As posttraumatic stress disorder (PTSD) becomes more commonly recognized, the number of studies examining the biological basis of this disorder are increasing. The majority of studies to date demonstrate alterations consistent with an enhanced negative feedback inhibition of cortisol on the pituitary, and/or an overall hyper-reactivity of the hypothalamic-pituitary-adrenal (HPA) axis. Paradoxically, however, the enhanced activity observed during either neuroendocrine or behavioral challenge, is typically manifested by lower ambient levels of cortisol. This article will present a summary of the data obtained to date in order to evaluate the degree to which different observations support the various models that have been proposed to explain the neuroendocrine basis of this disorder.

**LEVELS OF HPA AXIS HORMONES IN PTSD**

**Urinary and Plasma Cortisol in PTSD**

The initial finding in PTSD was a report of sustained, lower urinary cortisol levels in PTSD compared to veterans with other psychiatric diagnoses. A major point emphasized by the authors was that cortisol levels in PTSD fell within the normal range of 20 to 90 μg/d, indicating that the alteration was not in the hypoadrenal or endocrinopathological range. Attempts to replicate this initial finding yielded different results, although the majority of studies have supported this initial observation and have reported an association between low urinary cortisol excretion and PTSD. A comprehensive analysis of each of these studies and the methodologic issues associated with the different findings, has been provided elsewhere. There is a growing attempt to resolve issues related to disparate findings by simply counting the number of papers reporting one finding versus the number reporting another finding without consideration to potential methodologic differences in studies. Numerous variables that can affect ambient cortisol levels and the determination of the extent to which PTSD might be associated with cortisol alterations will require a careful consideration of these issues. The failure to consistently observe either low or high cortisol levels indicates that levels of this hormone are related to specific, or state-dependent features of the disorder, such as comorbid depression or the time course of the disorder. The divergent findings also raise the possibility that there are different phenotypic expressions of this disorder, and suggest that low cortisol levels may not be a neces-

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sary feature of PTSD, just as cortisol elevations are only observed in about half of depressed patients.³

Similar to studies of urinary cortisol, investigations of plasma and salivary cortisol levels have also provided inconsistent findings in PTSD. However, the use of a single sampling of cortisol, particularly at a set time of the day, may not represent an appropriate method for estimating cortisol levels because of moment-to-moment fluctuations in cortisol levels due to transient stressors in the environment (including the actual stress of venipuncture or anticipatory anxiety). Of particular note, however, has been the demonstration of low cortisol in a large epidemiologic sample of more than 2000 Vietnam veterans with PTSD compared to those without PTSD, reported by Boscariño.⁴ Although this study demonstrated low morning (8 AM) plasma cortisol, the effect size was small, and thus it is certainly possible that studies using small number of subjects will fail to observe differences at this time point.
Study of Circadian Rhythm of Cortisol and Its Neuroendocrinological Significance

An initial study of circadian parameters in PTSD was conducted by obtaining 49 consecutive blood samples from three groups of subjects—Vietnam combat veterans with PTSD, subjects (largely veterans) with major depression, and nonpsychiatric comparison subjects—every 30 minutes over a 24-hour period under carefully controlled laboratory conditions. The mathematical mean of basal cortisol release was found to be significantly lower in the PTSD subjects at several points, primarily in the late evening and early morning hours compared to the other groups. The major difference between PTSD and non-PTSD groups was that cortisol levels were lower in the late night and very early morning and remained lower for a longer period of time in PTSD during hours when subjects are normally sleeping. By the time of awakening, the peak cortisol release was comparable in PTSD subjects and age-matched subjects.

Since the cortisol peak was not statistically different but the trough was lower among those with PTSD, the range of cortisol release over the diurnal cycle was greater in PTSD. In contrast, depressed patients showed a less dynamic circadian release of cortisol, reflected in an increased mesor of cortisol release over the 24-hour cycle, a decreased amplitude-to-mesor ratio, and an elevated trough. A second study, examining serial cerebrospinal fluid (CSF) sampling over a 6-hour period, also reported significantly higher CSF CRF concentrations, but did not observe a relationship between CRF and 24-hour urinary cortisol release.

Corticotropic Levels in PTSD

If the pituitary is functioning normally, it will mediate between CRF stimulation from the hypothalamus and the inhibition of corticotropin release resulting from the negative feedback of adrenal corticosteroids. In a situation of increased CRF, baseline corticotropin levels may appear to be normal even though the pituitary gland may be receiving excessive stimulation from CRF.

Most studies have demonstrated that corticotropin levels between PTSD and comparison subjects were comparable even when cortisol levels obtained from the same sample were found to be significantly lower. Lower cortisol levels in the face of normal corticotropin levels can reflect a relatively decreased adrenal output. Yet, under circumstances of classic adrenal insufficiency, there is usually increased corticotropin release compared to normal levels. Thus, in PTSD, there may be an additional component of feedback on the pituitary acting to depress corticotropin levels that appear normal rather than elevated. Indeed, elevations in corticotropin would be expected not only from a reduced adrenal output but also from increased CRF stimulation. It is possible, however, that adrenal output in PTSD is relatively decreased, but not substantially enough to affect corticotropin levels.

Some investigators have reported that cortisol levels were higher in PTSD relative to corticotropin levels. Although corticotropin levels were not significantly different in PTSD compared to controls, the increase in cortisol

<table>
<thead>
<tr>
<th>Author (yr)</th>
<th>DEX dose/d</th>
<th>PTSD % Suppression (n)</th>
<th>Control % Suppression (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thaller et al. (1999)*</td>
<td>1</td>
<td>67.0 (34)</td>
<td>85.0 (17)</td>
</tr>
<tr>
<td>Yehuda et al. (1993)†</td>
<td>0.5</td>
<td>87.5 (21)</td>
<td>68.3 (12)</td>
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<tr>
<td>Stein et al. (1997)†</td>
<td>0.5</td>
<td>89.1 (13)</td>
<td>80.0 (21)</td>
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<tr>
<td>Yehuda et al. (1995)†</td>
<td>0.5</td>
<td>90.0 (14)</td>
<td>73.4 (14)</td>
</tr>
<tr>
<td>Yehuda et al. (1995)†</td>
<td>0.25</td>
<td>54.4 (14)</td>
<td>36.7 (14)</td>
</tr>
<tr>
<td>Kellner et al. (1997)‡</td>
<td>0.50</td>
<td>90.1 (7)</td>
<td>77.9 (n = 23)</td>
</tr>
</tbody>
</table>

*significantly less suppressed than controls.
†significantly more suppressed than controls.
‡no control group was studied.
Includes subjects without depression; subjects with both PTSD and major depressive disorder (n=17) showed a percent suppression of 78.8, which differs from our previous report (Yehuda et al., 1993) in younger combat veterans. Data are expressed as percent suppression of cortisol from baseline.
DST = dexamethasone suppression test. PTSD = posttraumatic stress disorder. DEX = dexamethasone.
relative to corticotropin is reminiscent of classic models of HPA dysregulation in depression where there is hypercortisolism but a reduced corticotropin negative feedback inhibition, (but without the hypercortisolism).

**Glucocorticoid Receptors in PTSD**

A greater number of 8 AM, but not 4 PM, mononuclear leukocytes (presumably lymphocyte) Type II glucocorticoid receptors was reported in Vietnam veterans with PTSD compared to a normal comparison group. An inverse relationship between 24-hour urinary cortisol excretion and lymphocyte glucocorticoid receptor number in PTSD and depression (ie, low cortisol and increased receptor levels were observed in PTSD whereas in major depressive disorder, elevated cortisol and reduced receptor number were observed).  

**CORTISOL AND CORTICOTROPIN RESPONSES TO NEUROENDOCRINE CHALLENGE**

**The Dexamethasone Suppression Test in PTSD**

Four out of five of the early studies of the cortisol response to dexamethasone (DEX) noted that PTSD did not appear to be associated with cortisol nonsuppression, using the established criterion of 5 μg/100 ml at 4 PM. Although the 1.0 mg dexamethasone suppression test (DST) studies primarily focused on evaluating failure of normal negative feedback inhibition, Halbreich et al. noted that post-DEX cortisol levels in the PTSD group were particularly lower than subjects with depression and even comparison subjects, raising the possibility that the 1 mg dose produced a floor effect in the PTSD group. Yehuda et al. hypothesized that PTSD patients would show an enhanced, rather than reduced, cortisol suppression to DEX and administered lower doses of DEX—0.50 mg and 0.25 mg—to examine this possibility. A hyperresponsiveness to low doses of DEX, as reflected by significantly lower post-DEX cortisol levels, was observed in PTSD patients compared to non-exposed subjects. The Table provides a summary of studies that have examined the cortisol response by comparing the pre-DEX and post-DEX cortisol levels at 8 AM.

**Other HPA Axis Challenge Tests in PTSD**

Kellner et al. administered a 50 μg bolus of cholecystokinin tetrapeptide (CCK-4) to subjects with PTSD and found substantially attenuated elevations of corticotropin in PTSD, which occurred despite comparable corticotropin levels at baseline. Cortisol levels were lower in PTSD at baseline, but rose to a comparable level in PTSD and control subjects. However, the rate of decline from the peak was faster, leading to an overall lower total cortisol surge. The attenuated corticotropin response to CCK-4 is compatible with the idea of corticotropin-releasing hormone override in PTSD. That less corticotropin can produce a similar activation of the adrenal but a more rapid decline of cortisol is also consistent with a more sensitive negative feedback inhibition secondary to increased glucocorticoid receptor activity at the pituitary.

**The Metyrapone Stimulation Test**

Metyrapone prevents adrenal steroidogenesis by blocking the conversion of 11-deoxy cortisol to cortisol, thereby unmasking the pituitary gland from the influences of negative feedback inhibition. The administration of 2.5 mg metyrapone in the morning resulted in an almost complete reduction in cortisol levels in both PTSD and normal subjects (and removal of negative feedback inhibition), but in a higher increase in corticosterone and 11-deoxycortisol in combat Vietnam veterans with PTSD, compared to non-exposed subjects. In the context of low cortisol levels and increased CSF CRF levels, the findings supported the hypothesis of a stronger negative feedback inhibition in PTSD. Kanter et al. did not find evidence for an exaggerated negative feedback inhibition using a metyrapone stimulation paradigm. In this study, a lower dose of metyrapone was used administered over a 3-hour period (750 mg at 7 AM and 10 AM), and, rather than simply examining the corticotropin response to this manipulation, the cortisol levels were introduced by means of an infusion, theoretically allowing the effects of negative feedback inhibition to be evaluated more systematically. Under conditions of enhanced negative feedback inhibition, the introduction of cortisol following metyrapone administration should result in a greater suppression of corticotropin in PTSD. However, no significant differences in the corticotropin response to cortisol infusion between PTSD and comparison subjects (but a nonsignificant trend, P = .10, for such a reduction) were observed. Because the metyrapone produced a significantly greater decrease in cortisol in the comparison subjects, while not producing a significant difference in corticotropin concentrations, it might be that the lack of an corticotropin reduction in PTSD.

In posttraumatic stress disorder, there may be an additional component of feedback on the pituitary acting to depress corticotropin levels that appear normal rather than elevated.
following cortisol infusion may have been due to a floor effect due to the fact that the endogenous cortisol present was already high enough to suppress corticotropin secretion in the PTSD group, rather than a demonstration of lack of reactivity of the system. The interesting finding in this study is that the same relatively low dose of metyrapone did not result in as great a decline cortisol in PTSD, but did result in the same level of cortisol inhibition implying differences in the activity of the enzyme 11-β-hydroxylase.

The idea of reduced adrenal capacity as a possible model for PTSD has also been recently raised by Heim et al., who concluded that low cortisol may not be a unique feature of PTSD, but may represent a more universal phenomenon related to bodily disorders, having an etiology related to chronic stress. In one study, a decreased cortisol response to low dose dexamethasone was observed, but a blunted corticotropin response to CRF in women with chronic pelvic pain, some of whom had PTSD, was not.

The CRF Challenge Test and Corticotropin Stimulation Test in PTSD

An initial study demonstrated that the corticotropin response to CRF was blunted, even though the cortisol response was not significantly affected. These findings are consistent with an increased negative feedback inhibition of the pituitary secondary to increased glucocorticoid receptor number or sensitivity. In contrast, reported an augmented corticotropin response to CRF in 12 women with PTSD compared to 11 healthy controls was more recently reported. Yet, the magnitude of the corticotropin response was substantially larger in subjects with PTSD than the cortisol response. Thus, although corticotropin levels were more elevated in PTSD, this did not result in a comparable stimulation of cortisol. The authors also performed a neuroendocrine challenge with 250 µg of corticotropin in these women to determine the response of the pituitary gland to this maximally stimulating dose. An exaggerated cortisol response to corticotropin was observed in PTSD, which tended to suggest that the adrenal glands may actually be overactive, rather than show a reduced activity, as implied by the results of the CRF tests. Basal assessments did not reveal group differences in either 24-hour urinary cortisol levels, or basal plasma cortisol or corticotropin levels. These paradoxical results warrant further investigation.

An increased corticotropin response to CRF in abused women with and without major depressive disorder compared with nonabused depressed women and comparison subjects has also been observed. Abused women without depression showed an augmented corticotropin response to CRF, but a reduced cortisol response to corticotropin compared to other groups. Only a small proportion (4/20) met criteria for PTSD. The study is noteworthy for suggesting that early abuse may be associated in and of itself with a profile of pituitary-adrenocortical alterations (particularly, low ambient cortisol as a function of a diminished adrenal responsiveness) that are opposite to those seen in depression.

MODELS OF HPA AXIS ALTERATIONS IN PTSD

Cortisol levels are most often found to be lower than normal in PTSD, but can also be similar to or greater than those in comparison subjects. Findings of changes in circadian rhythm suggest that there may be regulatory influences that result in a greater dynamic range of cortisol release over the diurnal cycle in PTSD. Thus, the adrenal gland is certainly capable of producing adequate amounts of cortisol in response to challenge. The model of enhanced negative feedback inhibition posits that chronic or transient elevations in CRF release stimulate the pituitary release of corticotropin, which in turn stimulates the adrenal release of cortisol. However, an increased negative feedback inhibition would result in reduced cortisol levels under ambient conditions.

The explanation that PTSD is associated with reduced adrenal output accounts for why ambient cortisol levels would be lower than normal, and even for the relatively smaller magnitude of differences in corticotropin relative to cortisol, but does not account for why basal corticotropin levels are not significantly higher in PTSD than in comparison subjects, particularly in light of evidence of CRF hypersecretion. CRF hypersecretion may result in a down regulation of pituitary CRF receptors leading to a decreased corticotropin response. However it remains to be elucidated why in such cases CRF hypersecretion would lead to pituitary desensitization and low cortisol as opposed to the more classic model of HPA dysfunction articulated for major depressive disorder in which the effect of hypothalamic CRF release on the pituitary would ultimately result in hypercortisolism. Under conditions of reduced adrenal
output, it is possible that compensatory changes in hypothalamic CRF might occur to the extent that there is a weaker negative feedback inhibition as a result of decreased cortisol output. But if this were occurring, it is not clear how there could be an increased corticotropin response to CRF and psychological stressors.23,27

Findings of the cortisol response to DEX are compatible with both the enhanced negative feedback inhibition model and adrenal insufficiency. However, in the latter case, one would not expect a reduced cortisol level to result from, or even be accompanied by, changes in the glucocorticoid receptor, but, would reflect reduced adrenal output rather than an enhanced containment of corticotropin.

CORTISOL IN THE ACUTE AFTERMATH OF TRAUMA

Low cortisol levels in the immediate aftermath of a motor vehicle accident predicted the development of PTSD in a group of accident victims consecutively presenting to an emergency department.29 Delahanty et al. also reported that low cortisol levels in the immediate aftermath of a trauma contributed to the prediction of PTSD symptoms at one month.30 In persons who survived a natural disaster, cortisol levels were similarly found to be lowest in those with highest PTSD symptom severity scores at one month posttrauma, however cortisol levels were not predictive of symptoms at one year.31 Similarly, lower morning but higher evening cortisol levels were observed in subjects with high levels of PTSD symptoms 5 days following a mine accident in Lebanon, compared to subjects with lower levels of PTSD symptoms.32

In a study examining the cortisol response in the acute aftermath of rape, low cortisol levels were associated with prior rape or assault, themselves risk factors for PTSD.29 but not with the development of PTSD per se, implying that cortisol levels might have been lower in trauma survivors who subsequently develop PTSD even before their exposure to trauma, and might therefore represent a pre-existing risk factor. Consistent with this, low 24-hour urinary cortisol levels in adult children of Holocaust survivors were specifically associated with the risk factor of parental PTSD. These studies raise the possibility that low cortisol levels represent an index of risk, and may actually contribute to the secondary biological alterations that ultimately lead to the development of PTSD. Interestingly, the risk factor of parental PTSD in offspring of Holocaust survivors was also associated with an increased incidence of traumatic childhood antecedents.3 Thus, low cortisol levels may occur in those who have experienced an adverse event early in life, and then remain different from those not exposed to early adversity. Although there might reasonably be HPA axis fluctuations in the aftermath of stress, and PTSD at one month, there is an active process of adaptation and attempt at achieving homeostasis, and that PTSD symptoms themselves are determined by biological responses, rather than the opposite. Hawk et al. found that at one month post trauma, urinary cortisol levels were elevated among men with PTSD symptoms (but not women).35 By six months, there were no group differences in cortisol, but emotional numbness at one month predicted lower cortisol levels six months after the accident.

The development of PTSD may be facilitated by the hormonal milieu at the time of trauma, which may reflect an interaction of pretraumatic and peritraumatic influences. These responses may be further modified in the days and weeks preceding it by a variety of other influences. The neuroendocrinologic response to trauma of a person with lower cortisol levels at the outset might be fundamentally different from that of someone with a greater adrenal capacity and higher ambient cortisol levels.

CONCLUSION

The HPA axis alterations in PTSD support the idea that HPA axis alterations are complex and may be associated with different aspects of PTSD, including risk for the development of this disorder. Future research is necessary to determine whether some features of the HPA axis may be altered prior to the exposure to a focal trauma or whether components of the HPA axis are differentially regulated. In PTSD, the HPA axis appears to be more dynamic and may therefore show transient increases or hyperresponsivity under certain environmental conditions. There is a need to examine the contribution of other regulatory influences that may affect HPA axis regulation in PTSD, and to systematically test for different biologic variants of PTSD with relatively similar phenotypic expressions.
REFERENCES


