Biology of Posttraumatic Stress Disorder

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Most biological findings in posttraumatic stress disorder (PTSD) are compatible with those of the chronic stress response, such as increased corticotropin-releasing factor (CRF) concentrations, catecholamine depletion within the central nervous system, and reduced hippocampal volume. However, over the last 10 years, biological observations have been made in PTSD that are different from what has been typically associated with chronic stress, notably certain hypothalamic-pituitary-adrenal (HPA) axis findings. In particular, urinary and plasma cortisol levels are considerably lower in PTSD patients than in non-PTSD trauma survivors and normal controls. Furthermore, the circadian pattern of cortisol release from the adrenal glands follows a greater dynamic range in PTSD than in patients with major depression or in normal controls. The reduction in cortisol levels results from an enhanced negative feedback by cortisol, which is secondary to an increased sensitivity of glucocorticoid receptors in target tissues. This HPA axis alteration contrasts with the well-known chronic stress cascade in which CRF release results in erosion of negative feedback and down-regulation of glucocorticoid receptors. Sensitization of the HPA axis is consistent with the clinical picture of hyperreactivity and hyperresponsiveness in PTSD. *(J Clin Psychiatry 2001;62[suppl 17]:41–46)*

Posttraumatic stress disorder (PTSD) was finally recognized as a distinct clinical entity in 1980, and, over the last 20 years, understanding of the biology of PTSD has evolved considerably. Originally, PTSD was thought to be a natural process of adaptation to an unusually severe traumatic event, with a similar neurobiological profile to stress. However, contrary to initial expectations, PTSD represents a specific type of adaptation to trauma that does not reflect typical stress responsiveness. Chronic PTSD is associated with a distinct set of biological modifications, primarily involving the hypothalamic-pituitary-adrenal (HPA) axis. In contrast to the classic profile of increased adrenocortical activity and resultant adrenocortical dysregulation described in studies of stress and other psychiatric disorders, trauma survivors with PTSD show evidence of a highly sensitized HPA axis characterized by decreased basal cortisol levels and increased negative feedback regulation.[1] This review briefly describes the HPA alterations in PTSD, illustrating the role of these alterations in the pathophysiology of the disorder.

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Presented at the advisory board meeting "Understanding Posttraumatic Stress Disorder," which was held March 8–9, 1999, in Cannes, France, and supported by an unrestricted educational grant from Janssen-Cilag.

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HPA ALTERATIONS IN STRESS

The HPA axis plays a major role in the adaptive response to stress. Following exposure to a stressor, a cascade of biochemical activity is initiated, known as the basic HPA axis stress-response cascade.[2] In the initial stage of this pathway, brain neuropeptides stimulate the release of corticotropin-releasing factor (CRF, or corticotropin-releasing hormone [CRH]), vasopressin, and other regulatory neuropeptides from the hypothalamus.[3] The release of CRF promotes, among other things, the secretion of adrenocorticotropic hormone (ACTH) from the pituitary, and this hormone, in turn, leads to the release of cortisol from the adrenal glands.[2]

During response to acute stress, there is a dose-dependent increase in both catecholamines and cortisol; the levels of both hormones increase relative to the severity of the stressor. In addition, the actions of these 2 systems appear to be synergistic. Whereas catecholamines facilitate the availability of energy to vital organs, cortisol functions as an "antistress" hormone, helping to contain or shut down the neural defensive reactions that have been initiated by stress.[4] As stress-activated biological reactions shut down, the activity of the HPA axis is suppressed by the negative feedback inhibition of cortisol on the pituitary, hypothalamus, and other sites.[5,6] These sites contain a large concentration of glucocorticoid receptors[6,7] and are important targets of action of cortisol.[8] Once the acute stressor has been removed and the amygdala no longer detects the external threat, it activates negative feedback inhibition of the HPA axis in tandem with the hippocampus,[8] leading to the restoration of basal hormone levels.

Chronic stress can also result in sustained increases in cortisol. However, depending on the nature of the stressor, the HPA axis may also become tonically inhibited due to a chronic adaptation to the stressor. This response would result in normal or lower than normal cortisol levels.[9] Selye[10] referred to this tonic inhibition of the HPA axis following chronic stress as "adrenal exhaustion." Under these conditions, the entire HPA axis appears to be suppressed, with no evidence of suprahypothalamic activation of the HPA axis (e.g., increased CRF levels). Thus, in classic stress theory, stressors that result in the activation of CRF release from paraventricular neurons in the hypothalamus also result in elevated cortisol levels, whereas lower levels of cortisol are thought to result directly from a cessation of activation by CRF.

NEUROENDOCRINE ALTERATIONS IN PTSD

Cortisol Levels in PTSD

Initial hypotheses based on classic stress theory suggested that cortisol levels would be elevated in PTSD. Despite reports of increased CRF concentrations in PTSD,[11–13] cortisol levels were actually shown to be lower in subjects with PTSD than in normal comparison groups, other psychiatric patients, or similarly exposed non-PTSD groups regardless of age, gender, or type of trauma.[14–17]

Three independent studies[18–20] of 24-hour urinary cortisol excretion have reported increased levels of cortisol in PTSD; however, this difference can be attributed to methodological errors or collection procedures that distort urinary cortisol values (reviewed in reference 9). For example, the normal range of cortisol excretion over a 24-hour period is estimated to be between 20 and 90 µg/day.[21] Consequently, values that are either above or below this range may indicate abnormality. In those studies that reported higher levels of cortisol in PTSD subjects, the cortisol levels for both the PTSD and normal groups were either outside this normal range or at the very high end of it (Table 1).[18–20]

Single-point estimates of cortisol levels from plasma and salivary samples have also reported the presence of reduced cortisol levels in PTSD.[22–24] Generally, single-point measurements do not provide an optimal method for evaluating low cortisol levels because of the enormous amount of transient fluctuations in cortisol release as well as individual differences in stress response to venipuncture. Studies employing large sample numbers, however, are able to detect subtle group differences and may overcome sources of between-subject error. For example, in a study of 2490 Vietnam veterans by Boscarino,[22] plasma cortisol levels were lower in 293 veterans with PTSD than in those veterans without PTSD. In addition, Goenjian and colleagues[23] reported lower basal salivary cortisol levels in children who had been close to the epicenter of the Armenian earthquake 5 years earlier and who still had substantial PTSD symptoms, compared with children who had been further away from the epicenter and who, as a group, had fewer symptoms.

Table 1. Summary of Urinary Cortisol Levels in Posttraumatic Stress Disorder (PTSD) Studies[a]

Study	Trauma Survivors With PTSD	Trauma Survivors Without PTSD	Normal Controls	Psychiatric Controls
Mason et al, 1986[14]	33.3	...	...	51.0[b]
Yehuda et al, 1990[16]	40.9	...	62.8	…
Pitman and Orr, 1990[18]	107.3	80.5	...	
Yehuda et al, 1993[15]	38.6	...	...	69.0[c]
Lemieux and Coe, 1995[19]	111.8	83.1	87.8	...
Yehuda et al, 1995[17]	32.6	62.7	51.9	...
Maes et al, 1998[20]	840.0	...	118.0	591.0[d]

[a]Data presented as mean cortisol levels (expressed as µg/day) for PTSD and control groups.
[b]Psychiatric diagnoses included major depressive disorder (N = 8), mania (N = 8), schizophrenia (N = 7), and paranoid schizophrenia (N = 12).
[c]Psychiatric diagnoses included major depressive disorder (N = 10), mania (N = 7), psychotic disorder (N = 9), and panic disorder (N = 6).
[d]Psychiatric subjects were diagnosed with major depressive disorder (N = 10).

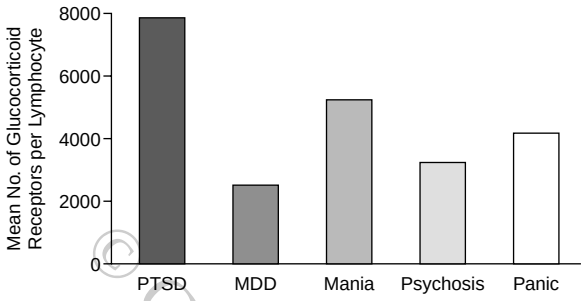
The circadian release of cortisol over the 24-hour diurnal cycle has been investigated by Yehuda et al.[24] In this study, blood samples were obtained every 30 minutes over a 24-hour period of bed rest from 15 combat veterans with PTSD, 14 subjects with major depression, and 15 normal male subjects. The results showed that basal plasma cortical release was substantially lower in the evening in PTSD subjects, whereas morning levels were comparable to those in the other 2 groups. In addition, there was a greater degree of circadian rhythm and a higher signal-to-noise ratio of cortisol release in subjects with PTSD than in both depressed patients and normal controls.

Low cortisol levels have also been observed in trauma survivors who appear to have been symptomatic at the time of assessment but were not specifically evaluated for PTSD.[25–27] For example, reduced plasma cortisol was observed in a sample of 29 recently liberated detainees from a prisoner of war camp in Bosnia[25] and in a group of 84 refugees who had fled from East to West Germany and who were still symptomatic 6 weeks after their arrival in West Berlin.[26]

Glucocorticoid Receptors in PTSD

In order to exert physiologic and behavioral effects, cortisol must bind to glucocorticoid receptors.[28] Consequently, alterations in the sensitivity of glucocorticoid receptors influence the dynamic functioning of the HPA axis. In major depression, although cortisol levels are higher, both the number and sensitivity of lymphocyte glucocorticoid receptors are reduced compared with values in normal subjects.[15,29,30] Therefore, decreased sensitivity of the receptor may actually cause attenuation of the normal biobehavioral effects of steroids. This phenomenon of

Figure 1. Glucocorticoid Receptor Density in Psychiatric Disorders[a]



[a]Data from Yehuda et al.[15] Abbreviations: MDD = major depressive disorder, PTSD = posttraumatic stress disorder.

"glucocorticoid resistance"[31] explains why chronically depressed patients with very high cortisol levels do not tend to develop evidence of endocrinopathies such as Cushing's syndrome (a disease characterized by excessively high release of cortisol).

In contrast to the decreased number of glucocorticoid receptors observed in major depression and stress, the situation appears to be reversed in PTSD. Three studies of combat veterans[15,32,33] and one study of adult survivors of childhood sexual abuse[34] demonstrated that lymphocyte glucocorticoid receptors are higher in PTSD patients than in nontraumatized subjects without psychiatric disorders. For example, analysis of the number of glucocorticoid receptors in patients with psychiatric disorders showed that the number of receptors in the PTSD group was 3 times greater than the number observed in those patients with major depression (Figure 1).[15] Glucocorticoid receptors also appear to be more sensitive in PTSD.[32] This was determined by examining glucocorticoid receptor levels on lymphocytes before and after dexamethasone administration. The results showed that treatment with dexamethasone produced a significant decrease or down-regulation of the lymphocyte glucocorticoid receptor number in combat veterans with PTSD but not in trauma survivors without PTSD or normal controls. This finding suggests that the glucocorticoid receptors of PTSD subjects show a greater response to the administration of the synthetic steroid.[32]

Cortisol Response to Dexamethasone in PTSD

The strength of the cortisol negative feedback mechanism can be evaluated by the dexamethasone suppression test (DST); dexamethasone is a synthetic steroid that mimics the effects of cortisol. High cortisol levels following the administration of dexamethasone indicate relatively weak negative feedback, and low levels, a stronger feedback mechanism.

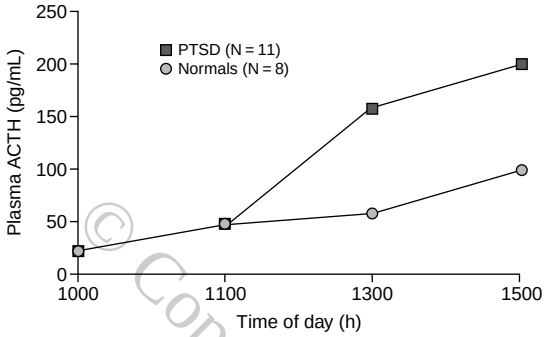
The initial DST studies in PTSD used a 1.0-mg dose of dexamethasone.[35–39] However, the studies were unable to find evidence for a nonsuppression of cortisol following dexamethasone in nondepressed PTSD patients, and most also failed to demonstrate nonsuppression in depressed PTSD patients (except for the findings of Kudler et al.,[38] who reported nonsuppression in about half of their subjects with PTSD). Nevertheless, the findings of Halbreich et al.[36] showed that the low mean cortisol observed (0.90 ± 0.53 μg/dL) was well below the cutoff for nonsuppression and suggested the possibility of hypersuppression in PTSD.[36] Consequently, Yehuda et al.[32] administered lower doses of dexamethasone (0.50 and 0.25 mg) in order to cause a partial suppression of cortisol in the comparison group and to determine whether PTSD subjects would show significantly lower post-dexamethasone cortisol levels. Augmented suppression was observed in PTSD subjects, indicating relatively strong negative feedback. This effect appeared dose dependent and was shown to be accompanied by a decrease in glucocorticoid receptor number. In addition, the hyperresponsiveness to dexamethasone was also present in combat veterans with PTSD who met diagnostic criteria for major depression[40] and, importantly, was not present in combat veterans without PTSD.[32] The finding of an enhanced cortisol suppression to 0.50 mg of dexamethasone in veterans has now been independently replicated in adult survivors of childhood sexual abuse,[34] adult victims of sexual abuse,[41] children exposed to natural disasters,[23] and Desert Storm returnees.[42]

HPA AXIS ALTERATIONS IN PTSD

The presence of low cortisol concentrations alongside high CRF levels in PTSD suggests that there is enhanced negative feedback inhibition of cortisol in the disorder. In this model, chronic CRF release[17] leads to an altered responsiveness of the pituitary. However, because the number and sensitivity of glucocorticoid receptors are increased, negative feedback inhibition is strengthened, resulting in an attenuation of tonic cortisol levels. The enhanced negative feedback response contrasts to the well-known cascade in depression whereby chronic CRF release produces a decrease in the level of negative feedback inhibition and resultant hypercortisolism and glucocorticoid receptor down-regulation.[43] The model implies that low cortisol is not the salient feature of the neuroendocrinology of PTSD. Rather, low cortisol is a downstream manifestation of a more primary alteration, which is an enhanced negative feedback inhibition resulting from an increased glucocorticoid receptor sensitivity.

Further evidence for the enhanced negative feedback theory has been provided by the results of the metyrapone stimulation test. Metyrapone blocks the conversion of 11-deoxycortisol (the immediate precursor of cortisol) into cortisol and therefore provides a pharmacologic mechanism that removes negative feedback inhibition for several hours.[44] Metyrapone administration resulted in an aug-

Figure 2. Mean Plasma Adrenocorticotropic Hormone (ACTH) Levels in PTSD and Normal Subjects After Metyrapone Treatment[a]



[a]Data from Yehuda et al.[11] Metyrapone, 2500 mg, was administered orally at 1000 h.

mented ACTH response in combat veterans with PTSD compared to nontraumatized men who showed ACTH increases in the normal endocrinologic range (Figure 2).[11] The increased ACTH response to metyrapone demonstrates that when the pituitary is unconstrained by negative feedback inhibition, there is clearly evidence of suprapituitary activation (increased CRF). It therefore follows that under basal conditions, the increased negative feedback inhibition at the level of the pituitary results in lower ambient cortisol levels.

IMPLICATIONS OF LOW CORTISOL IN THE IMMEDIATE AFTERMATH OF A TRAUMA

The presence of low cortisol levels in trauma survivors is intriguing because this is counterintuitive to the idea that stress (and psychiatric symptoms) would be associated with high cortisol levels. One of the important questions that have arisen regarding the data concerns when in the course of adaptation to trauma low basal cortisol levels are first observable. In the above mentioned studies, cortisol levels were generally obtained several months, years, or even decades after exposure to the stressor. Consequently, low basal cortisol levels in PTSD were suggested to reflect a chronic adaptation of the HPA axis. Implicit in this hypothesis is the possibility that if cortisol levels were obtained while the individual was undergoing the traumatic event, or at least in the immediate aftermath of it, then cortisol levels would have been elevated—particularly in individuals who would subsequently develop long-term psychiatric problems and/or PTSD. In fact, this idea that cortisol levels must have been extremely high at the time of the trauma in individuals who develop PTSD has been stated numerous times in the literature as if it were an obvious, foregone conclusion (e.g., reference 45). However, cortisol levels can be low in response to an extremely traumatic experience. For example, Bourne et al.[46] measured urinary cortisol metabolites in Vietnam soldiers while they were stationed in Vietnam during a threat of imminent enemy attack. Contrary to stress theory that would predict cortisol levels to be quite high in individuals undergoing this stressful situation, the investigators actually found lower levels of the cortisol metabolite 17-hydroxycorticosteroid compared with normal.

Studies examining trauma survivors while they are experiencing an extremely stressful situation are rare due to the impracticality, and in most cases, infeasibility, of obtaining such observations in experimental research settings. Indeed, it was almost 30 years after the initial observations that attempts were made to measure the hormonal response to a traumatic event while it was occurring, or at least, in its immediate aftermath. Recently, however, 2 prospective longitudinal studies[47,48] have examined the cortisol response to trauma within hours after the trauma occurred. In contrast to the study design employed by Bourne et al.,[46] these studies attempted to directly relate the acute cortisol response to a traumatic event with the subsequent development of PTSD.

The first study by McFarlane et al.[47] measured the cortisol response to motor vehicle accidents in persons presenting to the emergency room in the immediate aftermath (usually within 1 or 2 hours) of this trauma. Six months later, subjects were evaluated for the presence or absence of psychiatric disorder. In subjects who had developed PTSD, the cortisol response in the immediate aftermath of the motor vehicle accident was significantly lower than the cortisol response of those who subsequently developed major depression. The mean cortisol levels after motor vehicle accidents in those who did not subsequently develop psychiatric disorder was in between that of those who developed PTSD and those who developed major depression.[47,49] This study suggests that PTSD-like HPA axis alterations are present in the immediate aftermath of a traumatic event.

In the second study, Resnick et al.[48] demonstrated that women with a prior history of rape or assault had lower cortisol levels immediately after rape than women without such histories. Cortisol levels did not predict the subsequent development of PTSD in these women (possibly owing to the small sample size). Thus, cortisol levels in the immediate aftermath of a traumatic event may be predicted by factors that precede trauma exposure or by previous exposure.

Taken together, the results of both studies demonstrate that the acute cortisol responses to trauma in individuals who develop PTSD, or who show characteristic risk factors for PTSD such as prior exposure to trauma, may be different from those of individuals who do not develop PTSD in response to a similar trauma or do not have prior trauma histories.

One question raised by these studies is whether or not individuals may have had low cortisol levels even before

the traumatic event or had some abnormality that accounts for their aberrant response to the traumatic event they sustained. In this regard, we have previously demonstrated that cortisol levels are low in the high-risk group of adult children of Holocaust survivors.[50] Adult children of Holocaust survivors are 3 times more likely to develop PTSD compared with demographically matched comparison subjects.[51] Risk of PTSD is greater in offspring whose parents had chronic PTSD compared with those whose parents did not develop or sustain PTSD.[52] Although low cortisol was present in offspring with their own PTSD, it was also associated with the specific risk factor of parental PTSD in the offspring and was present in high-risk offspring (those with parental PTSD) who had not been exposed to traumatic events and therefore had not developed PTSD. These types of studies need to be performed on a wider scale with multiple high-risk groups before this issue is resolved. Ultimately, the best resolution of this question will necessitate prospective studies that assess cortisol levels in persons before and after they experience traumatic events or the study of other groups at risk for PTSD (e.g., owing to increased familial risk for the development of PTSD).

IMPLICATIONS OF ENHANCED NEGATIVE FEEDBACK INHIBITION FOR OTHER BIOLOGICAL ALTERATIONS IN PTSD

Recent findings of smaller hippocampal volumes in PTSD might explain the increased sensitivity of brain glucocorticoid receptors. The hippocampus is an area that is rich in glucocorticoid receptors. The current explanation in the published literature is that smaller hippocampal volumes occur as a result of increased cortisol levels released in response to the traumatic event that caused neurotoxicity and ultimately reduced volume.[53] However, as stated above, cortisol levels are neither low in the immediate aftermath of a trauma nor low during the chronic PTSD illness. However, if PTSD were characterized by increased sensitivity not only of lymphocyte glucocorticoid receptors but also of hippocampal glucocorticoid receptors, this could increase the vulnerability of the hippocampus to atrophy even if cortisol levels were not increased. Indeed, it is the activation of receptors that leads to the cascade that results in the events (i.e., primarily activation of glutamate receptors) that contribute to the neuronal degeneration following stress. That glucocorticoid responsiveness is a more relevant contributor to hippocampal alterations than cortisol per se also explains why not all trauma survivors develop smaller hippocampal volumes following trauma exposure.

CONCLUSIONS

Chronic PTSD is associated with a distinct set of biological modifications, primarily involving the HPA axis. In contrast to the classic profile of increased adrenocortical activity and resultant adrenocortical dysregulation described in studies of stress and other psychiatric disorders, trauma survivors with PTSD show evidence of a highly sensitized HPA axis characterized by decreased basal cortisol levels and increased negative feedback regulation. In PTSD, chronic CRF release leads to an altered responsiveness of the pituitary gland, as is true in anxiety disorders. However, because there is increased sensitivity of glucocorticoid receptors in PTSD, negative feedback inhibition is stronger. This inhibition results in attenuation of cortisol levels and contrasts with the well-known cascade in which CRF release results in erosion of negative feedback, hypercortisolism, and down-regulation of glucocorticoid receptors (Table 2).

Table 2. HPA Axis Alterations: PTSD Versus Normal Stress Response[a]

PTSD	Normal
↓ Cortisol	↑ Cortisol
↑ Glucocorticoid receptors	↓ Glucocorticoid receptors
↑ Suppression on DST	↓ Suppression on DST
↑ Negative feedback inhibition	↓ Negative feedback inhibition

[a]Abbreviations: DST = dexamethasone suppression test, HPA = hypothalamic-pituitary-adrenal, PTSD = posttraumatic stress disorder.

Enhanced negative feedback inhibition secondary to altered glucocorticoid receptor responsivity is consistent with low cortisol levels, attenuated baseline ACTH, and enhanced suppression to dexamethasone. This "sensitization" of the HPA axis is consistent with the clinical presentation of PTSD, where patients typically show an unusually heightened response to stress and symptoms of increased startle, hypervigilance, and physiologic arousal.

The unique neuroendocrinology of PTSD provides an opportunity to explore further and consolidate current knowledge in this continually expanding yet still relatively new area of research, so that highly targeted diagnostic measures and therapeutic interventions may be developed. An important part of this process is to develop animal models representative of the neuroendocrinology of PTSD, so that differences between acute and chronic stress responses and individual variations in stress responsiveness may be further investigated. Molecular biological tools will facilitate the development of highly specific models, for example, with increased glucocorticoid sensitivity, and enable detailed exploration of the behavioral and biological characteristics of PTSD.

Drug names: dexamethasone (Decadron and others), metyrapone (Metopirone).

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