The Cortisol and Glucocorticoid Receptor Response to Low Dose Dexamethasone Administration in Aging Combat Veterans and Holocaust Survivors with and without Posttraumatic Stress Disorder

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Background: *Because alterations in cortisol negative feedback inhibition associated with aging are generally opposite of those observed in posttraumatic stress disorder (PTSD), we examined the cortisol and glucocorticoid receptor (GR) response to dexamethasone (DEX) in older trauma survivors.*

Methods: *Twenty-three Holocaust survivors (9 men, 14 women), 27 combat veterans (all male), and 10 comparison subjects (7 men, 3 women) provided samples for plasma or salivary cortisol and glucocorticoid receptor determination in mononuclear leukocytes at 8:00 AM on the day of, and following, 0.5 mg of DEX at 11:00 PM.*

Results: *Greater percent suppression of cortisol and lymphocyte GR was observed in older trauma survivors with PTSD compared to survivors without PTSD and comparison subjects. There was a significant main effect of depression in the direction of reduced suppression following DEX, consistent with the effects of DEX in major depressive disorder patients. Responses to DEX were uncorrelated with PTSD symptom severity, but cortisol suppression was associated with years elapsed since the most recent, but not focal, traumatic event.*

Conclusions: *The response to DEX is generally similar in older and younger trauma survivors, but the findings suggest that age, symptom severity, and lifetime trauma exposure characteristics may influence this response.*
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Key Words: Posttraumatic stress disorder, depression, cortisol, dexamethasone suppression test, glucocorticoid receptors, aging

Introduction

There are now several demonstrations of a greater cortisol suppression following dexamethasone (DEX) administration in subjects with posttraumatic stress disorder (PTSD) compared to similarly exposed or non-trauma exposed subjects, particularly when a low dose (0.50 mg) of dexameathsone is used (Goenjian et al 1996; Halbreich et al 1989; Heim et al 1998; Stein et al 1997; Yehuda et al 1993b, 1995a). To date, however, studies using the low-dose dexamethasone suppression test (DST) in PTSD have examined subjects within a restricted age range and an average duration of PTSD of less than 20 years. The mean age of subjects in published studies has ranged from 13.5 years to 44.1 years.

The extent to which neurobiological changes observed in younger PTSD populations also apply to older subjects is of particular interest, because age may be associated with differences in both clinical symptoms of PTSD and its concomitant neurobiology. Both longitudinal and cross-sectional studies of older trauma survivors demonstrate a reduction in the percent of subjects meeting criteria for PTSD 40 and 50 years following exposure, compared to PTSD symptom levels in closer proximity to the trauma (Fontana and Rosenbeck 1994; Kluznik et al 1986; Tennant et al 1993, 1997). In studies of Holocaust survivors, those who met criteria for PTSD tended to endorse mild to moderate symptom severity on diagnostic assessments rather than symptom severity in the extreme range (Yehuda et al 1995c, al 1996a, 1997).

Despite such differences in age-related PTSD phenomenology, Holocaust survivors with PTSD had lower cortisol levels compared to both Holocaust survivors without PTSD and non-exposed persons (Yehuda et al 1995b). The mean 24-hour urinary cortisol excretion in Holocaust survivors with PTSD was comparable to that observed in combat Vietnam veterans with this disorder (Yehuda et al 1990, 1993a). This finding may reflect the observation that basal cortisol concentrations appear to remain fairly con-

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stant throughout the normal life span (Svec 1997; Waltman et al 1991; Weiner et al 1987). That is, although there is evidence for an age-related decline in cortisol production from the adrenals (West et al 1979), an accompanying decline in the clearance and circadian rhythm (Ferrari et al 1995) of cortisol may serve to present the appearance of stable ambient cortisol levels as reflected by a mean integrated 24-hour urine, at least until subjects become very old.

In contrast to the relative stability of ambient cortisol levels over the lifespan, investigations of the hypothalamic–pituitary–adrenal (HPA) axis response to glucocorticoid feedback inhibition have generally provided evidence for a reduction in negative feedback sensitivity in aging (Ferrari et al 1995; Parnetti et al 1990; Wilkinson et al 1997, 2001; Zovato et al 1996), and an associated decline in the number of basal Type II glucocorticoid receptors (GR) in mononuclear leukocytes (Zovato et al 1996). These changes have been hypothesized as resulting from age-related alterations in the circadian rhythm of cortisol that can lead to changes in GR activity, even in the absence of detectable changes in ambient cortisol levels (Sapolsky 1992).

Additionally, whereas ambient cortisol levels have been reported to partially reflect more long-term individual "trait" characteristics (Holsboer et al 1995; Young et al 2000), the cortisol response to DEX appears to be more associated with clinical state (Huizenga et al 1998). Studies of depressed patients have shown that for subjects with non-suppression on the DST, successful treatment restores both DST suppression and GR function to normal (Grunhaus et al 1987; Hunter et al 1988; Ribeiro et al 1993). Although similar pre- and post-treatment studies have not been performed in PTSD, the extent of cortisol suppression following DEX has been found to be correlated with severity of PTSD symptoms (Goenjian et al 1996; Yehuda et al 1995a). Furthermore, combat veterans with past, but not current PTSD, do not show an exaggerated cortisol suppression to DEX (Yehuda et al 1995a).

Because the alterations in cortisol negative feedback inhibition that are associated with aging are opposite to those observed in PTSD, and because the clinical presentation of PTSD appears to decline over time, it was of interest to examine DST suppression in aging trauma survivors. The current research studied a mixed population of trauma survivors aged 50 years or older: Holocaust survivors, veterans of World War II, the Korean War, and Vietnam veterans approaching late middle age. Because traumatic events occurring subsequent to the focal trauma are particularly related to symptom severity in older trauma survivors (Yehuda et al 1995), we also examined the contribution of significant traumatic events occurring subsequent to the focal trauma (i.e., exposure to combat or the Holocaust) to PTSD-related biological alterations. Thus, we examined the cortisol and GR response to low dose DEX administration in older trauma survivors with and without PTSD compared to subjects who had not experienced comparable levels of traumatic stress, and we considered the relationship of these variables to severity of symptoms and other traumatic exposure-related characteristics.

Methods and Materials

Participants

Trauma-exposed participants were Holocaust survivors (n = 23) or combat veterans (n = 27) who were at least 50 years old at the time of the study. At the time of assessment, an average of 41.6 ± 15.1 years had elapsed since the focal trauma for the exposed groups. The Holocaust survivors (9 men, 14 women; mean age = 67.0 ± 6.2 years) were defined by having been interned in concentration camps, and/or having had other traumatic wartime experiences, such as being in hiding or fleeing Nazi-occupied territory. Combat veterans (all male; mean age = 63.3 ± 10.7 years) were defined as having seen active duty in one or more wars (e.g., primarily World War II, the Korean War, and the Vietnam conflict). Four career veterans participated in the Gulf War and endorsed this experience as their focal trauma event, although they had all participated in previous combat. The study also included 10 normal, age-comparable participants (7 men, 3 women; mean age = 68.5 ± 10.3) who had not been exposed to combat or to the Holocaust and were free from current or lifetime psychiatric diagnoses. Participants were recruited through advertisements for research participants placed on bulletin boards around the hospital and in newspapers and magazines. Combat veterans were recruited through a specialized PTSD program at the Bronx Veterans Affairs Medical Center, and Holocaust survivors through the Mount Sinai Specialized Treatment Program for Holocaust Survivors and Their Families. The study was approved by the Institutional Review Boards at the Mount Sinai School of Medicine and Bronx Veterans Affairs, and all participants gave written informed consent to participate following a detailed explanation of all study procedures.

Thirty-four participants (27 men and 7 women; mean age = 63.0 ± 8.3 years) met criteria for current PTSD, and 26 did not meet current criteria (16 men and 10 women; 69.0 ± 8.3 years). In the group without current PTSD, four subjects met the criteria for lifetime PTSD, which when present was usually confined to the first several years following trauma exposure. Thus, subjects in the no-current-PTSD group had not met criteria for PTSD for several decades. Fifty percent (n = 17) of individuals with current PTSD also met criteria for major depressive disorder (MDD), relative to only 11.5% (n = 3) of those without current PTSD.

Participants were excluded from the study if they had a history of psychotic disorder or bipolar illness, current alcohol or substance abuse/dependence, a smoking habit of more than three cigarettes per day, were clinically obese, or if they were taking

β-blockers, lithium, or other psychotropic medications within 2 months of the study. With regards to medication status, only participants who met the requirements described were enrolled in the study; participants were not withdrawn from medications to participate in this protocol. Subjects were also free from major medical, endocrinological, and neurological illness, as determined by history, physical examination, and routine clinical laboratory tests. One participant who completed the protocol was excluded from analyses when it emerged that he had lymphoma at the time of biological testing.

Clinical Assessments

All participants were interviewed by a trained psychologist or psychiatrist rater (RY, JG, RG, CW) using the Structured Clinical Interview for DSM-IV (Spitzer et al 1995). A comprehensive trauma history was obtained for each participant using the Trauma History Questionnaire (Green 1996), specifically obtaining information about the earliest, most recent, and most severe negative life events. Endorsed events were reviewed with the subject in order to ascertain whether they met the diagnostic criterion "A" for a traumatic event (American Psychiatric Association 1994). Following this exploration, the Clinician-Administered PTSD Scale (CAPS) (Blake et al 1995) was administered to all participants who reported a traumatic event, using the subject's "worst" experience as the focal trauma. This scale has recently been validated for use in elderly trauma survivors (Hyer et al 1996). Holocaust and combat veterans all reported some aspect of their respective grouping exposures as being the focal event. No comparison participants reported being exposed to an event that subsequently evoked symptoms of PTSD. Diagnostic groupings were confirmed by consensus, in consideration of the results of the structured clinical assessments and reports of clinicians, when available. For participants interviewed prior to the introduction of standardized interviews based on DSM-IV criteria, DSM-III-R–based clinical interviews were used; however, all diagnoses were subsequently standardized to DSM-IV criteria.

Biological Measures

The extent of corticosteroid suppression in response to DEX was assessed through either plasma ($n = 50$) or salivary ($n = 10$) cortisol measurement. The subjects who collected saliva samples (four trauma exposed individuals with no diagnosis and six with PTSD only) did so either out of reluctance to undergo two sets of venipuncture or because it was not possible for them to arrive at the hospital by 8:00 AM.

Baseline blood or saliva samples were obtained at 8:00 AM prior to DEX administration. Each participant then received an oral dose of 0.5 mg of DEX, and was instructed to take the DEX at 11:00 PM. To increase standardization of administration times, participants were called by a research assistant at 10:55 PM. Blood or saliva samples for determination of cortisol and DEX (plasma only) were obtained at 8:00 AM the following day. Plasma and salivary cortisol levels were determined by radioimmunoassay, as previously described (Yehuda et al 1990). The interassay and intrassay coefficients of variation for this method in our laboratory were 4.0% and 6.8% respectively. DEX levels were also assayed by radioimmunoassay in both plasma and saliva using commercially available antibodies (IgG Corporation, Nashville, TN) according to the method of Lowy and Meltzer (1987). The intra- and interassay coefficients of variation in our laboratory are 8.0% and 9.0%. Results of the DST were expressed as both post-DEX cortisol levels (μg/dL) and percent suppression of cortisol [(pre-DEX cortisol − post-DEX cortisol/pre-DEX cortisol) × 100]. The latter variable allowed us to account for individual variance in cortisol suppression resulting from differences in basal cortisol levels, and to obtain a dependent variable that would allow us to pool data from both plasma and salivary samples. Our laboratory has indicated a high correlation ($r = .99$; $n = 7$; $p < .0005$; Yehuda et al, unpublished observations) between plasma and salivary indices of percent cortisol suppression (defined above).

Twenty-five mL of plasma were obtained for assessment of glucocorticoid receptor number. Mononuclear cells were isolated using Ficoll Hypaque within 1 hour following blood draw, and cells were centrifuged at 300 *g* at 4°C, washed four times in ice-cold Hank's buffer and pelleted. An aliquot of the suspension was counted by a hemocytometer and the final pellet stored at −70°C. Glucocorticoid receptor binding was measured with using ^{3}H-DEX as ligand after suspending the frozen lymphocyte pellets (containing $0.6–2 \times 10^7$ cells) in an assay buffer (consisting of 10 mmol/L Tris, 1 mmol/L ethylenediaminetetraaceticacid (EDTA), 2.5 mmol/L dithiothreitol, 10% glycerol, 20 mmol/L Na_2MoO_4; pH 7.4), mixing vigorously in the cold for 30 min, and subjecting to centrifugation at 250,000 *g* for 30 min. Total binding of ^{3}H-DEX was measured in 0.25 mL aliquots of cytosol, which were incubated overnight at 4°C with 20 mmol/L of ligand. Specific binding was defined as that inhibited by a 500-fold excess of unlabeled DEX. That the 20 mmol/L ^{3}H-DEX concentration measures 90% of available receptors and correlates highly ($r = .99$) with B_{max} values has been confirmed by Scatchard analysis in our laboratory (Yehuda et al 1995a). An estimation of glucocorticoid receptor activity was expressed as percent suppression of GR [(pre-DEX GR − post-DEX GR/pre-DEX GR) × 100], as previously described (Yehuda et al 1995a).

Statistical Analysis

Analysis of variance (ANOVA) or covariance (ANCOVA) was used to assess the effects of PTSD and/or MDD on the biologic parameters. Secondary analyses considered the contribution of type of exposure (i.e., combat vs. Holocaust) on dependent variables. Covariates were considered (e.g., age, gender, DEX concentrations) and used where there were either group differences in potentially confounding variables, or significant associations with dependent measures. Post hoc comparisons were performed using Tukey's Honestly Significant Difference (HSD) test. Pearson's correlational analyses were performed to determine relationships among these biologic and symptom measures, controlling for age and gender where appropriate. Multivariate analysis of variance was used to analyze group differences in PTSD symptoms on the intrusion, avoidance, and hyperarousal

Table 1. Clinical Characteristics and DST Percent Cortisol Suppression in the Posttraumatic Stress Disorder (PTSD) versus No PTSD Groups, Reported by Presence or Absence of Major Depressive Disorder (MDD)

	PTSD Symptoms (frequency + intensity)								% Cortisol suppression	
	Intrusion		Avoidance		Hyperarousal		Total			
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
No PTSD (n = 26)	6.19	5.90	8.38	9.14	7.19	5.52	21.19	12.87	77.91	14.10
No major depression (n = 23)[a]	6.15	6.48	6.15	7.59	7.15	6.14	19.46	13.18	80.00	12.14
Major depression (n = 3)	6.33	3.06	18.00	10.44	7.33	1.53	28.67	9.87	60.66	14.73
PTSD (n = 34)	19.91	8.75	27.92	7.91	24.47	7.69	72.29	19.63	83.91	15.78
No major depression (n = 17)	16.71	9.63	23.71	7.92	21.24	7.91	61.65	20.99	88.99	10.57
Major depression (n = 17)	23.12	6.58	32.12	5.36	27.71	6.10	82.94	10.66	78.82	18.61

On all measures, No PTSD (n = 26) are significantly different from PTSD (n = 34).
DST, dexamethasone suppression test; CAPS, Clinician-Administered PTSD Scale.
[a]Includes 10 comparison participants without trauma exposure with no PTSD symptoms (i.e., means and SDs of CAPS total symptom scores and subscale scores are all zero for these participants). Cortisol suppression data for this subgroup appears in Figure 1.

subscales of the CAPS in relation to Holocaust versus combat exposure and the presence or absence of PTSD.

Results

Diagnostic Status and the Dexamethasone Suppression Test

The effect of percent cortisol suppression using salivary versus plasma samples was assessed using a two-way ANOVA to examine possible differences in the "type" of DST (i.e., salivary vs. plasma) in conjunction with PTSD diagnosis as predictors of percent cortisol suppression. There was no main effect of type of DST in relation to cortisol suppression [F (1, 56) = 0.01; n.s.], further supporting our decision to combine data regarding percent suppression of cortisol from saliva and plasma in the current analyses.

Because the PTSD group was significantly younger than the no-PTSD group at the time of assessment [$t(58)$ = 2.63, p = .011; see Methods], and had a higher incidence of MDD [$\chi^2(1)$ = 9.81, p = .002], an ANCOVA was used to examine the effect of current PTSD on percent cortisol suppression, with age at assessment and the presence or absence of MDD as covariates. This analysis showed a significant main effect of PTSD on percent suppression of cortisol [F (1, 56) = 6.42; p = .014], with mean percent suppression being higher in individuals with current PTSD (data reported in Table 1). MDD was found to be a significant covariate [F (1, 56) = 10.23; p = .002], but age was not [F (1, 56) = 2.46; *n.s.*].

Accordingly, a two-way ANOVA was conducted to examine further the impact of MDD and PTSD on the cortisol response to DEX, revealing significant main effects of both PTSD [F (1, 56) = 3.15; p = .006] and MDD [F (1, 56) = 8.36; p = .005) on percent cortisol suppression, but no significant interaction of these variables [F(1, 56) = 0.69; n.s.]. As shown in Figure 1, PTSD was associated with higher, and MDD with reduced, suppression of cortisol in response to DEX. When this

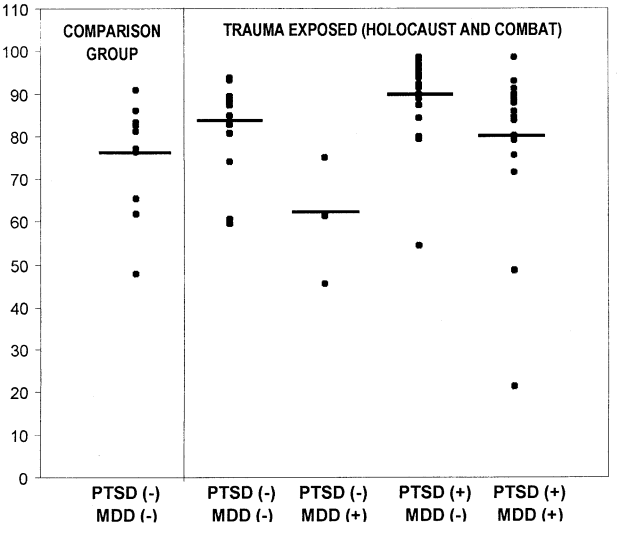

Figure 1. Percent cortisol suppression in response to .5 mg dexamethasone, reported by the presence or absence of posttraumatic stress disorder (PSTD), major depression (MDD), and trauma exposure. Trauma-exposed participants without any psychiatric diagnoses showed cortisol suppression that was marginally higher than that in non-exposed comparison participants, but lower than subjects with PTSD only. When analysis of variance was used to examine this effect, there was a significant main effect of the three-level grouping variable [i.e, comparison subjects, exposed subjects without a diagnosis, and exposed subjects with PTSD only: F(2, 37) = 4.75 p = .015] in relation to percent cortisol suppression. Post hoc testing using Tukey's Honestly Significant Difference (HSD) indicated a significant difference only between the PTSD and comparison groups (p = .01).

Table 2. Plasma Concentrations of Dexamethasone (DEX), Cortisol, and Mononuclear Leukocytes Glucocorticoid Receptor (GR) Concentrations in Response to the Low-Dose Dexamethasone Suppression Test (DST)

	Dexamethasone (ug/dL)[a]		Plasma cortisol (ug/dL)				Mononuclear leukocyte GR (number/cell)[a]			
			Pre-DEX[b]		Post-DEX[c]		Pre-DEX[d]		Post-DEX[e]	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
No PTSD (n = 22)	124.10	44.21	11.40	3.75	2.70	1.62	2383	845	2362	1026
No major depression (n = 19)	126.33	43.72	11.26	3.77	2.43	1.57	2474	549	2414	983
No trauma (n = 10)	121.56	49.29	10.94	3.63	2.81	1.92	2346	506	2411	1194
Trauma (n = 9)	131.11	39.75	11.60	4.11	2.00	1.02	2603	590	2417	792
Major depression (n = 3)	110.67	54.60	12.33	4.26	4.43	0.42	1835	2013	2053	1467
PTSD (n = 28)	113.89	47.90	9.91	2.84	1.81	1.99	2538	1211	2235	1253
No major depression (n = 11)	127.45	48.37	9.54	3.50	1.01	0.95	2848	1366	2580	1463
Major depression (n = 17)	105.12	46.91	10.15	2.41	2.32	2.33	2337	1095	2012	1085

Data are reported by diagnoses for the subset of participants (n = 50) who completed the plasma DST. PTSD, Posttraumatic Stress Disorder.

[a] n = 49; assays for plasma DEX and mononuclear leukocyte GR could not be performed for one comparison participant.

[b] Two-way analysis of variance (ANOVA) examining baseline plasma cortisol levels in relation to PTSD and MDD found no significant main effect of PTSD [F(1, 46) = 2.57; p = .11] or MDD [F(1, 47) = 0.48] and no PTSD × MDD interaction [F(1, 46) = .04].

[c] Two-way analysis of covariance (ANCOVA) examining post-DEX cortisol concentrations in relation to PTSD and MDD while covarying for plasma DEX concentrations indicated significant and opposite main effects of PTSD [F(1, 44) = 7.75 ; p = .008] and MDD [F(1, 44 = 5.63; p = .022], but no interaction (F = .24), and no effect of plasma DEX concentration as a covariate (F = .33).

[d] Two-way ANOVA examining pre-DEX receptor levels in relation to PTSD and MDD indicated no main effect of either diagnosis in relation to receptor number [for PTSD, F(1, 45) = 1.68: for MDD, F = 1.88], and no PTSD × MDD interaction (F = .10).

[e] Two-way ANCOVA examining post-DEX receptor number in relation to PTSD and MDD while covarying for plasma concentrations of DEX indicated no main effect of either PTSD [F(1, 44) = .07] or MDD (F = 2.11) and no interaction (F = .03). There was a significant effect of covarying for plasma DEX [F(1, 44) = 9.43; p = .004], DEX concentrations correlating negatively with post-DEX receptor concentrations (Pearson's r = −.37, n = 49, p = .008).

analysis was repeated in the subset of 50 participants (28 with current PTSD, 22 without) who completed the plasma DST, the results were the same (means and SDs for plasma data are reported separately in Table 2). Two-way ANCOVA examined percent cortisol suppression in relation to the presence or absence of both PTSD and MDD, covarying for plasma DEX concentration. There were significant main effects of PTSD [F (1, 44) = 8.56; p = .005], and MDD [F(1, 44) = 7.04; p = .011] but no interaction [F (1, 46) = 0.34; *ns*]. Plasma DEX concentration was not a significant covariate [F (1, 44) = 0.08; *ns*].

To further determine whether differences in percent suppression of cortisol were associated with an exaggerated suppression in response to dexamethasone, a repeated-measures ANCOVA was carried out on log transformed plasma cortisol concentrations, examining pre- to post-DEX change (assessment) in concentration in relation to PTSD and MDD, covarying for plasma DEX concentration. There was a significant cortisol assessment × PTSD diagnosis interaction [F(1, 44) = 11.4; p = .002], confirming that this suppression is exaggerated in individuals with current PTSD. In addition, there was a significant assessment × MDD interaction [F (1, 44) = 6.3 ; p = .016], confirming the weaker suppression observed in association with current MDD. The assessment × PTSD × MDD interaction was not significant (F = 0.003).

For the subset with plasma DST cortisol values, (Table 2) a two-way ANOVA confirmed that there were no differences in mean post-test plasma DEX concentration in relation to either PTSD [F (1, 45 = 0.02; n.s.] or MDD [F (1, 45) = 1.24; n.s.]. Examinations of mononuclear leukocyte GR number were also carried out. A preliminary examination of these data revealed a significant outlier among the participants with both PTSD and MDD, the −241.9% suppression for this participant being more than three SDs outside the group mean (4.09 ± 73.77%). Analyses of the data were therefore carried out excluding this outlying value. A two-way ANCOVA examined current PTSD and MDD status in relation to percent change in concentration of GRs following administration of DEX, covarying for post-test DEX concentration, because we found this to correlate with percent GR change.[1] There was a significant main effect of PTSD [F(1, 43) = 12,19; p = .001], reflecting larger percent reductions in GR concentration in individuals with PTSD. There was also a trend for a main effect of MDD [F(1, 43) = 3.01; p = .09], indicating that individuals with MDD tended to show lower percent suppression than those without, and a significant PTSD × MDD interaction [F(1, 43) = 9.95;

[1] Plasma DEX concentration was found to correlate with percent change in GR, r = .38. If DEX was not included as a covariate in the analysis, ANOVA indicated a significant main effect of PTSD [F (1, 44) = 9.98; p = .003], a significant main effect of MDD [F = 4.24; df = 1,44; p = .007] and a PTSD × MDD interaction [F (1,44) = 7.98; p = .007].

Table 3. Clinical Characteristics and Percent Cortisol Suppression in Response to Dexamethasone in Holocaust Survivors versus Combat Veterans

	Age at trauma exposure				PTSD Symptoms (frequency + intensity)						% Cortisol suppression	
	Focal		Most recent		Intrusion		Avoidance		Hyperarousal			
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Holocaust survivors												
No PTSD (n = 11)	10.36	6.42	55.91	13.69	7.18	6.18	7.73	7.90	7.73	4.78	80.14	14.80
No MDD (n = 9)	11.44	6.54	55.78	15.28	7.00	6.87	6.78	8.50	7.78	5.29	84.55	9.95
MDD (n = 2)	5.50	3.54	56.50	2.12	8.00	1.41	12.00	1.41	7.50	2.12	60.28	20.81
PTSD (n = 12)	12.58	4.38	47.58	17.25	19.58	10.81	23.58	7.79	21.75	9.28	82.13	22.22
No MDD (n = 7)	13.29	5.06	50.57	14.30	14.57	10.24	19.43	6.50	17.00	6.58	87.97	15.15
MDD (n = 5)	11.60	3.51	43.40	21.78	26.60	7.64	29.40	5.55	28.40	8.79	73.95	29.49
Combat veterans												
No PTSD (n = 5)	21.80	4.21	52.00	25.29	4.00	5.15	9.80	12.38	6.00	7.38	73.02	12.45
No MDD (n = 4)	22.75	4.19	49.00	28.01	4.25	5.91	4.75	5.85	5.75	8.50	75.92	12.27
MDD (n = 1)	18.00	—	65.00	—	3.00	—	30.00	—	7.00	—	61.42	—
PTSD (n = 22)	26.05	11.92	44.50	17.07	20.09	7.68	30.27	7.07	25.95	6.43	84.87	11.39
No MDD (n = 10)	28.40	14.02	41.70	19.01	18.20	9.43	26.70	7.69	24.20	7.66	89.70	6.65
MDD (n = 12)	24.08	10.07	48.83	15.72	21.67	5.84	33.25	5.08	27.42	5.07	80.85	13.14

PTSD, posttraumatic stress disorder; MDD, major depressive disorder.

$p = .003$].[2] The small number of individuals in the MDD only group ($n = 3$) made interpretation of the latter finding difficult. Reductions in receptor levels appeared to be highest in individuals with both PTSD and MDD, but lowest (i.e., reflecting a small increase, rather than decrease, in GR concentration following DEX) in those with MDD alone. Post-DST plasma levels of DEX were also significant as a covariate [$F(1, 43) = 9.61$; $p = .003$].

In a second analysis of GR number, we repeated the above examination of GR change without the correction for starting values that is included in the % suppression variable. Log transformed pre- and post-DEX GR concentrations were subject to a repeated-measures ANCOVA with PTSD and MDD status as predictors and plasma DEX concentrations as covariate. The results confirmed the above findings with regards to PTSD, there being a significant assessment (pre- to post-DEX) × PTSD interaction [F (1, 43) = 6.1; $p = .018$], indicating enhanced GR "down-regulation" in individuals with PTSD. There was no assessment × MDD interaction (F = .16), but the three-way interaction of assessment × PTSD × MDD was significant [F(1,43)=5.04, p = .030], replicating the above reported analysis.

Correlational analyses were carried out in the 34 subjects with PTSD, examining associations between percent cortisol suppression and change in GR number in relation to PTSD symptoms. There were no correlations with total CAPS symptom scores ($r = -.152$, $n = 34$, n.s.) or any of the symptom subscale scores (intrusion $r = -.23$, avoidance $r = .05$, hyperarousal $r = -.18$; $n = 34$; all n.s.). Percent change in GR number was similarly uncorrelated with total PTSD symptoms ($r = -.05$, $n = 28$, n.s.), and with all subscale scores (intrusion $r = .15$; avoidance $r = -.21$; hyperarousal r = −.09; $n = 28$; n.s.). Partial correlations controlling for the presence or absence of MDD, and also for plasma DEX in the case of GR concentrations, did not substantively alter any of these findings.

Impact of Exposure: Holocaust versus Combat

Clinical characteristics for Holocaust survivors and combat veterans are reported in Table 3. Age at exposure to the focal trauma was substantially lower for Holocaust survivors (mean = 11.5 ± 5.4 years; range = 3–24 years) compared to combat veterans (mean = 25.3 ± 11.0 years; range = 17–55 years) [$t(48) = 5.45$, $p < .0005$]. Correspondingly, the time elapsed between their focal event and assessment was longer for Holocaust survivors (mean = 55.5 ± 4.6 years) than for combat veterans (mean = 38.1 ± 16.3 years) [$t(30,80) = 5.33$, $p < .0005$: correction made for unequal variances]. For Holocaust survivors, exposure to traumatic events prior to the focal trauma tended to occur in the context of the Holocaust (for example, a subject could have witnessed her child, parent or sibling being murdered at age 20, before being placed in

[2] When analyses were repeated including the outlier, there was still a significant main effect of PTSD [F (1,44) = 4.11; df = 1, 44; $p = .049$], but there was no main effect of MDD [F (1,44) = 2.33; $p = .13$]. The interaction was reduced to trend level [$F = 3.23$; df = 1,44; $p = .079$]. MDD interaction ($F = 0.16$), but the three-way interaction of assessment × PTSD × MDD was significant [$F(1,43) = 5.04$; $p = .030$], replicating the above reported analysis.

a concentration camp at age 22; or they could be subjected to anti-Semitic violence during Krystallnacht at age 7, forced to live in a ghetto at age 13, and in a death march at age 16). Only 17.4% of survivors reported trauma exposure for unrelated events occurring prior to the Holocaust. In contrast, for combat veterans, exposure to prior events tended to be independent of the exposure to the combat trauma. Of the combat veterans, 55.6% reported traumatic events prior to combat exposure, including muggings, motor vehicle accidents, natural and man-made disasters, witnessing murder, the death of a relative, and physical or sexual abuse in childhood, and for veterans reporting the Gulf War as focal trauma, prior combat.

The incidence of PTSD was higher among the combat veterans than among the Holocaust survivors [81.5% vs. 52.2%: χ^2 (1) = 4.90, p = .027]. The PTSD symptoms on the intrusion, avoidance, and hyperarousal subscales of the CAPS were examined in relation to Holocaust versus combat exposure and the presence or absence of PTSD using MANOVA. There was no main effect of type of exposure in relation to symptoms [Pillai's Trace $F(3,44)$ = 1.13; n.s.] when diagnosis was taken into account [$F(3,44)$ = 25.10; $p < .0005$], and no exposure × PTSD interaction [$F(3, 44)$ = 0.60; n.s.]. Thus, symptom levels were similar in combat veterans and Holocaust survivors with PTSD, and in veterans and Holocaust survivors without PTSD. Of the combat veterans, 48.1% met criteria for MDD at the time of study, compared to 30.4% of Holocaust survivors [$\chi^2(1)$ = 1.63; n.s.].

Dexamethasone suppression test responses were also examined in relation to type of trauma exposure comparing the combat (n = 27) and Holocaust survivor (n = 23; 16 male, 7 female) participants. Because the combat veterans were all male but the Holocaust sample contained both men and women, we first conducted a three-way ANOVA, with gender, PTSD, and MDD as predictors and percent cortisol suppression as the dependent variable. This allowed us to examine whether there was an effect of gender on responses on the DST, accounting for any diagnostic differences. There was no main effect of gender [$F(1, 43)$ = 0.62 n.s.] on percent cortisol suppression, and the main effects of PTSD [$F(1,43)$ = 5.38; p = .025] and MDD [$F(1,43)$ = 8.49; p = .006] were retained in this trauma-exposed subset. A second three-way ANOVA examined the effect of type of exposure (combat vs. Holocaust) on percent cortisol suppression, taking into account the effects of PTSD and MDD. There was no effect of type of exposure on percent cortisol suppression [$F(1, 43)$ = 0.002; n.s.].

Time Since Trauma Exposure

Correlational analyses examined responses on the DST in relation to the presumed duration of PTSD symptoms (i.e., time since the focal trauma). In addition, because intervening events may have changed the course and severity of PTSD symptoms, time since exposure to the most recent trauma experienced (not necessarily the focal event) was also examined in relation to responses on the DST. These analyses were carried out within the subset of 34 participants who had current PTSD. For percent cortisol suppression, Pearson's correlation coefficient indicated no relationship with years since the focal trauma (r = −.14, n = 34, n.s.), but a significant negative correlation with time since the most recent trauma (r = −.40, n = 34, p = .019). For percent change in GR concentration (available for 28 participants with PTSD), there were no correlations with either symptom duration (r = −.18, n = 28, n.s.) or time since the most recent event (r = −.02, n = 28, n.s.).

Discussion

The main finding of this study is that there is a greater suppression of cortisol in response to DEX in older trauma survivors with PTSD compared to similarly exposed survivors without PTSD, and non-exposed comparison subjects. The percent suppression of cortisol in the PTSD group was virtually identical to that previously reported in younger subjects (Yehuda et al 1993b, 1995a); however, in the current study we additionally found a significant main effect of depression, MDD being associated with reduced cortisol suppression following DEX, consistent with the effects of DEX reported for MDD populations (Holsboer et al 1995; The APA Task Force on Laboratory Tests in Psychiatry 1987). We have previously observed that there was no effect of MDD on cortisol hypersuppression in Vietnam combat veterans with PTSD (Yehuda et al 1993b). Thus, the current finding suggests that the response to DEX is similar in older and younger trauma survivors in some ways but that there might also be some important differences.

The current findings differ from prior reports in terms of the lack of correlation between measures reflecting cortisol negative feedback inhibition and those relating to symptom severity. The failure to observe such an association may reflect the fact that PTSD and MDD had opposite effects on the biologic measures but synergistic effects on symptom severity. It was certainly the case that individuals suffering from both disorders reported more symptoms in the CAPS interview in the current study, although the extent to which this observation reflects more severe PTSD in the presence of MDD versus the detection of depressive symptoms directly on the CAPS is not known. Indeed, the mean total CAPS score was 34% higher in subjects with both PTSD and MDD compared to those with PTSD alone. Controlling for the presence of MDD did not strengthen the correlation between cortisol

suppression and symptom severity; however, the use of such a dichotomous measure may not have been sensitive enough to provide a reasonable examination of this question. Future studies should examine this issue by controlling for the intensity of depression rather than simply its presence or absence.

The current research also demonstrated a significant effect of PTSD on the percent suppression of cytosolic mononuclear leukocyte GR in response to DEX. This is consistent with research with younger trauma survivors. We have previously reported that although combat Vietnam veterans with and without PTSD did not significantly differ in the number of baseline lymphocyte GR, Vietnam veterans with PTSD showed a reduced number of GR in response to DEX compared with veterans without PTSD and non-exposed subjects (Yehuda et al 1995a). The procedure used to measure GR measures cytosolic but not nuclear receptors, therefore a reduction in post-DEX cytosolic receptor number may provide an estimation of the percent receptors that translocated into the nucleus following in vivo administration of DEX (Gormley et al 1985). The enhanced cortisol response to similarly low doses of DEX in PTSD would, at least theoretically, be expected to occur due to an increased activity of the GR at the level of the pituitary (Holsboer et al 1995, 2000; Pariante and Miller 2001). To the extent that lymphocyte GR have similar characteristics to pituitary receptors (Lowy 1989), the percent suppression of cytosolic lymphocyte GR may provide a measure of the activity of the GR following DEX administration.

We have not previously examined differences in the percent suppression of GR in trauma survivors with and without MDD. Therefore, the current finding of an apparent decrease in GR translocation following DEX constitutes the first such observation in depressed trauma survivors with and without PTSD. A reduced GR number following the administration of 1.0 mg of DEX has been previously observed in subjects with MDD and is consistent with theories of the pathophysiology of depression. Alterations of the HPA axis in MDD are hypothesized to be associated with an impaired sensitivity of the GR, possibly secondary to corticotrophic releasing factor (CRF) hypersecretion, that leads to a reduced negative feedback inhibition of the HPA axis (Holsboer 2000). Because the current difference was significant at trend level only, and this finding did not replicate when absolute change in GR number was assessed rather than percent change, it will be important to re-examine this issue in a larger data set and in a wider range of trauma survivors. At present, it is difficult to know whether the effect of MDD on GR suppression would also be present in a younger or different sample of trauma survivors with PTSD, particularly if MDD-related differences in cortisol hypersuppression are not present (i.e., Vietnam veterans).

One notable difference between the current findings and our prior reports of GR number is that 0.5 mg DEX had almost no effect on GR number in non-PTSD subjects in the current study. We have previously reported a strong effect of DEX on GR number in Vietnam veterans (Yehuda et al 1995a). Age-related changes might provide one possible explanation for this discrepancy. For example, the possibility that glucocorticoid receptors become generally less sensitive with age in all groups would be consistent with the idea of hypercortisolism in aging, and may represent an initial alteration; however, changes in our assay procedure (e.g., from using a more selective Type II antagonist as a ligand to using radioactive dexamethasone) may also contribute to this finding.

The inclusion of both combat veterans and Holocaust survivors allowed us to examine possible differences that might be related to exposure characteristics as well as other variables that differentiate these two groups of subjects. In this study, there were differences between Holocaust survivors and combat veterans in age of exposure to the focal trauma and prior trauma history. The two groups also differed in the percent of subjects meeting criteria for current PTSD. This observation, however, is likely to be an artifact of recruitment rather than a reflection of actual population differences in the prevalence of PTSD; the majority of Holocaust survivors were recruited from the community, whereas combat veterans tended to be recruited from within the VA. Despite the differences between the two samples, Holocaust survivors and combat veterans were similar in terms of symptom severity within their respective diagnostic subgroups. In terms of responses to the DST, the difference in suppression for Holocaust survivors with versus without PTSD appeared somewhat smaller than that for combat veterans, primarily due to a relatively high level of suppression in the survivors without PTSD. Although this combat versus Holocaust exposure effect was not statistically significant, it raises the possibility that not all groups of trauma survivors will show equivalent biological alterations. Should this be the case, it will be of particular importance to delineate the factors that explain such discrepancies and to adjust our models of the psychobiology of PTSD accordingly.

One of the major variables associated with geriatric PTSD is the vulnerability to developing a recrudescence of PTSD in response to recent stressors, such as retirement, illness, or death of a loved one (Macleod 1994). Posttraumatic stress disorder may also re-emerge in response to actual physical danger. For example, during the Persian Gulf War, Holocaust survivors showed greater levels of psychological distress than other civilians exposed to the

same threat of SCUD missiles (Solomon and Prager 1992). Under these circumstances, older trauma survivors suffer from the classic symptoms of PTSD, which may not be less severe than the syndrome which they had experienced at earlier stages in their lives (Hierholzer et al 1992; Kuch and Cox 1992; Macleod 1994). The current observation of a negative correlation between the extent of cortisol hypersuppression and the duration in years since exposure to the most recent traumatic event is in support of the idea that repeated exposure intensifies the biologic response associated with PTSD. There was no relationship between percent cortisol suppression and years since exposure, to the focal trauma.

The presence of depression in older trauma survivors may occur for reasons related or unrelated to either the initial exposure to trauma, or to subsequent exposures. Regardless of why depression is present in older trauma survivors, its presence may add to PTSD symptomatology while exerting an opposite effect on cortisol hypersuppression, such that the response to DEX might appear "normal" in these most severely symptomatic subjects. Studies of the cortisol response to DEX in relation to MDD in younger trauma survivors with PTSD have thus far been confined to Vietnam veterans. To determine whether the effect of MDD on cortisol suppression observed in the current study is limited to older trauma survivors, studies using a diverse group of younger trauma survivors with and without both PTSD and MDD are needed.

Finally, there are methodological limitations that must be considered in interpreting the broader applicability and significance of these observations. Already mentioned is the problem of having a very small number of observations in the group of trauma survivors with only MDD, precluding interpretation of the findings in this respect. Thus, at this time conclusions regarding the biological similarity of trauma-related MDD to MDD in other populations are premature. Additionally, the study was performed using a convenience sample of trauma survivors who were both healthy enough to meet the rather stringent physical, medical, and diagnostic inclusion/exclusion criteria, and willing to participate in a study that required both ingesting a foreign substance (i.e., DEX) and discussing traumatic material. Less than half of older trauma subjects inquiring about research opportunities were willing to participate in the current protocol, and less than half of those willing were eligible. Our clinical impression is that the ingestion of the DEX was a mitigating factor for participation, particularly among Holocaust survivors, whereas World War II and Korean War veterans were more likely to avoid participating when it became clear that trauma-related material would be discussed as a condition of participation. The difficulty of recruiting older trauma survivors for biologic studies constitutes a potential source of selection bias in the data. A final consideration is the validity of combining plasma and salivary DST data; this concern primarily relates to the exploratory analysis of combat versus Holocaust exposure, where relatively small *n*s precluded replicating the analysis in plasma data alone. Although we made every effort to ensure that the combination of plasma and salivary DST data was a reasonable step, any conclusions relating to biological differences between combat and Holocaust survivors must be considered in the light of this potential limitation.

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