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Neuroendocrine Aspects of PTSD

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Abstract This chapter discussed how neuroendocrine findings in posttraumatic stress disorder (PTSD) potentially inform hypothalamic-pituitary-adrenal (HPA) alterations in PTSD and highlight alterations relevant to the identification of targets for drug development. Most studies demonstrate alterations consistent with an enhanced negative feedback inhibition of cortisol on the pituitary, an overall hyperreactivity of other target tissues (adrenal gland, hypothalamus), or both in PTSD. However, findings of low cortisol and increased reactivity

of the pituitary in PTSD are also consistent with reduced adrenal output. The observations in PTSD are part of a growing body of neuroendocrine data providing evidence of insufficient glucocorticoid signaling in stress-related neuropsychiatric disorders.

Keywords Posttraumatic stress disorder · Cortisol · Neuroendocrine alterations · Negative feedback inhibition · Glucocorticoid receptors · CRF

1 Introduction

The development of drugs that might be effective in treating anxiety disorders in part depends on the ability of clinical neuroscience to identify biologic alterations that might serve as targets for drug development. Unfortunately, an observable biologic change—even one that is directly correlated with severity of symptoms or the absence or presence of a disorder—does not always constitute a core pathophysiologic process requiring biologic "repair." Biologic alterations may be present in specific anxiety disorders because they are correlates or proxies for other pathophysiologic processes, or even because they represent compensatory mechanisms of adaptation.

The study of the neuroendocrinology of posttraumatic stress disorder (PTSD) has been illuminating in highlighting alterations that have not historically been associated with pathologic processes. The most infamous of these findings—low cortisol levels—has been subjected to much discussion and scrutiny, likely because it has been a counterintuitive result, given modern interpretations of the damaging effects of stress hormones. Indeed, the initial observation of low cortisol in a disorder precipitated by extreme stress directly contradicted the popular formulation of hormonal responses to stress, the "glucocorticoid cascade hypothesis" (Sapolsky 1986), which was emerging as a cogent rationale for antiglucocorticoid treatments in depression, and other psychiatric disorders thought to be driven by hypercortisolism.

This chapter discusses how cortisol findings in PTSD potentially inform hypothalamic–pituitary–adrenal (HPA) alterations in PTSD and highlights what might be true targets of drug development. The observations in PTSD are part of a growing body of neuroendocrine data providing evidence of insufficient glucocorticoid signaling in stress-related neuropsychiatric disorders (Raison and Miller 2003). The majority of studies demonstrates alterations consistent with an enhanced negative feedback inhibition of cortisol on the pituitary, an overall hyperreactivity of other target tissues (adrenal gland, hypothalamus), or both in PTSD. This model explains most of the reported observations in PTSD. Theoretically, however, findings of low cortisol and increased reactivity of the pituitary in PTSD are also consistent with reduced adrenal output (Maes et al. 1998; Heim et al. 2000), but this latter model is only supported by the minority of HPA alterations observed in PTSD.

It may be that models of enhanced negative feedback, increased HPA reactivity, and reduced adrenal capacity explain different facets of the neuroendocrinology of PTSD, or that the tendency for reduced adrenal output may represent a pre-existing risk factor related to certain types of early experiences, at least in certain persons who develop PTSD. On the other hand, alterations associated with enhanced negative feedback inhibition may develop over time in response to the complex biologic demands of extreme trauma and its aftermath. Moreover, the findings of increased HPA reactivity may reflect a more nonspecific response to ongoing environmental challenges associated with having chronic PTSD. Furthermore, the absence of cortisol alterations in some studies imply that alterations associated with low cortisol and enhanced negative feedback are only present in a biologic subtype of PTSD. The observations in the aggregate, and the alternative models of pathology or adaptation suggested by them, must be clearly understood in using neuroendocrine data in PTSD to identify targets for drug development.

2
Basal HPA Hormone Levels in PTSD

The first report on cortisol levels in PTSD was that of Mason et al. who found that the mean 24-h urinary excretion of cortisol was significantly lower in combat Vietnam veterans with PTSD compared to psychiatric patients in four other diagnostic groups (Mason et al. 1986). The authors noted surprise at the fact that cortisol levels were low, since "certain clinical features such as depression and anxiety [in PTSD] might have been expected to be associated with increased activity of the pituitary-adrenal cortical system." Since this initial observation, the majority of the evidence supports the conclusion that cortisol alterations in PTSD are different from those observed in acute and chronic stress, and major depression, but more importantly, that the HPA axis appears to be regulated differently.

2.1
Urinary Cortisol Levels in PTSD

The initial report of sustained, lower urinary cortisol levels in PTSD highlighted the disassociation between cortisol and catecholamine levels in PTSD. Norepinephrine and epinephrine levels assayed from the same urine specimens revealed elevations in both of these catecholamines, while cortisol levels in PTSD fell within the "normal range" of 20–90 μg/day, indicating that the alteration was not in the "hypoadrenal" or endocrinopathologic range (Mason et al. 1986). This finding established the expectation that alterations in basal levels of cortisol might be subtle, and not easily differentiated from normal values (Mason et al. 1986).

Table 1 shows that this is in fact the case. Whereas the majority of studies has found evidence of low cortisol in PTSD, it is clear that group differences are not always present between subjects with and without PTSD. The inconsistency in published reports examining urinary 24-h cortisol levels has been widely noted. There are numerous sources of potential variability in such studies related to the selection of subjects and comparison groups, adequate sample size, and sample inclusion/exclusion criteria, as well as considerations that are specific to the methods of collecting and assaying cortisol levels, that can explain the discrepant finding. However, the simplest explanation for disparate observations is that cortisol levels can show day to day fluctuations, making it difficult to consistently observe group differences.

Table 1 Summary of data from studies of 24-h urinary cortisol excretion in adults with PTSD

Author(s), year	Trauma survivors with PTSD Cortisol μg/day (*n*)		Trauma w/out PTSD Cortisol μg/day (*n*)		Normal comparison Cortisol μg/day (*n*)		Psychiatric comparison Cortisol μg/day (*n*)	
Mason et al. 1986*	33.3	(9)					48.5	(35)
Kosten et al. 1990*	50.0	(11)			55.0	(28)	70.0	(18)
Pitman and Orr 1990**	107.3	(20)	80.5	(15)				
Yehuda et al. 1990*	40.9	(16)			62.8	(16)		
Yehuda et al. 1993a*	38.6	(8)					69.4	(32)
Yehuda et al. 1995b*	32.6	(22)	62.7	(25)	51.9	(15)		
Lemieux and Coe 1995**	111.8	(11)	83.1	(8)	87.8	(9)		
Maes et al. 1998**	840.0	(10)			118	(17)	591.0	(10)
Thaller et al. 1999*	130.9	(34)			213.9	(17)		
Baker et al. 1999	84.4	(11)			76.2	(12)		
DeBellis et al. 1999**	57.3	(18)			43.6	(24)	56.0	(10)
Yehuda et al. 2000*	48.3	(22)			65.1	(15)		
Rasmusson et al. 2001	42.8	(12)			34.6	(8)		
Glover and Poland 2001*[a]	9.8	(14)	16.5	(7)	12.8	(8)		

*Denotes findings in which cortisol levels were significantly lower than comparison subjects, or, in the case of Kosten et al., from depression only. **Denotes findings in which cortisol levels were significantly higher than comparison subjects. [a]Results are from a 12-h rather than 24-h urine collection and are expressed as μg/12 h.

2.2 Cortisol Levels Over the Diurnal Cycle in PTSD

Among the many potential methodologic problems associated with 24-h urine collections is the possibility that persons who are asked to collect 24-h samples at home may not provide complete collections. To the extent that there may be a systematic bias in protocol nonadherence between subjects with and without PTSD, in that the former might be more likely to miss collections than the latter, this could contribute to observed low cortisol levels. One of the initial rationales for performing a comprehensive circadian rhythm analysis was to corroborate and extend findings from the 24-h urine excretion studies and those using single-point estimates (Yehuda et al. 1990). 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 non-psychiatric comparison subjects—every 30 min over a 24-h period under carefully controlled laboratory conditions.

Mean basal cortisol release was found to be significantly lower in the PTSD, and cortisol levels were also reduced, at several points during the circadian period, 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 A.M., 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. In a second study, these findings were replicated and extended in a sample of 52 women with and without a history of early childhood sexual abuse and PTSD. Cortisol levels obtained every 15 min over a 24-h period demonstrated significantly low cortisol levels, this time in the afternoon and evening hours in the PTSD group.

Thaller et al. also reported that PTSD subjects seemed to show a greater dynamic range as evidenced by a greater disparity between 8:00 A.M. and 5:00 P.M. cortisol levels compared to those of normal controls (Thaller et al. 1999). In PTSD, mean cortisol levels were 21.6 μg/dl in the A.M. and 8.8 μg/dl in the P.M. compared to 21.4 μg/dl in the A.M. and 14.6 μg/dl at 5:00 P.M. for comparison subjects. These findings are consistent with those obtained from the more comprehensive circadian rhythm analysis, indicating that cortisol levels are comparable at their peak, but lower at the nadir in PTSD. In contrast, Hoffman et al. also reported a greater A.M. to P.M. decline in PTSD, but in this case subjects with PTSD went from 18.2 μg/dl to 10.1 μg/dl, compared to control subjects who diminished from 14.1 μg/dl to 9.9 μg/dl (Hoffman et al. 1989).

In Yehuda et al., the raw cortisol data were then subjected to single and multi-oscillator cosinor analyses to determine circadian rhythm parameters (Yehuda et al. 1996b). An increased amplitude-to-mesor (midline estimating statistic of

rhythm) ratio reflected the fact that PTSD subjects displayed a greater dynamic range of cortisol compared to controls. That is, although the cortisol peak among individuals without PTSD was not statistically different from the peak among individuals with PTSD, the lower trough among those with PTSD, and the longer period spent at the nadir, resulted in a decreased mesor. Considering differences in the peak of cortisol relative to the mesor also provides an estimate of the "signal-to-noise" ratio of the system. In contrast, depressed patients showed a less dynamic circadian release of cortisol, reflected in an increased mesor of cortisol release over the 24-h cycle, a decreased amplitude-to-mesor ratio, and an elevated trough (Yehuda et al. 1996b). These findings suggest that the main feature of basal cortisol release in PTSD is potential for a greater reactivity of the system.

2.3 Cortisol Levels in Response to Stress

The potential significance of the findings of an increased range of cortisol is that the HPA axis may be maximally responsive to stress-related cues in PTSD, whereas major depressive disorder may reflect a condition of minimal responsiveness to the environment. That is, an enhanced amplitude-to-mesor ratio describes a system with particularly low background activity and, accordingly, a potentially increased capacity to respond to environmental cues. In support of this, Liberzon et al. observed an increased cortisol [but not increased corticotrophin (ACTH)] response in combat veterans with PTSD compared to controls who were exposed to white noise and combat sounds (Liberzon et al. 1999). Elizinga et al. also observed that women with PTSD related to childhood abuse had substantially higher salivary cortisol levels in response to hearing scripts related to their childhood experiences compared to controls, who had relatively lower cortisol levels in response to hearing scripts of other people's traumatic stories (Elzinga et al. 2003). Similarly, Bremner et al. also observed an increased salivary cortisol response in anticipation of a cognitive challenge test relative to controls in women with PTSD related to childhood abuse (these were a subset of the same women in whom plasma cortisol levels had been low at baseline) (Bremner et al. 2003a). The authors suggest that although cortisol levels were found low at baseline, there did not appear to be an impairment in the cortisol response to stressors in PTSD. These studies demonstrate transient increases in cortisol levels that are consistent with the notion of a more generalized HPA axis reactivity in PTSD.

2.4 Observations About Baseline Cortisol Based on Single Estimates of Plasma or Saliva

Investigations of single plasma and salivary cortisol levels have become increasingly popular in the last decade given the relative ease in acquiring samples.

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). Variability in single sampling estimates of cortisol may also reflect individual variation in sleep cycles. Because cortisol levels steadily decline from their peak, which is usually observed at 30 min post-awakening (Hucklebridge et al. 1999), differences in wake-time of several minutes to an hour may increase the variability substantially.

Table 2 provides a summary of cortisol levels in studies that specifically obtained 8:00 A.M. cortisol concentrations, and highlights the lack of uniform findings in relation to cortisol levels, possibly reflecting the above-mentioned methodologic considerations. Of particular note, however, is Boscarino's report of low cortisol in a large epidemiologic sample of over 2,000 Vietnam veterans with PTSD compared to those without PTSD, which implies that to consistently observe low morning cortisol would require an extremely large sample size (Boscarino 1996). The magnitude of difference between PTSD and non-PTSD subjects at 8:00 A.M. was very modest—there was only a 4% difference between veterans with and without current or lifetime PTSD. Cortisol levels were significantly lower in combat veterans with very high exposure (17.9 μg/day) compared to those with no or low exposure (19.1 μg/day). The finding of an inverse relationship between combat exposure severity and 8:00 A.M. cortisol levels had been reported earlier in a much smaller sample of Vietnam veterans (Yehuda et al. 1995a).

The use of salivary assessments has helped supply data in studies of children and adolescents, for whom even a blood draw may be too invasive, and also helped in our evaluation of longitudinal outcomes. King et al. (2001) observed significantly low cortisol levels in children aged 5–7 years who had been sexually abused compared to control subjects. Goenjian et al. (1996) demonstrated a relationship between low salivary cortisol levels and PTSD symptoms in adolescents exposed to the Armenian earthquake. However, both Lipschitz et al. (2003) and Carrion et al. (2002) failed to note differences in salivary cortisol levels at baseline in multiply traumatized adolescents.

Using repeated salivary cortisol assessments in a single individual, Kellner et al. (1997) demonstrated that salivary cortisol decreased dramatically 3 months after a traumatic event, and in the course of further research showed an inverse relation to fluctuating, but gradually improving PTSD symptoms. Post-dexamethasone (post-DEX) cortisol was suppressed below the detection limit early after trauma, and rose again more than 1 year post-trauma. In a similar case report, Heber et al. demonstrated an increase in basal salivary cortisol and an increasingly attenuated cortisol response to dexamethasone (DEX) in PTSD patients who were successfully treated using eye-movement desensitization reprocessing therapy (EMDR) (Heber et al. 2002), suggesting some relationship between low cortisol and PTSD symptoms.

Table 2 Plasma A.M. cortisol levels in PTSD and comparison subjects

Reference	Trauma survivors with PTSD Cortisol µg/day (*n*)		Trauma w/out PTSD Cortisol µg/day (*n*)		Normal comparison Cortisol µg/day (*n*)		Psychiatric comparison Cortisol µg/day (*n*)	
Hoffman et al. 1989**	18.2	(21)			14.1	(20)		
								(23)
Halbreich et al. 1989	7.7	(13)			7.3	(21)	12.3	(MDD)
Yehuda et al. 1991b	14.3	(15)			14.9	(11)		
Yehuda et al. 1993b	14.3	(21)			15.1	(12)		
Yehuda et al. 1995a*	12.7	(14)	16.4	(12)	15.0	(14)		
								(14)
Yehuda et al. 1996a[#]	11.6	(15)			14.2	(15)	12.2	(MDD)
Yehuda et al. 1996a[#]	11.8	(11)			9.8	(8)		
Boscarino 1996*	17.7	(293)	18.4	(2197)				
Jensen et al. 1997*	4.6	(7)			8.9	(7)	9.9	(7)
								(Panic)
Liberzon et al. 1999**	12.1	(17)	7.9	(11)	9.3	(14)		
Thaller et al 1999	21.6	(34)			21.4	(17)		
Kellner et al. 2000*	7.8	(8)			13.3	(8)		
Kanter et al. 2001*[#]	7.6	(13)			10.6	(16)		
Atmaca et al. 2002**	12.9	(14)			10.7	(14)		
Gotovac et al. 2003*	14.4	(28)			17.2	(19)		
Seedat et al. 2003*	10.3	(10)	10.6	(12)	13.4	(16)		
								(45)
Oquendo et al. 2003[#]*	11.8	(13)			14.8	(24)	16	(MDD)
Lueckeh et al. 2004[#]*	8.7	(13)			14.4	(47)		(Cancer)
Yehuda et al. 2004a,b								

[#]No means reported in the text; data estimated from the figures provided. *Significantly lower in PTSD than normal comparison. **Significantly higher in PTSD than normal comparison. MDD, major depressive disorder.

2.5 Correlates of Cortisol in PTSD

Even in cases where there is failure to find group differences, there are often correlations within the PTSD group with indices of PTSD symptom severity. Baker et al. (1999) failed to find group differences between Vietnam veterans with PTSD compared to non-exposed controls, but did report a negative correlation between 24-h urinary cortisol and PTSD symptoms in combat veterans. A negative correlation between baseline plasma cortisol levels and PTSD symptoms, particularly avoidance and hyperarousal symptoms, were observed in adolescents with PTSD (Goenjian et al. 2003). Rasmusson et al. (2003) failed to observe a significant difference in urinary cortisol between premenopausal women with PTSD and healthy women, but noted an inverse correlation between duration since the trauma and cortisol levels, implying that low cortisol is associated with early traumatization. This finding is consisted with Yehuda and colleagues' observation of an inverse relationship between childhood emotional abuse and cortisol levels in adult children of Holocaust survivors (Yehuda et al. 2002a).

Cortisol levels have also been correlated with findings from brain imaging studies in PTSD. In one report, there was a positive relationship between cortisol levels and hippocampal acetylaspartate (NAA)—a marker of cell atrophy presumed to reflect changes in neuronal density or metabolism—in subjects with PTSD, suggesting that rather than having neurotoxic effects, cortisol levels in PTSD may have a trophic effect on the hippocampus (Neylan et al. 2003a). Similarly, cortisol levels in PTSD were negatively correlated with medial temporal lob perfusion, while anterior cingulate perfusion and cortisol levels were positively correlated in PTSD, but negatively correlated in trauma survivors without PTSD (Bonne et al. 2003b). The authors suggest that the negative correlation may result from an augmented negative hippocampal effect secondary to increased sensitivity of brain glucocorticoid receptors (GRs), which would account for the inverse correlation in PTSD despite equal cortisol levels in both the PTSD and non-PTSD groups. On the other hand, the positive correlation between regional cerebral blood flow in the fronto-cingulate transitional cortex and cortisol levels in PTSD may reflect unsuccessful attempts of the fronto-cingulate transitional cortex to terminate the stress response, which has also been linked to low cortisol.

Cortisol may be related to specific, or state-dependent features of the disorder, such as comorbid depression or the time course of the disorder. Mason et al. (2001) have underscored the importance of examining intrapsychic correlates of individual differences in cortisol levels in PTSD, and have hypothesized that cortisol levels in PTSD may be related to different levels of emotional arousal, and opposing antiarousal disengagement defense mechanisms or other coping styles. Further, Wang et al. have posited that adrenal activity may change

over time in a predicted manner reflecting stages of decompensation in PTSD (Wang et al. 1996).

2.6 CRF Levels in PTSD

There have been three published reports examining the concentration of corticotrophin-releasing factor (CRF) in cerebrospinal fluid (CSF) in PTSD. The assessment of CSF CRF does not necessarily provide a good estimate of hypothalamic CRF release, but rather, an estimate of both hypothalamic and extrahypothalamic release of this neuropeptide (Yehuda and Nemeroff 1994). An initial report using a single lumbar puncture indicated that CRF levels were elevated in combat veterans with PTSD (Bremner et al. 1997). A second study, examining serial CSF sampling over a 6-h period by means of an indwelling catheter, also reported significantly higher CSF CRF concentrations, but did not observe a relationship between CRF and 24-h urinary cortisol release (Baker et al. 1999). A third report demonstrated that PTSD subjects with psychotic symptoms had significantly higher mean levels of CRF than either subjects with PTSD without psychotic symptoms or controls subjects (Sautter et al. 2003).

2.7 ACTH Levels in PTSD

Among the challenges in assessing pituitary activity under basal conditions is the fact that the normal positive and negative feedback influences on the pituitary can mask the true activity of this gland. Because the pituitary mediates between CRF stimulation from the hypothalamus and the inhibition of ACTH release resulting from the negative feedback of adrenal corticosteroids, baseline ACTH levels may appear to be "normal" even though the pituitary gland may be receiving excessive stimulation from CRF. In most studies ACTH levels in PTSD patients were reported to be comparable to non-exposed subjects.

The majority of studies has reported no detectible differences in ACTH levels between PTSD and comparison subjects even when cortisol levels obtained from the same sample were found to be significantly lower. This pattern was observed in Kellner et al. who reported that cortisol levels were 41% lower, but that ACTH levels were only 7.4% lower in PTSD compared to normals (Kellner et al. 2000), and Hockings et al. who showed that cortisol levels were 12% lower in PTSD but ACTH levels identical to controls (Hockings et al. 1993). Kanter et al. also reported that cortisol levels were substantially lower in PTSD, while ACTH levels were comparable to controls (Kanter et al. 2001). In Yehuda et al. cortisol levels were lower at baseline on the placebo day in PTSD, but not at the baseline time point on the metyrapone day (i.e., prior

to metyrapone administration) compared to comparison subjects, but ACTH levels were comparable in both groups on both days (Yehuda et al. 1996a). Similar data were reported by Neylan et al. (2003a).

Lower cortisol levels in the face of normal ACTH levels can reflect a relatively decreased adrenal output. Yet under circumstances of classic adrenal insufficiency, there is usually increased ACTH release compared to normal levels. Thus, in PTSD there may be an additional component of feedback on the pituitary that is acting to depress ACTH levels, making them appear normal. Indeed, elevations in ACTH would be expected not only from a reduced adrenal output but also from increased CRF stimulation (Baker et al. 1999; Bremner et al. 1997). On the other hand, the adrenal output in PTSD may be relatively decreased, but not substantially enough to affect ACTH levels. In any event, the "normal" ACTH levels in PTSD in the context of the other findings suggest a more complex model of the regulatory influences on the pituitary in this disorder than reduced adrenal insufficiency.

In contrast to the above-mentioned findings, Hoffman et al. reported that cortisol levels were 22.5% higher in PTSD, but ACTH was only 4% lower compared to controls (Hoffman et al. 1989). In this report, mean plasma β-endorphin (co-localized and released with ACTH) was reported as lower in PTSD. Liberzon et al. also reported mean cortisol levels to be 33% higher, but ACTH 31% lower in PTSD compared to controls (Liberzon et al. 1999). Smith et al. also reported cortisol levels were 48% higher and ACTH 32% lower in PTSD than controls, but this was in the afternoon (Smith et al. 1989). Although ACTH levels were not significantly different in PTSD compared to controls, the increase in cortisol relative to ACTH is reminiscent of classic models of HPA dysregulation in depression where there is hypercortisolism but a reduced ACTH negative feedback inhibition. Rasmusson et al. (2001) demonstrated a 13% increase in cortisol with no differences in ACTH in PTSD at 8:00 P.M., which is consistent with the idea of an overall, but somewhat mild, HPA hyperactivity.

2.8 Corticosteroid Binding Globulin

Kanter et al. reported an increase concentration of the corticosteroid binding globulin (CBG) (Kanter et al. 2001). Most cortisol is bound to CBG, and is biologically inactive. A greater concentration of CBG is consistent with low levels of measurable free cortisol, and provides a putative explanation for how cortisol levels could be measurably low even though other aspects of HPA axis functioning do not seem hypoactive. However, the extent to which CBG levels are a contributing cause of low cortisol requires further examination.

3 Glucocorticoid Receptors in PTSD

Type II GRs are expressed in ACTH- and CRF-producing neurons of the pituitary, hypothalamus, and hippocampus, and mediate most systemic glucocorticoid effects, particularly those related to stress responsiveness (deKloet et al. 1991). Low circulating levels of a hormone or neurotransmitter can result in increased numbers of available receptors (Sapolsky et al. 1984) that improve response capacity and facilitate homeostasis. However, alterations in the number and sensitivity of both type I (mineralocorticoid) and type II GRs can also significantly influence HPA axis activity, and in particular, can regulate hormone levels by mediating the strength of negative feedback (Svec 1985; Holsboer et al. 2000).

Lymphocyte and brain GRs have been found to share similar regulatory and binding characteristics (Lowy 1989). A greater number of 8:00 A.M., but not 4:00 P.M., mononuclear leukocytes (presumably lymphocyte) type II GRs was reported in Vietnam veterans with PTSD compared to a normal comparison group (Yehuda et al. 1991b). Subsequently, Yehuda et al. reported an inverse relationship between 24-h urinary cortisol excretion and lymphocyte GR number in PTSD and depression (i.e., low cortisol and increased receptor levels were observed in PTSD, whereas in major depressive disorder, elevated cortisol and reduced receptor number were observed) (Yehuda et al. 1993a). Although it is not clear whether alterations in GR number reflect an adaptation to low cortisol levels or some other alteration, the observation of an increased number of lymphocyte GRs provided the basis for the hypothesis of an increased negative feedback inhibition of cortisol secondary to increased receptor sensitivity (Yehuda et al. 1995a).

Following the administration of a 0.25-mg dose of DEX, it was possible to observe that the cortisol response was accompanied by a concurrent decline in the number of cytosolic lymphocyte receptors (Yehuda et al. 1995a). This finding contrasted with the observation of a reduced decline in the number of cytosolic lymphocyte receptors in major depression, implying that the reduced cortisol levels following DEX administration may reflect an enhanced negative feedback inhibition in PTSD (Gormley et al. 1985).

Observations regarding the cellular immune response in PTSD are also consistent with enhanced GR responsiveness in the periphery. In one study, beclomethasone-induced vasoconstriction was increased in women PTSD subjects compared to healthy, non-trauma-exposed comparison subjects (Coupland et al. 2003). Similarly, an enhanced delayed-type hypersensitivity of skin test responses was observed in women who survived childhood sexual abuse vs those who did not (Altemus et al. 2003). Because immune responses, like endocrine ones, can be multiply regulated, these studies provide only indirect evidence of GR responsiveness. However, when considered in the context of the observation that PTSD patients showed increased expression of the re-

ceptors in all lymphocyte subpopulations, despite a relatively low quantity of intracellular GR as determined by flow cytometry, and in the face of lower ambient cortisol levels (Gotovac et al. 2003), the findings convincingly support an enhanced sensitivity of the GR to glucocorticoids. Furthermore, Kellner et al. reported an absence of alterations of the mineralocorticoid receptor in PTSD as investigated by examining the cortisol and ACTH response to spironolactone following CRF stimulation (Kellner et al. 2002a).

Finally, a recent study provided the first demonstration of an alteration in target tissue sensitivity in glucocorticoids using an in vitro paradigm. Mononuclear leukocytes isolated from the blood of 26 men with PTSD and 18 men without PTSD were incubated with a series of concentrations of DEX to determine the rate of inhibition of lysozyme activity; a portion of cells was frozen for the determination of GRs. Subjects with PTSD showed evidence of a greater sensitivity to glucocorticoids as reflected by a significantly lower mean lysozyme $IC_{50\text{-}DEX}$ (nM). The lysozyme $IC_{50\text{-}DEX}$ was significantly correlated with age at exposure to the first traumatic event in subjects with PTSD. The number of cytosolic GRs was correlated with age at exposure to the focal traumatic event (Yehuda et al., in press).

4
Cortisol and ACTH Responses to Neuroendocrine Challenge

4.1
The Dexamethasone Suppression Test in PTSD

In contrast to observations regarding ambient cortisol and ACTH levels, results using the DEX suppression test (DST) have presented a more consistent view of reduced cortisol suppression in response to DEX administration. The DST provides a direct test of the effects of GR activation in the pituitary on ACTH secretion, and cortisol levels following DEX administration are thus interpreted an estimate of the strength of negative feedback inhibition, provided that the adrenal response to ACTH is not altered. There are several hundred published studies reporting on the use of the DST in depression, all reporting that approximately 40%–60% of patients with major depression demonstrate a failure to suppress cortisol levels below 5.0 µg/100 dl in response to 1.0 mg of DEX (Ribeiro et al. 1993). Nonsuppression of cortisol results from a reduced ability of DEX to exert negative feedback inhibition on the release of CRF and ACTH (Holsboer 2000).

The initial DST studies in PTSD using the 1.0-mg dose of DEX did not consider the possibility of a hypersuppression to DEX and tested the hypothesis that patients with PTSD might show a nonsuppression of cortisol similar to patients with major depressive disorder. A large proportion of the PTSD subjects studied also met criteria for major depression. Four (Dinan et al.

1990; Halbreich et al. 1989; Kosten et al. 1990; Reist et al. 1995) out of five (Kudler et al. 1987) of the earlier studies noted that PTSD did not appear to be associated with cortisol nonsuppression, using the established criterion of 5 µg/100 ml at 4:00 P.M. A more recent study did not use the established criterion to determine nonsuppression, but nonetheless reported a greater mean cortisol in PTSD compared to normal subjects at 8:00 A.M. (Thaller et al. 1999). In this study, Thaller et al. reported that DEX resulted in 67% suppression in PTSD (*n*=34) compared to 85% suppression in comparison (*n*=17) subjects. Similarly, Atmaca et al. showed a significantly higher DST nonsuppression in the PTSD group (63.12%) compared to healthy controls (79.6%) using the 1.0 mg DST (Atmaca et al. 2002).

Although the 1.0-mg 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 (Halbreich et al. 1987). The mean post-DEX cortisol levels were 0.96±0.63 µg/dl in PTSD compared to 3.72±3.97 µg/dl in depression and 1.37± µg/dl in comparison subjects, raising the possibility that the 1-mg dose produced a "floor effect" in the PTSD group. Based on this observation, and on findings of low cortisol and increased GR number, 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 (Yehuda et al. 1993a, 1995a). 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 enhanced suppression of cortisol was present in combat veterans with PTSD who met the diagnostic criteria for major depressive disorder (Yehuda et al. 1993a) and was not present in combat veterans without PTSD (Yehuda et al. 1995a).

The finding of an exaggerated suppression of cortisol in response to DEX was also observed by Stein et al. who studied adult survivors of childhood sexual abuse (Stein et al. 1997), and by Kellner et al. who evaluated Gulf War soldiers who were still in active duty about a year an a half after their deployment to the Persian Gulf (Kellner et al. 1997). More recently, an exaggerated suppression following 0.50 mg DEX was also observed in older subjects with PTSD (i.e., Holocaust survivors and combat veterans) compared to appropriate comparison subjects (Yehuda et al. in 2002b) in a sample of depressed women with PTSD resulting from early childhood abuse (Newport et al. 2004), and a mixed group of trauma survivors with PTSD (Yehuda et al. 2004b; Table 3).

Results from these studies are expressed as the extent of cortisol suppression, evaluated by the quotient of 8:00 A.M. post-DEX cortisol to 8:00 A.M. baseline cortisol. Expressing the data in this manner accounts for individual differences in baseline cortisol levels and allows for a more precise characterization of the strength of negative feedback inhibition as a continuous rather than as a dichotomous variable. Whereas studies of major depression empha-

size the 4:00 P.M. post-DEX value as relevant to the question of nonsuppression (Stokes et al. 1984), studies of PTSD have been concerned with the degree to which DEX suppresses negative feedback at the level of the pituitary, rather than the question of "early escape" from the effects of DEX. Goeinjian et al. observed an enhanced suppression of salivary cortisol at 4:00 P.M. following 0.50 mg of DEX in adolescents who had been closer to the epicenter of an earthquake 5 years earlier (and had more substantial PTSD symptoms) compared to those who had been further from the epicenter (Goeinjian et al. 1996). However, the percentage suppression of cortisol in these two groups was comparable at 8:00 A.M. The authors concluded that the suppression of cortisol to DEX may last longer in PTSD. Unfortunately, the authors were not able to study a non-exposed comparison group. Similarly, Lipschitz et al. failed to observe cortisol hypersuppression at 8:00 A.M. in adolescents with PTSD exposed to multiple traumatic events (Lipschitz et al. 2004). Unfortunately, the authors were not able to obtain data at the 4:00 P.M. time point.

There is some debate about whether DST hypersuppression reflects trauma exposure in psychiatric patients or PTSD per se. Using the combined DEX/CRF challenge in women with borderline personality disorder with and without PTSD relating to sustained childhood abuse, Rinne et al. (2002) demonstrated that chronically abused patients with borderline personality disorder had a significantly enhanced ACTH and cortisol response to the DEX/CRF challenge

Table 3 Summary of data from studies of using the dexamethasone suppression test

Reference	Dex dose/day	PTSD: % supp (*n*)		Comparison: % supp (*n*)	
Yehuda et al. 1993b*	0.5	87.5	(21)	68.3	(12)
Stein et al. 1997*	0.5	89.1	(13)	80.0	(21)
Yehuda et al. 1995a*	0.5	90.0	(14)	73.4	(14)
Yehuda et al. 1995*	0.25	54.4	(14)	36.7	(14)
Kellner et al. 1997***	0.50	90.1	(7)		
Yehuda et al. 2002b*	0.50	89.9	(17)[#]	77.9	(23)
Grossman et al. 2003*[a]	0.50	83.6	(16)	63.0	(36)
Newport et al. 2004*[b]	0.50	92.3	(16*)	77.78	(19)
Yehuda et al. 2004b*	0.50	82.5	(19)	68.9	(10)

[#]Includes subjects without depression; subjects with both PTSD and MDD (*n*=17) showed a percentage suppression of 78.8, which differs from our previous report (Yehuda et al. 1993b) in younger combat veterans. *Significantly more suppressed than controls. **Significantly less suppressed than controls. ***No control group was studied. [a]Comparison subjects were those with personality disorders but without PTSD. [b]It is impossible from this paper to get the correct mean for the actual 15 subjects with PTSD. These 16 subjects had MDD, but 15/16 also had PTSD, so this group also contains 1 subject who had been exposed to early abuse with past, but not current, PTSD.

compared with nonabused subjects, suggested a hyperresponsiveness of the HPA axis. The authors attribute the finding to trauma exposure. On the other hand, Grossman et al. (2003) examined the cortisol response to 0.50 mg DEX in a sample of personality disordered subjects and found that cortisol hypersuppression was related to the comorbid presence of PTSD, but not trauma exposure.

In the study by Newport and colleagues (2004), the authors attempted to determine whether cortisol hypersuppression was related to early abuse in PTSD and major depression. However, insofar as all the exposed subjects with current depression had PTSD (all except one), it was difficult to attribute the observed hypersuppression to PTSD or depression. Recently, however, Yehuda et al. observed cortisol hypersuppression following 0.50 mg DST in PTSD, and subjects with both PTSD and depression, but noted that hypersuppression was particularly prominent in persons with depression comorbidity if there had been a prior traumatic experience. Thus, cortisol hypersuppression in response to DEX appears to be associated with PTSD, but in subjects with depression, hypersuppression may be present as a result of early trauma, and possibly past PTSD (Yehuda et al. 2004b).

4.2 The Cholecystokinin Tetrapeptide Challenge Test in PTSD

Cholecystokinin tetrapeptide (CCK)-4 is a potent stimulator of ACTH. Kellner et al. administered a 50-μg bolus of CCK-4 to subjects with PTSD and found substantially attenuated elevations of ACTH in PTSD, which occurred despite comparable ACTH levels at baseline (Kellner et al. 2000). 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 ACTH response to CCK-4 is compatible with the idea of CRF overdrive in PTSD, and is a similar to the administration of CRF. That less ACTH can produce a similar activation of the adrenal gland, 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. Although the comparatively greater effects on cortisol relative to ACTH is also compatible with an increased sensitivity of the adrenal gland to ACTH, rather than an enhanced negative feedback sensitivity on the pituitary, this explanation only accounts for the greater rise cortisol, but not the more rapid rate of decline of cortisol, following CCK-4.

4.3 The Metyrapone Stimulation Test

Whereas both the results of the DST and CCK challenge tests are consistent with the idea of an enhanced negative feedback inhibition in PTSD, these alter-

ations do not directly imply that an enhanced negative feedback inhibition is a primary disturbance in PTSD. Yehuda et al. used the metyrapone stimulation test as a way of providing further support for the enhanced negative feedback hypothesis (Yehuda et al. 1996a). Metyrapone prevents adrenal steroidogenesis by blocking the conversion of 11-deoxycortisol to cortisol, thereby unmasking the pituitary gland from the influences of negative feedback inhibition. If a sufficiently high dose of metyrapone is used such that an almost complete suppression of cortisol is achieved, this allows a direct examination of pituitary release of ACTH without the potentially confounding effects of differing ambient cortisol levels. When metyrapone is administered in the morning—when HPA axis activity is relatively high—maximal pituitary activity can be achieved, facilitating an evaluation of group differences in pituitary capability. The administration of 2.5 mg metyrapone in the morning resulted in a similar and almost complete reduction in cortisol levels in both PTSD and normal subjects (i.e., and removal of negative feedback inhibition), but a higher increase in ACTH and 11-deoxycortisol in combat Vietnam veterans with PTSD compared to non-exposed subjects (Yehuda et al. 1996a). 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. Both pituitary and adrenal insufficiency would not likely result in an increased ACTH response to removal of negative feedback inhibition, since the former would be associated with an attenuated ACTH response and reduced adrenal output would not necessarily affect the ACTH response. To the extent that ambient cortisol levels are lower than normal, an increased ACTH response following removal of negative feedback inhibition implies that when negative feedback is intact, it is strong enough to inhibit ACTH and cortisol. The increased ACTH response is most easily explained by increased suprapituitary activation; however, a sufficiently strong negative feedback inhibition would account for the augmented ACTH response even in the absence of hypothalamic CRF hypersecretion.

Kanter et al. failed to find evidence for an exaggerated negative feedback inhibition using a different type of metyrapone stimulation paradigm (Kanter et al. 2002). In this study, a lower dose of metyrapone was used, administered over a 3-h period (750 mg at 7:00 A.M. and 10:00 A.M.), and rather than simply examining the ACTH response to this manipulation, the cortisol levels were introduced by means of an infusion, 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 ACTH in PTSD. However, no significant differences in the ACTH response to cortisol infusion between PTSD and comparison subjects (but a non-significant trend, p=.10, for such a reduction) were observed. There was, however, a reduced response of 11-*b*-deoxycortisol. The authors concluded that their findings provided evidence of sub-clinical adrenocortical insufficiency.

In evaluating this finding, it must be noted, as the authors do, that at the dose used, metyrapone did not accomplish a complete suppression of cortisol in this study. Furthermore, the manipulation produced a more robust suppression of cortisol in comparison subjects, suggesting that the control group was significantly more perturbed by the same does of metyrapone prior to the cortisol infusion than the PTSD group. The authors suggest that the lack of decline in ACTH following cortisol infusion in the PTSD group argues against an enhanced negative feedback inhibition. However, insofar as the drug produced a significantly greater decrease in cortisol in the comparison subjects, while not producing a significant difference in ACTH concentrations, it might be that the lack of an ACTH reduction in PTSD following cortisol infusion may have been caused by a floor effect, rather than a demonstration of lack of reactivity of the system. Indeed, because metyrapone at the dose used did not fully suppress cortisol, the endogenous cortisol present may have already been high enough to suppress ACTH secretion in the PTSD group. Interestingly, although metyrapone did not result in as great a decline of cortisol in PTSD, it did result in the same level of cortisol inhibition, implying differences in the activity of the enzyme 11-β-hydroxylase, which merits further investigation.

To the extent that there was a significant reduction of the 11-deoxycortisol response in PTSD in the absence of an attenuated ACTH response, this would indeed support the idea of a reduced adrenal output. However, the trend for an ACTH response suggests that part of the failure to achieve statistical significance may have also occurred because of limited power, particularly given the lack of evidence for increased ambient ACTH levels in PTSD relative to normal controls. Dose–response studies using the higher vs lower dose of metyrapone should certainly be conducted to further address this critical issue.

A third study used metyrapone to evaluate CRF effects on sleep, but in the process also provided information relevant to negative feedback inhibition. Metyrapone (750 mg) was administered at 8:00 A.M. every 4 h for 16 h, and cortisol, 11-deoxycortisol and ACTH levels were measured at 8:00 A.M. the following morning. Cortisol, 11-deoxycortisol, and ACTH levels were increased in the PTSD group relative to the controls, suggesting that the same dose of metyrapone did not produce the same degree of adrenal suppression of cortisol synthesis. Under these conditions, it is difficult to evaluate the true effect on ACTH and 11-deoxycortisol, which depends on achieving complete cortisol suppression, or at least the same degree of cortisol suppression in the two groups. The endocrine response to metyrapone in this study does not support the model of reduced adrenal capacity, since this would have been expected to yield a large ratio of ACTH to cortisol release; yet the mean ACTH/cortisol ratio prior to metyrapone was no different in PTSD vs controls. On the other hand, the mean ACTH/cortisol ratio post-metyrapone was lower, though non-significantly, suggesting, if anything, an exaggerated negative feedback rather than reduced adrenal capacity (Neylan et al. 2003a).

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 (Heim et al. 2000). There are numerous stress-related disorders such as chronic fatigue syndrome, fibromyalgia, rheumatoid arthritis, chronic pain syndromes, and other disorders that are characterized by hypocortisolism. In one study, Heim et al. showed decreased cortisol responses to low-dose DEX, but failed to observe blunted ACTH responses to CRF in women with chronic pelvic pain, some of whom had PTSD, compared to women with infertility (Heim et al. 1998). Since the data were not analyzed on the basis of the subgroup with and without trauma and/or PTSD, it is not possible to directly compare results of that study to other reports examining PTSD directly.

4.4
The CRF Challenge Test and ACTH Stimulation Test in PTSD

Infusion of exogenous CRF increases ACTH levels and provides a test of pituitary sensitivity. In several studies of major depression, the ACTH response to CRF was shown to be "blunted," reflecting a reduced sensitivity of the pituitary to CRF (e.g., Krishnan 1993). This finding has been widely interpreted as reflecting a downregulation of pituitary CRF receptors secondary to CRF hypersecretion, but may also reflect increased cortisol inhibition of ACTH secondary to hypercortisolism (Krishnan 1993; Yehuda and Nemeroff 1994).

A study of eight PTSD subjects demonstrated that the ACTH response to CRF is also blunted (Smith et al. 1989). However, although the authors noted a uniform blunting of the ACTH response, this did not always occur in the context of hypercortisolism. Furthermore, although the ACTH response was significantly blunted, the cortisol response was not (however, though not statistically significant, it should be noted that the area under the curve for cortisol was 38% less than controls). Bremner et al. also observed a blunted ACTH response to CRF in women with PTSD as a result of early childhood sexual abuse (Bremner et al. 2003b). Yehuda et al. previously suggested that the blunted ACTH response in PTSD might reflect an increased negative feedback inhibition of the pituitary secondary to increased GR number or sensitivity (Yehuda et al. 1995a). This explanation supports the idea of CRF hypersecretion in PTSD, and explains the pituitary desensitization and resultant lack of hypercortisolism as arising from a stronger negative feedback inhibition.

A blunted ACTH response to CRF in the context of a normal cortisol response was also observed in sexually abused girls, but the diagnosis of PTSD was not systematically made in this study (deBellis et al. 1994). When living in the context of ongoing abuse, abused children with depression showed an enhanced ACTH response to CRF in comparison with abused children without depression and normals (Kauffman et al. 1997). Again, although such subjects

were considered at greater risk for the development of PTSD, it is difficult to draw direct conclusions from these studies about the neuroendocrinology of PTSD because this variable was not directly measured.

In contrast, Rasmusson et al. (2001) recently reported an augmented ACTH response to CRF in 12 women with PTSD compared to 11 healthy controls. In the same subjects, the authors also performed a neuroendocrine challenge with 250 μg of cosyntropin (ACTHα1-24) to determine the response of the pituitary gland to this maximally stimulating dose. Women with PTSD demonstrated an exaggerated cortisol response to ACTH compared to healthy subjects. Basal assessments did not reveal group differences in either 24-h urinary cortisol levels, or basal plasma cortisol or ACTH levels. The authors concluded that their findings suggested an increased reactivity of both the pituitary and adrenal in PTSD.

What is particularly interesting about the finding of the increased ACTH in response to CRF is that the magnitude of the ACTH response appeared to be much higher than the cortisol response. The ACTH response was 87% greater in the subjects with PTSD, but the cortisol response was only 35% higher. Thus, although ACTH levels were more increased in PTSD than controls, this increased ACTH level did not result in a comparable stimulation of cortisol, suggesting a reduced adrenal capacity or an enhanced inhibition of cortisol. On the other hand, Rasmusson and colleagues' demonstration of an increased cortisol response to cosyntropin in the same patients suggests the opposite. The authors do not discuss the possibility that the results of the CRF test suggest reduced adrenal capacity, nor do they suggest a model that accounts for the co-existence of these two apparently disparate observations.

Attempting to resolve the two discrepant observations in the Rasmusson et al. finding (2001) will by necessity require viewing HPA axis alterations as reflecting a more complex set of processes than are currently described in classical clinical endocrinology, and will be aided, no doubt, by the appearance of currently unavailable information. However, the discrepancy may also result from a methodologic artifact owing to the administration of the cosyntropin at variable times during the day (ranging from 8:15 A.M. to 4:15 P.M.). It may be that if the cortisol data were corrected for time of day of administration of cosyntropin that the findings might no longer be significant, and it would be important to rule this out. Indeed, to conclude that a greater reactivity of the pituitary gland occurs in the context of a more reduced cortisol response would be a simpler observation to contend with.

In fact, the observation of an increased ACTH response to CRF would be compatible with a recent study by Heim et al. who examined such responses in abused women with and without major depressive disorder compared with nonabused depressed women and comparison subjects (Heim et al. 2000). Abused women without depression showed an augmented ACTH response to CRF, but a reduced cortisol response to ACTH compared to other groups. Only a small proportion (4/20) met criteria for PTSD. Abused women with

depression (14/15 with PTSD) showed a blunted ACTH response to CRF compared to controls, as did nonabused women with depression. These findings are compatible with those of Smith et al. (1989). Although the study by Heim et al. (2000) did not focus directly on the issue of HPA alterations in PTSD, the model presented by the authors is extremely informative in suggesting the possibility 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. However, when depression is present, these alterations may be "overridden" by the results of depression-related CRF hypersecretion. Early trauma exposure is a risk factor not only for depression, but also for PTSD in the absence or presence of depression. It is possible that low cortisol levels resulting from this risk factor may also be influenced by PTSD-related alterations (i.e., increased GR responsiveness and increased responsiveness of negative feedback inhibition).

4.5
The Naloxone Stimulation Test in PTSD

Another strategy for examining CRF activity involves the assessment of ACTH and cortisol after administration of agents that normally block the inhibition of CRF. Naloxone increases CRF release by blocking the inhibition normally exerted by opioids in the hypothalamus. Naloxone was administered to 13 PTSD patients and 7 normal comparison subjects (Hockings et al. 1993). Of the PTSD subjects, 6/7 showed an increased ACTH and cortisol response to naloxone. These findings appear to contradict those of Smith et al. (1989) who showed a blunted ACTH response to CRF; however, here too the absence of information about ambient CRF complicates the interpretation of these findings. This finding is noteworthy for illustrating that only a proportion of subjects in a particular group may exhibit evidence of pituitary adrenocortical alterations.

5
Drawing Conclusions from Challenge Studies: Do They Provide a Window into the Brain?

Although the neuroendocrine challenges described above directly assess ACTH and cortisol, hypothalamic CRF release may be inferred from some of the results. For example, because metyrapone administration results in the elimination of negative feedback inhibition, its administration allows an exploration of suprapituitary release of ACTH, without the potentially confounding effects of differing ambient cortisol levels. To the extent that metyrapone administration results in a substantially higher increase in ACTH and 11-deoxycortisol

in PTSD compared to controls, it is possible to infer that the increase in ACTH results occurs as a direct result of hypothalamic CRF stimulation.

Similarly, the CRF challenge test has also been used to estimate hypothalamic CRF activity, since a blunted ACTH response is suggestive of a downregulation of pituitary receptors secondary to CRF hypersecretion. Using this logic, an augmented ACTH response to CRF would reflect a decreased hypothalamic CRF release, or at least an upregulation of pituitary CRF receptors. Rasmusson et al. (2001) assert that the finding of an increased ACTH response to CRF is analogous to the increased ACTH response to metyrapone obtained by Yehuda et al. (1996a). Although this might not be the most likely explanation for the finding, insofar as the subjects in Rasmusson et al. did not show increases in either basal ACTH or cortisol levels, it is possible that the finding of an augmented ACTH response to CRF does indeed reflect an enhanced negative feedback on the pituitary, particularly in view of the relatively weaker effect of CRF on cortisol relative to ACTH. However, the model of enhanced negative feedback inhibition would not explain the increased cortisol response to ACTH observed in the same patients.

6 Putative 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. Together, these findings imply that although cortisol levels may be generally lower, the adrenal gland is certainly capable of producing adequate amounts of cortisol in response to challenge.

The model of enhanced negative feedback inhibition is compatible with the idea that there may be transient elevations in cortisol, but would suggest that when present, these increases would be shorter-lived due to a more efficient containment of ACTH release as a result of enhanced GR activation. This model posits that chronic or transient elevations in CRF release stimulate the pituitary release of ACTH, which in turn stimulates the adrenal release of cortisol. However, an increased negative feedback inhibition would result in reduced cortisol levels under ambient conditions. In contrast to other models of endocrinopathy, which identify specific and usually singular primary alterations in endocrine organs and/or regulation, the model of enhanced negative feedback inhibition in PTSD is in large part descriptive. The model currently offers little explanation for why some individuals show such alterations of the HPA axis following exposure to traumatic experiences while others do not, but it represents an important development in the field of neuroendocrinology of PTSD by accounting for a substantial proportion of the findings observed.

On the other hand, the model of reduced adrenal output accounts for why ambient cortisol levels would be lower than normal, and even for the relatively smaller magnitude of differences in ACTH relative to cortisol, but does not account for why basal ACTH levels are not significantly higher in PTSD than in comparison subjects, particularly in light of evidence of CRF hypersecretion. One of the challenge in elucidating a neuroendocrinology of PTSD is in being able to resolve the apparent paradox that cortisol levels are low when CRF levels appear to be elevated, as well as to accommodate a dynamic process in that accounts for observed diurnal fluctuations and potential responsivity to environmental cues. Heim et al. (2001) have again argued that in response to early trauma, CRF hypersecretion may result in a downregulation of pituitary CRF receptors leading to a decreased ACTH response. However, it is not quite clear according to this 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.

Findings of increased CRF levels in PTSD are important to the theory of enhanced negative feedback inhibition in PTSD, but are not necessarily relevant to theories of adrenal insufficiency. That is, to the extent that there are increases in CRF, these would not necessarily occur as a direct response to reduced adrenal output, but might have a different origin. Under conditions of reduced adrenal output, it is possible, as implied by Heim et al. (2000), that compensatory changes in hypothalamic CRF might occur to the extent that there is a weaker negative feedback inhibition because of decreased cortisol output. But if this were occurring, it would be difficult to find an explanation for why the ACTH response to CRF (Heim et al. 2001) and psychologic stressors (Heim et al. 2000) were augmented in relation to early traumatization.

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 that a reduced cortisol level to result from, or even be accompanied by, changes in the GR, but rather, would reflect reduced adrenal output rather than an enhanced containment of ACTH.

Findings of a blunted ACTH response to CRF are compatible with the enhanced negative feedback model, but not the adrenal insufficiency hypothesis. Adrenal insufficiency would not be expected to result in a blunted ACTH response to CRF. On the contrary, primary adrenal insufficiency is characterized by increased ACTH at baseline and in response to CRF. Findings demonstrating an augmented ACTH to metyrapone are also consistent with enhanced negative feedback inhibition, but not adrenal insufficiency. Adrenal insufficiency is also incompatible with findings showing a greater activation of cortisol in the context of reduced ACTH responses to pituitary challenges.

Table 4 summarizes these HPA findings in PTSD and the explanations compatible with these findings. This table demonstrates that the model of enhanced negative feedback is compatible with 15/21 observations of HPA alterations in PTSD, whereas reduced adrenal capacity is consistent with 9/21 observations.

6.1 Findings of Cortisol in the Acute Aftermath of Trauma

Recent data have provided some support for the idea that low cortisol levels may be an early predictor of PTSD rather than a consequence of this condition. Low cortisol levels in the immediate aftermath of a motor vehicle accident predicted the development of PTSD in a group of 35 accident victims consecutively presenting to an emergency room (Yehuda et al. 1998). Delahanty et al. (2000) also reported that low cortisol levels in the immediate aftermath of a trauma contributed to the prediction of PTSD symptoms at 1 month. In a sample of 115 people who survived a natural disaster, cortisol levels were similarly found to be lowest in those with highest PTSD scores at 1 month post-trauma, however cortisol levels were not predictive of symptoms at 1 year (Anisman et al. 2001). Similarly, lower morning, but higher evening cortisol levels were observed in 15 subjects with high levels of PTSD symptoms 5 days following a mine accident in Lebanon compared to 16 subjects with lower levels of PTSD symptoms (Aardal-Eriksson et al. 2001).

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 (Resnick et al. 1995), but not with the development of PTSD per se. A post hoc analysis of the data reported in (Yehuda et al. 1998) confirmed the observation that low cortisol levels were also associated with prior trauma exposure in this group as well (A.C. McFarlane et al., personal communication).

These findings imply 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-h 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 biologic 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 (Yehuda et al. 2001). In this study, both the presence of subject-rated parental PTSD and scores reflecting childhood emotional abuse were associated with low cortisol levels in offspring. Thus, it may be that low cortisol levels 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 even differences in

Table 4 Summary of data from studies supporting enhanced negative feedback or reduced adrenal output in PTSD

Finding in PTSD	Enhanced negative feedback	Reduced adrenal output
Lower ambient cortisol levels	Yes	Yes
Normal or variable cortisol levels	Yes	No
Higher cortisol levels	Yes[a]	No
Increased circadian rhythm of cortisol	Yes	No
Decreased circadian rhythm of cortisol	No	Yes
Normal ACTH levels	Yes	No
Low β-endorphin levels	Yes[b]	No
Increased CRF levels in CSF	Yes	Yes
Increased glucocorticoid receptor sensitivity/number	Yes	No[c]
Normal cortisol levels to 1 mg DEX	Yes	Yes
Decreased cortisol levels following 0.5 DEX	Yes	Yes
Increased cortisol levels following 1 mg DEX	No	No
Decreased number of cytosolic glucocorticoid receptors following DEX compared to baseline receptors	Yes	No[d]
Increased ACTH levels to high dose metyrapone	Yes	No
Decreased ACTH levels to low dose metyrapone	No[e]	Yes
Decreased ACTH levels following CRF	Yes	No
Increased ACTH levels following CRF	No	Yes
Increased cortisol responses to ACTH	No	No
Decreased ACTH levels following CCK-4	Yes	No
Increased ACTH levels following naloxone	No	Yes
Increased ACTH levels following stress	Yes	Yes

*Also observed in samples of subjects with early abuse, depression, or somatic illnesses with or without comorbid PTSD. [a]Higher cortisol levels are only consistent with enhanced negative feedback to the extent that they represent transient elevations. [b]To the extent that β-endorphin is co-released with ACTH and reflects ACTH, this finding is compatible. What is problematic is the lack of relationship in this paper between ACTH and β-endorphin, which raises methodologic questions. [c]This conclusion is based on empirical findings from studies of endocrinologic disorders that have generally failed to observe accommodation in glucocorticoid receptors in response to either very high or very low cortisol levels (reviewed in Yehuda 2002). It is theoretically possible, however, that low levels of ambient cortisol would result in an "upregulation" of glucocorticoid receptors. [d]Based on c. [e]See extensive discussion on this paper in text.

the magnitude of such responses compared to those not exposed to trauma early in life, HPA parameters would subsequently recover to their pre-stress baseline.

Low cortisol levels may impede the process of biologic recovery from stress, resulting in a cascade of alterations that lead to intrusive recollections of the event, avoidance of reminders of the event, and symptoms of hyperarousal. This failure may represent an alternative trajectory to the normal process of adaptation and recovery after a traumatic event.

Additionally, it is possible that, within the time frame between several hours or days following a trauma and the development of PTSD at 1 month, there is an active process of adaptation and an attempt at achieving homeostasis, and that PTSD symptoms themselves are determined by biologic responses, rather than the opposite. For example, Hawk et al. (2000) found that at 1 month post-trauma, urinary cortisol levels were elevated among men with PTSD symptoms (but not women). By 6 months, there were no group differences in cortisol, but emotional numbing at 1 month predicted lower cortisol levels 6 months after the accident. Similarly, in a prospective study in which plasma cortisol and continuous measures of PTSD symptoms were obtained from 21 survivors at 1 week and 6 months post-trauma, cortisol levels at 1 week did not predict subsequent PTSD, but cortisol levels at 6 months negatively correlated with self-reported PTSD symptoms within PTSD subjects (Bonne et al. 2003a).

PTSD may arise from any number of circumstances, one of which may be the hormonal milieu at the time of trauma, which may reflect an interaction of pre- and peri-traumatic influences. These responses may be further modified in the days and weeks preceding it by a variety of other influences. For example, under normal circumstances, CRF and ACTH are activated in response to stress, and ultimately culminate in cortisol release, which negatively feeds back to keep the stress response in check. A reduced adrenal capacity might initially lead to a stronger activation of the pituitary due to increased CRF stimulation in synergy with other neuropeptides, such as arginine vasopressin, resulting in a high magnitude ACTH response. This might lead to a greater internal necessity by the pituitary for negative feedback inhibition. Achieving regulation under these conditions might necessitate a progressive decline in the ACTH/cortisol ratio, possibly facilitated by accommodations in the sensitivity of GRs and other central neuromodulators, ultimately leading to an exaggerated negative feedback inhibition. Affecting these hormonal responses might also be the demands made by posttraumatic factors. Although such a model is hypothetical, it is consistent with the adaptational process of allostatic load described by McEwen (1999): that is, that physiologic systems accommodate to achieve homeostasis based on already existing predispositions to stress responses. Thus, 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.

One of most compelling lines of evidence supporting the hypothesis that lower cortisol levels may be an important pathway to the development of PTSD symptoms involves results of studies by Schelling et al. (2001) who administered stress doses of hydrocortisone during septic shock and evaluated the

effects of this treatment on the development of PTSD and traumatic memories. Indeed, the results of a randomized, double-blind study demonstrated that administration of hydrocortisone in high, but physiologic-stress, doses was associated with reduced PTSD symptoms compared to the group that received saline. These findings support the idea that low cortisol levels may facilitate the development of PTSD in response to an overwhelming biologic demand—at least in some circumstances.

7 Conclusions

The HPA axis alterations in PTSD support the idea that HPA axis alterations are complex and might be associated with different aspects of PTSD, including risk for the development of this disorder. For the findings to coalesce into an integrative neuroendocrine hypothesis of PTSD, it would be necessary to assert that (1) some features of the HPA axis may be altered prior to the exposure to a focal trauma; (2) that components of the HPA axis are not uniformly regulated (e.g., circadian rhythm patterns, tonic cortisol secretion, negative feedback inhibition, and the cortisol response to stress are differentially mediated; (3) that the system is dynamic, and may therefore show transient increases or hyperresponsivity under certain environmental conditions; that (4) other regulatory influences might affect HPA axis regulation in PTSD; and probably (though not necessarily), that (5) there might be different biologic variants of PTSD with relatively similar phenotypic expressions, as is the case with major depressive disorder.

The wide range of observations observed in the neuroendocrinology of PTSD underscores the important observation of Mason et al. (1986) that HPA response patterns in PTSD are fundamentally in the normal range and do not reflect endocrinopathy. In endocrinologic disorders, where there is usually a lesion in one or more target tissues or biosynthetic pathways, endocrine methods can usually isolate the problem with the appropriate test(s), and then obtain rather consistent results. In psychiatric disorders, neuroendocrine alterations may be subtle, and therefore, when using standard endocrine tools to examine these alterations, there is a high probability of failing to observe all the alterations consistent with a neuroendocrine explanation of the pathology in tandem, or of obtaining disparate results within the same patient group owing to a stronger compensation or re-regulation of the HPA axis following challenge.

The next generation of studies should aim to apply more rigorous tests of neuroendocrinology of PTSD based on the appropriate developmental issues and in consideration of the longitudinal course of the disorder, and the individual differences that affect these processes. No doubt such studies will require a closer examination of a wide range of biologic responses, including

the cellular and molecular mechanisms involved in adaptation to stress, and an understanding of the relationship between the endocrine findings and other identified biologic alterations in PTSD.

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References

Aardal-Eriksson E, Eriksson TE, Thorell L (2001) Salivary cortisol, posttraumatic stress symptoms and general health in the acute phase and during 9-month follow-up. Biol Psychiatry 50:986–993

Altemus M, Cloitre M, Dhabhar FR (2003) Enhanced cellular immune responses in women with PTSD related to childhood abuse. Am J Psychiatry 160:1705–1707

Anisman H, Griffiths J, Matheson K, Ravindran AV, Merali Z (2001) Posttraumatic stress symptoms and salivary cortisol levels. Am J Psychiatry 158:1509–1511

Atmaca M, Kuloglu M, Tezcan E, Onal S, Ustundag B (2002) Neopterin levels and dexamethasone suppression test in posttraumatic stress disorder. Eur Arch Psychiatry Clin Neurosci 252:161–165

Baker DG, West SA, Nicholson WE, Ekhator NN, Kasckow JW, Hill KK, Bruce AB, Orth DN, Geracioti TD Jr (1999) Serial CSF corticotropin-releasing hormone levels and adrenocortical activity in combat veterans with posttraumatic stress disorder [published erratum appears in Am J Psychiatry 1999 Jun;156(6):986]. Am J Psychiatry 156:585–588

Bonne O, Brandes D, Segman R, Pitman RK, Yehuda R, Shalev AY (2003a) Prospective evaluation of plasma cortisol in recent trauma survivors with posttraumatic stress disorder. Psychiatry Res 119:171–175

Bonne O, Gilboa A, Louzoun Y, Brandes D, Yona I, Lester H, Barkai G, Freedman N, Chisin R, Shalev AY (2003b) Resting regional cerebral perfusion in recent posttraumatic stress disorder. Biol Psychiatry 54:1077–1086

Boscarino JA (1996) Posttraumatic stress disorder, exposure to combat, and lower plasma cortisol among Vietnam veterans: findings and clinical implications. J Consult Clin Psychol 64:191–201

Bourne PG, Rose RM, Mason JW (1968) 17 OHCS levels in combat. Special forces "A" team under threat of attack. Arch Gen Psychiatry 17:104–110

Bremner JD, Licinio J, Darnell A, Krystal JH, Owens MJ, Southwick SM, Nemeroff CB, Charney DS (1997) Elevated CSF corticotropin-releasing factor concentrations in posttraumatic stress disorder. Am J Psychiatry 154:624–629

Bremner JD, Vythilingma M, Vermetten E, Adil J, Khan S, Nazeer A, Afzal N, McGlashan T, Elzinga B, Anderson GM, Heninger G, Southwick SM, Charney DS (2003a) Cortisol response to a cognitive stress challenge in posttraumatic stress disorder related to childhood abuse. Psychoneuroendocrinology 28:733–750

Bremner JD, Vythilingam M, Anderson G, Vermetten E, McGlashan T, Heninger G, Rasmusson A, Southwick SM, Charney DS (2003b) Assessment of the hypothalamic-pituitary-adrenal axis over a 24-hour period and in response to neuroendocrine challenges in women with and without childhood sexual abuse and posttraumatic stress disorder. Biol Psychiatry 54:710–718

Carrion VG, Weems CF, Ray RD, Glaser B, Hessl D, Reiss AL (2002) Diurnal salivary cortisol in pediatric posttraumatic stress disorder. Biol Psychiatry 51:575–582

Coupland NJ, Hegadoren KM, Myrholm J (2003) Increased beclomethasone-induced vasoconstriction in women with posttraumatic stress disorder. J Psychiatr Res 37:221–228

De Bellis MD, Chrousos GP, Dorn LD, Burke L, Helmers K, Kling MA, Trickett PK, Putnam FW (1994) Hypothalamic-pituitary-adrenal axis dysregulation in sexually abused girls. J Clin Endocrinol Metab 78:249–255

De Bellis MD, Baum AS, Birmaher B, Keshavan MS, Eccard CH, Boring AM, Jenkins FJ, Ryan ND (1999) A.E. Bennett Research Award. Developmental traumatology. Part I: Biological stress systems [see comments]. Biol Psychiatry 45:1259–1270

de Kloet ER, Joels M, Oitzl M, Sutanto W (1991) Implication of brain corticosteroid receptor diversity for the adaptation syndrome concept. Methods Achiev Exp Pathol 14:104–132

Delahanty DL, Raimonde AJ, Spoonster E (2000) Initial posttraumatic urinary cortisol levels predict subsequent PTSD symptoms in motor vehicle accident victims. Biol Psychiatry 48:940–947

Dinan TG, Barry S, Yatham LN, Mobayed M, Brown I (1990) A pilot study of a neuroendocrine test battery in posttraumatic stress disorder. Biol Psychiatry 28:665–672

Elzinga BM, Schmahl CG, Vermetten E, van Dyck R, Bremner JD (2003) Higher cortisol levels following exposure to traumatic reminders in abuse-related PTSD. Neuropsychopharmacology 28:1656–1665

Glover D, Poland R (2002) Urinary cortisol and catecholamines in mothers of child cancer survivors with and without PTSD. Psychoneuroendocrinology 27:805–819

Goeinjian AK, Pynoos RS, Steinberg Am, Endres D, Abraham K, Geffner ME, Fairbanks LA (2003) Hypothalamic-pituitary-adrenal activity among Armenian adolescents with PTSD symptoms. J Trauma Stress 16:319–323

Goenjian AK, Yehuda R, Pynoos RS, Steinberg AM, Tashjian M, Yang RK, Najarian LM, Fairbanks LA (1996) Basal cortisol, dexamethasone suppression of cortisol and MHPG in adolescents after the 1988 earthquake in Armenia. Am J Psychiatry 153:929–934

Gormley GJ, Lowy MT, Reder AT, Hospelhorn VD, Antel JP, Meltzer HY (1985) Glucocorticoid receptors in depression: relationship to the dexamethasone suppression test. Am J Psychiatry 142:1278–1284

Gotovak K, Sabioncello A, Rabatic S, Berki T, Dekaris D (2003) Flow cytometric determination of glucocorticoid receptor expression in lymphocyte subpopulations: lower quantity of glucocorticoid receptors in patients with posttraumatic stress disorder. Clin Exp Immunol 131:335–339

Grossman R, Yehuda R, New A, Schmeidler J, Silverman J, Mitropoulous V, Sta Maria N, Bgolier J, Siever L (2003) Dexamethasone suppression test findings in subjects with personality disorders: associations with posttraumatic stress disorder and major depression. Am J Psychiatry 160:1291–1298

Halbreich U, Olympia J, Carson S, Glogowski J, Yeh CM, Axelrod S, Desu MM (1989) Hypothalamo-pituitary-adrenal activity in endogenously depressed posttraumatic stress disorder patients. Psychoneuroendocrinology 14; :365–370

Hawk LW, Dougall AL, Ursano RJ, Baum A (2000) Urinary catecholamines and cortisol in recent-onset posttraumatic stress disorder after motor vehicle accidents. Psychosom Med 62:423–434

Heim C, Newport JJ, Heit S, Graham YP, Wilcox M, Bonsall R, Miller AH, Nemeroff CG (2000) Pituitary-adrenal and autonomic responses to stress in women after sexual and physical abuse in childhood. JAMA 284:592–597

Heim C, Ehlert U, Rexhausen J, Hanker JP, Hellhammer DH (1998) Abuse-related posttraumatic stress disorder and alterations of the hypothalamic-pituitary-adrenal axis in women with chronic pelvic pain. Psychosom Med 60:309–318

Heim C, Ehlert U, Hellhammer DH (2000) The potential role of hypocortisolism in the pathophysiology of stress-related bodily disorders. Psychoneuroendocrinology 25:1–35

Heim C, Newport DJ, Bonsall R, Miller AH, Nemeroff CB (2001) Altered pituitary-adrenal axis responses to provocative challenge tests in adult survivors of childhood abuse. Am J Psychiatry 158:575–581

Hockings GI, Grice JE, Ward WK, Walters MM, Jensen GR, Jackson RV (1993) Hypersensitivity of the hypothalamic-pituitary-adrenal axis to naloxone in posttraumatic stress disorder. Biol Psychiatry 33:585–593

Hoffmann L, Burges Watson P, Wilson G, Montgomery J (1989) Low plasma b-endorphin in posttraumatic stress disorder. Aust NZ J Psychiatry 23:269–273

Holsboer F (2000) The corticosteroid receptor hypothesis of depression. Neuropsychopharmacology 23:477–501

Holsboer F, Lauer CJ, Schreiber W, Krieg JC (1995) Altered hypothalamic-pituitary-adrenocortical regulation in healthy subjects at high familial risk for affective disorders. Neuroendocrinology 62:340–347

Hucklebridge FH, Clow A, Abeyguneratne T, Huezo-Diaz P, Evans P (1999) The awakening cortisol response and blood glucose levels. Life Sci 64:931–937

Jensen CF, Keller TW, Peskind ER, McFall ME, Veith RC, Martin D,Wilkinson CW, Raskind M (1997) Behavioral and neuroendocrine responses to sodium lactate infusion in subjects with posttraumatic stress disorder. Am J Psychiatry 154:266–268

Kanter ED, Wilkinson CW, Radant AD, Petrie EC, Dobie DJ, McFall ME, Peskind ER, Raskind MA (2001) Glucocorticoid feedback sensitivity and adrenocortical responsiveness in posttraumatic stress disorder. Biol Psychiatry 50:238–245

Kauffman J, Birmaher B, Perel J, Dahl RE, Moreci P, Nelson B, Wells W, Ryan ND (1997) The corticotrophin-releasing hormone challenge in depressed abused, depressed nonabused, and normal control children. Biol Psychiatry 42:669–679

Kellner M, Baker DG, Yehuda R (1997) Salivary cortisol in Operation Desert Storm returnees. Biol Psychiatry 42:849–850

Kellner M, Wiedemann K, Yassouridis A, Levengood R, Guo LS, Holsboer F, Yehuda R (2000) Behavioral and endocrine response to cholecystokinin tetrapeptide in patients with posttraumatic stress disorder. Biol Psychiatry 47:107–111

Kellner M, Baker DG, Yassouridis A, Bettinger S, Otte C, Naber D, Wiedemann K (2002a) Mineralocorticoid receptor function in patients with posttraumatic stress disorder. Am J Psychiatry 159:1938–1940

Kellner M, Yehuda R, Arlt J, Wiedemann K (2002b) Longitudinal course of salivary cortisol in posttraumatic stress disorder. Acta Psychiatr Scand 105:153–155

King JA, Mandansky D, King S, Fletcher KE, Brewer J (2001) Early sexual abuse and low cortisol. Psychiatry Clin Neurosci 55:71–74

Kosten TR, Wahby V, Giller E, Mason J (1990) The dexamethasone suppression test and thyrotropin-releasing hormone stimulation test in posttraumatic stress disorder. Biol Psychiatry 28:657–664

Krishnan KRR, Rayasam K, Reed D, Smith M, Chapell P, Saunders WB, Ritchie JC, Carroll BJ, Nemeroff CB (1993) The corticotropin releasing factor stimulation test in patients with major depression: relationship to dexamethasone suppression test results. Depression 1:133–136

Kudler H, Davidson J, Meador K, Lipper S, Ely T (1987) The DST and posttraumatic stress disorder. Am J Psychiatry 14:1058–1071

Lemieux AM, Coe CL (1995) Abuse-related posttraumatic stress disorder: evidence for chronic neuroendocrine activation in women. Psychosom Med 57:105–115

Liberzon I, Abelson JL, Flagel SB, Raz J, Young EA (1999) Neuroendocrine and psychophysiologic responses in PTSD: a symptom provocation study. Neuropsychopharmacology 21:40–50

Lipschitz DS, Rasmusson AM, Yehuda R, Wang S, Anyan W, Gueoguieva R, Grilo CM, Fehon DC, Southwick SM (2003) Salivary cortisol response to dexamethasone in adolescents with posttraumatic stress disorder. J Am Acad Child Adolesc Psychiatry 42:1310–1317

Lowy MT (1989) Quantification of type I and II adrenal steroid receptors in neuronal, lymphoid and pituitary tissues. Brain Res 503:191–197

Luecken LJ, Dausche B, Gulla V, Hong R, Compas BE (2004) Alterations in morning cortisol associated with PTSD in women with breast cancer. J Psychosom Res 56:13–15

Maes M, Lin A, Bonaccorso S, van Hunsel F, Van Gastel A, Delmeire L, Biondi M, Bosmans E, Kenis G, Scharpe S (1998) Increased 24-hour urinary cortisol excretion in patients with post-traumatic stress disorder and patients with major depression, but not in patients with fibromyalgia. Acta Psychiatr Scand 98:328–335

Mason JW, Giller EL, Kosten TR, Ostroff RB, Podd L (1986) Urinary free-cortisol levels in posttraumatic stress disorder patients. J Nerv Ment Dis 174:145–159

Mason JW, Wang S, Yehuda R, Riney S, Charney DS, Southwick SM (2001) Psychogenic lowering of urinary cortisol levels linked to increased emotional numbing and a shame-depressive syndrome in combat-related posttraumatic stress disorder. Psychosom Med 63:387–401

McEwen BS, Seeman T (1999) Protective and damaging effects of mediators of stress: elaborating and testing the concepts of allostasis and allostatic load. Ann NY Acad Sci 896:30–47

Newport DJ, Heim C, Bonsall R, Miller AH, Nemeroff CB (2004) Pituitary-adrenal responses to standard and low-dose dexamethasone suppression tests in adult survivors of child abuse. Biol Psychiatry 55:10–20

Neylan TC, Lenoci M, Maglione ML, Rosenlicht NZ, Metlzer TJ, Otte C, Schoenfeld FB, Yehuda R, Marmar CR (2003a) Delta sleep response to metyrapone in posttraumatic stress disorder. Neuropsychopharmacology 28:1666–1676

Neylan TC, Schuff N, Lenoci M, Yehuda R, Weiner MW, Marmar CR (2003b) Cortisol levels are positively correlated with hippocampal N-acetylaspartate. Biol Psychiatry 54:1118–1121

Oquendo MA, Echavarria G, Galfalvy HC, Grunebaum MF, Burke A, Barrera A, Cooper TB, Malone KM, Mann JJ (2003) Lower cortisol levels in depressed patients with comorbid posttraumatic stress disorder. Neuropsychopharmacology 28:591–598

Pitman RK, Orr SP (1990) Twenty-four hour urinary cortisol and catecholamine excretion in combat-related posttraumatic stress disorder. Biol Psychiatry 27:245–247

Raison CL, Miller AH (2003) When not enough is too much: the role of insufficient glucocorticoid signaling in the pathophysiology of stress related disorders. Am J Psychiatry 160:1554–1565

Rasmusson AM, Lipschitz DS, Wang S, Hu S, Vojvoda D, Bremner JD, Southwick SM, Charney D (2001) Increased pituitary and adrenal reactivity in premenopausal women with posttraumatic stress disorder. Biol Psychiatry 12:965–977

Reist C, Kauffmann ED, Chicz-Demet A, Chen CC, Demet EM (1995) REM latency, dexamethasone suppression test, and thyroid releasing hormone stimulation test in posttraumatic stress disorder. Prog Neuropsychopharmacol Biol Psychiatry 19:433–443

Resnick HS, Yehuda R, Pitman RK, Foy DW (1995) Effect of previous trauma on acute plasma cortisol level following rape. Am J Psychiatry 152:1675–1677

Ribeiro SC, Tandon R, Grunhaus L, Greden JF (1993) The DST as a predictor of outcome in depression: a meta-analysis [see comments]. Am J Psychiatry 150:1618–1629

Rinne T, deKloet ER, Wouters L, Goekoop JG, DeRijk RH, van de Brink W (2002) Hyperresponsiveness of hypothalamic-pituitary-adrenal axis to combined dexamethasone/corticotropin-releasing hormone challenge in female borderline personality disorder subjects with a history of sustained childhood abuse. Biol Psychiatry 52:1102–1112

Sapolsky RM, Krey LC, McEwen BS (1984) Stress down-regulates corticosterone receptors in a site-specific manner in the brain. Endocrinology 114:287–292

Sapolsky RM, Krey LC, McEwen BS (1986) The neuroendocrinology of stress and aging: the glucocorticoid cascade hypothesis. Endocr Rev 7:284–301

Sautter FJ, Bisette G, Wiley J, Manguno-Mire G, Schoenbachler B, Myers L, Johnson JE, Cerbone A, Malaspina D (2003) Corticotropin-releasing factor in posttraumatic stress disorder with secondary psychotic symptoms, nonpsychotic PTSD, and health control subjects. Biol Psychiatry 54:1382–1388

Schelling G, Briegel J, Roozendaal B, Stoll C, Rothenhausler HB, Kapfhammer HP (2001) The effect of stress doses of hydrocortisone during septic shock on posttraumatic stress disorder in survivors. Biol Psychiatry 50:978–985

Schulte HM, Chrousos GP, Avgerinos P, Oldfield EH, Gold PW, Cutler GB, Loriaux DL (1984) The corticotrophin-releasing hormone stimulation test: a possible aid in the evaluation of patients with adrenal insufficiency. J Clin Endocrinol metab 58:1064–1067

Seedat S, Stein MB, Kennedy CM, Hauger RL (2003) Plasma cortisol and neuropeptide Y in female victims of intimate partner violence. Psychoneuroendocrinology 28:796–808

Smith MA, Davidson J, Ritchie JC, Kudler H, Lipper S, Chappell P, Nemeroff CB (1989) The corticotropin-releasing hormone test in patients with posttraumatic stress disorder. Biol Psychiatry 26:349–355

Stein MB, Yehuda R, Koverola C, Hanna C (1997) Enhanced dexamethasone suppression of plasma cortisol in adult women traumatized by childhood sexual abuse. Biol Psychiatry 42:680–686

Stokes PE, Stoll PM, Koslow SH, Maas JW, Davis JM, Swann AC, Robins E (1984) Pretreatment DST and hypothalamic-pituitary-adrenocortical function in depressed patients and comparison groups. A multicenter study. Arch Gen Psychiatry 41:257–267

Svec F (1985) Glucocorticoid receptor regulation. Life Sci 36:2359–2366

Thaller V, Vrkljan M, Hotujac L, Thakore J (1999) The potential role of hypocortisolism in the pathophysiology of PTSD and psoriasis. Coll Antropol 23:611–619

Wang S, Wilson JP, Mason JWL (1996) Stages of decompensation in combat-related posttraumatic stress disorder: a new conceptual model. Integr Physiol Behav Sci 31:237–253

Yehud R, Hallig SL, Grossman R (2001) Childhood trauma and risk for PTSD: relationship to intergenerational effects of trauma, parental PTSD, and cortisol excretion. Dev Psychopathol 13:733–753

Yehuda R (1999a) Risk factors for posttraumatic stress disorder. American Psychiatric Press, Washington

Yehuda R (1999b) Biological factors associated with susceptibility to posttraumatic stress disorder. Can J Psychiatry 44:34–39

Yehuda R (2002) Current status of cortisol findings in post-traumatic stress disorder. Psychiatr Clin North Am 25:341–368

Yehuda R, Nemeroff CB (1994) Neuropeptide alterations in affective and anxiety disorders. In: DenBoer JA, Sisten A (eds) Handbook on depression and anxiety: a biological approach. Marcel Dekker, New York, pp 543–571

Yehuda R, Southwick SM, Nussbaum G, Wahby V, Giller EL, Mason JW (1990) Low urinary cortisol excretion in patients with posttraumatic stress disorder. J Nerv Ment Dis 178:366–369

Yehuda R, Giller EL, Southwick SM, Lowy MT, Mason JW (1991a) Hypothalamic-pituitary-adrenal dysfunction in posttraumatic stress disorder. Biol Psychiatry 30:1031–1048

Yehuda R, Lowy MT, Southwick S, Shaffer D, Giller EL (1991b) Lymphocyte glucocorticoid receptor number in posttraumatic stress disorder. Am J Psychiatry 148:499–504

Yehuda R, Boisoneau D, Mason JW, Giller EL (1993a) Glucocorticoid receptor number and cortisol excretion in mood, anxiety, and psychotic disorders. Biol Psychiatry 34:18–25

Yehuda R, Southwick SM, Krystal JH, Bremner D, Charney DS, Mason JW (1993b) Enhanced suppression of cortisol following dexamethasone administration in posttraumatic stress disorder. Am J Psychiatry 150:83–86

Yehuda R, Boisoneau D, Lowy MT, Giller EL (1995a) Dose-response changes in plasma cortisol and lymphocyte glucocorticoid receptors following dexamethasone administration in combat veterans with and without posttraumatic stress disorder. Arch Gen Psychiatry 52:583–593

Yehuda R, Kahana B, Binder-Brynes K, Southwick S, Mason JW, Giller EL (1995b) Low urinary cortisol excretion in Holocaust survivors with posttraumatic stress disorder. Am J Psychiatry 152:982–986

Yehuda R, Levengood RA, Schmeidler J, Wilson S, Guo LS, Gerber D (1996a) Increased pituitary activation following metyrapone administration in post-traumatic stress disorder. Psychoneuroendocrinology 21:1–16

Yehuda R, Teicher MH, Trestman RL, Levengood RA, Siever LJ (1996b) Cortisol regulation in posttraumatic stress disorder and major depression: a chronobiological analysis. Biol Psychiatry 40:79–88

Yehuda R, Bierer LM, Schmeidler J, Aferiat DH, Breslau I, Dolan S (2000) Low cortisol and risk for PTSD in adult offspring of holocaust survivors. Am J Psychiatry 157:1252–1259

Yehuda R, Halligan S, Grossman R (2001) Childhood trauma and risk for PTSD: relationship to intergenerational effects of trauma, parental PTSD and cortisol excretion. Stress Dev 13:731–751

Yehuda R, Halligan SL, Bierer LM (2002a) Cortisol levels in adult offspring of Holocaust survivors: relation to PTSD symptom severity in the parent and child. Psychoneuroendocrinology 27:171–180

Yehuda R, Halligan SL, Grossman R, Golier JA, Wong C (2002b) The cortisol and glucocorticoid receptor response to low dose dexamethasone administration in aging combat veterans and holocaust survivors with and without posttraumatic stress disorder. Biol Psychiatry 52:393–403

Yehuda R, Golier J, Yang RK, Tischler L (2004a) Enhanced sensitivity to glucocorticoids in peripheral mononuclear leukocytes in posttraumatic stress disorder. Biol Psychiatry 55:1110–1116

Yehuda R, Halligan SL, Golier J, Grossman R, Bierer LM (2004b) Effects of trauma exposure on the cortisol response to dexamethasone administration in TPSD and major depressive disorder. Psychoneuroendocrinology 29:389–404