Low Urinary Cortisol Excretion in Holocaust Survivors With Posttraumatic Stress Disorder

Rachel Yehuda, Ph.D., Boaz Kahana, Ph.D., Karen Binder-Brynes, Ph.D., Steven M. Southwick, M.D., John W. Mason, and Earl L. Giller, M.D., Ph.D.

Objective: The authors' objective was to compare the urinary cortisol excretion of Holocaust survivors with posttraumatic stress disorder (PTSD) (N=22) to that of Holocaust survivors without PTSD (N=25) and comparison subjects not exposed to the Holocaust (N=15). Method: Twenty-four-hour urine samples were collected, and the following day, subjects were evaluated for the presence and severity of past and current PTSD and other psychiatric conditions. Results: Holocaust survivors with PTSD showed significantly lower mean 24-hour urinary cortisol excretion than the two groups of subjects without PTSD. Multiple correlation analysis revealed a significant relationship between cortisol levels and severity of PTSD that was due to a substantial association with scores on the avoidance subscale. Conclusions: The present findings replicate the authors' previous observation of low urinary cortisol excretion in combat veterans with PTSD and extend these findings to a non-treatment-seeking civilian group. The results also demonstrate that low cortisol levels are associated with PTSD symptoms of a clinically significant nature, rather than occurring as a result of exposure to trauma per se, and that low cortisol levels may persist for decades following exposure to trauma among individuals with chronic PTSD.

(Am J Psychiatry 1995; 152:982–986)

We have previously demonstrated that combat veterans with posttraumatic stress disorder (PTSD) have significantly lower mean 24-hour urinary cortisol excretion (1–3), lower mean basal plasma cortisol levels at several times during the circadian cycle (4), and greater numbers of lymphocyte cytosolic glucocorticoid receptors than nonpsychiatric normal subjects and depressed patients (3, 5). In addition, veterans with PTSD show hypersuppression of cortisol in response to low doses of dexamethasone (5, 6). We have hypothesized that these changes are consistent with the idea of an enhanced negative feedback regulation of cortisol in PTSD (5–8). As such, these alterations in PTSD may reflect a type of adaptation that is different from the more traditionally described "desensitization" or dysregulation, in which the hypothalamic-pituitary-adrenal (HPA) axis becomes more sensitized after exposure to trauma (4).

Despite the internal consistency of the HPA axis alterations in combat veterans with PTSD, several questions remain concerning the long-term course and generalizability of the previously cited findings to other groups of trauma survivors with PTSD, particularly to non-treatment-seeking civilians and women who suffer from PTSD. Further points that require clarification concern the nature of HPA axis abnormalities in individuals who are exposed to similar trauma but who do not meet the diagnostic criteria for PTSD. To address these issues in the present study, we examined 24-hour urinary cortisol excretion in male and female Holocaust survivors with and without PTSD and in a demographically matched comparison group. To our knowledge, the present study represents the first neurobiological study of Holocaust survivors.

METHOD

The study group consisted of 47 individuals between the ages of 56 and 75 years of age who had been interned in Nazi concentration camps and 15 individuals (10 American-born and five European-born) who were comparable in age, sex, height, weight, race, religion,

Received July 11, 1994; revision received Nov. 28, 1994; accepted Jan. 12, 1995. From the Post-traumatic Stress Disorder Program, Department of Psychiatry, Mount Sinai School of Medicine, New York, N.Y., and Bronx VA Medical Center; Department of Psychology, Center for Aging, Cleveland State University, Cleveland, Ohio; and the Clinical Neurosciences Division, National Center for Posttraumatic Stress Disorder, West Haven, Conn. Address reprint requests to Dr. Yehuda, Psychiatry 116/A, Bronx VA Medical Center, 130 West Kingsbridge Rd., Bronx, NY 10468.

Supported by NIMH grant MH-49536 (Dr. Yehuda).

The authors acknowledge the technical assistance of Dr. Ren Kwei Yang and Mr. David Boisoneau, the administrative and editorial assistance of Ms. Skye Wilson, and the statistical consultation of Dr. James Schmeidler.

TABLE 1. Clinical Characteristics of Holocaust Survivors and Comparison Subjects

	Holocaust Survivors[a]						Pairwise Comparisons					
	With PTSD (A) (N=22)		Without PTSD (B) (N=25)		Comparison Subjects (C) (N=15)		A Versus B (df=45)		A Versus C (df=35)		B Versus C (df=38)	
Characteristic	Mean	SD	Mean	SD	Mean	SD	t	p	t	p	t	p
Cortisol level (μg/day)	32.6	17.0	62.7	25.3	51.9	23.7	4.94	0.001	3.12	0.002	1.33	n.s.
Civilian Mississippi PTSD Scale score	105.1	19.2	80.9	18.9	65.4	12.3	4.29	0.001	6.66	0.0001	2.67	0.01
Clinician-Administered PTSD Scale score												
Intrusive subscale	14.4	5.4	10.7	7.3	—	—	1.96	0.06				
Avoidance subscale	20.4	5.2	6.8	5.2	—	—	8.87	0.0001				
Hyperarousal subscale	20.4	9.9	9.2	7.7	—	—	4.32	0.0003				
Total	55.1	15.3	26.8	17.0	—	—	5.96	0.0001				

[a]Diagnostic groupings of Holocaust survivors were made with the Clinician-Administered PTSD Scale and were based on DSM-III-R criteria.

and income but who had not undergone the trauma of the Holocaust. Subjects were randomly selected from publicly available lists of Holocaust survivors provided by the local historical society and local synagogue membership rosters and were invited through a mailing to participate in studies exploring the biological basis of survival and adaptation. Comparison subjects were also recruited from the Jewish community by advertising in the local synagogue and community center. Subjects who agreed to participate provided written informed consent and then received a complete medical health assessment with the OARS checklist (9). Medical information on all subjects was carefully reviewed by a physician (E.L.G.), and patients with major medical conditions were excluded from the study, as were patients who had used benzodiazepines, antidepressants, lithium, β blockers, and psychotropic medication within 2 months of the study.

The Civilian Mississippi PTSD Scale was administered to all subjects to determine the global effect of stressful events on individuals' lives (10). Current and past psychiatric disorder was evaluated by using the Structured Clinical Interview for DSM-III-R (SCID) (11) for all subjects. The presence and severity of current and past PTSD were determined by using the Clinician-Administered PTSD Scale (12). This scale was administered to all Holocaust survivors and to comparison subjects who had undergone a past traumatic event according to DSM-III-R criterion A for the diagnosis of PTSD. On the basis of the results of the diagnostic assessment, the survivor group was further subdivided into those with (N=22) and those without (N=25) PTSD. Subjects who met the criteria for any primary axis I disorder other than PTSD were excluded from this study. Normal comparison subjects who met the criteria for any current or lifetime primary axis I psychiatric disorder, including PTSD, were also excluded. Data from 19 of the 62 subjects have been previously reported by Yehuda et al. (13).

Urine was collected beginning at 9:00 a.m. in exact 24-hour portions in 2-liter polyethylene bottles kept in freezers in the subjects' residences in order to ensure stability of cortisol and to avoid the possibility of falsely high urinary-free cortisol values in urine samples collected in acid. Collections were scheduled to occur on days when subjects planned to be at home for the 24-hour period. Clinical assessments took place following the completion of the 24-hour collection. Urinary-free cortisol levels were determined by using an extraction procedure and radioimmunoassay kit from Clinical Assays, Inc. (Cambridge, Mass.) (interassay coefficient of variation=4.0%).

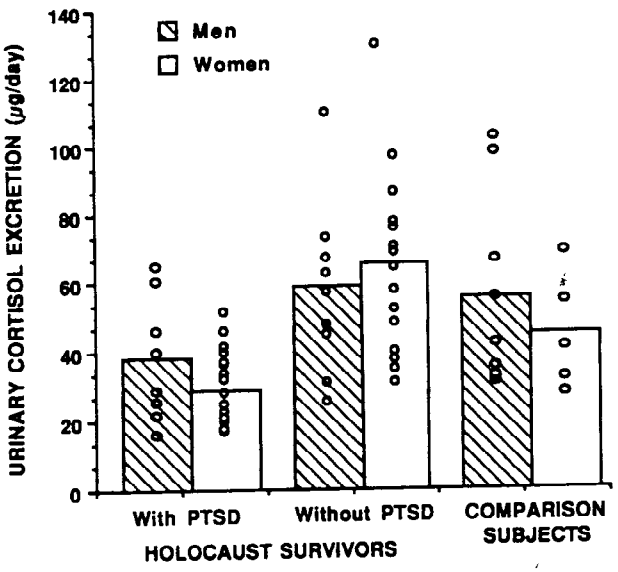
We used t tests to compare pairs of the three groups—survivors with PTSD, survivors without PTSD (as determined by the Clinician-Administered PTSD Scale), and demographically matched individuals who were not exposed to the Holocaust—on cortisol levels and scores on the Civilian Mississippi PTSD Scale. The effects and interaction of gender and group on cortisol were assessed by using two-way analysis of variance (ANOVA). Pearson correlations were used to assess the association between cortisol levels and scores on the Civilian Mississippi PTSD Scale for the entire cohort, and scores on the Clinician-Administered PTSD Scale (total and subscales) for the Holocaust survivors. Multiple correlation was used to assess the association between cortisol levels and scores on the Clinician-Administered PTSD Scale subscales (Holocaust survivors only).

RESULTS

Group means and standard deviations for cortisol and clinical variables are presented in table 1. Pairwise t tests showed that survivors with PTSD had significantly lower cortisol levels than survivors without PTSD and comparison subjects. Cortisol excretion in the last two groups did not differ significantly. Two-way ANOVAs revealed no significant cortisol differences by gender (N=28 men and 34 women) ($F=0.56$, $df=1, 56$) or Group by Gender interactions ($F=1.01$, $df=2, 56$). The individual cortisol values are plotted in figure 1. Eleven of the 25 Holocaust survivors who did not meet diagnostic criteria for current PTSD met the criteria for past PTSD. No group differences in cortisol excretion were present between survivors without current PTSD and with or without past PTSD (past PTSD: mean=58.7 μg/day, SD=19.4; no past PTSD: mean=67.8, SD=31.6).

Pairwise t tests revealed that the survivor group with current PTSD had significantly higher scores on the Civilian Mississippi PTSD Scale than both other groups. Scores on this scale for the survivor group without PTSD were also significantly higher than those of the comparison group (table 1). Consistent with the criteria for PTSD, Holocaust survivors with PTSD endorsed a significantly greater severity of PTSD symptoms, as assessed by the Clinician-Administered PTSD Scale (i.e., intrusive, avoidance and hyperarousal subscales), than Holocaust survivors without PTSD. It should be noted that many of the survivors without PTSD also had substantial symptoms even though they did not meet full DSM-III-R criteria for the disorder. Thirty-five percent of survivors who did not meet criteria for PTSD had total scores on the Clinician-Administered PTSD Scale that were as high as those of at least some survivors in the PTSD group, and 85% of survivors with PTSD had

FIGURE 1. Mean 24-Hour Urinary Cortisol Excretion in Holocaust Survivors With (N=22) and Without (N=25) PTSD and Comparison Subjects (N=15)



total scores on the scale that were as low as those of some individuals in the non-PTSD group.

Table 2 summarizes correlational analyses relating cortisol excretion to clinical symptoms. Simple correlation with the entire cohort failed to demonstrate a significant association with Civilian Mississippi PTSD Scale scores, which are thought to reflect not only the severity of PTSD, but the effect of PTSD on the individual's life. When Holocaust survivors were examined separately, there was still no significant relationship between cortisol levels and Civilian Mississippi PTSD Scale scores. There was, however, a trend for an association with total scores on the Clinician-Administered PTSD Scale; the trend was due to the substantial association with scores on the avoidance subscale. When all three subscales of the Clinician-Administered PTSD Scale were employed in a multiple correlation, the result was significant and was due only to the avoidance subscale (t for beta=3.54, df=41, p=0.001).

DISCUSSION

The main finding in the present study is that Holocaust survivors with chronic PTSD had significantly lower urinary cortisol excretion than individuals who were not exposed to the Holocaust and who did not meet criteria for current or past PTSD as a result of any other traumatic event. This observation agrees with our previous finding of lower urinary cortisol excretion in combat veterans with chronic PTSD than in a noncombat comparison group (2). In addition, the present results extend those findings by demonstrating that Holocaust survivors with PTSD have significantly lower cortisol levels than Holocaust survivors without PTSD,

TABLE 2. Correlations and Multiple Correlation of Cortisol Levels With Clinical Variables for 46 Holocaust Survivors and 13 Comparison Subjects[a]

Clinical Variable	N	Correlation	df	p
All subjects: Civilian Mississippi PTSD Scale	59	–0.16	58	n.s.
Holocaust survivors only				
Civilian Mississippi PTSD Scale	46	–0.14	44	n.s.
Clinician-Administered PTSD Scale				
Total	47	–0.29	45	0.05
Intrusive subscale	47	–0.09	45	n.s.
Avoidance subscale	47	–0.49	45	0.0005
Hyperarousal subscale	47	–0.40	45	n.s.
Three Clinician-Administered PTSD Scale subscales	47	0.53[b]	3, 43	0.003

[a]One Holocaust survivor and two comparison subjects did not have completed clinical data sets and were eliminated from correlational analyses.
[b]Multiple correlation.

while the latter have cortisol levels that do not significantly differ from those of the group not exposed to the Holocaust.

Cortisol levels among Holocaust survivors without PTSD were measured to determine whether differences in the excretion of this hormone were related to the presence of PTSD or, rather, were associated with having experienced a traumatic event. Consistent with a previous study (6), the Holocaust survivors without PTSD in the present study were significantly more symptomatic than the comparison group on measures of symptom severity. Nonetheless, Holocaust survivors without PTSD were not significantly different from the comparison group in regard to the mean 24-hour urinary excretion of cortisol. Furthermore, when the survivor group without PTSD was divided into those who met or did not meet criteria for past PTSD, no significant differences were observed. Although it is impossible to know whether the cortisol levels of the Holocaust survivors without PTSD were low at the time they met the criteria for PTSD, it can safely be concluded that exposure to trauma per se is not associated with long-term cortisol abnormalities. Rather, neurobiological alterations in cortisol release are associated with current symptoms of a clinically significant nature.

When the survivor group was considered as a whole (i.e., those with and those without PTSD), multiple correlation revealed that cortisol excretion was associated with severity of trauma-related symptoms, as reflected by scores on the Clinician-Administered PTSD Scale. In particular, severity of avoidance symptoms predicted cortisol levels, whereas intrusive and hyperarousal scores did not correlate with cortisol levels in this group. Although there was no a priori hypothesis for the specific association between cortisol levels and avoidance symptoms, it may be that avoidance is particularly common among subjects with PTSD who do not seek treatment and therefore especially reflects

PTSD in this group. Indeed, survivors with PTSD had a mean avoidance score that was 300% higher than that of survivors without PTSD.

In evaluating specific differences between the present results and previous studies of war veterans, it is important to note that although Holocaust survivors and combat veterans share many similarities in having been exposed to chronic and severe stress and in developing PTSD symptoms, these groups differ substantially on several important variables such as length of time since the original trauma (i.e., 25 versus 50 years) and the potential duration of PTSD symptoms. The present findings suggest that low cortisol levels are a persistent feature of PTSD that can be present even 50 years after a traumatic event. Consequently, this study provides preliminary data concerning longitudinal aspects of biological alterations in PTSD.

Given the age of the subjects in this study, it is important to consider the extent to which the present cortisol findings may have been confounded by the process of aging. Although there is now evidence for both decreases (13–15) and increases (16, 17) in cortisol levels with age, the majority of studies to date have shown no differences in plasma or urinary cortisol levels in elderly and younger subjects (18–26). A lower concentration of cortisol metabolites, apparently reflecting a lower rate of cortisol clearance from circulation, has been noted; however, in those studies there were no changes in the production or concentration of corticosteroids (18, 19, 24). Most studies that have examined the negative feedback sensitivity in elderly humans have shown normal responses of the adrenocortical axis to dexamethasone (22, 23, 26–28). Moreover, the responsiveness of the adrenal glands to ACTH infusion (18) and insulin (16) appears to be normal in the elderly. It should also be noted that the mean cortisol excretion for the PTSD and comparison groups in the current study was comparable to what we have previously reported for subjects with a mean age of approximately 40 years (2, 3). Therefore, it seems unlikely that the present results were influenced by the process of aging.

The present findings also represent the first reports of HPA axis abnormalities in woman with chronic PTSD. Given that the majority of biological studies have used male combat veterans, information about neuroendocrine abnormalities in women has been lacking. The present results failed to indicate gender differences in cortisol levels. However, the women studied were all menopausal. Therefore, gender-related differences should be evaluated in younger women before definitive conclusions can be made regarding the influence of gender on HPA axis measures in PTSD.

Other differences between survivors studied in the present report and previously studied war veterans are treatment-seeking status, past and current psychiatric comorbidity, and past and current substance dependence. Indeed, the present study provides one of the first demonstrations of neuroendocrine differences in a nontreatment-seeking group with chronic PTSD that is free of confounding factors such as psychiatric comorbidity, particularly major depression and substance abuse, and difficulties in social and occupational functioning. Despite these important differences, the mean urinary cortisol excretion in the current group of Holocaust survivors with PTSD is comparable to what we have previously reported for treatment-seeking combat veterans (1–3). Therefore, it can be concluded that the marked differences in the previously mentioned variables between Holocaust survivors and combat veterans with PTSD are not relevant to the mean 24-hour urinary excretion of cortisol. Rather, low cortisol levels appear to reflect the presence of a current and chronic posttraumatic stress syndrome.

REFERENCES

1. Mason JW, Giller EL, Kosten TR, Ostroff R, Harkness L: Urinary-free cortisol in posttraumatic stress disorder. J Nerv Ment Dis 1986; 174:145–149
2. Yehuda R, Southwick SM, Nussbaum G, Wahby V, Giller EL, Mason J: Low urinary cortisol excretion in patients with posttraumatic stress disorder. J Nerv Ment Dis 1990; 187:366–369
3. Yehuda R, Boisoneau D, Mason JW, Giller EL: Relationship between lymphocyte glucocorticoid receptor number and urinary-free cortisol excretion in mood, anxiety, and psychotic disorder. Biol Psychiatry 1993; 34:18–25
4. Yehuda R, Teicher MH, Trestman RL, Levengood RA, Siever LJ: Cortisol regulation in posttraumatic stress disorder: a chronobiological analysis, in New Research Program and Abstracts, 146th Annual Meeting of the American Psychiatric Association. Washington, DC, APA, 1993
5. Yehuda R, Boisoneau D, Lowy MT, Giller EL: 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 (in press)
6. Yehuda R, Southwick SM, Krystal JH, Bremner D, Charney DS, Mason JW: Enhanced suppression of cortisol following dexamethasone administration in posttraumatic stress disorder. Am J Psychiatry 1993; 150:83–86
7. Yehuda R, Lowy MT, Southwick SM, Shaffer D, Giller EL Jr: Lymphocyte glucocorticoid receptor number in posttraumatic stress disorder. Am J Psychiatry 1991; 148:499–504
8. Yehuda R, Giller EL, Southwick SM, Lowy MT, Mason JW: Hypothalamic-pituitary-adrenal dysfunction in posttraumatic stress disorder. Biol Psychiatry 1991; 30:1031–1048
9. Blazer D: Durham Survey: description and application, in Multidimensional Functional Assessment OARS Methodology: A Manual, 2nd ed. Durham, NC, Duke University Center for the Study of Aging and Human Development, 1978
10. Keane TM, Caddell JM, Taylor KL: The Civilian Mississippi PTSD Scale. Boston, National Center for Posttraumatic Stress Disorder, 1991
11. Spitzer RL, Williams JBW, Gibbon M: Structured Clinical Interview for DSM-III-R (SCID). New York, New York State Psychiatric Institute, Biometrics Research, 1987
12. Blake D, Weathers F, Nagy D, Kaloupek G, Klauminzer D, Charney D, Keane T: A clinician rating scale for current and lifetime PTSD. Behavior Therapist 1990; 13:187–188
13. Yehuda R, Resnick H, Kahana B, Giller EL: Persistent hormonal alterations following extreme stress in humans: adaptive or maladaptive? Psychosom Med 1993; 55:287–297
14. Sharma M, Palacios-Bois G, Schwartz H, Iskandar M, Thakur M, Quirion R, Nair NPV: Circadian rhythms of melatonin and cortisol in aging. Biol Psychiatry 1989; 25:305–319
15. Drafta D, Schindler AE, Stroe E, Neascu E: Age-related changes of plasma steroids in normal adult males. J Steroid Biochem 1982; 17:683–687
16. Sherman B, Wysham C, Pfohl B: Age-related changes in the cir-

cadian rhythm of plasma cortisol in man. J Clin Endocrinol Metab 1985; 61:439–443
17. Friedman M, Green MF, Sharland DE: Assessment of hypothalamic-pituitary-adrenal function in the geriatric age group. J Gerontol 1969; 24:292–297
18. Halbreich U, Asnis GM, Zumoff B, Swai Nathan R, Shindledecker R: Effect of age and sex on cortisol secretion in depressives and normals. Psychiatry Res 1984; 13:221–229
19. West C, Brown H, Simons E, Carter D, Kumagai L, Englebert E: Adrenocortical function and cortisol metabolism in old age. J Clin Endocrinol Metab 1961; 21:1197–1203
20. Blichert-Toft M: The adrenal glands in old age, in Geriatric Endocrinology. Edited by Greenblatt RB. New York, Raven Press, 1978
21. Andras R, Tobin JD: Endocrine systems, in Handbook of the Biology of Aging. Edited by Finch CE, Hayflick L. New York, Van Nostrand, 1977
22. Tourigny-Rivard MF, Raskind M, Rivard D: The dexamethasone suppression test in an elderly population. Biol Psychiatry 1981; 16:1177–1184
23. Rosenbaum AH, Schatzberg AF, MacLaughlin RA, Snyder K, Jiang NS, Ilstrup D, Rothschild AJ, Kliman B: The dexamethasone suppression test in normal control subjects: comparison of two assays and effect of age. Am J Psychiatry 1984; 141:1550–1555
24. Stokes PE, Stoll PM, Koslow SH, Maas JW, Davis JM, Swann AC, Robins E: Pretreatment DST and hypothalamic-pituitary-adrenocortical function in depressed patients and comparison groups. Arch Gen Psychiatry 1984; 41:257–267
25. Jensen HK, Blichert-Toft M: Serum corticotrophin, plasma cortisol and urinary excretion of 17-ketogenic steroids in the elderly (age group: 66–94 years). Acta Endocrinol (Copenh) 1971; 6: 625–634
26. Krieger DT, Allen W, Rizzo F, Krieger HP: Characterization of the normal temporal pattern of plasma corticosteroid levels. J Clin Endocrinol Metab 1971; 32:266–284
27. Touitou Y, Sulon J, Nogdan A, Touitou C, Reinberg A, Beck H, Sodoyz JC, Demy-Ponsart E, Van Cauwenberge H: Adrenal circadian system in young and elderly human subjects: a comparative study. J Endocrinol 1982; 93:201–210
28. Zimmerman M, Coryell W: The dexamethasone suppression test in healthy controls. Psychoneuroendocrinology 1987; 1:245–253