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Chapter 3.3

Fluvoxamine Reduces Hyperresponsiveness of HPA-Axis in Adult Female BPD Patients with a History of Sustained Childhood Abuse

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Submitted for publication
Abstract

Objective: The aim of the study is to test whether fluvoxamine can reduce the increased responsiveness of the hypothalamic pituitary adrenal (HPA) in female borderline (BPD) patients with a history of severe childhood abuse, using a reduction in the adrenocorticotropin hormone (ACTH) and cortisol hyperresponsivity to a combined dexamethasone corticotropin releasing hormone (DEX/CRH) test as the central indicator.

Method: Thirty female BPD patients with (N=17) and without (N=13) sustained childhood abuse histories were submitted to a DEX/CRH challenge before and after 6 (N=14) or 12 (N=16) weeks of fluvoxamine treatment (150 mg/day).

Results: Both six weeks and twelve weeks of fluvoxamine treatment were associated with a significant reduction of the ACTH and cortisol response to the DEX/CRH test in the total group of BPD patients. BPD patients with a history of sustained childhood abuse exhibited a significantly larger reduction in the ACTH and cortisol response to DEX/CRH than BPD patients without sustained childhood abuse. No significant interaction effects were observed between treatment and the presence of a comorbid major depressive disorder or a post traumatic stress disorder (PTSD).

Conclusion: A six-week treatment with fluvoxamine can reduce the responsiveness of the HPA axis in BPD patients and especially the chronic hyperresponsiveness in those BPD patients with a history of sustained childhood abuse.
Introduction

Many borderline patients report a history of sustained childhood abuse and many of them meet criteria for comorbid major depressive disorder (MDD) and/or posttraumatic stress disorder (PTSD) (Zanarini et al 1998). Sustained childhood abuse is associated with a permanently increased responsiveness of the hypothalamic pituitary adrenal (HPA) axis, as reflected by an increased adrenocorticotrope hormone (ACTH) and cortisol response to a combined dexamethasone corticotropin releasing hormone (DEX/CRH) test and by hyperarousal in response to a psychological stressor (Rinne et al 2001b; Heim et al 2000a; Heim et al 2000b). Preclinical studies suggest that an enhanced expression of CRH is involved in the pathogenesis of this hyperresponsiveness of the HPA axis is an enhanced expression of CRH and its potent co-regulator arginine vasopressin (AVP) in the hypothalamic nucleus paraventricularis (PVN) (Coplan et al 1996; Hatalski et al 1998). In addition, this hyperresponsiveness of the HPA axis may render the abused BPD patients very susceptible to stress and in case of sustained stress to depression comparable with subjects with a heritable predisposition for MDD (Holsboer et al 1995). As far as the treatment of psychiatric disorders related to a hyperactive HPA-axis concerns there is evidence that the recovery from MDD due to antidepressant drug treatment is paralleled by attenuation of the hyperactive HPA axis (Holsboer et al 1996; Barden et al 1995).

Moreover, animal studies have shown that antidepressants may restore HPA-axis feedback deficiency (Rowe et al 1997).

In the present study we hypothesized that treatment with an antidepressant drug (e.g. the SSRI fluvoxamine) will reduce the hyperresponsiveness of the HPA axis in BPD patients with a history of sustained childhood abuse. Since concurrent major depressive disorder and/or posttraumatic stress disorder could confound the outcome of the DEX/CRH test, they were taken into consideration in an analysis of covariance.

To investigate the hypothesis and to explore the timeframe of the functional reduction of the HPA axis activity, a combined DEX/CRH challenge test is performed before and after 6 or 12 weeks of fluvoxamine treatment in a group of patients with a borderline personality disorders including both patients with and without severe childhood traumatization.

Method

Subjects:
Thirty healthy female borderline patients with and without sustained childhood abuse were included in the study (for sample characteristics see table 1). Subjects were recruited from outpatient mental health care centers and by advertising. In order to be included in the fluvoxamine trial all of the patients had to obtain a score of 110 or more on the borderline trait and distress scale of a self-report screener Assessment of DSM-IV Personality Disorder (ADP-IV) (Schotte et al 1998), meet more than 5 of the BPD criteria on the Structured Interview for DSM-IV Personality Disorders (SIDP-IV) (Pfohl et al 1995; Jong et al 1996) and receive a score of 20 or more on the fully-structured Borderline Personality Disorder Severity Index (BPDSI) (Arntz et al 2002; Weaver et al 1993).

All eligible subjects were screened for somatic conditions and examined physically; an electrocardiogram, a complete blood count, routine blood chemistry analyses, and urine
analyses were performed to exclude somatic illness. Exclusion criteria were: schizophrenia, a life-time episode of mania, current major depression not lasting more than 4 weeks, current drug or alcohol abuse or dependence according to a fully structured psychiatric interview: Composite International Diagnostic interview (CIDI) (WHO 1997; Smitten et al 1997) Specially trained psychologists who were blind for the diagnoses performed diagnostic interviews. Subgroups were defined according to the presence of sustained childhood abuse, as was assessed with the Structured Trauma Interview (STI) (Draijer 1989). Diagnosis of concurrent MDD and PTSD were obtained by the CIDI. All of the subjects had to be medication free at least 14 days prior to the neuroendocrine challenge test (fluoxetine six weeks). They were also not allowed to drink alcohol one week prior to the test. All of the patients provided their -fully informed- written consent. The ethical committee of our clinic approved the study.

**Design:**
After diagnostic baseline assessment the first combined DEX/CRH test was performed just before the start of fluvoxamine treatment (150 mg/day). The second DEX/CRH test was performed for one group (n=14) after 6 weeks of fluvoxamine treatment and for the other group (n=16) after 12 weeks of fluvoxamine treatment.

**Neuroendocrine challenge procedure**
For the combined dexamethasone suppression corticotropine releasing hormone challenge test (DEX/CRH), the refined procedure developed at the Max Planck Institute in Munich was adopted. (Heuser et al 1994) Participants had to ingest an oral dosage of 1.5 mg of dexamethasone at 11:00 p.m. the evening before the challenge. 50 mg of riboflavin was added to the capsule in order to check for the ingestion of dexamethasone. Riboflavin has a rapid renal clearing, and the subjects were therefore asked to collect their first urine on the morning of the test procedure. On the same morning, the participants had a light breakfast and were instructed to not eat or drink after 11:00 a.m. with the exception of water or herbal tea. The participants arrived at the research unit at 1:30 p.m. The riboflavin concentrations in their morning urine were analyzed before 3:00 p.m. They were asked to rest supine on a bed: a cannula was inserted in the forearm vein and kept open by heparinization. At 3:00 p.m. (after baseline sampling), 100 mg of CRH (Ferring BV, Hoofddorp, The Netherlands) reconstituted in 1 ml of 0.9% saline was administered in the cannula within 30 seconds. Blood samples for cortisol and ACTH plasma level measurement were taken at five time points: 3:00 p.m. (baseline level before CRH ), 3:30 p.m., 3:45 p.m., 4:00 p.m., and 4:15 p.m. Blood pressure, heart rate, and temperature were also measured at the same time points. Afternoon cortisol and ACTH baseline plasma levels without a challenge probe were measured on a different day. These baseline measurements were taken at the same timepoints as the DEX/CRH challenge test measurements.
All of the blood samples were extracted by vacuum into three plain tubes (5 ml); the first tube
was discarded. The tubes were immediately placed on ice; after centrifugation, the plasma was kept frozen at -70°C until analysis. Cortisol and ACTH plasma levels were analysed with commercially available assays. The cortisol assay was obtained from Boehringer Mannheim and the ACTH assay from Nichols Institute Diagnostics. The intra-interassay coefficients of variation for cortisol measurement were less than 6% and 10% respectively. The intra-interassay coefficients of variation for ACTH measurement were less than 3.2% and 6.3% respectively.

Statistical analysis:
The efficacy of fluvoxamine to reduce the increased responsiveness of the HPA axis in BPD patients could be reflected in the lower cortisol and ACTH afternoon baseline levels or in the decreased ACTH or cortisol responses to CRH after DEX pre-treatment. The latter data were calculated using the area under the concentration time curve (AUC) of ACTH and cortisol response.
The effect of fluvoxamine on the response of the HPA axis to the DEX/CRH challenge tests in BPD patients was analyzed using paired student t-tests to compare the ACTH and cortisol AUC’s before and after treatment. To assess the probable statistical interactions of the factors severe childhood abuse, comorbid PTSD and comorbid MDD with the effect of fluvoxamine on the HPA axis, a stepwise backward analysis for each dependent variable was performed, starting from a full repeated model with pre- and post-treatment measures of the dependent variable as the within-subject factor and severe childhood abuse, comorbid PTSD and MDD as between-subject factors. Interaction of a between-subject factor with the within-subject factor indicates an effect of the between-subject factor on the relevant change.
In all the analyses corrections for age, body mass index and contraceptive pill usage were made, if required.
Results

ACTH and Cortisol response pre/post fluvoxamine

No significant overall changes in mean afternoon baseline cortisol and ACTH baseline levels were detected after 6 or 12 weeks of fluvoxamine treatment. However, fluvoxamine treatment was associated with a significant decrease of the mean AUC of the ACTH and cortisol response to DEX/CRH challenge: Mean AUC of the cortisol concentration time curve decreased from 85.3 (sd=110.7) to 16.65 (sd=44.42); (t=3.77, df=29, p=0.001) and mean AUC of the ACTH concentration time curve from 8.77 (sd=9.21) to 2.21 (sd=5.18); (t=3.70, df=29 p=0.001).

Covariates: childhood abuse, MDD and PTSD

Regarding the question whether the reduction of the hyperresponsiveness of the HPA axis by fluvoxamine treatment is expressed more in BPD subjects with a history of sustained childhood abuse and whether this effect is affected by comorbid PTSD or MDD, a stepwise backward analyses of covariance has been performed. This revealed no effects for changes in mean cortisol and ACTH afternoon baseline levels. However, changes in AUC’s of the cortisol and ACTH response to the DEX/CRH test were significantly dependent on a history of sustained childhood abuse, but not on the various forms of psychiatric comorbidity. Mean AUC ACTH response for those subjects with sustained childhood abuse dropped from 12.70 (sd=10.41) to 2.37 (sd=5.82); while for those subjects without childhood abuse the mean AUC ACTH response dropped from 3.63 (sd=3.19) to 2.00 (sd=4.43) (F(1,28)=7.19, p=0.012; (see also figure 1). Mean AUC of the cortisol response for those subjects with sustained childhood abuse this AUC dropped from 113.2 (sd=121.0) to 13.9 (sd=30.7); while for those subjects without sustained childhood abuse the mean AUC cortisol response dropped from 48.9 (sd=87.0) to 20.2 (sd=59.1) (F(1,28)=4.08, p=0.058; (see also figure 2).

Figure 1

Concentration time curve of ACTH response to DEX/CRH challenge pre and post fluvoxamine (FLVX) treatment for abused (N=17) and not abused (N=13) BPD subjects. Students-t test for independent samples of mean AUC’s of ACTH of the abused versus not abused subjects pre fluvoxamine treatment

a) t=3.390 df=28, p=0.005 and post fluvoxamine

b) t=0.199, df=28, p=0.84. Students paired t-test of mean AUC’s of ACTH pre versus post fluvoxamine treatment for the abused and not abused subjects

c) t = -3.80, df = 16, p = 0.002 and
d) t = 1.61, df = 12, p = 0.134 respectively.
The time frame of the fluvoxamine effect on the HPA axis

The AUC of ACTH response after DEX/CRH challenge decreased from 8.99 (SD=9.70) to 2.60 (SD=4.07) and from 8.57 (SD=9.08) to 1.87 (SD=6.10) after 6 weeks of fluvoxamine treatment (n=14) and after 12 weeks of fluvoxamine treatment (n=16) respectively.

Because of the equal decrease in both groups no statistically significant group by time effect could be found ( F(1.28)=0.007, p=0.933), indicating that fluvoxamine exerts its effect in the first six weeks of treatment.

Figure 2

Concentration time curve of cortisol response to DEX/CRH challenge pre and post fluvoxamine (FLVX) treatment for abused (N=17) and not abused (N=13) BPD subjects. Students-t test for independent samples of mean AUC’s of cortisol of the abused versus not abused subjects pre fluvoxamine treatment

a) t=1.69, df=27.93, p=0.10 and post fluvoxamine

b) t=0.352, df=16.93, p=0.73.

Students paired t-test of mean AUC’s of cortisol pre versus post fluvoxamine treatment for the abused and not abused subjects

c) t=3.57, df=16, p=0.001 and

d) t=1.75, df=12, p=0.106 respectively.
Discussion

Fluvoxamine treatment was associated with a significant reduction of the ACTH and cortisol response to the combined DEX/CRH challenge test in all BPD subjects. The BPD subjects with a history of sustained childhood abuse exhibited a significantly larger decrease of the ACTH and cortisol response to DEX/CRH as compared to the not abused subjects, whereas PTSD and depression did not show any interaction effect (Rinne et al 2001b). (figure 1 and 2) Additional analysis revealed that the decrease of the ACTH and cortisol response is established in the first six weeks of the fluvoxamine treatment. The marked decrease of the ACTH and cortisol response to the DEX/CRH test after fluvoxamine treatment in the chronically childhood abused BPD subjects may reflect a reduction of the enhanced CRH/AVP drive (Rinne et al 2001b). Interestingly, fluvoxamine treatment of 8 weeks does not restore the severely blunted prolactin and cortisol response to the challenge with the serotoninergic agonist meta-chlorophenylpiperazine (m-CPP) in BPD subjects (Rinne et al 2001a), whereas the blunted prolactin response was highly correlated with sustained childhood abuse (Rinne et al 2000).

The combination of these findings directs our attention to the HPA axis as primary target of SSRI treatment in the chronically abused BPD subjects and not to the central serotoninergic system.

Preclinical research has provided some clues as to how these effects of childhood abuse and fluvoxamine on the HPA-axis evolve (Levine et al 2000). It appeared that early life stressors such as maternal deprivation persistently enhance responsiveness of the HPA axis in adulthood (Ma et al 1998; Oitzl et al 2000). The effect exerted by maternal deprivation resulted into altered expression of the hippocampal mineralo and glucocorticoid receptor sites (Oitzl et al 2000) in a manner that would explain the enhanced HPA responsiveness (De Kloet et al 1998). In other studies early stress was found to induce an increase in the number of hypothalamic CRH neurons and an increase in CRH and AVP m-RNA expression. (De Goeij et al 1992; Plotsky et al 1993; Coplan et al 1996; Hatalski et al 1998; Lim 2000; Coplan et al 2001). This elevated AVP/CRH release is likely to enhance the expression of pro-melanocortin synthesis and the release of its peptide product ACTH in the pituitary corticotrophs.

Preclinical studies on the effects of the chronic administration of different antidepressants demonstrate that a decrease of the HPA axis activity is a final common pathway of antidepressant effects, but that the different antidepressants unfold their specific pharmacological efficacy on varying HPA axis levels and receptor subsystems.

Tricyclic antidepressants as well as the SSRI fluoxetine are likely to increase either GR m-RNA or MR m-RNA expression in the hippocampus depending on the type of drug (Brady et al 1992; Seckl et al 1992; Barden et al 1995; Holsboer et al 1996; Okugawa et al 1999; Jensen et al 1999; DeRijk et al 2001). Owing to the increase of hippocampal mineralo- and glucocorticoid receptors they are thought to regain their balance re-establishing the inhibitory tone on the PVN in the hypothalamus. In accordance with this assumption CRH m-RNA in the hypothalamic PVN and CSF CRH as well as AVP turn out to be decreased after fluoxetine treatment. (Brady et al 1992; De Bellis et al 1993)

In this context another (hypothetical) pathway of SSRI's action on the HPA axis may be of
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interest (Brady 1994). The CRH neurons of the PVN and the locus coeruleus (LC) maintain a positive feedback loop in case of stress (Holsboer et al 1996; Valentino et al 1983). Sustained SSRI treatment leads to a reduced firing rate of noradrenergic neurons of the LC (Szabo et al 1999; Szabo et al 2000) which is expected to have its repercussion on the hypothalamic CRH neurons and thus on the release of ACTH secretagogues. In conclusion, the above mentioned factors may contribute to a normalization of the hyperresponsive stress axis of the chronically childhood abused BPD subjects, as reflected by a decreased ACTH and cortisol response to the DEX/CRH test after fluvoxamine treatment. The failure to detect the expected neuro-endocrinological effects of concurrent MDD (Barden et al 1995) in 11 BPD subjects on the ACTH and cortisol response to the DEX/CRH test after fluvoxamine treatment in our BPD sample might be due to the considerable overlap of concurrent PTSD and MDD. Six of the eleven subjects who suffered from MDD also had comorbid PTSD. In a previous study we demonstrated that the same BPD subjects with concurrent MDD and PTSD exhibited a strongly increased negative feedback inhibition of the pituitary corticotrophs, as demonstrated by hypersuppression to dexamethasone challenge. This effect is comparable to the results from subjects suffering from PTSD without MDD (Rinne et al 2001b). The expected neuroendocrine effects of MDD are most likely obscured by comorbid PTSD. The childhood abuse subgroup was significantly older than the non-abuse subgroup, which was taken into account in the statistical analysis. The lower education level of the abused group may be a reflection of the adverse rearing conditions in which they grew up. This study contributes to the knowledge of the effect of fluvoxamine in chronically childhood abused and not abused borderline patients. Whereas childhood abuse seems to leave a persistent increase of the excitability of the HPA-axis, fluvoxamine turns out to reduce these effects as demonstrated by an attenuated ACTH and cortisol response after the combined DEX/CRH test. This normalization takes place in the first 6 weeks of fluvoxamine treatment. Therefore, it can be concluded that SSRI treatment might be a supportive strategy in addition to cognitive training in stress management to reduce the susceptibility of the severely abused BPD subjects to stress and stress related disorders like MDD.

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