Assessment of the Hypothalamic-Pituitary-Adrenal Axis over a 24-Hour Diurnal Period and in Response to Neuroendocrine Challenges in Women with and without Childhood Sexual Abuse and Posttraumatic Stress Disorder

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Background: Preclinical studies showed that early stress results in long-term alterations in the hypothalamic-pituitary-adrenal (HPA) axis. We performed a comprehensive assessment of the HPA axis in women with and without a history of early childhood sexual abuse and posttraumatic stress disorder (PTSD).

Methods: Fifty-two women with and without a history of early childhood sexual abuse and PTSD underwent a comprehensive assessment of the HPA axis, including measurement of cortisol in plasma every 15 min over a 24-hour period and cortisol and corticotropin (ACTH) following corticotropin-releasing factor (CRF) and ACTH challenge.

Results: Abused women with PTSD had lower levels of cortisol during the afternoon hours (12:00 – 8:00 PM) of a 24-hour period compared with non-PTSD women. Their ACTH response to a CRF challenge was blunted compared with nonabused non-PTSD (but not abused non-PTSD) women. There were no differences in cortisol response to CRF and ACTH challenges between the groups. Increased PTSD symptom levels were associated with low afternoon cortisol levels.

Conclusions: These findings suggest that early abuse is associated with increased CRF drive as evidenced by decreased pituitary sensitivity to CRF, whereas in abuse with PTSD there is a specific hypocortisolemia that is most pronounced in the afternoon hours.

Key Words: HPA axis, posttraumatic stress disorder, childhood abuse, cortisol, ACTH

Introduction

The “invisible epidemic” of childhood sexual abuse is a major public health problem in our country (McCawley et al 1997; MacMillan et al 1997). Sixteen percent of women have a history of childhood sexual abuse (MacMillan et al 1997), and sexual abuse is the most common cause of posttraumatic stress disorder (PTSD) in women, affecting 10% of women at some time in their lives (Kessler et al 1995). Given the sheer magnitude of this problem, it is especially important to understand the effects that early abuse can have on women throughout the lifetime, including both behavioral and biological consequences (Saigh and Bremner 1999; Bremner 2002).

Little is known about the long-term consequences of early abuse on neurobiological function in women. Exposure to early stressors such as separation from the mother result in long-term alterations in the hypothalamic-pituitary-adrenal (HPA) axis (Yehuda et al 1995b). Corticotropin-releasing factor (CRF) released during stress (Chapell et al 1986) from nerve terminals originating in the paraventricular nucleus of the hypothalamus increases the secretion of corticotropin hormone (ACTH) from the anterior pituitary, which in turn stimulates release of glucocorticoids from the adrenal (Owens and Nemeroff 1991). The hippocampus inhibits CRF release from the hypothalamus (Herman et al 1989; Jacobson and Sapolsky 1991). Studies in animals showed that chronic stress
results in sustained increases in plasma glucocorticoid levels associated with a potentiation of glucocorticoid responsiveness to subsequent stressors (Dallman and Jones 1973; Ottenweller et al 1989), resistance to suppression of dexamethasone, increased neuronal secretion of CRF, a compensatory blunting of ACTH responses to CRF (Coplan et al 1996; Fride et al 1986; Ladd et al 1996; Levine et al 1993; Makino et al 1995; Plotsky and Meaney 1993; Sapolsky et al 1997; Smith et al 1997; Stanton et al 1988; Takahashi et al 1998) and alterations in the hippocampus (Sapolsky 1996). Other studies, however, suggest that chronic stress is associated with a decrease in glucocorticoid response to subsequent stressors (Katz et al 1981; Rivier and Vale 1987; Young and Akil 1985). These observations from animal studies suggest that early adverse experience permanently affects the HPA axis.

Studies of HPA axis function in human populations exposed to traumatic stressors with the diagnosis of PTSD have not been entirely consistent with the animal literature. Studies comparing men with chronic combat-related PTSD with healthy nontraumatized control subjects found long-term alterations in HPA axis function including increased levels of CRF in cerebrospinal fluid (CSF; Baker et al 1999; Bremner et al 1997), blunted ACTH response to CRF challenge (consistent with decreased pituitary sensitivity to CRF, which may be seen with elevated levels of CRF; Smith et al 1989), decreased cortisol measured in 24-hour urine in some studies (Mason et al 1986; Yehuda et al 1991b, 1995c) but not others (Mason et al 2002; Pitman and Orr 1990), decreased cortisol based on plasma samples during the 7–10 PM segment of a 24-hour period (Yehuda et al 1994), normal cortisol response to standard dexamethasone suppression test (Kudler et al 1987), and excessive suppression of cortisol with low dose dexamethasone (Yehuda et al 1993). Other findings include increased number of glucocorticoid receptors on peripheral lymphocytes (Yehuda et al 1991; Yehuda et al 1995), and increased ACTH and 11-deoxycortisol response to metyrapone (Yehuda et al 1996). A study of girls or women with early childhood sexual abuse that did not specifically look at PTSD diagnosis found a blunted ACTH response to CRF, consistent with hypersecretion of CRF (De Bellis et al 1994), whereas others found increased ACTH response (Kaufman et al 1997), increased cortisol in 24-hour urines (Lemieux and Coe 1995), and increased suppression with low-dose dexamethasone (Stein et al 1997). Emotionally neglected children from a Romanian orphanage had elevated cortisol levels over a diurnal period compared with control subjects (Gunnar et al 2001). Maltreated school-age children with clinical-level internalizing problems had elevated cortisol compared with control subjects (Cicchetti and Rogosch 2001; Hart et al 1996). One study of boys and girls with the diagnosis of PTSD found elevated cortisol in 24-hour urine (De Bellis et al 1999). Adult women with PTSD related to a variety of causes had increased pituitary responses to CRF challenge (Rasmusson et al 2001). Studies of adult women with depression and early abuse found increased cortisol and ACTH responses to a stressful cognitive challenge (Heim et al 2000) and blunted ACTH response to CRF challenge (Heim et al 2001). Subjects with abuse-related PTSD had increased cortisol in anticipation of a stressful cognitive challenge (Bremner et al, in press) and with exposure to traumatic reminders in the form of personalized scripts (Elzinga et al, in press).

Findings to date have presented a confusing picture of the HPA axis in PTSD. Some of these inconsistent findings may be related to factors such as behavioral state of the individual at the time of the assessment, specificity of PTSD, phase of the disease, age, developmental epoch, and ongoing stressors. We hypothesize that acute trauma early in life and the early phases of PTSD are associated with increased central release of CRF with resultant elevations in ACTH, peripheral hypercortisolemia, and potentiated responses to stressors. As individuals move from the childhood to the adult developmental phase and PTSD becomes a chronic disorder, there is continued increased central release of CRF, resultant elevations in ACTH, and blunted ACTH response to CRF due to down-regulation of pituitary CRF receptors. With chronic PTSD and adulthood, however, there may be peripheral hypocortisolemia when the individual is in a compensated state, and exaggerated cortisol response to stressors or traumatic reminders. The repeated episodes of stressors in the form of daily traumatic reminders or an abnormal lack of coping for minor stressors of daily life may result in periods of disrupted homeostasis with excessive HPA responses, with intervening periods of relative hypocortisolemia related to an overcompensatory reaction to the periods of excessive response. This may result in a situation in which cortisol is lower over an extended time period when there are no traumatic reminders or other stressors.

The purpose of this study was to assess comprehensively the HPA axis, including measures of ACTH and cortisol response to CRF and ACTH challenge and measures of cortisol every 15 min over a 24-hour period, in women with early childhood sexual abuse with and without PTSD and in nonabused non-PTSD women. This study attempted to address limitations of previous studies, including the absence of comprehensive assessments of traumatized individuals with and without PTSD, the use of 24-hour urinary samples of cortisol that do not provide information about abnormalities over the diurnal cycle, and the absence of studies that include comprehensive...
measures of the HPA axis in the same individuals. We hypothesized that women with PTSD would have a blunted ACTH response to CRF challenge, lower cortisol levels following CRF and ACTH challenge, and lower levels of cortisol during a 7–10 PM time period compared with control subjects.

Methods and Materials

The study was approved by the Yale University Institutional Review Board, and all subjects gave written informed consent prior to participation. Fifty-two premenopausal women aged 18 years or older underwent comprehensive assessment of the HPA axis. Subjects included women with a history of early childhood (premenarchal) penetrative sexual abuse as measured with the Early Trauma Inventory (ETI; Bremner et al. 2000), the instrument used in this study. All subjects were medication free for at least 4 weeks before the study. The onset of abuse occurred at some time before the study. The entire protocol was performed at 1 and 2 week intervals. Subjects were admitted to the unit on an elective basis and received appointment dates for their admission. Only subjects who were clinically stable and not in crisis were admitted. The entire protocol represented a time commitment of several weeks, and not all of the subjects completed every aspect of the protocol; however, the 24-hour diurnal assessment of cortisol was performed first, and most women were able to complete this portion of the study.

Abused PTSD women were included with a history of early childhood (premenarchal) penetrative sexual abuse as measured by the ETI and the diagnosis of PTSD based on the Structured Clinical Interview for the DSM-IV (SCID) (Spitzer et al. 1987). In all subjects, PTSD was related to early trauma; there were no subjects with PTSD related to adult traumas. Subjects were excluded if they presented with a history of alcohol or substance abuse or dependence within the past 6 months, with schizophrenia, or with an eating disorder as determined by the SCID. They were likewise excluded if they presented with a serious medical disorder as determined by laboratory tests and physical examination, organic mental disorder, neurologic disorder, or head trauma. All subjects were medication free for at least 4 weeks before the study. The onset of abuse occurred at some time between ages 4 and 13 years (mean = 7).

Abused non-PTSD women met the same inclusion criteria for abused PTSD women with the exception of their having a diagnosis of PTSD based on the SCID. Nonabused non-PTSD women did not have a history of early childhood sexual abuse or other major traumas as measured by the ETI and did not have a history of psychiatric disorder as measured by the SCID. There was no difference in age between the groups (Table 1).

Table 1. Demographic and Psychometric Data in Women with and without Abuse and Posttraumatic Stress Disorder (PTSD)

<table>
<thead>
<tr>
<th></th>
<th>Women with Abuse and PTSD (n = 22)</th>
<th>Women with Abuse without PTSD (n = 14)</th>
<th>Women without Abuse or PTSD (n = 16)</th>
<th>F</th>
<th>p</th>
</tr>
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<tbody>
<tr>
<td>Age</td>
<td>34 (7)</td>
<td>31 (8)</td>
<td>32 (10)</td>
<td>1.05</td>
<td>.36</td>
</tr>
<tr>
<td>Height (inches)</td>
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<td>65 (3)</td>
<td>64 (3)</td>
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<td>.74</td>
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<tr>
<td>Weight (lbs.)</td>
<td>168 (47)</td>
<td>152 (41)</td>
<td>139 (29)</td>
<td>2.42</td>
<td>.10</td>
</tr>
<tr>
<td>Age of Trauma Onset</td>
<td>7.5 (3.4)</td>
<td>10.2 (4.5)</td>
<td>—</td>
<td>3.99</td>
<td>.054</td>
</tr>
<tr>
<td>ETI General Trauma</td>
<td>345 (271)</td>
<td>157 (159)</td>
<td>31 (83)</td>
<td>10.73a</td>
<td>.0002</td>
</tr>
<tr>
<td>Severity Index</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ETI Physical Abuse</td>
<td>310 (473)</td>
<td>119 (253)</td>
<td>19 (27)</td>
<td>3.39a</td>
<td>.04</td>
</tr>
<tr>
<td>Severity Index</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ETI Emotional Abuse</td>
<td>1255 (468)</td>
<td>517 (746)</td>
<td>122 (226)</td>
<td>11.86a</td>
<td>&lt;.0001</td>
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<td>Severity Index</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ETI Sexual Abuse</td>
<td>245 (468)</td>
<td>130 (256)</td>
<td>4 (7)</td>
<td>2.39</td>
<td>.13</td>
</tr>
<tr>
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<tr>
<td>ETI Trauma Severity</td>
<td>2154 (1542)</td>
<td>921 (1131)</td>
<td>154 (213)</td>
<td>12.44a</td>
<td>&lt;.0001</td>
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<tr>
<td>Index (total)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>CAPS Score</td>
<td>59 (24)</td>
<td>8 (9)</td>
<td>1 (2)</td>
<td>36.6a</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Mississippi Scale Score</td>
<td>120 (24)</td>
<td>76 (12)</td>
<td>70 (11)</td>
<td>31.6a</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>CADSS Score</td>
<td>14 (14)</td>
<td>2 (3)</td>
<td>0 (1)</td>
<td>6.88a</td>
<td>.003</td>
</tr>
<tr>
<td>HAM-D Score</td>
<td>18 (12)</td>
<td>4 (4)</td>
<td>1 (3)</td>
<td>18.15a</td>
<td>.0001</td>
</tr>
</tbody>
</table>

Data are mean (SD). CADSS, Clinician Administered Dissociative States Scale; CAPS, Clinician Administered PTSD Scale; ETI, Early Trauma Inventory; HAM-D, Hamilton Depression Scale; Mississippi Scale, Civilian Version of the Mississippi Scale for Combat-Related PTSD.

aPTSD group greater than abused non-PTSD and nonabused non-PTSD groups by Duncan Multiple Range Test (p < .05).

bPTSD greater than nonabused non-PTSD, but not abused PTSD (p < .05).
All subjects were evaluated with the SCID for comorbid psychiatric diagnoses. Of the 21 PTSD subjects, 12 (57%) fulfilled criteria for a lifetime history of major depression and 3 (14%) for current major depression. Two subjects (10%) fulfilled criteria for lifetime and current history of panic disorder without agoraphobia, two subjects (10%) fulfilled criteria for lifetime and current history of panic disorder with agoraphobia, one patient (5%) had a current and lifetime history of generalized anxiety disorder, and one (5%) current and lifetime social phobia. Two (10%) subjects met criteria for lifetime (not current) bulimia, and two (10%) for dissociative identity disorder. None of the subjects had current (past 6 months) alcohol or substance abuse or dependence. Four PTSD subjects (19%) fulfilled criteria for a lifetime history of alcohol dependence, two (10%) for lifetime history of alcohol abuse, one (5%) for lifetime history of polysubstance dependence, one (5%) for marijuana dependence, one (5%) for marijuana abuse, two (10%) for cocaine abuse, three (14%) for cocaine dependence, and one (5%) for opioid dependence. Onset of PTSD was typically in childhood and in all cases preceded all other psychiatric disorders by at least several years, including affective disorders.

Among the abused women without PTSD, six (40%) had lifetime histories of major depression (none had current depression), two (13%) had a lifetime (not current) history of panic disorder without agoraphobia, and one (7%) had a current and lifetime history of social phobia. One of the women (7%) had a lifetime (not current) history of bulimia. Three (20%) of the abused women without current PTSD had a past history of PTSD. None of the subjects had current (past 6 months) alcohol or substance abuse or dependence. Two of the abused non-PTSD women (13%) fulfilled criteria for a lifetime history of alcohol dependence, and one (7%) for a lifetime history of marijuana dependence. None of the nonabused non-PTSD women had a history of psychiatric disorder.

All subjects were assessed with the Clinician Administered PTSD Scale (CAPS) (Blake et al 1995), a reliable and valid measure of PTSD symptom level with subcomponents for the individual symptom clusters. Subjects were also assessed with the Civilian Version of the Mississippi Scale for Combat-Related PTSD, a self-report measure of current PTSD symptom severity that is a continuous measure (Vreven et al 1995). Severity of childhood abuse was evaluated with the ETI, a reliable and valid instrument for assessment of childhood and adult abuse and trauma (Bremer et al 2000). The ETI has components for measurement of general childhood trauma (such as being in an accident or a natural disaster) and for physical, emotional, and sexual abuse. We have developed indexes for measurement of severity of trauma in each of the subcomponents based on number of endorsed items, duration, and frequency. The ETI Trauma Severity Index is the sum of scores for severity indexes in the subcomponents. The scoring and psychometric properties of the ETI and ETI-based indexes are described in detail elsewhere (Bremer et al 2000). Baseline dissociative state symptom levels were assessed with the Clinician Administered Dissociative States Scale (CADSS), a reliable and valid instrument (Bremer et al 1998). Current depressive symptoms were assessed with the Hamilton Depression Scale (Hamilton 1960). Psychometric data collected with these instruments are presented in Table 1.

Subjects were admitted to the inpatient unit of the General Clinical Research Center for measurement of plasma cortisol over a 24-hour period. All subjects were studied during the early follicular phase of the menstrual cycle. Subjects underwent placement of an intravenous catheter at 4:00 PM of day 1 of the study. Normal saline with 3000 units/L of heparin was run at keep-vein-open speed for 24 hours. 5 mL blood samples were drawn every 15 min for 24 hours starting at 5:00 PM and placed in a chilled tube containing ethylenediaminetetraacetic acid. Samples were placed on ice, separated in a refrigerated centrifuge within 2 hours, and frozen for later analysis. During the time of the study, subjects stayed in a research hospital bed in a controlled environment. At the end of the 24-hour period, subjects were discharged from the inpatient unit.

At 4:00 PM on a day at least 2 weeks after the 24-hour study subjects underwent a CRF stimulation test. Thirty minutes before the procedure, an intravenous catheter was inserted for administration of CRF. Subjects were administered ovine CRF (1 μg/kg) in an intravenous bolus followed by plasma sampling for cortisol and ACTH every 10 min for 120 min. At 8:00 AM on a day at least 1 week after the CRF challenge, subjects were administered 40 units of adrenocorticotropin releasing hormone (ACTH) by intramuscular injection followed by plasma measurement of cortisol every 10 min over 120 min.

Plasma cortisol concentrations were determined using commercially available radiometric assay kits supplied by Incstar (Stillwater, MN); within-day and day-to-day coefficients of variation of 5%–9% were observed. The ACTH from the CRF challenge was assayed in duplicate 200-μL aliquots of ethyl-enediamine tetraacetate plasma using materials obtained from Diagnostic Systems Laboratories (Webster, TX) with inter- and intraassay coefficients of variation less than 9%. This assay is less specific than the commonly used Nichols assay. For this reason, we cannot exclude the possibility that peptides other than ACTH were included in the measurement. The within-subject design, however, involves the use of the subjects’ own baseline as the control.

Area under the curve (AUC) was determined for cortisol levels for the 7–10 PM hypothized time segment; AUC was then determined for three 8-hour time segments (12 to 8 PM, 8 PM to 4 AM, and 4 AM to 12 PM). t tests were used to compare PTSD to non-PTSD (abused non-PTSD and nonabused non-PTSD combined) for the three time segments with a Bonferroni correction for multiple comparisons. Data from AM and PM subjects also underwent log transformation with calculation of the slope of change of the log-transformed data in the AM and PM segments and comparison between groups. Repeated-measures analysis of variance with Duncan’s Multiple Range Test was used to compare cortisol and ACTH response with CRF and ACTH challenge between groups. Pearson correlations were used to compare behavioral data (trauma severity and age of onset measured with the ETI, PTSD symptoms measured with the CAPS and the Civilian Mississippi, depression measured with the Hamilton Depression Scale, and dissociation measured with the CADSS) and afternoon (12–8 PM) cortisol AUC. Bonferroni correction was used to correct for multiple comparisons between these behavioral variables and afternoon (12–8 PM) cortisol AUC.
Results

Diurnal Levels of Cortisol over a 24-Hour Period

There were no differences in cortisol levels in the 7–10 PM time segment. There was a significant difference in cortisol levels between PTSD women and abused women without PTSD in the afternoon time period (12–8 PM) of the 24-hour diurnal assessment period (t = 2.59 df = 2.37; p = .0134), which was significant after adjusting for multiple comparisons (p < .0167; Figure 1). Post hoc t tests showed that PTSD subjects had lower cortisol levels than both abused PTSD and nonabused non-PTSD subjects (p < .05); however, after adjustment for multiple comparisons between groups with the Dunnett test, the differences were significant for the abused PTSD versus abused non-PTSD comparison (adjusted p < .05) but not the abused PTSD versus nonabused non-PTSD comparison (adjusted p = .09). Mean levels of cortisol during this time period were 37% lower in the abused PTSD women than in abused non-PTSD women and 25% lower than in the nonabused non-PTSD women as measured by AUC (Figure 1).

Cortisol and ACTH Response to CRF and ACTH Challenge

The CRF challenge resulted in a blunted ACTH response in PTSD subjects relative to nonabused non-PTSD (but not abused non-PTSD) women [F = 4.71(1.18); p = .04; Figure 2]. The CRF challenge resulted in increased cortisol levels in all groups with no difference in cortisol response between groups. When the ratio of ACTH to cortisol following CRF challenge was assessed, there was no difference between the groups 60 min after the challenge. The ACTH challenge resulted in an increase in cortisol levels in all groups, with no significant difference between groups. There was no difference in ACTH values following ACTH challenge between the groups.

Relationship between Trauma Severity, Onset, and Symptoms and HPA Axis Measures

The relationship between age of trauma onset, trauma severity, and symptom severity and afternoon (12–8 PM) cortisol was assessed in the abused women with and without PTSD. Severity of childhood trauma as measured with the ETI was negatively correlated with afternoon cortisol levels measured as AUC from 12–8 PM in the abused group as a whole (r = −.43; df = 25; p = .027). Early onset of trauma was correlated with lower cortisol levels in the afternoon (r = .48; df = 27; p = .008). As measured by the CAPS score, PTSD symptoms were negatively correlated with afternoon cortisol levels (AUC for 12–8 PM) in abused women both with and without PTSD (r = −.45; df = 26; p = .01). As measured by the Civilian Mississippi Scale for PTSD, symptoms were negatively correlated with lower afternoon 12–8 PM AUC for cortisol levels in abused women (r = −.52; df = 26; p = .0046; Figure 3). There was no relationship between...
current depressive symptomatology as measured with the Hamilton Depression Scale and afternoon cortisol. Of these correlations, only the correlations between age of trauma onset and PTSD symptoms Civilian Mississippi and afternoon cortisol were significant after correcting for multiple comparisons ($p < .0083$).

**Effect of Comorbidity on HPA Axis Measures**

To examine the relationship between depression and PTSD, we compared PTSD women with and without comorbid current depression. There were no significant differences in 24-hour AUC for cortisol levels between women with PTSD and depression (155, 38 SD) compared with women with PTSD without depression (201, 52 SD).

To examine the effects of past comorbid alcohol and substance abuse, we compared PTSD subjects with and without past alcohol or substance abuse for 24-hour cortisol levels. No subjects had a current history of alcohol or substance abuse or dependence (past 6 months). There were no differences in 24-hour AUC for cortisol levels between PTSD subjects with (176, 39 SD) and without (197, 62 SD) a past history of alcohol or substance abuse.

Twenty percent of the abused women without PTSD had a past history of PTSD related to childhood abuse. When women with past (not current) PTSD were compared with women with abuse with no past history of PTSD, they showed a pattern of lower cortisol levels as measured by the afternoon (12–8 PM) AUC, although the sample was too small for statistical significance: 58.0 (1.5 SD) versus 96.9 (45.0 SD).

**Discussion**

Women with abuse-related PTSD had lower cortisol levels in the afternoon hours (12 PM–8 PM) compared with women without PTSD. Women with abuse and PTSD demonstrated blunted ACTH response to CRF relative to nonabused non-PTSD (but not abused non-PTSD women). There were no differences in cortisol levels following CRF and ACTH challenge between the groups in the study subjects. Symptom levels in the abused women with and without PTSD were negatively correlated with cortisol levels in the afternoon period (12 PM–8 PM). Age of trauma onset was positively correlated with low cortisol levels in the afternoon period (12 PM–8 PM).

These findings suggest that childhood abuse results in an increase in central release of CRF, with decreased sensitivity of the pituitary to CRF stimulation of ACTH release (related to CRF overdrive). The findings further suggest that in women who develop PTSD as a result of early abuse, there is a decrease in peripheral cortisol. The hypothesis of increased CRF release is consistent with prior reports of increased CRF concentrations in CSF (Baker et al 1999; Bremner et al 1997) in PTSD, and blunted ACTH response to CRF in some studies of PTSD. We did not measure CSF CRF in this study, however. Peripheral hypocortisolemia with no change in cortisol response to ACTH and CRF could be explained by a decrease in the adrenals responsiveness in PTSD. Differences in adrenals and possibly pituitary responsiveness may distinguish abused women who do and do not develop PTSD, possibly reflecting a long-term adaptation to the stressor occurring at the pituitary and adrenal levels. Another possibility is that PTSD is associated with increased cortisol during times of stress and traumatic reminders and that the baseline period measured here is an adaptive suppression to compensate for periods of excessive cortisol release. This is consistent with findings in both abuse-related PTSD (Bremner et al, in press) and abused women with depression (with high PTSD comorbidity; Heim et al 2000) of enhanced cortisol release associated with a stressful cognitive challenge and of increased cortisol response to traumatic scripts in abuse-related PTSD (Elzinga et al, in press), with cortisol returning to normal levels in the aftermath of the challenge in all of these studies.

The time period of decreased cortisol in PTSD (12 PM–8 PM) differs from the prior finding of Yehuda et al (1994) of lower cortisol from 7 PM–10 PM. Although the differences were not statistically significant, cortisol levels were about 20% lower during the 7 PM–10 PM time period. Differences in study population (abuse victims vs. combat veterans) or gender (women vs. men) may account for the difference in findings. Yehuda et al (1995c), in addition to
lower baseline cortisol, have found excessive suppression of cortisol with low-dose dexamethasone (Yehuda et al. 1993), increased number of glucocorticoid receptors on peripheral lymphocytes (Yehuda et al. 1991a, 1995a), and increased ACTH and 11-deoxycortisol response to metyrapone (Yehuda et al. 1996). These findings have been interpreted as being secondary to increased negative feedback at the level of brain areas that regulate the HPA axis (e.g., hippocampus, hypothalamus, or pituitary). Our study suggests that PTSD is associated with decreased cortisol; however, blunted ACTH response is consistent with increased CRF drive. If increased suppression occurs at the level of the hypothalamus or above, one would expect decreased CRF, however increased suppression at the pituitary level could conceivably be associated with increased CRF. It is also possible that there are transitory periods of increased CRF (e.g., with traumatic reminders) driven by brain regions above the level of the hypothalamus that are not sensitive to inhibitory control, whereas the ongoing baseline is characterized by increased suppression.

It should be noted that although our study found correlations between psychiatric symptoms and differences in HPA axis function, changes in HPA axis function are not necessarily involved in the etiology of these symptoms. Another possibility is that psychiatric symptoms may lead to differences in HPA axis function. In fact, a number of studies have shown that cortisol is acutely sensitive to psychologic states. It is also possible that some third factor (e.g., dysfunction in frontal cortex) determines both the HPA axis profile and development of psychiatric symptoms.

There are several limitations to our study. For instance, we did not measure multiple baseline samples of cortisol and ACTH before the CRF and ACTH challenges; therefore, it is difficult to fully assess baseline function. Also, we did not sample beyond 2 hours after challenges, and cortisol levels did not return to baseline by that time. Data on smoking history, which may affect HPA function, was not collected. We attempted to verify abuse histories by contacting family members, but this proved to be impossible. The reasons for this probably include disrupted family relationships in victims of abuse and impaired social function directly related to PTSD. All assessments of abuse are therefore based on self-report; however, we have previously shown good test–retest reliability of self-reports of childhood abuse as measured with the ETI, the instrument used in this study.

Findings of our study of abused women with PTSD suggest that abuse-related PTSD is associated with a different HPA profile than depression, a disorder that has also been linked to stress. Subjects with depression have been found to have elevated CRF concentrations, blunted ACTH response to CRF, increased cortisol levels in the periphery, and enhanced negative feedback of dexamethasone on cortisol release. The PTSD subjects in our study had high levels of comorbid depression, as is typical of studies in PTSD; however, onset of depression was, in all cases, several years or more after onset of PTSD, and there were no differences in cortisol levels between PTSD subjects with and without comorbid depression. Therefore the results do not appear to be attributable to depression and are consistent with other studies showing that biological markers in subjects with PTSD and comorbid depression are not similar to those in subjects with unipolar depression. In fact, Friedman and Yehuda (1995) have argued that “comorbid” depression in PTSD is not really a distinct disorder, but an artifact of the multifaceted response to trauma. In fact, interpreting low cortisol as a biological marker for PTSD disease severity (e.g., based on the correlations between low cortisol and high symptom severity), the pattern of lower cortisol levels in PTSD subjects with comorbid depression suggests that the presence of comorbidity is a marker of disease severity rather than an indicator of the presence of a comorbid and distinct condition.

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