Brain 5-HT function in obsessive–compulsive disorder

Prolactin responses to d-fenfluramine

N. A. FINEBERG, A. ROBERTS, S. A. MONTGOMERY and P. J. COWEN

Background Drugs that potentiate brain serotonin (5-HT) neurotransmission are effective in the treatment of obsessive–compulsive disorder (OCD), but it is unclear whether disturbances in brain 5-HT function play a role in the pathophysiology of OCD.

Method We studied the prolactin response to the selective 5-HT releasing agent d-fenfluramine in 14 non-depressed, drug-free OCD patients, and 14 healthy controls matched for age and gender.

Results The prolactin response to d-fenfluramine was significantly increased in OCD patients compared with controls.

Conclusions The disparate results of studies of 5-HT neuroendocrine function in OCD make it unlikely that disturbances of brain 5-HT function play a central role in the pathophysiology of OCD. Increased brain 5-HT neurotransmission in non-depressed OCD subjects may represent an adaptive neurobehavioural mechanism which can be amplified to therapeutic advantage by treatment with 5-HT potentiating drugs.

It is well established that drugs that produce potent blockade of serotonin (5-HT) reuptake, such as clomipramine and selective serotonin reuptake inhibitors (SSRIs), have efficacy, albeit limited, in the treatment of obsessive–compulsive disorder (OCD) (Piccinelli *et al*, 1995). This raises the possibility that abnormalities in brain 5-HT function may play a pathophysiological role in OCD. Neuroendocrine challenge tests provide one way of assessing 5-HT function in the human brain, but the findings in OCD patients have been contradictory, with normal, decreased and increased 5-HT-mediated responses reported (Hewlett *et al*, 1992; Hollander *et al*, 1992; Lucey *et al*, 1992; Fineberg *et al*, 1994; Lopez-Ibor *et al*, 1994). 5-HT neuroendocrine responses in OCD patients may be confounded by the presence of major depression and previous drug treatment (see Cowen, 1993). The aim of the present study was to assess prolactin responses to the selective 5-HT releasing agent, d-fenfluramine, in non-depressed, untreated OCD patients.

METHOD

Subjects

We recruited 14 patients (7 men, 7 women) with a mean age of 39.9 years (range 23–52 years). Ten were recruited from general practice while the remaining four were referrals from other psychiatric teams. On the basis of a standard clinical interview, all met DSM–III–R criteria for OCD (American Psychiatric Association, 1987). None of the patients met DSM–III–R criteria for any other axis I disorder, including major depression. They were drug-free for a minimum period of ten weeks, and six were drug-naïve. Two had failed to respond to previous trials of SSRIs. Fourteen healthy controls were matched for age and gender with the patients (mean age 37.8 years, range 26–50 years). The controls had no personal history of psychiatric disorder and were medication-free for at least 12 weeks. Female subjects were all tested in the early follicular phase of the menstrual cycle. Subjects gave informed consent to the study, which was approved by the local ethics committees.

Neuroendocrine testing

Subjects were tested after an overnight fast. At approximately 0900 hours an indwelling venous cannula was inserted and maintained with heparinised saline. Following a 30-minute baseline blood sampling period, d-fenfluramine (30 mg orally) was administered and blood samples taken at 30-minute intervals for the following 240 minutes for estimation of plasma prolactin. Additional samples were taken at 60-minute intervals for measurement of plasma d-fenfluramine and its major metabolite, d-norfenfluramine.

Biochemical methods

Plasma was separated by centrifugation and stored at −30°C. Plasma prolactin and cortisol were determined by standard immunoradiometric assays (reagents provided by Netria, London). The inter- and intra-assay coefficients of variation over the ranges encompassed by the standard curve were 4.8 and 2.4% for prolactin, and 4.1 and 2.6% for cortisol respectively. D-fenfluramine and d-norfenfluramine were assayed by a modified gas liquid chromatographic technique with a nitrogen/phosphorus detector. The inter- and intra-assay coefficients of variation for d-fenfluramine were 6.9 and 6.1%, and for d-norfenfluramine 16.6 and 6.1%.

Statistics

The prolactin data were plotted against time and analysed as a two-way repeated measures analysis of variance (ANOVA). The main between-subject factors were diagnosis (patient *v.* control) and gender. Time was treated as a within-subject factor. Baseline prolactin (at time 0) and plasma levels of d-fenfluramine and d-norfenfluramine (measured as the area under the curve; AUC) were added as covariates. Significant diagnosis by time interactions were tested with *post hoc* unpaired *t*-tests (two-tailed). The prolactin response to d-fenfluramine was also measured as AUC using the trapezoid method, with subtraction of 'basal' prolactin secretion extrapolated from +60 minutes. The reason for using the +60-minute time point as the baseline is that placebo-controlled studies have shown that

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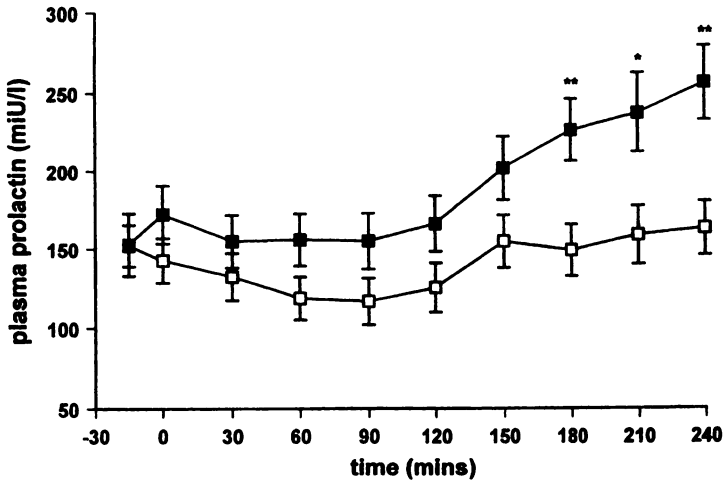

Fig. 1 Mean ± SEM plasma prolactin in 14 patients with OCD and 14 matched healthy controls before and following administration of d-fenfluramine (30 mg at time 0). Plasma prolactin levels are significantly higher in the patients (F=5.14; P=0.002). *P < 0.05; **P < 0.01 (unpaired t-test). ■, OCD patients; □, controls.

administration of d-fenfluramine (30 mg orally) does not increase plasma prolactin compared with placebo until after this time (Park & Cowen, 1995). The AUC prolactin responses of patients and controls were compared by a factorial ANOVA with diagnosis and gender as factors and plasma d-fenfluramine and d-norfenfluramine levels as covariates. Correlations were carried out with Pearson's product.

RESULTS

The d-fenfluramine was well tolerated by both patients and controls. The d-fenfluramine and d-norfenfluramine levels of one of the patients were not available because of technical difficulties. Plasma prolactin levels in the patients with OCD were significantly higher than those of controls following d-fenfluramine administration (Fig. 1). The repeated measures ANOVA of the prolactin data, with baseline prolactin and d-fenfluramine and d-norfenfluramine levels as covariates, showed significant main effects of diagnosis (F=8.36; d.f.=1,20; P=0.009) and time (F=12.64; d.f.=8,184; P<0.001). There was also a significant diagnosis by time interaction (F=3.36; d.f.=8,184; P=0.001). There were no significant main or interactive effects of gender (all P values >0.2). Repeating the ANOVA without d-fenfluramine and d-norfenfluramine as covariates enabled all 14 patients to be entered in the analysis. This ANOVA also showed a significant main effect of diagnosis (F=5.14; d.f.=1,24; P=0.033) and a diagnosis by time interaction (F=3.12; d.f.=9,216; P=0.002).

The factorial ANOVA of the AUC prolactin data showed a significant effect of diagnosis (F=7.74; d.f.=1,21; P=0.011). Adjusted mean AUCs were 156.5 *v.* 42.2 *miU* × *h/l* for patients and controls respectively. Mean ± standard error of the mean (SEM) levels of d-fenfluramine and d-norfenfluramine tended to be lower in patients than in controls (d-fenfluramine: 37.0 ± 5.4 *v.* 65.7 ± 12.6 ng × h/ml; P=0.058; and d-norfenfluramine: 7.1 ± 2.2 *v.* 12.0 ± 3.1 ng × h/ml; P=0.23, unpaired t-test). There were significant correlations in the subject group considered together between the prolactin AUC and that of d-fenfluramine (r=0.44; P=0.023) and d-norfenfluramine (r=0.48; P=0.023). Baseline cortisol levels (at time 0) did not differ between patients and controls (18.2 ± 2.2 *v.* 20.7 ± 2.2; P=0.44).

DISCUSSION

5-HT neuroendocrine function in OCD

While there is some evidence from work with L-tryptophan and clomipramine that 5-HT-mediated neuroendocrine responses may be increased in drug-free patients with OCD (see above), this is the first report, as far as we are aware, of an increased prolactin response to d-fenfluramine. Other studies using either dl-fenfluramine or d-fenfluramine have reported either no change or a decrease in prolactin responses in OCD patients (Hewlett *et al*, 1992; Hollander *et al*, 1992; Lucey *et al*, 1992). It is possible that methodological factors play a part in these disparate results. For example, it is difficult to know whether standard drug wash-out periods are adequate to exclude persisting effects of psychotropic drugs on brain 5-HT function. We believe, however, that the major factor is likely to be differences in the clinical characteristics of the patients studied.

Effects of depression and cortisol hypersecretion

Patients with OCD often have significant depressive symptomatology, and major depression is clearly associated with blunted prolactin responses to L-tryptophan, clomipramine and d-fenfluramine (see Cowen, 1993). In addition, Lopez-Ibor *et al* (1994) found that prolactin responses to clomipramine in OCD were significantly lower in patients with depressive symptomatology, even after those who fulfilled criteria for concomitant major depression had been excluded. A related factor is the presence of elevated plasma cortisol levels which may result in blunted prolactin responses to d-fenfluramine through cortisol-induced changes in 5-HT receptor sensitivity (Dinan, 1994). Thus while the OCD patients studied by Lucey *et al* (1992) were 'normothymic', their mean baseline plasma cortisol levels, in contrast to the present study, were higher than controls and in the same range as those of depressed patients. Like the depressed subjects, their prolactin responses to d-fenfluramine were blunted (Lucey *et al*, 1992).

Brain 5-HT function in OCD

From this it is possible to conclude that 5-HT-mediated neuroendocrine responses in patients with OCD can be increased, normal or low compared with healthy controls. This makes it unlikely that changes in brain 5-HT function play an important pathophysiological role in the core syndrome of OCD. It seems probable, however, that in some OCD patients 5-HT neurotransmission is decreased because of concomitant depressive symptomatology or accompanying cortisol hypersecretion.

Increased brain 5-HT function, resilience and OCD

What might be the significance of increased 5-HT neurotransmission in non-depressed patients with OCD? Deakin & Graeff (1991) proposed that increases in brain 5-HT function may produce two major behavioural effects in anxiety-provoking

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situations. The first enables disengagement of aversive cues from their emotional consequences, while the second restrains 'flight' in the presence of danger signals. From this it is possible that increased brain 5-HT activity in some patients with OCD may represent an adaptive process which permits a certain degree of functioning in spite of prevailing obsessions and compulsions. From this viewpoint the therapeutic effect of clomipramine and SSRIs in OCD may be to facilitate an intrinsic neuropsychological defence mechanism. This would fit with the common clinical impression that while patients with OCD can show definite improvement in functioning following SSRI treatment, significant levels of symptomatology often remain (Piccinelli *et al*, 1995).

CLINICAL IMPLICATIONS

- Alterations in brain 5-HT function are unlikely to play a key role in the aetiology of OCD.
- Lowered brain 5-HT function in some OCD patients may be attributable to concomitant depression and cortisol hypersecretion.
- SSRIs may have limited efficacy in OCD because they act by promoting intrinsic neuropsychological defence mechanisms, rather than by reversing a key pathophysiological abnormality.

LIMITATIONS

- The small number of subjects studied may be unrepresentative.
- There was a lack of placebo control challenge.
- Indirect measures of brain 5-HT function were used.

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