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BRIEF COMMUNICATION

5-HT_{1A} dysfunction in borderline personality disorder

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ABSTRACT

Background. A number of challenge studies have reported abnormalities of serotonergic function in borderline personality disorder (BPD). There are, however, problems with the pharmacological probes used in these studies since fenfluramine and m-CPP are not only serotonergic agents but also induce release of catecholamines, particularly dopamine. Therefore, we tested whether subjects with BPD showed a blunted prolactin (PRL) response to flesinoxan, a highly potent and selective 5-HT_{1A}agonist.

Methods. Flesinoxan challenge test was carried out in 20 BPD in-patients and 20 healthy controls matched for gender but not for age. Since 16 BPD in-patients exhibited major depressive co-morbidity, a group of 20 depressed in-patients matched for gender but not for age was also included.

Results. BPD in-patients exhibited blunted PRL responses as compared to controls, whereas depressed in-patients did not differ from controls. Moreover, PRL responses were lower among BPD in-patients than among depressed in-patients. Among the BPD in-patients, PRL responses to flesinoxan were lower in patients with past history of suicide attempts ($N = 8$) than in those with a negative history.

Conclusions. The results show major involvement of serotonergic function in BPD and are consistent with previous studies linking lower serotonergic activity with impulsivity. More particularly, our data suggest that BPD is characterized by lower 5-HT_{1A} receptor sensitivity. Moreover, the data support the involvement of 5-HT_{1A} activity in suicidal behaviour. However, this conclusion is limited because other hormonal responses such as ACTH and cortisol were not assessed, and because BPD was assessed by a self-report questionnaire and not a structured clinical interview.

INTRODUCTION

Borderline personality disorder (BPD) is defined in DSM-IV (American Psychiatric Association, 1994) as a pattern of instability in interpersonal relationships, self-image, and affects, and marked impulsivity. The syndrome of BPD may be classified into four groups of symptoms: affective, impulsive, ego/interpersonal and psychotic. Several of these symptoms are associated with serotonergic dysfunction, and more particularly affective lability, suicidal behaviours, and impulsive aggression. Based on this statement, serotonin uptake inhibitors were openly studied in BPD patients soon after the release of fluoxetine. Three reports demonstrated the efficacy of fluoxetine in treating the depressive and impulsive symptoms of patients with BPD

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(Norden, 1989; Cornelius *et al*. 1990; Markovitz *et al*. 1991). However, these studies were not double blind, which could lead to bias in collecting the data.

The first double-blind, placebo-controlled study conducted among a small group of BPD patients demonstrated clear efficacy for fluoxetine over placebo on a number of dimensions, including depression, anxiety and global function (Markowitz, 1995). The second controlled fluoxetine study among BPD patients reported improvement in a number of symptoms, but this improvement was not statistically significant, except for aggression against objects (Salzman *et al*. 1995). In another controlled trial of 40 outpatients with personality disorders including 13 with BPD, fluoxetine had an antiaggressive effect on impulsive aggressive individuals with personality disorder including BPD (Cocarro & Kavoussi, 1997). In an open trial with sertraline, significant reduction in irritability and aggression were reported in BPD (Kavoussi *et al*. 1994). However, more controlled trials with larger patient populations were necessary to replicate these results.

Platelet studies have been carried out in BPD to assess serotonergic function in this disorder. Platelet serotonin (5-HT) content was higher in patients with BPD than in non-borderline patients and normal controls, and were positively correlated with the disposition to experience anger (Verkes *et al*. 1996, 1998).

Another way to assess further the role of the 5-HT function in BPD was to use specific pharmacological probes. Cocarro *et al*. (1989) administered the non-specific 5-HT releaser/reuptake blocker fenfluramine to patients with major depressive disorders and/or personality disorders including BPD and found that prolactin (PRL) response was blunted compared to non-borderline personality disorder and normal control subjects, independent of co-morbid major affective disorder. Moreover, PRL responses were negatively correlated with impulsive aggression and with history of suicide attempts. However, Martial *et al*. (1997) reported higher PRL responses and lower cortisol responses to fenfluramine in five BPD women as compared to controls. They argued that the different direction of effect for PRL and cortisol is consistent with evidence that the release of the two hormones is regulated by different serotonergic receptor subtypes. In fact, Meltzer & Maes (1995) suggested that the PRL response needs activation of both 5-HT_{1A} and 5-HT_{2C} receptors whereas cortisol secretion is induced by stimulation of 5-HT_{2C} receptors. Recently, Soloff *et al*. (2000) performed a study using positron-emission tomography (PET) during fenfluramine challenge test in BPD. The results showed that patients with BPD have diminished responses to serotonergic stimulation in areas of prefrontal cortex, a region associated with the regulation of impulsive behaviour.

Hollander *et al*. (1994) found higher cortisol levels and marginally blunted PRL responses to the 5-HT agonist effect of meta-chlorophenylpiperazine (m-CPP) in eight male patients with BPD as compared to controls. However, the results in the female patients (four subjects) were not significant. The authors noted that this gender difference could be attributable to circulating ovarian hormones because the subjects were not studied during the first 10 days of the menstrual cycle. Moreover, the opposite direction of hormonal responses suggested different mechanisms of cortisol and PRL release. In another study with m-CPP, women with a BPD diagnosis had PRL and cortisol blunted responses to this challenge (Rinne *et al*. 2000). Furthermore, these authors reported a significant negative correlation between delta peak PRL values and abuse characteristics, such as the severity and the duration of physical and sexual abuse. They concluded that the alteration of the serotonergic system was probably not related to BPD diagnosis *per se*, but to sustained traumatization during childhood.

Overall, these findings support a role for serotonin in BPD. There are, however, methodological problems with the pharmacological probes used in these studies. It has been reported by some investigators that fenfluramine and m-CPP are not only serotonergic agents causing the release of serotonin and the blockade of 5-HT uptake, but that they also cause release of catecholamines, particularly dopamine (Rowland & Carlton, 1986; Invernizzi *et al*. 1989; Eriksson *et al*. 1999).

Against this background the present study investigates the serotonergic function in BPD using the flesinoxan challenge test. Flesinoxan is a highly potent and selective 5-HT_{1A} agonist inducing a significant and dose-dependent re-

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lease of PRL in normal subjects (Pitchot *et al.* 1995). In fact, pindolol (a 5-HT_{1A} antagonist) significantly blocks the PRL response to flesinoxan. This result supports the role of 5-HT_{1A} mechanisms in the PRL response to flesinoxan. Based on previous studies, a blunted PRL response to flesinoxan among BPD in-patients is expected.

METHOD

Subjects

The study was conducted among 20 BPD in-patients (14 women and six men) with a mean age of 30·5 years (S.D. = 10·2) and 20 depressive in-patients matched for gender (mean age 46·1 years, S.D. = 13·2) admitted to the Psychiatric Unit of the University Hospital of Liège, Belgium. The diagnosis of BPD was based on the DSM-IV criteria and on the self-questionnaire from the Structured Clinical Interview for DSM-III Axis II (SCID-II). Moreover, the depressive symptomatology of the BDP in-patients was assessed by the 17-item Hamilton Depression Rating Scale (HDRS) (Hamilton, 1967). The mean score of HDRS was 26·3 (S.D. = 7·2). According to the DSM-IV criteria, 16 BPD patients had a current diagnosis of major depressive disorder and four had an eating disorder. Among BPD in-patients, eight had a positive history of suicidal attempts and 12 had a negative history. The assessment of suicidal attempts was based on clinical history. Most of the attempts were self-poisoning with drugs ($N = 7$, 87·5%), with only one case of cutting. According to DSM-IV criteria and SCID-II, BPD in-patients had no antisocial personality disorder or other personality disorders. The depressed in-patients met DSM-IV criteria for major depressive disorder (American Psychiatric Association, 1994) with a mean score of 27·2 (S.D. = 6·7) on the HDRS. They were hospitalized principally for adaptation of medication. There was no Axis I or Axis II co-morbidity among depressed in-patients as assessed by DSM-IV criteria and the SCID-II. Moreover, the depressed in-patients had a negative history of suicidal attempts. All patients were free of medication for at least 3 weeks before the challenge. Clinical examinations assessed that the patients were free of medical illness. A group of 20 experimentally naive healthy volunteers was also included in the study. The subjects were six men and 14 women (mean age 37·2 years; S.D. = 9·6) recruited among the staff of the University Hospital of Liège, Belgium. They all underwent a medical interview to exclude psychiatric or somatic disorders, and had a score < 6 on the HDRS, with a mean score of 3·4 (S.D. = 1·6) and a score < 2 on item 1. The Ethical Committee of the University of Liège Medical School approved the protocol and all subjects gave their informed consent.

Neuroendocrine procedure

The flesinoxan challenge test was performed after an overnight fast, and after a drug-free period of at least 3 weeks. Because of the influence of the oestrogen on PRL levels during the menstrual cycle, the flesinoxan challenge test was performed between the 3rd and the 12th day of the menstrual cycle. At 08.30 h, an indwelling catheter was inserted into a forearm vein. Blood samples of 10 ml were collected 30 min before and immediately before the injection of flesinoxan at 09.30 h. Successive blood samples were collected 15, 30, 60, 90, and 120 min after the injection. Flesinoxan (1 mg/70 kg body weight), diluted in saline solution to obtain 20 ml, was injected intravenously over a period of 10 min. Blood samples were centrifuged within 2 h and the serum was immediately frozen and kept at -18 °C until analysis.

PRL was measured by radioimmunoassay (RIA) with intra-assay and inter-assay coefficients of variation of $10{\cdot}0 \pm 10{\cdot}0$% and a detection limit of 8 mIU/ml. Analyses were performed using PRL absolute values at the different times following the injection (t0, t15, t30, t60, t90, t120).

Statistical analyses

The analyses were carried out using Statistica (4.5) for Windows (Statsoft, 1993). Group differences over time between BPD in-patients, depressed in-patients and controls on PRL responses to flesinoxan were assessed by 3 (group) × 6 (time) mixed MANOVA design with time as repeated measure and HDRS and age as cofactors. Group differences over time between BPD in-patients with and without a history of suicidal attempts were assessed by a 2 (group) × 6 (time) mixed MANOVA design with time as repeated measure and HDRS and age as

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co-factors. Least significant difference (LSD) tests were used for subgroup comparisons. All statistical tests were two-tailed using a 5% level of significance.

RESULTS

Age was significantly different within the three groups ($F = 10{\cdot}2$, $P < 0{\cdot}001$). *Post hoc* comparisons showed that depressed in-patients were significantly older than both BPD in-patients ($P < 0{\cdot}001$) and control subjects ($P = 0{\cdot}02$). Moreover, BPD in-patients were significantly younger than controls ($P = 0{\cdot}04$).

HDRS scores were significantly different within the three groups ($F = 81{\cdot}4$, $P < 0{\cdot}001$). *Post hoc* comparisons showed that control subjects had significantly lower scores than both BPD in-patients ($P < 0{\cdot}001$) and depressed in-patients ($P < 0{\cdot}001$). In contrast, BPD in-patients and depressed in-patients did not differ on HDRS scores ($P = 0{\cdot}90$).

Fig. 1 shows the mean PRL responses to flesinoxan over time among the three groups. Repeated measure analysis of covariance yielded a main effect of time ($F = 38{\cdot}8$, $P < 0{\cdot}001$), and a group-by-time interaction ($F = 2{\cdot}3$, $P = 0{\cdot}01$), but the main effect of group was not significant ($F = 1{\cdot}4$, $P = 0{\cdot}25$). *Post hoc* tests showed that there were no differences between the three groups in the mean baseline PRL plasma levels (230·8 mIU/ml for control, 161·6 mIU/ml for depressed in-patients, and 188·3 mIU/ml for BPD in-patients). *Post hoc* tests revealed a significant difference between BPD in-patients and control at 15 ($P < 0{\cdot}001$), 30 ($P < 0{\cdot}001$), 60 ($P < 0{\cdot}001$), 90 ($P < 0{\cdot}001$), and 120 ($P < 0{\cdot}001$) minutes after flesinoxan. Significant differences at 15 ($P < 0{\cdot}001$), 30 ($P < 0{\cdot}001$), 60 ($P < 0{\cdot}001$), 90 ($P < 0{\cdot}001$) minutes following flesinoxan existed between depressed in-patients and BPD. In contrast, no differences appeared between depressed in-patients and controls.

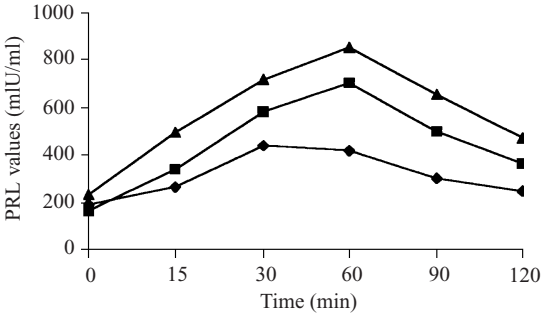


FIG. 1. Prolactin (PRL) responses among the three groups (◆, borderline personality disorder; ■, depression; ▲, controls). See text for statistical significance.

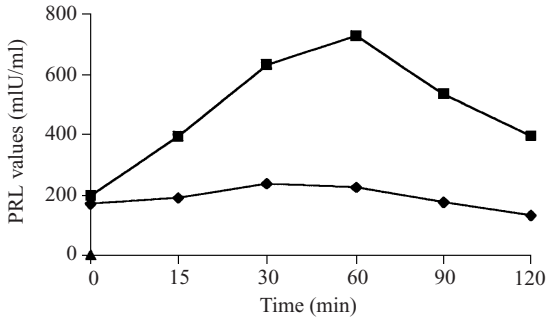


FIG. 2. Prolactin (PRL) responses to flesinoxan among the groups of BPD with a positive history (◆) of suicidal attempts ($N = 8$) and BPD with a negative history (■) of suicidal attempts ($N = 12$). See text for statistical differences.

Fig. 2 shows the mean PRL responses to flesinoxan over time among BPD in-patients with a positive and a negative history of suicide attempts. Repeated measure analysis of covariance yielded a main effect of group ($F = 4{\cdot}6$, $P = 0{\cdot}04$), a main effect of time ($F = 7{\cdot}6$, $P < 0{\cdot}001$), and a group-by-time interaction ($F = 4{\cdot}4$, $P < 0{\cdot}001$). *Post hoc* tests showed that there were no differences between the groups in the mean baseline PRL plasma levels (171·6 mIU/ml for BPD in-patients with positive history, and 196·9 for BPD in-patients with a negative history). *Post hoc* tests revealed a significant difference between groups at 30 ($P < 0{\cdot}001$), 60 ($P < 0{\cdot}001$), 90 ($P < 0{\cdot}001$) and 120 ($P < 0{\cdot}001$) minutes after flesinoxan.

DISCUSSION

The present results support the involvement of serotonin in BPD, and they are consistent with previous studies that reported lower PRL responses among BPD to serotonergic challenge tests (Cocarro *et al.* 1989; Hollander *et al.* 1994; Rinne *et al.* 2000). Since flesinoxan stimulates specifically the 5-HT_{1A} post-synaptic receptors, these results suggest that BPD patients are characterized by lower 5-HT_{1A} receptor sensitivity. To our knowledge, this is the first study that reports such results in BPD. Indeed,

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previous challenge studies among BPD were conducted with the non-specific fenfluramine and m-CPP challenge tests. However, the information is limited to PRL hormonal response to flesinoxan because other hormonal responses to flesinoxan, such cortisol and ACTH were not assessed in the present study. In fact, cortisol and ACTH hormonal responses are mediated with post-synaptic 5-HT_{1A} receptors. Without measuring these other responses in the present study, information of the implication of 5-HT_{1A} mechanism in BPD is limited.

The co-morbidity between Axis II and Axis I diagnostics among BPD in-patients may limit the conclusions. The PRL blunted responses observed among BPD patients may be attributed to the co-morbidity on Axis I, and more particularly with major depressive disorder. However, the present findings show that depressed in-patients do not present blunted PRL responses to flesinoxan as compared to controls. Furthermore, the depressed in-patients exhibit a higher PRL response to the challenge than BPD patients. It must be noted that differences in the depression in the BPD group compared to the depression group could explain the difference between the two groups, such as endogenicity or severity of depression. However, the severity of depression as assessed by HDRS did not differ between groups. Moreover, patients in both groups did not present characteristics of endogenicity. In contrast, it is possible that the level of anxiety differs between the two groups, and can influence the results. Indeed, in a recent positron emission tomography study with the selective 5-HT_{1A} antagonist [^{11}C] WAY-100635 Tauscher *et al.* (2001*a*) found a negative correlation between 5-HT_{1A} receptor binding potential and anxiety as assessed by the revised NEO personality inventory (Costa and McCrae, 1992) in healthy subjects. Unfortunately, we have not used a measure of anxiety in the present study.

The big age difference between groups also limits the conclusions. Depressed in-patients were significantly older than both BPD in-patients and control subjects, and BPD in-patients were significantly younger than controls. Relatively little is known about the influence of age on the 5-HT_{1A} receptor. However, a recent positron emission tomography study with [^{11}C]WAY-100635 suggested that 5-HT_{1A} binding potential declined at a rate of approximately 10% for every decade, except for mediotemporal cortex where a significant effect of age was not found (Tauscher *et al.* 2001*b*). Interestingly, Meltzer *et al.* (2001) observed an inverse relationship between age and the binding of [^{11}C]WAY-100635 to the 5-HT_{1A} receptor in men but not in women. Since women made up the majority of the subjects included in the present study, the age difference between groups was probably not relevant. Moreover, the younger group was BPD in-patients where blunted response to flesinoxan was observed.

Interestingly, we find blunted PRL responses to flesinoxan among BPD subjects with a past history of suicide attempts as compared to BPD subjects without history of suicidal behaviours. It is necessary to point out that all the subjects made non-violent suicide attempts, and these attempts were impulsive. Unfortunately, impulsivity and irritability were not assessed here, and therefore, correlations between PRL response and impulsivity were not computed. It should also be noted that the difference between BPD in-patients with a positive and a negative history of suicide attempts must be moderated since there are few subjects, and also because BPD in-patients co-morbidity with depression and eating disorders. Despite these limitations, this result is consistent with the inverse relationship between central 5-HT functioning and aggression, impulsivity and suicidal behaviour observed in different studies (Cocarro *et al.* 1989; New *et al.* 1997; Evans *et al.* 2000). Moreover, Pitchot *et al.* (1995) reported that PRL responses to flesinoxan were lower in a subgroup of depressed patients characterized by past suicidal history. However, even if altered serotonin indices have been reported in the brains of suicide victims, the 5-HT_{1A} receptors do not seem to be directly associated with suicidal behaviour. Stockmeier *et al.* (1997) reported no significant differences between suicide victims with major depression and comparison subjects who died of natural or accident causes in 5-HT_{1A} receptors in area 10 of the right prefrontal cortex or the hippocampus. Moreover, two studies found that the number of 5-HT_{1A} binding sites did not differ significantly between suicides and controls (Arranz *et al.* 1994; Lowther *et al.* 1997). However, Arango *et al.* (1995) found among a larger sample of suicide victims that 5-HT_{1A} receptor binding

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was higher. It should be noted however that these studies were conducted on suicide victims with the usual methodological limitations (e.g. delay between death and analysis). In contrast, the present results were obtained from a neuroendocrine procedure. In this context, several studies with fenfluramine challenge reported lower PRL response in depressed patients who had a history of suicide attempts (Cocarro *et al*. 1989; Malone *et al*. 1996).

Before concluding, several limitations in the design of this study should be listed. First, flesinoxan acts only on the complex and widely distributed 5-HT_{1A} receptors and not on the entire serotonergic system. In the brain, 5-HT_{1A} receptors are located pre-synaptically as somatodendritic receptors on 5-HT neurons and post-synaptically in particular limbic and cortical region (De Vry, 1995; Groenink *et al*. 1997). It should be noted that only hypothalamic receptors were assessed by the PRL response. Therefore, this study cannot be considered as definitive evidence for serotonergic (5-HT_{1A}) implication in BPD. Secondly, the study was carried out with only one dose of the drug, and it could be useful to explore both lower and higher doses since a previous study has reported that flesinoxan induced a dose-dependent PRL response (Pitchot *et al*. 1995). Moreover, a recent report has demonstrated a dose-dependent decrease in threshold for acute fear responses recorded in rats following administration of flesinoxan (Jenck *et al*. 1999). Thirdly, the lack of a placebo-controlled flesinoxan also limits the conclusions of this study. Without a placebo control for the flesinoxan challenge, it is difficult to be sure what confidence we can have in the PRL response of flesinoxan challenge. Fourthly, the use of a self-assessment only is problematical for personality assessment, and constitutes a serious limitation. Given the complexity of personality pathology, the use of structured clinical interview would have been preferable. Finally, the three groups were not weight matched, and recent weight loss, especially in the BDP group might complicate results and is a variable that needs to be accounted for carefully.

In conclusion, despite the limitations mentioned above, the results show a major implication of the serotonergic function in the aetiology of BPD and are consistent with previous studies, which linked lower serotonergic activity and impulsivity. These findings provide interesting area of study for the pharmacological treatment of this dramatic disorder. However, more controlled studies with larger patient populations are necessary to replicate the results of existing research.

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