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Plasma prolactin response to D-fenfluramine is blunted in bulimic patients with frequent binge episodes

P. MONTELEONE,[1] F. BRAMBILLA, F. BORTOLOTTI, C. FERRARO AND M. MAJ

From the Institute of Psychiatry, School of Medicine, University of Naples SUN, Naples, Italy

ABSTRACT

Background. Abnormalities of brain serotonin (5-HT) transmission have been implicated in the pathophysiology of bulimia nervosa (BN), but no conclusive data have yet been provided. The purpose of this study was to assess 5-HT transmission via the measurement of the prolactin (PRL) response to the specific 5-HT releasing agent D-fenfluramine (D-FEN) in both patients with BN and comparison subjects.

Methods. According to a double-blind placebo-controlled design, plasma PRL response to D-FEN was measured in 14 drug-free bulimics and 14 matched healthy controls. In both patients and controls, eating-related psychopathology, depressive and obsessive–compulsive symptoms, and aggressiveness were measured by rating scales.

Results. Baseline plasma levels of PRL and 17β-oestradiol were significantly reduced in bulimic patients, whereas basal plasma levels of cortisol did not significantly differ from healthy controls. PRL response to D-FEN was not different between patients and controls as groups, but it was significantly blunted in bulimics with high frequency bingeing ($\geqslant 2$ binge episodes per day; $N = 7$) as compared to both those with low frequency bingeing ($\leqslant 1$ binge episode per day; $N = 7$) and matched controls. A significant negative correlation emerged between the frequency of binge episodes and the hormone response to D-FEN. Moreover, although patients scored higher than healthy subjects on rating scales assessing depressive and obsessive–compulsive symptoms and aggressiveness, no significant correlation was found between these measures and the PRL response to D-FEN.

Conclusions. These results support the idea that serotonin transmission is impaired in bulimic patients with frequent binge episodes.

INTRODUCTION

Bulimia nervosa (BN) is an eating disorder of unknown aetiology. Several lines of evidence support the idea that brain serotonin (5-HT) may be implicated in its pathogenesis. Experimental data on the role of 5-HT in feeding and satiety show that, in experimental animals, the decrease in brain serotonergic function may lead to reduced satiety and increased food consumption, both of which could be linked to binge eating, a cardinal symptom of BN (Kaye *et al.* 1988; Blundell, 1991; Curzon, 1991). Conversely, fluoxetine and fluvoxamine, two selective 5-HT reuptake inhibitors, reduce the frequency of binge eating in patients with BN (Goldstein *et al.* 1995; Fichter *et al.* 1996).

Studies carried out in bulimics to assess the functional status of 5-HT transmission have provided inconsistent results. Cerebrospinal fluid (CSF) levels of 5-hydroxyindoleacetic acid (5-HIAA) have been reported to be either normal

[1] Address for correspondence: Dr Palmiero Monteleone, Institute of Psychiatry, School of Medicine, University of Naples SUN, Largo Madonna delle Grazie, 80138 Naples, Italy.

or reduced, according to the frequency of the binge episodes (Kaye *et al.* 1990; Jimerson *et al.* 1992). Platelet studies have shown either normal or increased 5-HT reuptake, decreased ^{3}[H]imipramine binding and increased 5-HT_2-mediated platelet aggregation (Goldbloom *et al.* 1988; Hallman *et al.* 1989; Marazziti *et al.* 1989; McBride *et al.* 1991; Halmi *et al.* 1993). Whole blood 5-HT levels and plasma L-tryptophan (TRP)/large neutral amino acid ratio have been found not to differ from normal controls (Lydiard *et al.* 1988; McBride *et al.* 1991). Thus, different studies have reported a decrease, an increase or no change of several neurochemical indices of 5-HT transmission in patients with BN.

Neuroendocrine investigations are now being used extensively to assess indirectly central neurotransmitter function in humans. The most widely employed neuroendocrine strategies to look at central 5-HT transmission in bulimics have involved the administration of the 5-HT precursor L-TRP (Brewerton *et al.* 1992), or the 5-HT releasing agent D,L-fenfluramine (Halmi *et al.* 1993; Jimerson *et al.* 1997), or the post-synaptic 5-HT receptor agonist meta-chlorophenylpiperazine (m-CPP) (Brewerton *et al.* 1992; Levitan *et al.* 1997). In summary, patients with BN appear to be characterized by reduced prolactin (PRL) and normal or decreased cortisol responses to these challengers. However, the probes used in those studies are not specific for the 5-HT system, because they affect also brain dopamine and norepinephrine transmission (Yatham & Steiner, 1993).

The now available dextro-rotatory isomer of fenfluramine, D-fenfluramine (D-FEN), differently from the racemic mixture of the compound, releases 5-HT from nerve terminals and inhibits its reuptake without affecting catecholaminergic transmission (Garattini *et al.* 1987). It is known that orally administered D-FEN induces a clear-cut increase of plasma PRL levels in humans, and this effect is believed to be a net index of the functional activity of the (hypothalamic) 5-HT system (Invernizzi *et al.* 1986).

In the present study, we measured the PRL response to D-FEN and placebo in a sample of drug-free non-hospitalized bulimic patients and in matched healthy subjects. Moreover, since 5-HT, in addition to playing a role in feeding behaviour, has been involved also in depression (Meltzer & Lowy, 1987), obsessionality (Katz, 1991) and aggressiveness (Fuller, 1996), all of which are common in patients with BN (Cooper & Fairburn, 1986; Pigott *et al.* 1991; Waller *et al.* 1996), we sought possible correlations between these psychopathological dimensions and the neuroendocrine response.

METHOD

Patients and controls

Twenty-eight subjects participated in the study: 14 out-patients and 14 healthy controls.

Patients met the DSM-IV criteria for BN, with no other axis I or axis II diagnosis, as ascertained by means of the Composite International Diagnostic Interview (CIDI) (World Health Organization, 1987). They were 13 females and one male, aged 18–29 years, with a duration of illness ranging from 0·5 to 10 years. All had been drug-free for more than 1 month; none had received fluoxetine treatment in the past. According to the bingeing frequency in the last month before the study, patients were subgrouped *a posteriori* on the basis of literature data (Kaye *et al.* 1990) in those with low binge frequency ($\leqslant 1$ binge episode per day; $N = 7$) and those with high binge frequency ($\geqslant 2$ binge episodes per day; $N = 7$). The frequency of the binge episodes was determined by the reported value on the specific sub-item of the Bulimic Investigation Test Edinburgh (BITE) (Henderson & Freeman, 1987). Of the 13 female patients, four were amenorrhoeic; the remaining ones had normal regular menses.

Control subjects were 13 women and one man matched to the patients on age (within 5 years). All controls were mentally healthy as assessed by the CIDI and had no positive family history of mental disorders as assessed by the Family History Research Diagnostic Criteria (Andreasen *et al.* 1977).

Both patients and healthy volunteers had normal physical examinations, normal values of routine blood and urine tests and a normal electrocardiogram. Female patients and controls who were normally menstruating were tested in the follicular phase of their menstrual cycle (day 5–10 from menses). None of the subjects was taking oral contraceptives or had a past history of alcohol or drug abuse.

After complete description of the study to the subjects, written informed consent was obtained.

Psychological ratings

Both bulimic patients and healthy subjects underwent a psychopathological assessment by means of the following instruments: (*a*) the Eating Disorder Inventory (EDI) (Garner *et al.* 1983) and the BITE (Henderson & Freeman, 1987) to assess the eating-related psychopathology; (*b*) the Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960) to measure concomitant depressive symptoms; (*c*) the Yale-Brown Obsessive–Compulsive Scale (Y-BOCS) (Goodman *et al.* 1989) to rate obsessive–compulsive symptoms after excluding food, body image and exercise-related obsessions and compulsions; (*d*) the Buss-Durkee Hostility Inventory (BDHI) (Buss & Durkee, 1957), which is a self-report questionnaire divided into eight subscales providing information on direct and indirect aggression, irritability, negativism, resentment, suspiciousness, verbal aggression and guilt.

Neuroendocrine testing

Subjects were admitted to our Clinical Investigation Unit at 8.30 a.m. They had been instructed not to take food or alcohol during the previous 12 h. Between 8.30 and 9.00 a.m. a butterfly needle was inserted into an antecubital vein and kept patent by saline solution, that was slowly infused. Fifteen and 30 min later ($T = -15$ and 0) blood samples were drawn, then 30 mg D-FEN or placebo was administered orally. The two tests were run in random order, according to a double-blind design, and were separated by at least 5 days. Further blood specimens were drawn 60, 120, 180, 240 and 300 min after placebo or drug administration. For the duration of the test, subjects rested (but did not sleep) and remained fasted except for water. The average day of the menstrual cycle for both active drug and placebo challenges was similar in the patient and control groups.

Biochemical methods

Blood was collected in tubes with lithium heparin as anticoagulant. Plasma was separated by centrifugation at 3000 rpm and stored at -20 °C until assayed for PRL, 17β-oestradiol and cortisol. Plasma PRL and 17β-estradiol levels were determined by an immunometric method (MAIA clone), using commercial kits purchased from Serono-Diagnostics (Milan, Italy). The lower detection limits of the assays were 0·4 ng/ml for PRL and 5 pg/ml for 17β-estradiol. Intra- and inter-assay coefficients of variation were 5·4% and 8·6% for PRL and 4·3% and 3·2% for 17β-oestradiol. Plasma cortisol concentrations were determined by a double-antibody RIA method, using commercial kits purchased from Serono-Diagnostics (Milan, Italy). The lower detection limit of the assay was 27 nmol/l. Intra- and inter-assay coefficients of variation were less than 5% and 8%.

Statistical methods

After tests were performed for normality of distribution and for homoscedasticity, since data resulted normally distributed, they were statistically analyzed by conventional repeated measure analysis of variance (ANOVA), *post-hoc* Tukey's test and two-tailed Student's *t* test for paired data, where appropriate. Moreover, the integrated areas under the PRL time-curves (AUC) from $T = 0$ to $T = 300$ min were calculated, and the net hormone response to D-FEN was expressed as the difference between the PRL AUC after D-FEN and the PRL AUC after placebo (ΔAUC). PRL ΔAUC values were normally distributed. The relationships of these values with subjects' clinical and demographic characteristics were evaluated by the Pearson's product-moment correlation test.

In our sample we had two male subjects (one patient and the matched control). Although the PRL response to serotonergic probes varies from women to men (McBride *et al.* 1990), the results of statistical analyses did not change with the exclusion of male data, so male and female results were pooled.

RESULTS

Clinical findings

No significant difference emerged between bulimic patients and matched controls in age, body weight (BW) and body mass index (BMI) (Table 1). Similarly, no significant difference was found between patients with high binge frequency and those with low binge frequency in the mean values of age ($23·3 \pm 4·2$ years *v.* $24·3 \pm 3·9$ years), BW ($53·5 \pm 9·6$ kg *v.* $57·0 \pm$

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Table 1. *Demographic, clinical and hormonal data of bulimic patients* (N = 14) *and matched healthy controls* (N = 14)

	Healthy subjects	Bulimic patients	*t*	*P*
Age (years)	25·0 ± 4·3	23·5 ± 3·7	1·49	0·08
Body weight (kg)	57·7 ± 9·3 (range: 46–80)	56·1 ± 7·6 (range: 46–70)	0·52	0·3
Body Mass Index (kg/m²)	21·5 ± 2·7 (range: 18·2–26·8)	22·2 ± 3·8 (range: 18–25)	1·27	0·1
Duration of the illness (years)	—	4·5 ± 3·2		
EDI total score	25·6 ± 8·1	102·3 ± 26·2	8·82	< 0·0001
BITE total score	8·3 ± 5·7	40·0 ± 9·9	8·23	< 0·0001
HDRS total score	3·0 ± 4·1	19·5 ± 8·0	5·75	< 0·0002
Y-BOCS				
Total score	0·4 ± 1·4	22·0 ± 7·7	9·62	< 0·0001
Obsession score	0·2 ± 0·6	11·2 ± 5·0	7·60	< 0·0001
Compulsion score	0·2 ± 0·8	10·7 ± 3·7	10·09	< 0·0001
BDHI total score	53·0 ± 9·4	69·1 ± 12·1	3·66	< 0·002
Baseline plasma PRL (ng/ml)	14·3 ± 6·5	10·2 ± 3·7	2·45	< 0·025
Baseline plasma cortisol (nmol/l)	283 ± 142	375 ± 167	1·33	0·1
Baseline 17β-oestradiol (pg/ml)	60·8 ± 33·9	36·4 ± 22·8	2·31	< 0·02

EDI, Eating Disorder Inventory; BITE, Bulimic Investigation Test Edinburgh; HDRS, Hamilton Depression Rating Scale; Y-BOCS, Yale-Brown Obsessive–Compulsive Scale; BDHI, Buss-Durkee Hostility Inventory; PRL, prolactin.

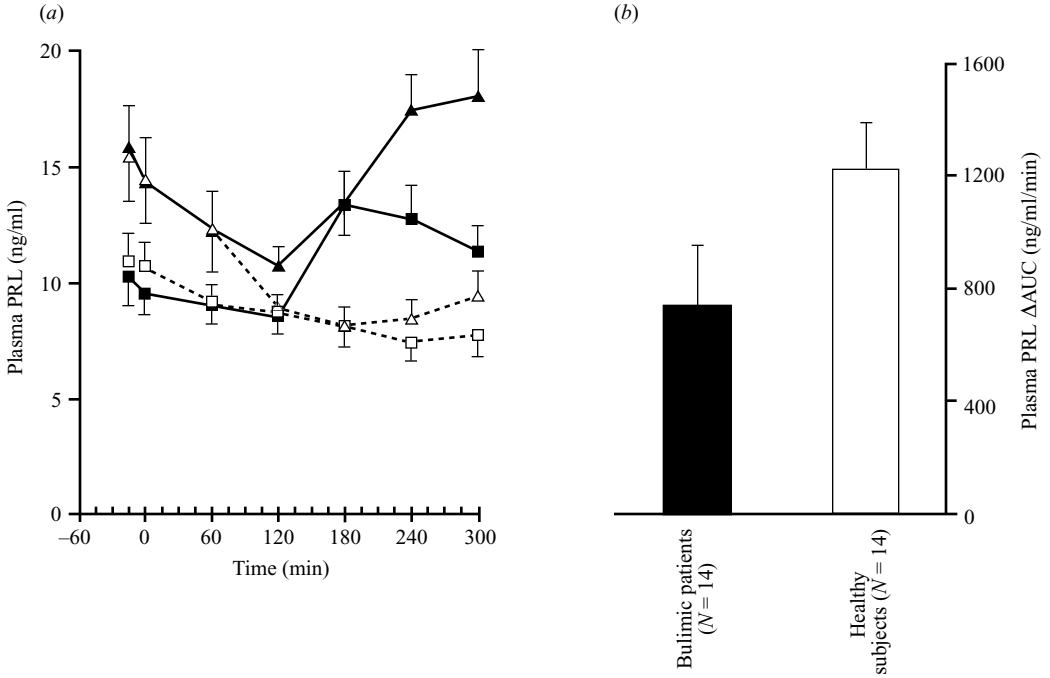

FIG. 1. (*a*) Mean (± S.E.M.) plasma prolactin response to D-fenfluramine (filled symbols and solid lines) and placebo (open symbols and dashed lines) in bulimic patients ($N = 14$) (squares) and in matched healthy controls ($N = 14$) (triangles). In both patients and controls, significant differences between D-fenfluramine and placebo were observed at T = 180, 240 and 300 min ($P < 0·001$, Tukey's test). There was no significant difference in the response between the two groups (for statistical analysis, see text). (*b*) Plasma prolactin response to D-fenfluramine expressed as the placebo-corrected area under the curve (ΔAUC).

4·3 kg) and BMI (21·6 ± 4·3 kg/m² *v.* 21·6 ± 1·8 kg/m²). The BW of the four amenorrhoeic women was above 85% of the ideal BW.

Compared with controls, bulimic patients displayed significantly higher EDI and BITE total scores, according to their abnormal eating

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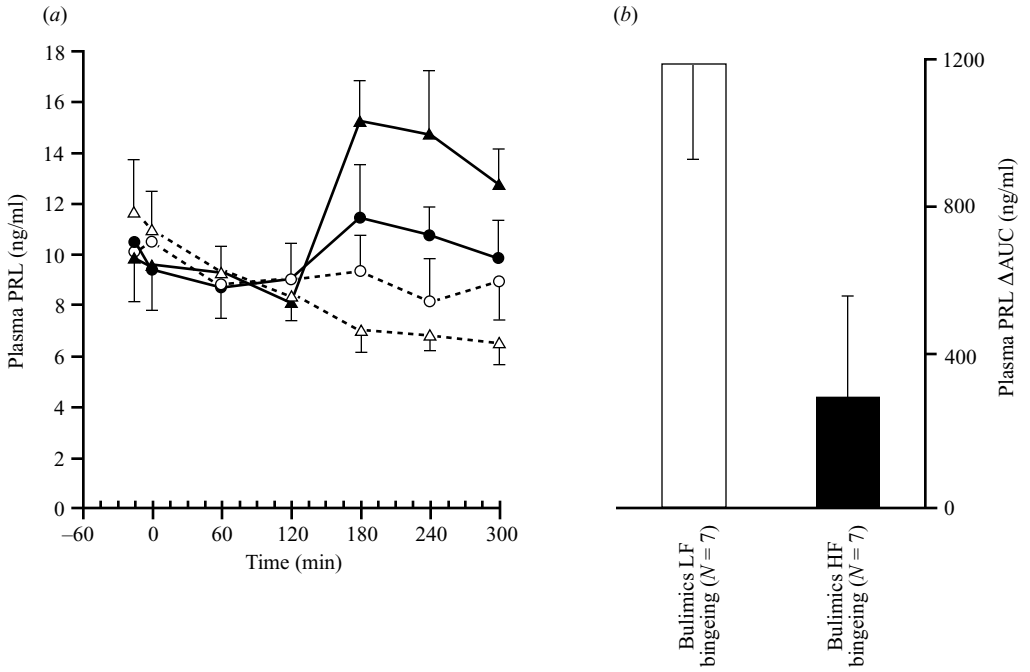

FIG. 2. (*a*) Mean (±S.E.M.) plasma prolactin response to D-fenfluramine (filled symbols and solid lines) and placebo (open symbols and dashed lines) in bulimic patients with high frequency (HF) bingeing ($N = 7$) (circles) and in bulimics with low frequency (LF) bingeing ($N = 7$) (triangles). In patients with LF bingeing, significant differences between D-fenfluramine and placebo were observed at T = 180, 240 and 300 min ($P < 0{\cdot}001$, Tukey's test). A significant difference in the response was found between patients with LF bingeing and those with HF bingeing ($F_{5,120} = 2{\cdot}509$; $P < 0{\cdot}04$). (*b*) Plasma prolactin response to D-fenfluramine expressed as the placebo-corrected area under the curve (ΔAUC). Significant difference was found between bulimics with HF bingeing and those with LF bingeing ($t = 2{\cdot}39$, df = 12, $P < 0{\cdot}02$).

habits (Table 1). Moreover, bulimics differed significantly from controls in the HDRS and Y-BOCS total scores and in the Y-BOCS obsession and compulsion scores (Table 1). With regard to aggressiveness, patients scored higher than controls on the BDHI total score (Table 1) and on the direct aggressiveness ($t = 2{\cdot}52$, df = 12, $P < 0{\cdot}02$), indirect aggressiveness ($t = 2{\cdot}18$, df = 12, $P < 0{\cdot}03$), irritability ($t = 3{\cdot}08$, df = 12, $P < 0{\cdot}005$), resentment ($t = 4{\cdot}24$, df = 12, $P < 0{\cdot}0007$), suspiciousness ($t = 2{\cdot}32$, df = 12, $P < 0{\cdot}02$) and guilt ($t = 3{\cdot}74$, df = 12, $P < 0{\cdot}002$) sub-item scores.

Neuroendocrine results

Baseline hormone levels

Hormone values before D-FEN and placebo (T = 0) were averaged together for each subject to obtain a baseline value.

In bulimic patients, the group mean plasma levels of PRL and 17β-oestradiol at baseline were significantly lower than those of the matched control group (Table 1). However, no significant difference was observed between the two groups in basal cortisol concentrations. Comparison of patient subgroups separated by their binge frequency did not reveal any significant difference in the mean values of baseline plasma PRL ($10{\cdot}1 \pm 4{\cdot}3$ ng/ml *v.* $10{\cdot}3 \pm 3{\cdot}3$ ng/ml), 17β-estradiol ($35{\cdot}1 \pm 25$ pg/ml *v.* $37{\cdot}7 \pm 22$ pg/ml) or cortisol levels (418 ± 199 nmol/l *v.* 333 ± 131 nmol/l).

In the patient group, baseline PRL, 17β-oestradiol and cortisol concentrations were not significantly correlated with frequency of binge eating or vomiting, age, BW, BMI or psychometric scores.

PRL response to D-FEN

As compared to placebo, D-FEN administration induced a clear-cut increase of plasma PRL levels in both healthy subjects and bulimic patients (Fig. 1). Three-way ANOVA with repeated measures was used to control for group

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(bulimics *v.* healthy controls), drug (D-FEN *v.* placebo) and time effects. There were significant effects for group ($F_{1,52} = 7{\cdot}252$, $P < 0{\cdot}01$) drug ($F_{1,52} = 10{\cdot}414$, $P < 0{\cdot}003$) and time ($F_{5,260} = 5{\cdot}525$, $P < 0{\cdot}0001$). Also group × time and drug × time interactions were significant ($F_{5,260} = 3{\cdot}638$, $P < 0{\cdot}004$; $F_{5,260} = 14{\cdot}68$, $P < 0{\cdot}0001$, respectively), whereas the group × drug × time interaction was not significant ($F_{5,260} = 1{\cdot}234$, NS), indicating that the timing of the PRL response to drug challenge was not significantly different between patients and healthy controls. Indeed, when the PRL response to D-FEN was evaluated as the placebo-corrected AUC, mean plasma PRL ΔAUCs did not differ between patients and controls (Fig. 1, right panel). In two bulimic women, negative values of plasma PRL ΔAUC were found. Although in both these patients blood PRL levels normally decreased from baseline value after placebo and slightly increased (one patient) or did not change (the other patient) after D-FEN, absolute values of plasma PRL at some time points after T = 0 were higher in the placebo condition, thus resulting in negative PRL ΔAUC values. This may be ascribed to the physiological day-to-day variability in plasma PRL values.

When patients were subgrouped according to their binge frequency, significant differences in plasma PRL response to D-FEN emerged between the two patient groups and between bulimics with high binge frequency and matched controls. Indeed, a blunted PRL response to D-FEN was evident in bulimics with high binge frequency, as compared to both low binge frequency patients and matched healthy subjects (Fig. 2). Three-way ANOVA with repeated measures showed a significant group × drug × time interaction in the comparison between the PRL response to D-FEN of high and low binge frequency bulimics ($F_{5,120} = 2{\cdot}509$, $P < 0{\cdot}04$) and of high binge frequency bulimics and matched controls ($F_{5,120} = 2{\cdot}354$, $P < 0{\cdot}05$). ΔPRL AUC was significantly lower in bulimics with high frequency bingeing than in both bulimics with low frequency bingeing and healthy controls (Fig. 2, right panel).

Correlations

No significant correlations emerged between PRL response to D-FEN, evaluated as ΔAUC, and baseline levels of PRL, cortisol or 17β-oestradiol in either patients or controls. Analogously, in both groups, no significant correlation was found between plasma PRL ΔAUC and age, BW or BMI. In bulimics, a significant negative correlation emerged between plasma PRL ΔAUC and the number of binge episodes per day ($r = -0{\cdot}68$, $P < 0{\cdot}005$) (Fig. 3).

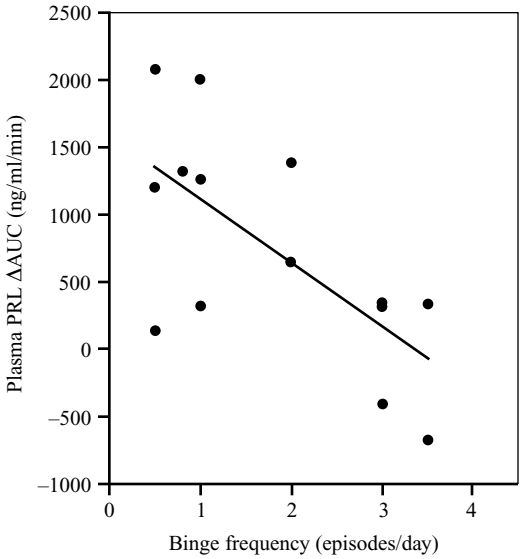

FIG. 3. Correlation between plasma prolactin response to D-fenfluramine, expressed as the placebo-corrected area under the curve (ΔAUC), and the number of binge episodes per day in bulimic patients ($r = -0{\cdot}68$, $P < 0{\cdot}005$).

When we correlated the PRL response to D-FEN with psychometric measures in bulimics, no statistically significant correlation emerged. Similar negative results were obtained in bulimics with high frequency bingeing.

DISCUSSION

In the present study, we explored, by a placebo-controlled double-blind design, the PRL response to a specific serotonergic probe in patients with BN. We found that drug-free bulimic patients had significantly lower baseline levels of PRL and 17β-oestradiol than matched controls, whereas they showed normal basal concentrations of cortisol. Moreover, as a group, bulimics did not differ from healthy subjects in the PRL response to D-FEN. When patients were subgrouped according to their history of binge frequency, those with high binge frequency

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exhibited a blunted PRL response to the 5-HT releasing agent, whereas those with low binge frequency did not.

Our finding of lower baseline PRL and 17β-oestradiol levels in bulimic patients is in line with previously reported data (Brewerton *et al.* 1992; Jimerson *et al.* 1997; Levitan *et al.* 1997). The extent to which an impaired 5-HT activity contributed to the decreased baseline PRL production in our bulimic patients is difficult to state, since experimentally-induced reduction in 5-HT activity, in the animal, did not always decrease baseline PRL levels (Tuomisto & Mannisto, 1985). Alternatively, an enhanced dopaminergic tone may account for reduced baseline PRL levels, since dopamine inhibits PRL secretion (Tuomisto & Mannisto, 1985). However, the empirical available evidence does not support the hypothesis of an increased dopaminergic tone in patients with BN (Jimerson *et al.* 1992, 1997).

The altered response to D-FEN in bulimics with high binge frequency cannot be ascribed to the controlled variables of age, weight, BMI or to the severity of psychopathological measures, since no significant difference was observed in these parameters between the two groups of patients. Furthermore, no correlation was found between these variables and the plasma PRL ΔAUC.

Previous neuroendocrine studies have found that 5-HT-mediated endocrine responses are inversely related to cortisol plasma levels (Dinan, 1994). Bulimics with high frequency bingeing exhibited higher baseline plasma concentrations of cortisol than patients with low frequency bingeing, although this difference was not statistically significant. Anyway, no significant correlation was found between baseline plasma cortisol levels and the PRL response to D-FEN. Therefore, it seems unlikely that the blunted neuroendocrine response in high frequency bingeing bulimics is to be ascribed to a negative influence of their plasma cortisol concentrations. Analogously, since ovarian oestrogens are known to facilitate the PRL response to D-FEN (O'Keane *et al.* 1991), one could speculate that the reduced plasma concentrations of 17β-oestradiol were responsible for the blunted PRL response to the 5-HT releasing agent in bulimics with high binge frequency. However, this does not seem to be the case because: (*i*) no correlation was found in our subjects between plasma levels of 17β-oestradiol and plasma PRL ΔAUC; and (*ii*) reduced baseline levels of 17β-oestradiol were found also in bulimics with low binge frequency, who had a normal PRL response to D-FEN.

Our data support the idea that serotonergic transmission is impaired in patients with severe bulimia. According to this hypothesis, Brewerton *et al.* (1992) showed a trend for a negative correlation between the PRL response to m-CPP and the frequency of binge eating in bulimic inpatients, while Jimerson *et al.* (1997) reported a significant inverse correlation between the frequency of the binge episodes and the PRL response to D,L-fenfluramine in drug-free bulimic out-patients. In addition, reduced levels of 5-HIAA have been found in the CSF of bulimics who binged more than 14 times a week, but not in those who had a lower binge frequency (Kaye *et al.* 1990; Jimerson *et al.* 1992). Whether bulimics with high binge frequency represent a neurochemically distinct subgroup with respect to those with low binge frequency, or merely patients with a higher degree of serotonergic dysfunction, cannot be stated at this point.

Since D-FEN is a 5-HT releasing agent, a blunted hormonal response to this probe is indicative of an overall reduction of 5-HT transmission, without differentiating between the pre-synaptic or the post-synaptic site of this dysfunction. Brewerton *et al.* (1992) and Levitan *et al.* (1997) reported a reduced PRL response to m-CPP in bulimic patients, which suggests decreased sensitivity of post-synaptic 5-HT receptors in BN. However, consistent with a deficit in pre-synaptic 5-HT release, reduced levels of 5-HIAA have been found in the CSF of bulimics with high frequency bingeing (Jimerson *et al.* 1992). To reconcile these observations, Jimerson *et al.* (1992) proposed that in bulimic patients a reduced pre-synaptic release of 5-HT does not induce a compensatory increase in post-synaptic 5-HT receptor sensitivity, as it would be expected, because during the recurrent binge episodes 5-HT synapses are temporally flooded with the neurotransmitter, resulting in persisting down-regulation of post-synaptic receptors. Therefore, the blunted PRL response to D-FEN in our patients with severe bulimia may be tentatively ascribed to both pre-synaptic and post-synaptic 5-HT dysfunction.

In our study, bulimic patients, besides the eating-related psychopathology, also showed the coexistence of depressive and obsessive–compulsive symptoms and a significant degree of aggressiveness. These findings are in line with those previously reported (Cooper & Fairburn, 1986; Pigott *et al*. 1991; Waller *et al*. 1996). In addition, we could not find any correlation between depressive and obsessive–compulsive symptoms or the measures of aggressiveness and the PRL response to D-FEN in our subjects. In line with these results, Brewerton *et al*. (1992) did not report any correlation between HDRS total score and the PRL response to both m-CPP and L-TRP in bulimic subjects, while Jimerson *et al*. (1997) could not find any relationship between PRL response to D,L-fenfluramine and Eating Attitude Test, HDRS and State-Trait Anxiety Inventory scores in bulimic out-patients. On the contrary, Waller *et al*. (1996) found a negative correlation between the resentment sub-item score of the BDHI and hormonal responses to ipsapirone, a 5-HT_{1A} receptor agonist, in six women with BN. In these patients, however, hormonal responses to the serotonergic probe did not differ from matched healthy controls.

To our knowledge, no study tried to correlate a serotonergic measure with the degree of obsessions and compulsions in bulimic patients. Our finding of a lack of correlation between the PRL response to D-FEN and the Y-BOCS scores in bulimics is worth of mention, because it diverges from what observed in patients with obsessive–compulsive disorder (OCD), in whom the neuroendocrine response was inversely related to the severity of obsessive–compulsive symptoms (Monteleone *et al*. 1997).

Some limitations of our study need to be discussed. First of all, subgrouping patients on the basis of the reported personal history of binge frequency may be misleading. Furthermore, this differentiation resulted in two relatively small groups of patients ($N = 7$) which may lead to a type II statistical error. Therefore, present results must be regarded as preliminary and need to be confirmed in larger studies. A further problem is the fact that we did not measure plasma levels of D-FEN and of its major metabolite, D-norfenfluramine. Therefore, even if no correlation has been found in healthy humans between plasma levels of these serotonergic probes and hormone responses (Gorad *et al*. 1993), we cannot exclude that pharmacokinetic differences between healthy subjects and bulimic patients may be responsible for the observed inter-group differences in the hormonal responses.

In conclusion, bulimic patients with frequent binge episodes exhibit a blunted PRL response to the specific serotonergic probe D-FEN. This alteration is not related to concomitant depressive and obsessive–compulsive symptoms or to aggressiveness. Whether such patients represent a neurochemically distinct subgroup of bulimics or merely subjects with a higher degree of serotonergic dysfunction needs to be assessed in future studies.

REFERENCES

Andreasen, N. C., Endicott, J., Spitzer, R. L. & Winokur, G. (1977). The family history method using diagnostic criteria: reliability and validity. *Archives of General Psychiatry* **34**, 1229–1235.

Blundell, J. E. (1991). Pharmacological approaches to appetite suppression. *Trends in Pharmacological Sciences* **12**, 147–157.

Brewerton, T. D., Mueller, E. A., Lesem, M. D.,Brandt, H. A., Quearry, B., George, D. T., Murphy, D. L. & Jimerson, D. C. (1992). Neuroendocrine responses to m-chlorophenylpiperazine and L-tryptophan in bulimia. *Archives of General Psychiatry* **49**, 852–861.

Buss, A. H. & Durkee, A. (1957). An inventory for assessing different kinds of hostility. *Journal of Consultation Psychology* **21**, 343–349.

Cooper, P. J. & Fairburn, C. G. (1986). The depressive symptoms of bulimia nervosa. *British Journal of Psychiatry* **148**, 268–274.

Curzon, G. (1991). 5-hydroxytryptamine in the control of feeding and its possible implications for appetite disturbance. In *5-hydroxytryptamine in Psychiatry: A Spectrum of Ideas* (ed. A. Sandler, A. Coppen and S. Harnett), pp. 279–302. Oxford University Press: Oxford.

Dinan, T. G. (1994). Glucocorticoids and the genesis of depressive illness. *British Journal of Psychiatry* **164**, 365–372.

Fichter, M. M., Kruger, R., Rief, W., Holland, R. & Dohne, J. (1996). Fluvoxamine in prevention of relapse in bulimia nervosa: effects on eating-specific psychopathology. *Journal of Clinical Psychopharmacology* **16**, 9–18.

Fuller, R. W. (1996). The influence of fluoxetine on aggressive behavior. *Neuropsychopharmacology* **14**, 77–81.

Garattini, S., Mennini, T. & Samanin, R. (1987). From fenfluramine racemate to D-fenfluramine: specificity and potency of the effects on the serotonergic system and food intake. *Annals of the New York Academy of Sciences* **199**, 156–166.

Garner, D. L., Olmstead, M. P. & Polivy, J. (1983). Development and validation of a multidimensional eating disorders inventory for anorexia nervosa and bulimia. *International Journal of Eating Disorders* **2**, 15–35.

Goldbloom, D. S., Hicks, L. K. & Garfinkel, P. E. (1988). Platelet serotonin uptake in bulimia nervosa. *Biological Psychiatry* **28**, 644–647.

Goldstein, D. J., Wilson, M. G., Thompson, V. L., Potvin, J. H. & Rampey, A. H. (1995). Long-term fluoxetine treatment of bulimia nervosa. *British Journal of Psychiatry* **166**, 660–666.

Goodman, W. K., Price, L. H., Rasmussen, S. A., Mazure, C., Fkeischmann, R. L., Hill, C. L., Heninger, G. R. & Charney, D. S. (1989). The Yale-Brown Obsessive–Compulsive Scale

(YBOCS): I. Development, use and reliability. *Archives of General Psychiatry* **46**, 1006–1011.

Gorad, D. A., Taylor, T. M., Medbak, S. H., Perry, L. A., Libby, G. W. & Farthing, M. J. G. (1993). Plasma prolactin, adrenocorticotrophic hormone and cortisol after administration of D-fenfluramine or placebo to healthy subjects. *International Clinical Psychopharmacology* **8**, 123–128.

Hallman, J., Sakurai, E. & Oreland, L. (1989). Blood platelet monoamine oxidase activity, serotonin uptake and release rates in anorexia and bulimia patients and in healthy controls. *Acta Psychiatrica Scandinavica* **81**, 73–77.

Halmi, K. A., McBride, P. A. & Sunday, S. R. (1993). Serotonin responsivity and hunger and satiety in eating disorders. In *Primary and Secondary Eating Disorders: A Psychoneuroendocrine and Metabolic Approach* (ed. E. Ferrari, F. Brambilla and S. B. Solerte), pp. 123–131. Pergamon Press: New York.

Hamilton, M. (1960). A rating scale for depression. *Journal of Neurology, Neurosurgery and Psychiatry* **23**, 56–62.

Henderson, M. & Freeman, C. P. L. (1987). A self-rating scale for bulimia: the BITE. *British Journal of Psychiatry* **150**, 18–24.

Invernizzi, R., Berettera, G., Garattini, S. & Samanin, R. (1986). D- and L-isomers of fenfluramine differ markedly in their interaction with brain serotonin and catecholamines in the rat. *European Journal of Pharmacology* **120**, 9–15.

Jimerson, D. C., Lesem, M. D., Kay, W. H. & Brewerton, T. D. (1992). Low serotonin and dopamine metabolite concentrations in cerebrospinal fluid from bulimic patients with frequent binge episodes. *Archives of General Psychiatry* **49**, 132–138.

Jimerson, D. C., Wolfe, B. E., Metzger, E. D., Finkelstein, D. M., Cooper, T. B. & Levine, J. M. (1997). Decreased serotonin function in bulimia nervosa. *Archives of General Psychiatry* **54**, 529–534.

Katz, R. J. (1991). Neurobiology of obsessive–compulsive disorder – a serotonergic basis of a Freudian depression. *Neurosciences and Biobehavioral Review* **15**, 375–381.

Kaye, W. H., Gwirstman, H. E., Brewerton, T. D. & Wurtman, R. J. (1988). Bingeing behavior and plasma amino acids: a possible involvement of brain serotonin in bulimia nervosa. *Psychiatry Research* **23**, 31–43.

Kaye, W. H., Ballenger, J. C., Lydiard, L. B., Stuart, G. W., Laraia, M. T., O'Neil, P., Fossey, M. D., Stevens, V., Lesser, S. & Hsu, G. (1990). CSF monoamine levels in normal-weight bulimia: evidence for abnormal noradrenergic activity. *American Journal of Psychiatry* **147**, 225–229.

Levitan, R. D., Kaplan, A. S., Joffe, R. T., Levitt, A. J. & Brown, G. M. (1997). Hormonal and subjective responses to intravenous meta-chlorophenylpiperazine in bulimia nervosa. *Archives of General Psychiatry* **54**, 521–527.

Lydiard, R. B., Brady, K. T., O'Neil, P. M., Schlesier-Carter, B., Hamilton, S., Rogers, Q. & Ballenger, J. C. (1988). Precursor amino acid concentrations in normal weight bulimics and normal controls. *Progress in Neuropsychopharmacology and Biological Psychiatry* **12**, 893–898.

McBride, P. A., Tierney, H., DeMeo, M., Chen, J.-S. & Mann, J. J. (1990). Effects of age and gender on CNS serotonergic responsivity in normal adults. *Biological Psychiatry* **27**, 1143–1155.

McBride, P. A., Anderson, G. M., Khait, V. D., Sunday, S. R. & Halmi, C. A. (1991). Serotonergic responsivity in eating disorders. *Psychopharmacology Bulletin* **27**, 365–372.

Marazziti, D., Macchi, E., Rotondo, A., Placidi, G. F. & Cassano, G. B. (1989). Involvement of serotonin system in bulimia. *Life Sciences* **43**, 2123–2126.

Meltzer, H. Y. & Lowy, M. T. (1987). The serotonin hypothesis of depression. In *Psychopharmacology. The Third Generation of Progress* (ed. H. Y. Meltzer), pp. 279–302. Raven Press: New York.

Monteleone, P., Catapano, F., Di Martino, S., Ferraro, C. & Maj, M. (1997). Prolactin response to D-fenfluramine in obsessive–compulsive patients, and outcome of fluvoxamine treatment. *British Journal of Psychiatry* **170**, 554–557.

O'Keane, V., O'Hanlon, M., Webb, M. & Dinan, T. G. (1991). D-Fenfluramine/prolactin response throughout the menstrual cycle: evidence for an oestrogen-induced alteration. *Clinical Endocrinology* **34**, 289–292.

Pigott, T. A., Altemus, M., Rubenstein, C. S., Hill, J. L., Bihari, K., L'Hereux, F., Bernstein, S. & Murphy, D. L. (1991). Symptoms of eating disorders in patients with obsessive–compulsive disorder. *American Journal of Psychiatry* **148**, 1552–1557.

Tuomisto, J. & Mannisto, P. (1985). Neurotransmitter regulation of anterior pituitary hormones. *Pharmacological Review* **73**, 249–332.

Waller, D. A., Sheinberg, A. L., Gullion, C., Moeller, F. G., Cannon, D. S., Petty, F., Hardy, D. W., Orsulak, P. & Rush, A. J. (1996). Impulsivity and neuroendocrine response to buspirone in bulimia nervosa. *Biological Psychiatry* **39**, 371–374.

World Health Organization (1987). *Composite International Diagnostic Interview*. WHO: Geneva.

Yatham, L. M. & Steiner, M. (1993). Neuroendocrine probes of serotonergic function: a critical review. *Life Sciences* **53**, 447–463.