



HPA axis activation in major depression and response to fluoxetine: a pilot study

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Summary Hypothalamic-pituitary–adrenal (HPA) axis activation is a frequently observed phenomenon in major depression. However, whether this activation has any implications for treatment is unknown. To address this question, we examined baseline response to metyrapone and 6-week response to fluoxetine. Premenopausal women ($n = 20$) who met criteria for major depression with no other confounding Axis I disorders, medications, or medical illnesses and were not taking hormonal contraceptives were evaluated with an evening metyrapone challenge before the onset of treatment. Twenty-one normal women were also studied with the evening metyrapone challenge. The depressed patients then entered an open label treatment with fluoxetine for 6 weeks. Subjects were classified as responders if they demonstrated a 50% or greater decrease in Hamilton Depression Rating Scale rating. As a group, the depressed women demonstrated significantly increased ACTH secretion compared to control women before the onset of treatment, during the metyrapone challenge. Before treatment, women who were non-responders to fluoxetine showed increased HPA axis activation compared to controls, while the fluoxetine responders did not differ significantly from normal subjects in their ACTH levels during metyrapone challenge. These results suggest that overactivity of the HPA axis may be one factor associated with slower response to fluoxetine. This may reflect the greater severity of subjects with HPA axis dysregulation or the need to normalize the HPA axis with medications for optimal response.

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1. Introduction

Dysregulation of the hypothalamic-pituitary–adrenal (HPA) axis in major depression has been

observed by a number of investigators (Halbreich et al., 1985; Pfohl et al., 1985; Carroll et al., 1981; Rubin et al., 1987; Holsboer et al., 1984; Gold et al., 1986; Nemeroff et al., 1984, 1988; Young et al., 1990, 1993, 1994). Both increased central corticotropin releasing hormone (CRH) drive and decreased sensitivity to negative feedback

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have been hypothesized as underlying pathophysiology contributing to these abnormalities (Halbreich et al., 1985; Pfohl et al., 1985; Rubin et al., 1987; Carroll et al., 1981; Young et al., 1993). Evidence in favor of increased CRH drive include the blunted ACTH response to exogenous CRH (Holsboer et al., 1984; Gold et al., 1986; Young et al., 1990), increased CRH in the CSF of individuals with major depression (Nemeroff et al., 1984; Roy et al., 1987), increased POMC mRNA in the pituitary (Lopez et al., 1992) and increased CRH mRNA in the paraventricular nucleus post-mortem (Raadsheer et al., 1994, 1995), decreased CRH receptors in the frontal cortex (Nemeroff et al., 1988) and increased responsiveness to evening metyrapone (Young et al., 1994). In previous studies, the increased responsiveness to metyrapone was specific to circadian phase, observed in the evening rather than the morning (Young et al., 1997).

While HPA axis dysregulation is universally acknowledged to occur in a subgroup of patients with major depression, particularly melancholic depression, the extent to which these abnormalities are related to prognosis is less certain. Recent studies suggest that the HPA axis may be a target of antidepressant action. Evidence is accumulating that older tricyclic antidepressants as well as monoamine oxidase inhibitors can directly regulate glucocorticoid receptor (GR) number and function (Heuser et al., 1996; Brady et al., 1991, 1992; Pepin et al., 1992; Lopez et al., 1998; Seckl and Fink, 1992; Reul et al., 1993; Pariante et al., 1997, 2001). In fact, this has been proposed as a common mechanism of action (Holsboer and Barden, 1996). These same agents can affect (CRH) mRNA in addition to actions on GR mRNA (Brady et al., 1991; Lopez et al., 1998). Similarly, these agents can alter 5HT_{2A} receptors (Blier and de Montigny, 1994; Welner et al., 1989; Klimek et al., 1994; Peroutka and Snyder, 1980). In contrast, selective serotonin re-uptake inhibitors (SSRIs) do not affect GR number or function (Brady et al., 1992; Lopez et al., 1998). Some data in rodents suggest that fluoxetine is able to regulate CRH mRNA in the PVN (Brady et al., 1991). However, these were under baseline (non-stressed) conditions. In contrast, using a chronic unpredictable stress paradigm, which leads to increased plasma glucocorticoids, fluoxetine is unable to reverse the increase in CRH mRNA in the PVN (Lopez et al., 1998).

Given these basic science data and the evidence of HPA axis dysregulation in a subpopulation of major depression, the links between treatment response and baseline HPA function is an area of interest. To address this, we examined the response to metyrapone before treatment in 20

women during an episode of major depression who were then treated with fluoxetine for 6 weeks. We hypothesized that fluoxetine responders would show less evidence of HPA dysregulation than those who did not respond to fluoxetine. We chose metyrapone as a challenge because our previous studies had demonstrated a robust effect with metyrapone, more so than observed with baseline measures alone (Young et al., 2001). Metyrapone acts by blocking the last step of cortisol synthesis, yielding the inactive precursor 11-deoxycortisol. By inhibiting cortisol synthesis, metyrapone produces an open loop system and thus amplifies the increased endogenous drive present in the evening in major depression.

2. Methods and subjects

2.1. Subjects

All studies were approved by the Institutional Review Board of the respective institutions and written informed consent was obtained for all subjects. A total of 20 premenopausal women (range 18–50) with major depression were recruited for this study to examine the relationship between baseline evening metyrapone response and fluoxetine response. Patients were recruited at both University of Michigan (13 subjects) and Weill Cornell Medical College (seven subjects). In order to qualify for the study, a minimum score of 20 on 24-item Hamilton Depression Rating Scale was necessary. Subjects with a failed trial of fluoxetine (at least 20 mg for at least 4 weeks) in the past year were excluded. History of non-response to other antidepressants was not obtained. In addition, 21 controls were recruited, 15 at Michigan and six at Cornell. Most patients and all controls were recruited by advertisement. All subjects were normally cycling women, on no other medications and untreated for the current episode of depression. None were on oral contraceptives or were regular smokers. None engaged in shift work or recent travel across more than three time zones. Depressed women received a SCID-IV to confirm the diagnosis. Normal control women had no other Axis I diagnosis as confirmed by a SCID-NP, and had no first-degree relatives with an Axis I diagnosis and no second-degree relatives with depression.

Subjects were studied at random phases of the menstrual cycle, since previous studies by us (Young et al., 2001) have shown no effect of menstrual cycle on basal ACTH and cortisol secretion. In addition, in normal women, no difference was

observed in response to metyrapone in follicular vs. luteal phase (Altemus, unpublished data).

2.2. Metyrapone protocol

All subjects were admitted to a general clinical research unit (GCRC) at 3 PM. An intravenous catheter for blood drawing was inserted at this time. A standardized meal was given at 6:30 PM. The first dose of metyrapone (750 mg) was administered at 4 PM and a repeat dose at 7:30 PM. Blood was drawn every 30 min between 4 PM and 10 PM, for measurement of ACTH, cortisol and 11-deoxycortisol. Blood was collected on ice and centrifuged and separated within 30 min of drawing. All samples were stored at -80°C until assayed.

2.3. Fluoxetine treatment

Following the completion of the metyrapone protocol, all subjects were begun on fluoxetine, 20 mg. They returned every 2 weeks for follow-up assessment. Raters were standardized between Michigan and Cornell sites. At week 4, if subjects had not met criteria for response, the dose of fluoxetine was increased to 40 mg, unless side effects prevented the increase. Of the 13 non-responders in this report, 10 were able to increase to 40 mg without side effect problems. Compliance with the treatment was monitored by pill counts on every return visit. Response was defined as $\geq 50\%$ decrease in HDRS score.

2.4. Hormone assays

All samples were assayed at the University of Michigan. Samples from Cornell were shipped to Michigan on dry ice. ACTH was assayed using Allegro HS ACTH IRMA (Nichols Diagnostics, San Juan Capistrano, CA). Cortisol was assayed using DPC Coat a Count kits (Los Angeles, CA). 11-Deoxycortisol was assayed using ICN Biomedical 11-deoxycortisol radioimmunoassay kits (Costa Rica, CA).

2.5. Data analysis

Subjects were divided into responders and non-responders based upon the 6-week HDRS score. Non-response was defined as $<50\%$ decrease in HDRS score. Hormone data were analyzed by repeated measures ANOVA, with ACTH values over the course of metyrapone study as dependent variables. Initial analyses compared depressed and normal subjects (two-way RM-ANOVA), while the second analyses compared normal subjects to responders and normal controls to non-responders

(three way RM-ANOVA). A final analysis compared only responders to non-responders.

3. Results

The mean age of patients was 33.8 ± 8.9 (SD) and the controls were 33.7 ± 9.9 . Responders and non-responders did not differ in age (responders = 25.2 ± 2.1 (SD); non-responders = 23.9 ± 2.1 (SD)). The mean baseline Hamilton was 24 ± 3 (SD). Responders did not significantly differ on baseline HDRS from non-responders (responders 25.2 ± 2.1 (SD); non-responders 23.9 ± 3.4 (SD)). Both groups were predominantly recurrent and the mean number of episodes did not differ between groups (3.3 ± 1.5 in responders and 2.5 ± 1.5 in non-responders). The mean 6-week HDRS in responders was 8 ± 2.7 while the mean 6-week HDRS in the non-responders was 22 ± 7 . Of the 20 subjects, eight subjects met research diagnostic criteria (RDC) for definite or probable endogenous and 12 for non-endogenous. Baseline HDRS did not differ in these two groups ($ED = 25 \pm 3.9$; non- $ED = 24 \pm 2.7$). In three subjects, dysthymia preceded the onset of depression; 17 subjects had recurrent depression and eight had comorbid anxiety disorders. This includes two subjects with GAD, three with anxiety NOS, and two with social phobia. All other Axis I diagnoses were excluded.

The ACTH data for the entire group is shown in Fig. 1. As in our previous study, where we only examined β endorphin secretion (Young et al., 1994), the depressed group as a whole demonstrates increased pituitary secretion (ACTH) during metyrapone challenge ($F = 3.9$, $df = 1$, $p = 0.05$ for group; $F = 6.89$, $df = 12$, $p = 0.0001$ for repeated measure, no significant interaction). Fig. 2 demonstrates that metyrapone was equally effective in blocking cortisol in both groups ($F = 1.44$, $df = 1$, $p = 0.236$ for group, $F = 28.8$, $df = 12$, $p = 0.0001$ for repeated measure and no significant interaction). Fig. 3 shows the 11-deoxycortisol (DOC) data for all subjects. Although the 11-DOC data appear higher in depressed patients, this did not achieve statistical significance ($F = 2.0$, $df = 1$, $p = 0.16$; repeated measure $F = 11.8$, $df = 10$, 38 ; $p = 0.0001$, no significant interaction).

Overall, eight patients met criteria for responders and 12 met criteria for non-responders. Fig. 4 shows the ACTH data by responder non-responder status. As can be observed, the non-responders demonstrate significantly greater ACTH activation during metyrapone challenge from control subjects ($F = 5.4$, $df = 1$, $p = 0.027$ for group, non-responders vs. controls). In contrast, the

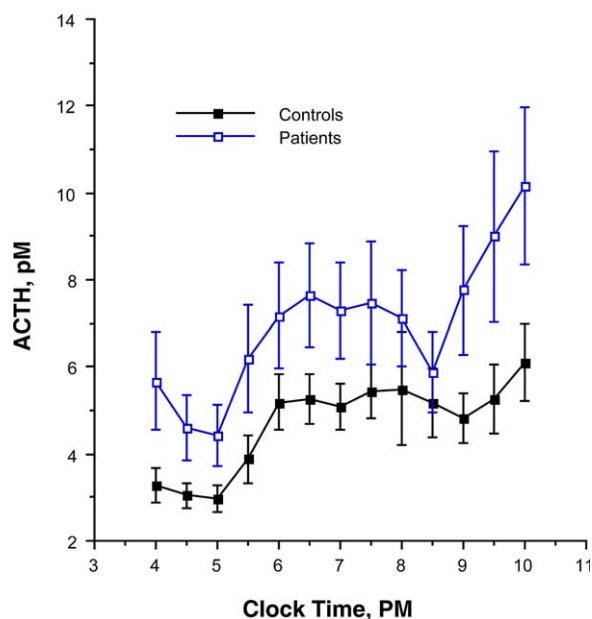


Fig. 1. Comparison of ACTH response to metyrapone in depressed patients and matched controls. The depressed patients show significantly greater ACTH response to metyrapone.

responders demonstrate an ACTH response to metyrapone that is similar to control subjects (Fig. 4; $F = 0.89$, $p = 0.35$ for responders vs. controls). However, the ACTH response to metyrapone did not differ between responders and non-responders ($F = 0.8$, $df = 1$, $p = 0.38$ for group, no significant interaction). There was no difference in the ACTH response to metyrapone between subjects who met criteria for non-endogenous vs. endogenous depression (data not shown).

We also examined the response to treatment by dividing patients based upon their mean ACTH during the metyrapone challenge. We used the mean (4.4) plus 2 SD of the normal subjects to define a cut-off value of 8.6 to define "high" ACTH. Five of the 20 subjects (25%) fell into the high ACTH group. Baseline HDRS did not differ between groups (24 ± 1.5 in high ACTH group vs. 24.9 ± 3.5 in low ACTH group). However, the 6-week HDRS was significantly different ($p = 0.027$) with a 6-week HDRS of 22 ± 8 in high ACTH group vs. 14 ± 6 in low ACTH group.

4. Discussion

These data confirm our previous studies with evening metyrapone demonstrating increased activation of the HPA axis in the evening in a group of depressed women. Unlike our previous study, this study examined ACTH rather than β -endorphin, and similar increased activation in patients with major depression was observed. However, the effect seen was a group effect rather than an interaction of group and time, raising the possibility that metyrapone administration was not necessary to demonstrate the group differences. However, because the metyrapone blocked the normal circadian fall in ACTH, it may have acted to maintain the initial baseline difference. In support of this is the observation that under basal (unstimulated) conditions that the differences in baseline ACTH in the evening between depressed and normal control women was approximately

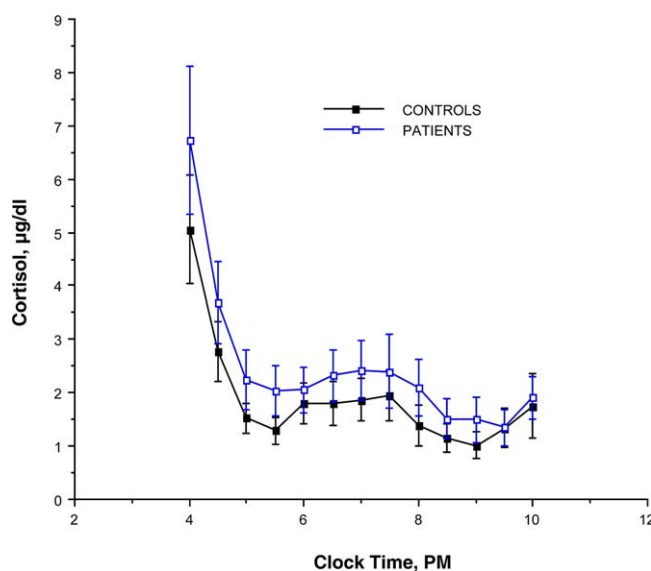


Fig. 2. Comparison of cortisol response to metyrapone in depressed patients and matched controls. Equivalent blockade of cortisol production was observed in both groups.

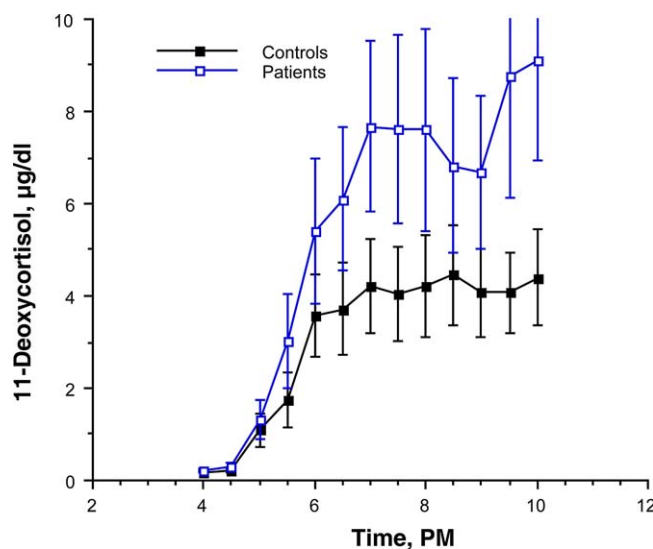


Fig. 3. Comparison of 11-DOC response to metyrapone in depressed patients and matched controls. There is no significant difference between groups.

0.2 SD (Young et al., 2001), while the ACTH of patients and controls over the course of this study differed by 1.5 SD.

This study suggests a possible association between baseline HPA axis abnormalities and treatment response to an SSRI, i.e. individuals who show activation of the HPA axis at baseline demonstrated a poorer response to 6 weeks of fluoxetine treatment. This hypothesis clearly needs to be tested on a larger sample with a

longer treatment before more definitive conclusions can be drawn. We chose to use the metyrapone challenge to evaluate this relationship, because evening metyrapone appears to be particularly sensitive to increased HPA axis activation in patients with major depression. In contrast, increased cortisol secretion is only seen in a small percent of unselected depressed patients (Young et al., 2001) and non-suppression of cortisol to

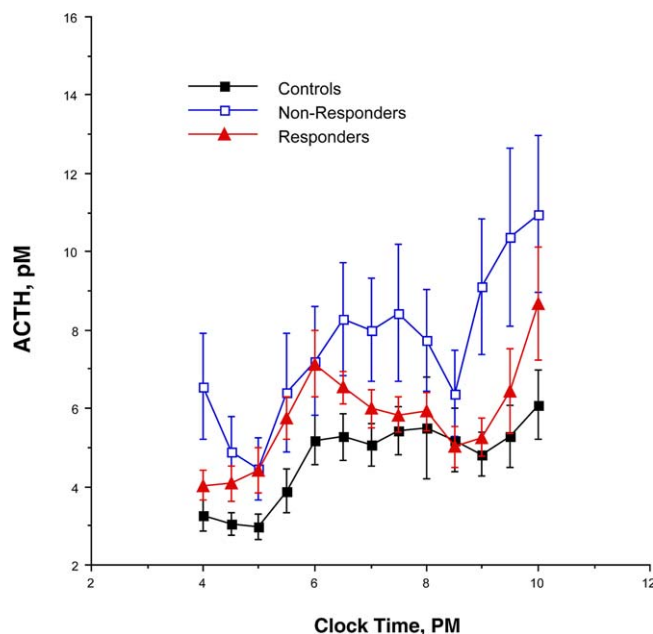


Fig. 4. Comparison of ACTH response to metyrapone in normal controls, fluoxetine responders and fluoxetine non-responders. Non-responders demonstrate significantly greater response to metyrapone than normal subjects, while the fluoxetine responders did not differ from normal subjects.

dexamethasone is also uncommon in an unselected population of depressed subjects (Young et al., 1993).

The current pilot data are consistent with basic science data demonstrating that SSRIs do not reverse HPA axis abnormalities in chronically stressed animals, and therefore may not be the most effective treatments for depressed individuals with HPA axis activation (Brady et al., 1992; Lopez et al., 1998). Furthermore, they suggest that SSRI non-responders are an enriched sample of individuals with HPA axis abnormalities and thus may be better treated with agents that correct the HPA axis (e.g., noradrenergic re-uptake inhibitors, CRH antagonists or GR antagonists) (Holsboer and Barden, 1996).

One surprising aspect of this study was the small number of fluoxetine responders (35%). This may reflect that 6 weeks is too short of a treatment period to classify subjects into responders and non-responders. It may also be that the "responders" at 6 weeks were placebo responders. Our design would not allow us to distinguish drug from placebo responders in this study. Furthermore, 6 weeks is too short of a treatment to label the subjects as true non-responders, since these individuals may be slow responders. A longer time course of treatment is needed to define non-responders than 6 weeks. The population studied was predominantly recurrent (17/20) and demonstrated comorbid anxiety (8/20) which may have contributed to the low 6-week response rate to fluoxetine. The low response rate may also reflect the proportion of individuals who met RDC criteria for probable or definite endogenous depression (60%). In fact the response rate for the non-endogenous subjects was five of 12 subjects (42%) while the response rate in the endogenous subjects was two of eight (25%). The large proportion of subjects meeting endogenous criteria by RDC is in contrast to only one who met DSM-IV melancholia, suggesting the melancholia criteria may be too stringent to pick up individuals who are less likely to respond to treatment with an SSRI.

While the current studies suggest a new lead towards understanding the effects of HPA axis activation on treatment response, the data demonstrate a group effect, and we cannot predict based upon an individual's response to metyrapone whether they will be a responder or non-responder to fluoxetine treatment. Indeed, because of the large variability in the depressed patients, the responders and non-responders did not differ from each other, only from the control subjects. Many further studies would be needed to

replicate this finding and to achieve such a predictive relationship. Furthermore, this is a medically healthy group of depressed women; we do not know if HPA axis activation from other medical disorders comorbid with depression might have similar influences on response to antidepressants. This also would be a future research interest. Finally, we cannot conclude that the suggested link between HPA axis activation and poor response would apply to other SSRIs.

In conclusion, these studies replicated the previous work that depression is accompanied by increased evening drive to the HPA axis. Furthermore, subjects who demonstrated a poor response to a 6 week course of fluoxetine demonstrated greater HPA axis activation than normal subjects, while responders did not differ from controls. These findings agree with basic science data suggesting that fluoxetine is unable to reverse the HPA axis activation induced by chronic stress. Finally, it may be necessary to correct HPA axis abnormalities for optimal treatment response.

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