A significant group effect on B_{max} for paroxetine binding differentiated lower density of binding sites in BN and BN-R groups from higher values obtained in HC participants, but not BN and BN-R groups. A plot of results (see Figure 1) shows the scatter of B_{max} values in BN-R participants to be much like that obtained in active BN cases, and to overlap minimally with scores in HC cases. To verify the extent to which variations in duration of abstinence from bingeing and purging might have influenced B_{max}, we computed the simple correlation between 'duration of abstinence' and B_{max} values for this group. A nonsignificant correlation was obtained ($r = 0.15$, $p > 0.50$). In addition, visual inspection of scores showed no evidence of systematically lower B_{max} in the most recently remitted cases. In a related vein, bivariate correlations between Age and BMI, on the one hand, and B_{max}, on the other, were negligible (and nonsignificant) in our BN ($r = -0.11$ and 0.07, respectively), BN-R ($r = 0.13$ and -0.13, respectively) or HC ($r = -0.11$ and 0.14, respectively) samples. Possible effects attributable to Age or BMI variations are, therefore, not indicated.

Data on lifetime history of selected Axis-I syndromes are shown in Table 2. Where empty cells exist, results are not

Table 1 Mean (±SD) Scores on Symptom Measures in BN, BN-R and HC Groups

	Active bulimic (BN)	*N*	Remitted bulimic (BN-R)	*N*	Healthy control (HC)	*N*	F (df, DF)
EAT-26	36.43 (11.88)[a]	22	12.03 (11.42)[b]	11	3.69 (3.47)[c]	22	71.54 (2,51)***
Drive for thinness	14.91 (5.45)[a]	22	7.25 (6.73)[b]	8	1.37 (3.25)[c]	19	38.25 (2,46)***
Bulimia	10.68 (5.34)[a]	22	3.25 (3.11)[b]	8	0.05 (0.23)[c]	19	41.16 (2,46)***
Interoceptive awareness	12.32 (7.94)[a]	22	5.00 (7.35)[b]	8	0.42 (0.84)[b]	19	19.64 (2,46)***
Body dissatisfaction	19.01 (6.57)[a]	22	10.88 (7.26)[b]	8	6.26 (7.08)[b]	19	17.84 (2,46)***
Barrat impulsivity	70.20 (8.34)	22	64.02 (6.11)	10	62.64 (8.52)	21	5.10 (2,50)**
CES-D	30.50 (13.35)[a]	22	11.10 (8.54)[b]	10	8.27 (7.44)[b]	22	27.49 (2,51)***
Identity problems	3.36 (0.93)[a]	22	2.16 (0.81)[b]	10	1.77 (0.73)[b]	22	21.21 (2,51)***
Affective instability	3.69 (0.78)[a]	22	2.78 (0.82)[b]	10	2.43 (0.82)[b]	22	13.90 (2,51)***
Stimulus seeking	2.82 (0.97)	22	2.32 (0.62)	10	2.54 (0.51)	22	1.72 (2,51) NS
Compulsivity	3.86 (0.92)[a]	22	3.15 (0.42)[b]	10	3.15 (0.78)[b]	22	5.29 (2,51)**
Restricted expression	3.36 (0.73)[a]	22	2.64 (0.87)[b]	10	2.16 (0.71)[b]	22	14.38 (2,51)***
Anxiousness	3.89 (0.82)[a]	22	3.06 (1.06)[b]	10	2.42 (0.92)[b]	22	14.46 (2,51)***
Paroxetine binding (B_{max})	549.05 (264.72)[a]	22	781.27 (345.56)[a]	11	1234.09 (513.7)[b]	22	16.69 (2,52)***
Paroxetine binding (K_d)	0.12 (0.08)	22	0.14 (0.15)	11	0.25 (0.39)	22	1.59 (2,52) NS

Means with different letters in their superscripts differ on Newman–Keuls tests at the 0.05 level or better.
*$p \leqslant 0.05$.
**$p \leqslant 0.01$.
***$p \leqslant 0.001$.
NS = nonsignificant.

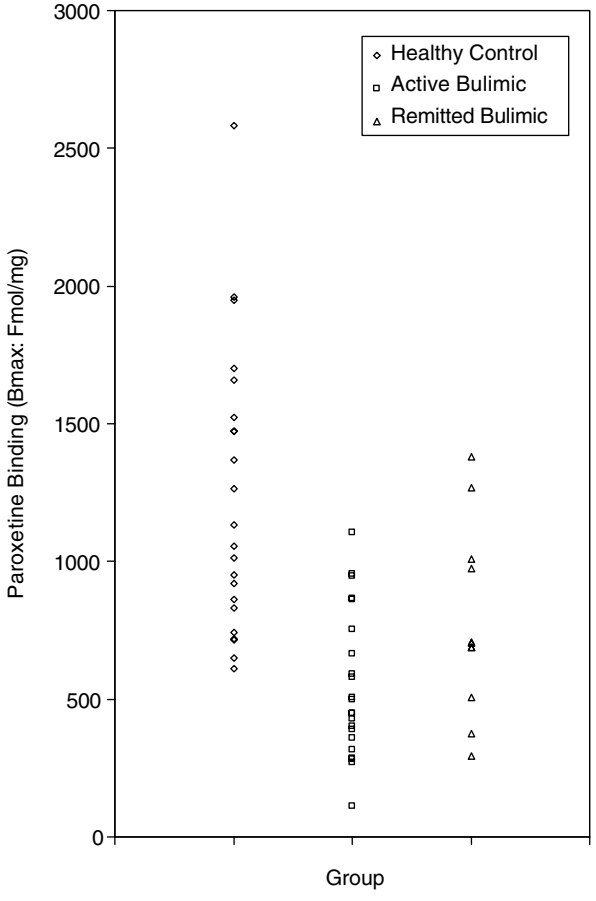

Figure 1 Scatter of values for density (B_{max}) of platelet [^{3}H]paroxetine-binding sites (fmol/mg) in BN, BN-R, and HC groups.

compared statistically. Meaningful χ^2 values could be computed for Major Depression and Post-Traumatic Stress Disorder. That for Major Depression was significant ($\chi^2_{(2)} = 29.99$, $p < 0.001$), with values indicating elevated disorder frequencies in both bulimic groups. That for Post-Traumatic Stress Disorder was also significant ($\chi^2_{(2)} = 7.61$, $p < 0.05$), results more ambiguously implying elevated symptomatology in both bulimic groups.

DISCUSSION

We find former DSM-IV bulimics 'in remission' to display markedly reduced density of platelet paroxetine-binding sites, comparable to that observed in fully active bulimics, and significantly lower than that obtained in normal eaters. This finding joins an accumulating set of results—generated using cerebrospinal fluid indices of 5-HT metabolism (Kaye *et al*, 1998), positron emission tomography of 5HT2a receptor binding (Kaye *et al*, 2001; Bailer *et al*, 2004), and behavioral measures after tryptophan depletion (Smith *et al*, 1999)—indicating abnormal 5-HT function in recovered bulimics. To these, our findings contribute evidence to suggest that a stable characteristic of individuals who have had BN (or who are BN-prone), even after substantial remission of symptoms, is low 5-HT reuptake.

Several uncertainties surround the attempt to draw causal inferences from these findings: A first ambiguity concerns the question of how fully 'recovered' were our abstinent patients. While caloric deprivation is known to affect central 5-HT function in animals (Huether *et al*, 1997; Zhou *et al*, 1996) and in humans (Goodwin *et al*, 1987), we are aware of no findings in either the animal or human

Table 2 Count (Percent) of Cases in BN, BN-R and HC Groups Meeting Criteria for Lifetime Major Psychiatric (Axis I) Disorders

	Active Bulimic (BN)		Remitted Bulimic (BN-R)		Healthy Control (HC)	
	n (%)	*N*	*n* (%)	*N*	*n* (%)	*N*
Major depression	19 (86.4%)	22	5 (50.0%)	10	2 (9.1%)	22
Obsessive-compulsive disorder	5 (22.7%)	22	0 (0%)	10	0 (0%)	22
Simple phobia	3 (13.6%)	22	0 (0%)	10	0 (0%)	22
Social phobia	11 (50%)	22	1 (10.0%)	10	2 (9.1%)	22
Agoraphobia	8 (36.4%)	22	0 (0%)	10	1 (4.5%)	22
Panic disorder	7 (31.8%)	22	2 (20.0%)	10	0 (0%)	22
Generalized anxiety disorder	5 (22.7%)	22	0 (0%)	10	0 (0%)	22
Post-traumatic stress disorder	8 (36.4%)	22	2 (20.0%)	10	1 (4.5%)	22

literature that would guide assumptions concerning the extent to which such effects may be long-lasting. Similarly, there is little guidance for decisions concerning when to consider an abstinent bulimic 'recovered', or to assume that nutritional sequelae will no longer be influencing a formerly bulimic individual's neurobiological activity. Serotonergic anomalies seen in our remitted bulimic group might, in other words, represent lasting 'injuries' or 'scars', associated with a previous period of nutritional distress.

While the preceding remains a concern, our remitted cases showed substantial freedom from eating and psychopathological symptoms, and a negligible correlation between the duration of abstinence and density of paroxetine-binding sites. At the least, this suggests that strikingly reduced paroxetine-binding density observed in our abstinent patients is unlikely to be attributable solely to residual symptomatology. Furthermore, several forms of evidence would support the concept that persistent 5-HT alterations in former bulimics might actually represent 'trait' variations, rather than eating-disorder sequelae: In various populations, traits such as impulsivity and compulsivity have been linked to altered 5-HT activity (Cloninger *et al*, 1993; Coccaro *et al*, 1996). In addition, in bulimic individuals, systematic associations have been reported between traits such as impulsivity or harm avoidance and variations on such indices, such as endocrine responses after a 5-HT agonist (Steiger *et al*, 2001a), platelet paroxetine binding (Steiger *et al*, 2001b), 5HT2a receptor activity (Bailer *et al*, 2004), and even 5-HT transporter gene variations (Steiger *et al*, 2005). All of the preceding encourage the speculation that an underlying serotonergic anomaly, existing independently of active ED symptoms, might be a risk factor for the development of both BN and associated trait pathology—and might (in turn) explain characteristic comorbidity patterns that emerge in bulimia sufferers. Speculations concerning an underlying serotonergic 'trait' ultimately require confirmation from longitudinal data reflecting individuals' premorbid status, family studies reflecting 5-HT status in first-degree relatives, and molecular-genetic studies.

Additional concerns surround the interpretation of our data: Foremost of these is that the value of the present findings rests upon the validity of inferences about central 5-HT functioning drawn from peripheral indices of 5-HT uptake. Platelet measures have obvious limitations in this regard, but there is also support for the belief that such indices provide an approximation to central 5-HT activity: (1) Platelet-binding sites display morphological and kinetic similarities to central 5-HT transporter sites (Lesch *et al*, 1993). (2) Previous demonstrations of reduced platelet-binding density for selective 5-HT reuptake inhibitors in actively bulimic women (Marazziti *et al*, 1988; Steiger *et al*, 2000, 2001b, 2005) are consistent with documented reduction of central transporter availability in BN (Tauscher *et al*, 2001). (3) Peripheral alterations in binding for selective 5-HT reuptake inhibitors correspond to response of depressive symptoms to pharmacotherapy (Freeman *et al*, 1993). (4) Paroxetine binding in platelets varies systematically with genotypic variations in the serotonin transporter gene promoter, 5HTTLPR (Steiger *et al*, 2005).

Compared to actively bulimic women, our abstinent bulimics showed relatively normal scores on various psychopathological indices (see Table 1 and 2). Evidence of normalization of psychopathological characteristics is observed in other studies in recovered bulimic patients (Kaye *et al*, 1998; Lilenfeld *et al*, 2000), and is therefore not altogether surprising. Nonetheless, a concern arises around the apparent tendency for findings on Axis-I disorders (see Table 2) to suggest that our remitted bulimics may have actually shown lesser lifetime psychopathology than did our active bulimics. If so, there is the possibility that, in selecting a group of bulimic patients who had achieved remission of BN, we may have been sampling from a fundamentally healthier subgroup. This remains a possibility. However, we note that any such tendencies would actually make our results all-the-more striking with respect to the hypothesis that there should exist ongoing reductions of 5-HT reuptake activity in abstinent patients—as this would imply that even less-disturbed bulimics had (and retained) a fundamental anomaly of the 5-HT system. The latter tendency would further disconnect the serotonergic anomaly in question from the sequelae of severe eating-disorder symptoms, and point to a possibly stable characteristic of the bulimia-prone individual.

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