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# Diurnal Salivary Cortisol in Pediatric Posttraumatic Stress Disorder

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**Background:** *The hypothalamic-pituitary-adrenal (HPA) axis has been implicated in the pathophysiology of post-traumatic stress disorder (PTSD). Additional information on basal cortisol levels in children exposed to trauma and experiencing PTSD symptoms may contribute to the understanding of the role of this axis in PTSD.*

**Methods:** *Fifty-one children (30 boys and 21 girls, mean age 10.7 years) with a history of exposure to trauma and PTSD symptoms were compared with 31 age- and gender-matched healthy control subjects. Salivary cortisol was obtained from participants during home measurements and was collected four times a day (prebreakfast, pre-lunch, predinner, and prebed) for up to 3 consecutive days.*

**Results:** *The clinical group demonstrated significantly elevated cortisol levels when compared with the control group. In addition, exploratory analyses revealed that girls with PTSD symptoms had significantly elevated cortisol levels when compared with boys with PTSD symptoms.*

**Conclusions:** *The physiologic response of children with history of trauma and with PTSD symptoms may be characterized by heightened adrenal activity.* Biol Psychiatry 2002;51:575–582 © 2002 Society of Biological Psychiatry

**Key Words:** Cortisol, PTSD, HPA axis, chronic stress, development

## Introduction

The hypothalamic-pituitary-adrenal (HPA) axis has been implicated in the pathophysiology of posttraumatic stress disorder (PTSD). To what extent this system is involved in the etiology or maintenance of this disorder still needs to be determined. Much of the research inves-

tigating the role of the HPA axis in PTSD has been conducted using cross-sectional designs or single-day assessments and employing adult samples. The purpose of this investigation was to increase our knowledge of baseline cortisol levels in children with symptoms of PTSD.

Decreased plasma basal cortisol levels have been observed in combat veterans when compared with traumatized veterans with no PTSD (Boscarino 1996). Low urinary cortisol excretion has been found in adult holocaust survivors with PTSD when compared with survivors without PTSD (Yehuda et al 1995a). In addition, glucocorticoid receptors have been investigated in peripheral lymphocytes of adults with PTSD. These studies report an elevation in the number of glucocorticoid receptors (Stein et al 1997; Yehuda et al 1993; Yehuda et al 1991). Yehuda and colleagues postulated that low basal cortisol levels and an increased number of glucocorticoid receptors may reflect enhanced suppression of cortisol via the negative feedback loop of the HPA axis in this population. This hypothesis has been supported by the observation of enhanced dexamethasone (a cortisol analog) suppression of plasma cortisol in adult women traumatized by childhood sexual abuse when compared with nontraumatized adults and in combat veterans with PTSD when compared with those veterans without PTSD (Stein et al 1997; Yehuda et al 1995b). The finding of increased adrenocorticotropin hormone (ACTH) release following metyrapone (which prevents conversion of 11-deoxycortisol to cortisol) administration in combat veterans with PTSD when compared with normal control subjects (Yehuda et al 1996) also supports a hypothesis of increased sensitization of the negative feedback loop by ruling out the possibility of pituitary hypoactivity. Other laboratories, however, have reported increased levels of cortisol in adults with PTSD. Specifically, three 24-hour urinary cortisol excretion studies have reported elevated cortisol levels in patients with PTSD (Lemieux and Coe 1995; Maes et al 1998; Pitman and Orr 1990). These findings underscore the existing controversy regarding HPA regulation in adult PTSD.

Data on the function of the HPA axis in children who experience trauma and develop PTSD symptoms may shed

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light on the pathogenesis of PTSD; however, limited information is available. Research has shown that individuals who experience trauma early in life may have altered HPA axis circadian rhythmicity. For example, maltreated children diagnosed with PTSD demonstrated increased urinary free cortisol levels after 24-hour urinary collection compared with matched control subjects (De Bellis et al 1999). In addition, the availability of salivary cortisol has facilitated cortisol collection in children while eliminating the confounds of venipuncture stress and renal clearance. Salivary cortisol is a valid and reliable reflection of the respective unbound hormone in blood for adults (Harris et al 1990; Kirschbaum and Hellhammer 1994) and children (Woodside et al 1991). Using this methodology, Goenjian and colleagues evaluated adolescents 5 years after their experience of the Armenian earthquake. They found that those adolescents close to the epicenter and who still had PTSD symptoms had lower basal salivary cortisol levels; a finding similar to those observed in some adult studies but different from those of De Bellis and colleagues (Goenjian et al 1996). Salivary cortisol has been investigated in other samples of traumatized children who have not been systematically evaluated for the diagnosis of PTSD. For example, King and colleagues collected morning salivary cortisol samples in girls aged 5 to 7 years who were scheduled for a physical exam. They found that girls with history of sexual abuse within the last 2 months had lower cortisol in comparison with control subjects (King et al 2001). In addition, afternoon salivary cortisol levels have been demonstrated to be elevated in depressed maltreated children when compared with depressed non-maltreated children (Hart et al 1996). As in adult studies, the interpretation of these results is limited by the different populations under study and the different methodologic procedures. Taken together, however, these results suggest a differential adrenal response in individuals exposed to traumatic experiences.

To date there is no clear consensus regarding whether cortisol levels are elevated or reduced in children with PTSD. Thus, the investigation of cortisol levels in children with PTSD and subthreshold PTSD symptoms warrants further study to help clarify the role of the HPA axis in pediatric PTSD pathophysiology. This article reports a study on the salivary cortisol levels of children with history of interpersonal trauma and PTSD symptoms. Our goal was to extend previous research by employing a large sample of children, assessing diurnal cortisol concentrations in children with salivary cortisol, and increasing reliability by collecting samples over 3 consecutive days across predetermined times of day. To the best of our knowledge, this is the first study reporting collection of repeated ambulatory samples of salivary cortisol for 3 consecutive days in children with history of trauma and

PTSD symptoms. The objective of this study was to identify baseline diurnal cortisol levels in children with history of trauma who already have manifested symptoms of PTSD and are thus at risk for chronic PTSD as adults. Given the findings of De Bellis and colleagues (see De Bellis et al 1999), we theorized that the eventual alterations in the adrenal response of adults with PTSD result from chronic hyperactivity of this axis during development. Thus, we hypothesized that children with history of interpersonal trauma and PTSD symptoms would demonstrate higher basal cortisol levels when compared with age- and gender-matched controls.

## Methods and Materials

### *Participants*

The sample was recruited from local social service departments and mental health clinics. All of the children in this sample were referred to the project because of exposure to traumatic events. All referred children underwent screening with the PTSD Reaction Index (Nader et al 1990) and were assessed further if they scored 12 or above (12 = mild PTSD). Sixty children were initially assessed; however, nine children did not fully complete the cortisol protocol. Thus, the final sample consisted of 30 boys and 21 girls for a total sample of 51 children exposed to trauma. The mean age of the children was 10.7 years with a range of 7 to 14 years. All participants fulfilled the following criteria: 1) experienced at least one episode of exposure to trauma, as defined by DSM-IV criterion A1 (“the person experienced, witnessed, or was confronted with an event or events that involved actual or threatened death or serious injury, or a threat to the physical integrity of self or others”; American Psychiatric Association 1994); 2) the trauma episode or episodes for which the individual was referred must have occurred at least 6 months before referral; 3) current home environment with no ongoing trauma and a caretaker willing to participate in the project. Exclusion criteria included: 1) history of neurologic disorders; and 2) history of alcohol or drug abuse/dependence.

Demographic characteristics of the PTSD and control sample are presented in Table 1. A healthy control group ( $n = 31$ ) was obtained from an archived sample in our laboratory. This sample was derived from the siblings of participants in a study of children with fragile X and selected for comparability to the age and gender composition of the PTSD group. Identical salivary collection methods were used for 2 consecutive days in this group. All control participants were clinically evaluated with the Child Behavior Checklist (CBCL; Achenbach 1991) and, with one exception, none scored in the clinical range (64 or more) for either internalizing or externalizing symptoms. One subject scored 66 on the internalizing subscale but was kept in the control group because of lack of subjective or parent-observed distress or dysfunction. These 31 healthy control subjects were comparable to the experimental subjects with regard to age (mean age 10.9 years; range 8–14 years), gender (18 boys 13 girls), and parent education level (see Table 1). The control group did differ with regard to family income and ethnicity.

Table 1. Demographic Characteristics for PTSD and Control Subjects

	Control	PTSD
Mean age (SD)	10.9 (1.6)	10.7 (1.9)
Gender		
% Female	40.6	41.2
Ethnicity % <sup>a</sup>		
White	93.8	45.1
African American	.0	37.3
Hispanic	3.1	9.8
Pacific Islander	3.1	.0
Other	.0	3.9
Median family income <sup>a</sup>	96,000	30,000
Parent education		
% college or higher	55.2	41.5

PTSD, posttraumatic stress disorder.

<sup>a</sup>Denotes significant difference between PTSD and Control.

Because research has indicated that socioeconomic status is associated with cortisol levels in child samples (Lupien et al 2000), family income was examined as a potential covariate before testing our main hypothesis. Supplemental analyses were also used to examine the potential influence of ethnicity on the findings.

### Clinical Evaluation

Consent was obtained from the participating counties' courts for those subjects in foster placement. The principle investigator (VC) presented all subjects and their caretakers, regardless of prior court consent, with a written internal review board-approved informed consent. All participants were given a copy of the consent. Subject's assent was required for participation. A procedure was in place to report any suspected ongoing maltreatment; however no cases were identified. Children who participated in the project were currently on stable home environments and their guardians agreed to participate in the project. An in-depth clinical evaluation was conducted on all referred children with PTSD Reaction Index score equal to or greater than 12. Evaluation instruments were as follows.

**THE CAPS-CA.** This is a structured clinical interview that allows for assessment of traumatic experiences through a trauma checklist and their completion of DSM-IV criteria. It is designed to be a developmentally adjusted counterpart to the CAPS for adults (Blake et al 1995; Nader et al 1996). The CAPS-CA interview assesses the 17 symptoms for PTSD outlined in DSM-IV and the overall severity of PTSD. The CAPS-CA has internal consistency for the intensity ratings and concurrent validity with the Child PTSD Checklist, a self-report measure of PTSD (Nader et al 1996). A board-certified child psychiatrist (VC) who was trained on the administration of this instrument conducted the interview. Moreover, an intraclass coefficient of .97 was established on a subsample of the interviews with one of the designers of the instrument (Dr. Elana Newman) who rated videotaped recordings of 10 interviews. All 51 experimental subjects were interviewed with the CAPS-CA. Full PTSD DSM-IV diagnosis was established in 12 children, and 39 had

subthreshold PTSD. In this article, we refer to the complete experimental group as the PTSD group except where noted (e.g., when cortisol differences between full PTSD and subthreshold PTSD are examined or discussed).

**THE PTSD REACTION INDEX.** This 20-item self-report instrument was used to assess PTSD symptoms after exposure to violence (Nader et al 1990; Pynoos et al 1987).

**SCHEDULE FOR AFFECTIVE DISORDERS AND SCHIZOPHRENIA FOR SCHOOL-AGE CHILDREN-PRESENT AND LIFETIME VERSION (K-SADS-PL).** This semistructured clinical interview is designed to identify Axis I DSM-IV disorders (Kaufman et al 1997a). A certified child psychiatrist (VC) conducted the K-SADS.

**TANNER STAGES.** Participants' pubertal development was determined by self-report. Participants selected from drawings with written descriptions representing the five Tanner Stages (Marshal and Tanner 1970) of pubic hair development and genital development for boys and breast development for girls. Previous research has demonstrated that self-report Tanner staging is a valid and reliable method that has been shown to correlate with physician ratings (Duke et al 1980).

**THE CHILD BEHAVIOR CHECKLIST (CBCL).** This measure was used to clinically evaluate the control group (Achenbach 1991). The CBCL provides scores for both internalizing and externalizing subscales.

**WECHSLER ABBREVIATED SCALES OF INTELLIGENCE (WASI).** This test was used to determine intelligence (Psychological Corporation 1999). The WASI is a nationally standardized test of intelligence that yields verbal, performance, and full scale IQ scores that correlate with subscales of the Wechsler Intelligence Scale for Children—Third Edition (WISC-III).

### Neuroendocrine Evaluation

**SALIVARY CORTISOL.** Salivary cortisol was obtained from the participant during home measurements. It was collected four times a day (prebreakfast, prelunch, predinner, and prebed) over the course of 3 days producing 12 samples. To maximize appropriate collection, detailed instructions and an illustration were provided to parents and children regarding the collection of saliva samples. A handout with a checklist indicating all 12 required collection times was provided for collection monitoring. Each of the samples was collected by having the participant place a cotton swab in his or her mouth for 1 minute. The cotton was then placed inside a sterile plastic tube and sealed. Salivary cortisol was extracted from the cotton by centrifuging the plastic tubes and cotton for 8 to 10 min. The cotton was then removed and the tubes sealed. All samples were kept at  $-20^{\circ}\text{C}$  and shipped on dry ice to the laboratory for assay. Samples were processed using the Magic Cortisol radioimmunoassay kit produced by Ciba-Corning (Giessen, Germany) as adapted for salivary cortisol analysis (see Kirschbaum et al 1989) by the

University of Minnesota Endocrine Laboratory. Inter- and intra-assay coefficients of variation are maintained at less than 12%. Cortisol is reported in  $\mu\text{g/dL}$ . As recommended for increased reliability (see Gunnar 2001) an aggregate score from the 3 days (i.e., the mean score across the assessment days) was created for each time period so that each participant had one prebreakfast, prelunch, predinner, and prebed sample. Participants missing three samples from the same time point were not included in this study ( $n = 9$ ). Individuals showed relative stability in their cortisol levels across the 3 days. Specifically, the correlation between day 1 and day 2 mean cortisol level was ( $r = .46, p < .001$ ) between day 1 and day 3 ( $r = .52, p < .001$ ) and day 2 and day 3 ( $r = .31, p < .001$ ).

### Statistical Methods

We used SPSS for all data analyses including descriptive statistics. To test the main hypothesis, a mixed design analysis of covariance (ANCOVA) was conducted with cortisol as the dependent variable, condition (PTSD vs. control) as the between subjects independent variable, time of day (prebreakfast, prelunch, predinner, and prebed) as the within subjects independent variable and family income as a covariate. Based on the sample size of the experimental and control group, the power to detect a significant difference (based on  $\alpha = .05$  with a medium effect size) is approximately .97. Additional comparisons of PTSD and control participants for each time of day were conducted using a nonparametric alternative, the Mann-Whitney  $U$  score if cortisol levels showed significant skew. The influence of gender was examined by comparing boys and girls cortisol levels using similar statistical procedures. Cohen's  $d$  was calculated to estimate effect size on significant between group mean differences.

### Results

Most children (51%) experienced multiple traumatic events. Traumatic events included separation and loss (51%), physical abuse (39%), witnessing violence (37%), sexual abuse (17%), physical neglect (11%), and emotional abuse (7%). The top six individual comorbid DSM-IV conditions were depressive disorder not otherwise specified (NOS; 12%), major depressive disorder (11%), attention-deficit/hyperactivity disorder (11%), specific phobia (9%), separation anxiety disorder (7%), and social phobia (7%). In terms of family income, 54.8% reported incomes between 0 and \$31,000, 15.6% reported incomes between \$31,000 and \$76,000, 17.8% of the families reported incomes over \$76,000, and 11.8% did not report income data (because children were in foster care, residential treatment, or other nontraditional rearing environment). With respect to education, caregivers reported partial high school education (3.9%), a high school education (23.5%), partial college (19.6%), college (13.7%), or graduate school education (19.6%). Educational background was not available for 19.6% of the

Table 2. Aggregated Cortisol Levels ( $\mu\text{g/dL}$ ) for Each Time of Day: Mean, Median, Standard Deviations, and Score Ranges

	Control	PTSD	Z	p	d
Prebreakfast					
Mean	.42	.43			.03
Median	.40	.44	.01 <sup>a</sup>	.99	
SD	.21	.16			
Range	.04-.87	.01-.86			
Prelunch					
Mean	.16	.22			.35
Median	.14	.20	1.85 <sup>a</sup>	.07	
SD	.09	.02			
Range	.01-.47	.03-.57			
Predinner					
Mean	.14	.17			.28
Median	.09	.15	2.27 <sup>a</sup>	.02	
SD	.13	.12			
Range	.02-.51	.01-.69			
Prebed					
Mean	.06	.12			.57
Median	.04	.07	2.15 <sup>a</sup>	.03	
SD	.06	.13			
Range	.00 <sup>b</sup> -.30	.00-.68			

d, Cohen's  $d$  statistic computed on mean differences; PTSD, posttraumatic stress disorder.

<sup>a</sup>Z score from Mann-Whitney  $U$  tests.

<sup>b</sup>Actual level was less than .01, i.e., =.0025.

sample, again because the children being in foster care, residential treatment, or other nontraditional rearing environment. Ethnic composition was European American ( $n = 23$ ), African American ( $n = 19$ ), Hispanic ( $n = 5$ ), Asian ( $n = 2$ ), and Other ( $n = 2$ ). Children's median pubic hair Tanner stage was 2; for girls, median breast Tanner stage was 3; for boys, median genital Tanner stage was 2. Full-scale IQs ranged from 62 to 142, average score 93, (5 subjects scored below 70; however, they were included in the sample because they did not meet criteria for mental retardation due to adaptive behavioral functioning within the normal range).

Ranges, means, and standard deviations for the cortisol level for each time of day are presented in Table 2. Examination of the cortisol level ranges and skew for each of the measures indicated considerable skew but only in the predinner and prebed measurements. As noted, because each of the cortisol measurements did not show skew, we used untransformed cortisol levels and employed nonparametric tests to supplement findings in parametric analyses.

Cortisol levels were examined using a mixed design repeated measures analysis of covariance (ANCOVA) with group (PTSD vs. control) as the between-subjects independent variable and time of day (prebreakfast, prelunch, predinner, and prebed) as the within-subjects independent variable controlling for family income level; however, family income was not a significant covariate

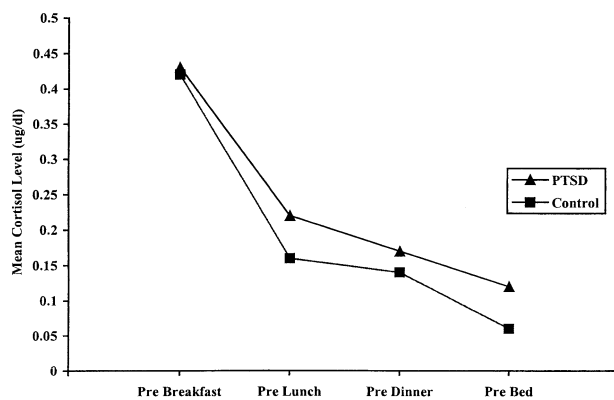


Figure 1. Cortisol levels as a function of group and time of collection. PTSD, posttraumatic stress disorder.

[ $F(1,68) = .846, p > .1$ ] in this model. Thus, ANOVA was used and revealed a significant effect of time [ $F(3,78) = 111.75, p < .0001$ ] and condition [ $F(1,80) = 4.09, p < .05$ ], Cohen's  $SD = .46$ , but no time by condition interaction [ $F(3,78) = .57, p > .1$ ]. The effect of condition (PTSD vs. control) was significant when controlling for family income as well. Overall, the PTSD group showed higher levels of cortisol than did the control group, and there was a significant decrease in cortisol levels over the course of the day (see Table 2 and Figure 1). Follow up Mann-Whitney  $U$  scores revealed a significant difference in predinner and prebed levels of salivary cortisol between the PTSD group and the control group (see Table 2).

Because the ethnic composition of the control group was predominately Caucasian, we conducted a supplemental ANOVA to determine if the ethnic diversity in the PTSD sample may have accounted for our main findings. Specifically, an ANOVA was conducted excluding all ethnic minorities from the analysis (i.e., comparing Caucasian PTSD children with Caucasian control children). ANOVA again revealed a significant effect of time [ $F(3,48) = 71.42, p < .001$ ] and condition [ $F(1,50) = 6.12, p < .05$ ], but no time by condition interaction [ $F(3,48) = 1.21, p > .1$ ].

We next examined whether children meeting full diagnostic criteria for PTSD according to DSM-IV CAPS-CA assessment (a categorical rather than continuous score) had significantly different cortisol levels than the rest of the trauma-exposed group. A mixed design repeated measures analysis of variance was performed with diagnostic group (full PTSD,  $n = 12$ ) versus trauma group meeting subthreshold diagnostic criteria ( $n = 39$ ) as the between-subjects variable and time of day as the within-subjects variable. Analyses of variance revealed a significant effect of time [ $F(3,44) = 34.77, p < .001$ ], but no effect of

diagnostic group [ $F(1,46) = .52, p > .1$ ] and no time by condition interaction [ $F(3,44) = 1.25, p > .1$ ].

Because of the comorbidity with depressive symptoms in this sample and prior research demonstrating a relationship between cortisol and depressive symptoms, we examined whether children with depression (i.e., the children meeting criteria for depressive disorder NOS or major depressive disorder) and PTSD symptoms had higher cortisol levels than children with PTSD symptoms only. No significant differences between these two groups were found [ $F(1,46) = .01, p > .1$ ].

### Age and Gender Findings

Although we matched participants on age and gender, we were interested in exploring the relation of age and gender to cortisol levels. No significant associations between age and cortisol level were found. Differences in the cortisol levels of boys and girls were found. Overall, results indicated that girls showed significantly higher cortisol levels than boys but only in the PTSD group. A mixed design repeated-measures ANOVA was performed, first using only the children in the PTSD group, with gender as the independent variable and time of day as the within-subjects variable. We did not first conduct a 2 (gender) by 2 (PTSD vs. control) by time ANOVA in these exploratory analyses because, given the size of the effect in our main analyses, we felt the cell sizes would be too small to detect a significant interaction effect. This analysis revealed a significant effect of time [ $F(3,47) = 32.26, p < .001$ ], and of gender [ $F(1,46) = 6.30, p < .05$ ], but no time by condition interaction [ $F(3,44) = 1.25, p > .1$ ]. Follow-up Mann-Whitney  $U$  scores revealed that girls had significantly higher levels of prebed salivary cortisol [ $z = 2.20, p < .05$ ]. No significant differences across gender were found in the control group.

### Discussion

Our hypothesis that children with a history of interpersonal trauma and PTSD symptoms would demonstrate higher basal cortisol levels than age- and gender-matched control subjects was supported by the findings of this study. There was a large diurnal reduction in cortisol levels across both groups. The control group, however, attained lower levels especially in the latter parts of the day when compared with children with full or subthreshold PTSD. Our results are consistent with those of De Bellis and colleagues, in which elevated levels of cortisol were observed from 24-hour urinary collection (De Bellis et al 1999) in children with history of maltreatment when compared with control subjects. They are in contrast, however, to results obtained from some adult studies and

an investigation of children reported by Goenjian and colleagues (Goenjian et al 1996). These investigators studied adolescents 5 years after the 1988 Armenian earthquake. They reported reduced levels of cortisol in children who were most closely exposed to a sudden, unexpected environmental disaster (earthquake) when compared with a less traumatized sample (children who lived farther away from the epicenter of the earthquake). The acute nature of the traumatic incident, the characteristics of the sample, and different methodology (e.g., collection times) may account for the discrepancy of these findings with those presented in our study. Understanding how these factors relate to cortisol regulation will be critical to decipher the role that the HPA axis plays at different stages of PTSD development.

The first question we can pose given our findings concerns whether the axis is responding normally to current stress or if there is an abnormality in the regulation of cortisol at some level of the HPA axis. Although the children in the experimental group were in nonabusing environments with increased structure and family support at the time of evaluation, one important limitation of this study is the lack of a systematic evaluation of ongoing stress. It will be important in future studies to assess the degree of stress experienced by the experimental group in comparison to the control group. Regarding the HPA regulation, several investigators have studied the axis at the hypothalamic–pituitary level in traumatized children. Kaufman and colleagues found that a cohort of depressed abused children had significantly greater peak, total, and net ACTH secretion post-corticotropin releasing factor (CRF) infusion, thus suggesting pituitary hyperactivity (Kaufman et al 1997b). Of note, increased ACTH secretion was observed only in depressed abused children experiencing ongoing chronic adversity. In contrast to these findings, De Bellis and colleagues found a blunted ACTH response to CRF infusion in 13 sexually abused girls when compared with control subjects. As in Kaufman's study, this group also had increased depressive symptoms. These investigators also found that these experimental subjects could still produce cortisol levels similar to the control group (De Bellis et al 1994). The authors suggest that these young girls may be correcting for pituitary hyporesponsiveness (e.g., pituitary CRF receptor downregulation) through an intact glucocorticoid feedback regulatory mechanism. Alternatively, however, the induced level of pituitary hyporesponsiveness may have dampened an otherwise hyperresponsive adrenal gland. To address this question, ACTH stimulation studies in PTSD are needed. To date there have been no ACTH stimulation studies in PTSD, adult or children (Heim et al 2001). Heim and colleagues, however, evaluated pituitary–adrenal responses to CRF and ACTH administration in adult survi-

vors of child abuse with and without major depressive disorder (Heim et al 2001). These authors found PTSD to be more common in the group with history of trauma and major depression. This group demonstrated a blunted ACTH response to CRF administration and lower basal cortisol levels upon ACTH administration. Of note, neither of the child studies systematically diagnosed PTSD in their samples. In addition, Heim and colleagues found that the adult group with comorbid Major Depressive Disorder and PTSD reported more recent chronic mild stress than comparison groups. Our results support the need for a study evaluating adrenal response to ACTH administration in children who have experienced early adversity and develop subsequent PTSD symptomatology.

The next question to address would be if the finding of high cortisol levels reflect sequelae of the experience of trauma, the onset of PTSD symptoms, or a marker of diagnosis. We found no differences between children with PTSD and children with subthreshold symptoms in terms of elevated levels of cortisol. This could indicate that high cortisol is not a marker of PTSD but that it results from the experience of trauma. Alternatively, it may suggest that the PTSD diagnosis in children needs further development to include those children who have subthreshold symptoms. In fact, we found similar findings while studying the phenomenology of this condition in children. Specifically, we found that there were no differences in terms of distress and dysfunction between children that fulfill all criteria for PTSD and children with subthreshold PTSD symptoms (Carrion et al, in press). Based on these findings, we feel behavioral descriptions may be limited in helping to identify children whose function become impaired by the experience of trauma. Promising biological markers, such as cortisol levels, may offer a more sensitive method to identify children in need of treatment.

Girls with PTSD symptoms had higher levels of cortisol than did boys in the clinical sample. This gender difference was not found in the healthy control group. It is known that girls and women are at greater risk of developing PTSD than are their male counterparts (Cuffe et al 1998; Kessler et al 1995). Interestingly, increased PTSD vulnerability for women has been related to early developmental trauma exposure (Breslau et al 1997). Our results suggest that the HPA axis may be implicated in this diathesis.

The interpretation of our preliminary results is limited by a number of factors. Although this study employed a relatively large sample size ( $n = 82$ ), only 12 of 51 subjects on the experimental group fulfilled DSM-IV PTSD criteria. In addition, the 31 control subjects were obtained from an archival sample. Larger samples of traumatized children comparing those with DSM-IV PTSD versus no PTSD will be necessary to decipher the

role of cortisol as a marker of PTSD. As discussed above, the study could have benefited from a measure of current life stress. Finally, the cross-sectional nature of the design limits interpretations on cause and effect.

The sequelae of a high cortisol environment during early development need to be elucidated. Clarifying the mechanism by which an altered HPA axis can lead to symptoms of anxiety and depression will have a direct impact in the development of more focused and targeted treatment interventions. PTSD, and especially pediatric PTSD, presents a unique opportunity to clarify the contributions of experiencing environmental stress, the genetics of stress susceptibility, and how their interaction may result in adult psychopathology.

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## References

- Achenbach TM (1991): *Manual for the Child Behavior Checklist and Revised Child Behavior Profile*. Burlington, VT: University of Vermont Department of Psychiatry.
- American Psychiatric Association (1994): *Diagnostic and Statistical Manual of Mental Disorders 4th ed.* Washington, DC: American Psychiatric Association.
- Blake DD, Weathers FW, Nagy LM, Kaloupek DG (1995): The development of a clinician-administered PTSD scale. *J Trauma Stress* 8:75–90.
- 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.
- Breslau N, Davis GC, Andreski P, Peterson EL, Schultz LR (1997): Sex differences in posttraumatic stress disorder. *Arch Gen Psychiatry* 54:1044–1048.
- Carrion VG, Weems CF, Ray RD, Reiss AL (in press): Towards an empirical definition of pediatric PTSD: the phenomenology of PTSD symptoms in youth. *J Am Acad Child Adolesc Psychiatry*.
- Cuffe SP, Addy CL, Garrison CZ, Waller JL, Kirby LA, McKeown RE, et al (1998): Prevalence of PTSD in a community sample of older adolescents. *J Am Acad Child Adolesc Psychiatry* 37:147–154.
- De Bellis MD, Baum AS, Birmaher B, Keshavan MS, Eccard CH, Boring AM, et al (1999): Developmental traumatology: I. Biological Stress Systems. *Biol Psychiatry* 45:1259–1270.
- De Bellis MD, Chrousos GP, Dorn LD, Burke L, Helmers K, Kling MA, et al (1994): Hypothalamic-pituitary-adrenal axis dysregulation in sexually abused girls. *J Clin Endocrinol Metab* 78:249–255.
- Duke PM, Litt IF, Gross RT (1980): Adolescents' self-assessment of sexual maturation. *Pediatrics* 66:918.
- Goenjian AK, Yehuda R, Pynoos RS, Steinberg AM, Tashjian M, Yang RK, et al (1996): Basal cortisol, dexamethasone suppression of cortisol, and MHPG in adolescents after the 1988 earthquake in Armenia. *Am J Psychiatry* 153:929–934.
- Gunnar MR (2001): The role of glucocorticoids in anxiety disorders: A critical analysis. In: Vasey MW, Dadds MR, editors. *The Developmental Psychopathology of Anxiety*. New York: Oxford University Press, 143–159.
- Harris B, Watkins S, Cook N, Walker RF, Read GF, Riad-Fahmy D (1990): Comparisons of plasma and salivary cortisol determinations for the diagnostic efficacy of the dexamethasone suppression test. *Biol Psychiatry* 27:897–904.
- Hart J, Gunnar M, Cichetti D (1996): Altered neuroendocrine activity in maltreated children related to symptoms of depression. *Dev Psychopathol* 8:201–214.
- Heim C, Newport JD, 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.
- Kaufman J, Birmaher B, Brent D, Rao U, Flynn C, Moreci P, et al (1997a): Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL): Initial reliability and validity data. *J Am Acad Child Adolesc Psychiatry* 36:980–988.
- Kaufman J, Birmaher B, Perel J, Dahl RE, Moreci P, Nelson B, et al (1997b): The corticotropin-releasing hormone challenge in depressed abused, depressed nonabused, and normal control children. *Biol Psychiatry* 42:669–679.
- Kessler RC, Sonnega A, Bromet E, Nelson CB (1995): Posttraumatic stress disorder in the National Comorbidity Survey. *Arch Gen Psychiatry* 52:1048–1060.
- King JA, Mandansky D, King S, Fletcher KE, Brewer J (2001): Early sexual abuse and low cortisol. *Psychiatry Clin Neurosciences* 55:71–74.
- Kirschbaum C, Hellhammer DH (1994): Salivary cortisol in psychoneuroendocrine research: Recent developments and applications. *Psychoneuroendocrinology* 19:313–333.
- Kirschbaum C, Strasburger CJ, Jammers W, Hellhammer DH (1989): Cortisol and behavior: I. Adaptation of a radioimmunoassay kit for reliable and inexpensive salivary cortisol determination. *Pharmacol Biochem Behav* 34:747–751.
- Lemieux AM, Coe CL (1995): Abuse-related posttraumatic stress disorder: Evidence for chronic neuroendocrine activation in women. *Psychosom Med* 57:105–115.
- Lupien SJ, King S, Meaney MJ, McEwen BS (2000): Child's stress hormone levels correlate with mother's socioeconomic status and depressive state. *Biol Psychiatry* 48:976–980.
- Maes M, Lin A, Bonaccorso S, van Hunsel F, Van Gastel A, Delmeire L, et al (1998): Increased 24-hour urinary cortisol excretion in patients with posttraumatic stress disorder and patients with major depression, but not in patients with fibromyalgia. *Acta Psychiatr Scand* 98:328–335.
- Marshal WA, Tanner JM (1970): Variations in the pattern of pubertal changes in girls. *Arch Dis Child* 45:13–23.
- Nader K, Pynoos RS, Fairbanks L, Frederick C (1990): Childhood PTSD reactions one year after a sniper attack. *Am J Psychiatry* 147:1526–1530.
- Nader KO, Kriegler JA, Blake DD, Pynoos RS, Newman E, Weather FW (1996): Clinician administered PTSD Scale,

- Child and Adolescent Version. White River Junction, VT: National Center for PTSD.
- Pitman R, Orr S (1990): Twenty-four hour urinary cortisol and catecholamine excretion in combat-related PTSD. *Biol Psychiatry* 27:245-247.
- Psychological Corporation (1999): *Wechsler Abbreviated Scale of Intelligence*. San Antonio, TX: Harcourt Brace & Company.
- Pynoos RS, Frederick C, Nader K, Arroyo W, Steinberg A, Eth S, et al (1987): Life threat and posttraumatic stress in school-age children. *Arch Gen Psychiatry* 44:1057-1063.
- 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.
- Woodside DB, Winter K, Fisman S (1991): Salivary cortisol in children: Correlations with serum values and effect of psychotropic drug administration. *Can J Psychiatry* 36:746-748.
- Yehuda R, Boisoneau D, Lowy MT, Giller EL Jr. (1995b): Dose-response changes in plasma cortisol and lymphocyte glucocorticoid receptors following dexamethasone administration in combat veterans with and without PTSD. *Arch Gen Psychiatry* 52:583-593.
- Yehuda R, Boisoneau D, Mason JW, Giller EL (1993): Glucocorticoid receptor number and cortisol excretion in mood, anxiety, and psychotic disorders. *Biol Psychiatry* 34:18-25.
- Yehuda R, Giller EL, Southwick SM, Lowy MT, Mason JW (1991): Hypothalamic-pituitary-adrenal dysfunction in PTSD. *Biol Psychiatry* 31:1031-1048.
- Yehuda R, Kahana B, Binder-Brynes K, Southwick SM, Mason JW, Giller EL (1995a): 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 (1996): Increase pituitary activation following metyrapone administration in post-traumatic stress disorder. *Psychoneuroendocrinology* 21:1-16.