The Dexamethasone/Corticotropin-Releasing Factor Test in Men with Major Depression: Role of Childhood Trauma

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Background: The dexamethasone/corticotropin-releasing factor (CRF) test is considered to be the most sensitive measure of hypothalamic–pituitary–adrenal (HPA) axis hyperactivity and has been demonstrated to be altered in patients with major depression (MDD). Although childhood trauma is a demonstrated risk factor for MDD and patients with a history of childhood abuse and MDD demonstrate HPA axis hyperactivity, the dexamethasone/CRF test remains unstudied in this population. We determined the impact of childhood trauma on dexamethasone/CRF test results in patients with MDD.

Methods: Forty-nine healthy men, ages 18–60 years, without mania or psychosis, active substance abuse, or eating disorder and medication-free were recruited into four study groups, including: 1) normal subjects with no childhood abuse history or psychiatric disorder ($n = 14$); 2) men with childhood abuse histories without current MDD ($n = 14$); 3) men with childhood abuse histories with current MDD ($n = 15$); and 4) men with current MDD and no childhood abuse history ($n = 6$). Plasma adrenocorticotropin (ACTH) and cortisol concentrations were measured in response to dexamethasone/CRF administration.

Results: Men with childhood trauma histories exhibited increases in ACTH and cortisol responses to dexamethasone/CRF compared with non-abused men. In particular, abused men with current MDD showed increased responsiveness compared with control subjects and depressed men without childhood abuse experience. Increased response was associated with the severity, duration, and earlier onset of the abuse. The effects were not explained by concurrent posttraumatic stress disorder.

Conclusions: Childhood trauma increases HPA axis activity as measured with the dexamethasone/CRF test in adult men with MDD, potentially reflecting environmental risk for developing depression.

Key Words: Cortisol, dexamethasone, HPA axis hyperactivity, MDD, trauma

Hyperactivity of the hypothalamic–pituitary–adrenal (HPA) axis in patients with major depression (MDD) is one of the most often reported findings in biological psychiatry. Thus, numerous studies have provided evidence that patients with MDD demonstrate increased cortisol production (i.e., increased urinary free cortisol secretion, increased cerebrospinal fluid [CSF] concentrations of cortisol, or increased circulating serum concentrations of cortisol) (1). Impaired glucocorticoid feedback has been demonstrated to contribute to HPA axis hyperactivity in MDD. Indeed, patients with MDD exhibit decreased glucocorticoid receptor (GR) function and non-suppression of cortisol secretion after administration of the synthetic glucocorticoid, dexamethasone (2). Relative glucocorticoid resistance is associated with a reduction in glucocorticoid negative feedback, resulting in hyperactivity of the hypothalamic corticotropin-releasing factor (CRF) system. Upon systemic injection of exogenous CRF, depressed patients exhibit a blunted adrenocorticotropin (ACTH) response, likely due to pituitary CRF receptor downregulation secondary to chronic CRF hypersecretion (3,4). Increased CSF concentrations of CRF have been repeatedly measured in drug-free depressed patients (5,6). Postmortem studies reported increased CRF concentrations and/or messenger RNA (mRNA) expression in the hypothalamic paraventricular nucleus (7,8), locus coeruleus (9), and frontal cortex (10) of patients with MDD. The CRF neurons interact with other neurotransmitter systems implicated in the pathophysiology of depression (11,12). When administered directly into the central nervous system (CNS), CRF produces many of the physiological and behavioral features of MDD (13,14). Chronic elevations of circulating glucocorticoids have been suggested to exert toxic effects on the hippocampus and prefrontal cortex, leading to cognitive impairment, deficits in emotional regulation, and further disinhibition of CNS CRF pathways and the HPA axis (1,15).

The combined dexamethasone/CRF test is considered to be the most sensitive measure of HPA axis activity and has been shown to be markedly altered in MDD (16–18). The test was developed as an improvement of the standard dexamethasone suppression test (DST) to measure the degree of GR-mediated feedback inhibition of the anterior pituitary gland during conditions of increased hypothalamic drive (16). In this test, CRF is injected after pretreatment the night before with dexamethasone. In normal control subjects, cortisol secretion after dexamethasone remains suppressed after CRF injection; however, patients with MDD show a characteristic "escape" from suppression with elevated ACTH and cortisol responses. The test has repeatedly been shown to be highly sensitive to detect HPA axis dysregulation in patients with a current episode of MDD and to distinguish depressed patients from normal volunteers (16–18). Escape from dexamethasone suppression after CRF usually normalizes with successful treatment or remission (17,19,20). However, some patients continue to exhibit escape after successful treatment, and these patients are at elevated risk for relapse (17,20–22). This latter finding suggests that stable escape in the dexamethasone/CRF test might reflect a trait-like marker of depression risk rather than a correlate of the illness state. In support of this hypothesis, asymptomatic first-degree relatives of

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patients with MDD exhibit increased cortisol responses in the dexamethasone/CRF test that is stable over time, suggesting that the test is sensitive to detect familial depression risk (23,24). Furthermore, dexamethasone/CRF test results vary with a polymorphism in the FKBP5 gene, a GR-regulating cochaperone of hsp-90, which is also associated with recurrence of depressive episodes and antidepressant response (25). In sum, the dexamethasone/CRF test is widely used in depression research to detect HPA axis dysfunction and is associated with relative risk, clinical course, and treatment response.

The onset of a depressive episode and relapse are often triggered by acute stress (26). Moreover, it is now well established that adverse experiences early in life, such as childhood abuse, neglect, or loss, is associated with marked increases in the risk to develop MDD in adulthood (27), particularly in response to additional life stressors (28). There is considerable evidence from animal models that early-life stress (ELS) leads to persistent hyperactivity of CNS CRF systems and sensitization of the HPA axis to subsequent stress (29,30). Recent rodent studies have shown that early adverse experience has epigenomic effects by altering DNA methylation of the GR gene promoter in the hippocampus, leading to functional impairment of the GR and consequently impaired feedback regulation and increased stress responsiveness (31). In a series of human clinical studies, we found evidence that many of the neuroendocrine features of MDD might well be secondary to childhood trauma and might reflect risk to develop MDD in response to stress (32). Childhood adverse experience also influences clinical course and treatment success in MDD (32). On the basis of the concatenation of these findings, we hypothesized that childhood trauma would be associated with increased response in the dexamethasone/CRF test in patients with MDD. The present study tested this hypothesis in adult men with and without MDD or childhood abuse experiences.

Methods and Materials

Subjects

The study group comprised 49 men, ages 18–60 years, including 14 men without significant ELS and no psychiatric disorder (normal control subjects), 14 men with a history of childhood abuse without current MDD (ELS/non-MDD), 15 men with a history of childhood abuse and current MDD (ELS/MDD), and 6 men without a history of childhood abuse and current MDD (non-ELS/MDD). For assignment to the ELS groups, men must have had experienced repeated moderate-to-severe sexual or physical abuse before the age of 13 years, defined as having been forced to touch another person's intimate parts; having been touched in intimate parts; attempted or completed intercourse; and/or having been spanked, kicked, or choked in a way that left bruises or injuries; having been attacked with a weapon; or tied up or locked in a room or a closet. Assignment to the MDD groups required a diagnosis of current MDD according to DSM-IV criteria (33). For the assignment to groups without significant ELS, men could not have experienced any traumatic or major stressful life event before the age of 13 years. General exclusion criteria were current medical illness, lifetime psychosis or bipolar disorder, alcohol or substance abuse within 6 months, or eating disorders within the past year. None of the participants was in current psychiatric treatment or took medication. Heavy smokers (>20 cigarettes/day) were excluded. All subjects were recruited from responses to advertising in newspaper and the local transportation system and screened for eligibility. Eligible subjects were invited and paid for participation. After description of the study to the participants, written informed consent was obtained. The study was approved by the Institutional Review Board of Emory University School of Medicine.

Procedure

The presence or absence of childhood trauma was assessed with the Early Trauma Inventory (ETI) (34). The ETI is a structured interview with high test-retest reliability, internal consistency, and external validity that assesses the number, frequency, and duration of various trauma types (i.e., physical abuse, sexual abuse, emotional abuse, and general trauma), resulting in a score for each trauma type and a total score. For diagnosis of MDD and other psychiatric disorders, the Structured Clinical Interview for DSM-IV was used (35). Symptoms of depression and posttraumatic stress disorder (PTSD) were quantified with the Hamilton Rating Scale for Depression 21 Items Version (HRSD21) and the Clinician Administered PTSD Scale (CAPS), respectively (36,37). We also measured major life events in the past year with the Life Event Survey (38) and recorded adulthood traumas (39).

For the dexamethasone/CRF test, a dose of 1.5 mg dexamethasone (Roxane Laboratories, Columbus, Ohio) was administered orally at 11:00 PM. On the following day, antecubital venous catheters were inserted at 12:00 PM and kept patent by saline infusion. Post-dexamethasone blood samples were collected at 2:00 PM (−60 min), 2:30 pm (−30 min), and 3:00 PM (0 min). Immediately after the 3:00 PM sample, a bolus injection of 1 μg/kg ovine CRF (Ferring, Suffern, New York) was administered through the catheter. Blood samples were collected at 5, 15, 30, 60, 90, and 120 min after CRF injection. It should be noted that the dexamethasone/CRF test was originally validated with human CRF (16), which is less potent and has different pharmacokinetics than ovine CRF (40). Because of these pharmacological differences, ovine CRF is usually administered in an adjusted dose of 1 μg/kg bodyweight (avoiding a biphasic response), whereas human CRF is typically administered in a 100-μg dose regardless of bodyweight (40). The mechanism of the dexamethosone/CRF test (i.e., stimulating pituitary corticotrophs to induce escape from suppression) remains unchanged.

Blood was collected in ethylenediaminetetraacetic acid (EDTA) tubes, placed immediately on ice, and centrifuged at 4°C for 10 min at 3000 rpm. Plasma was separated, coded, and stored at −80°C until assayed. Plasma was assayed with commercial radioimmunoassays (ACTH: Nichols, San Juan Capistrano, California; cortisol: DiaSorin, Stillwater, Minnesota). Dexamethasone concentrations were measured in the 2:30 PM sample for control purposes with radioimmunoassay (IGG Corporation, Nashville, Tennessee). Assay sensitivity was .38 pg/mL for ACTH, .04 μg/dL for cortisol, and 38 pg/mL for dexamethasone. Intra-assay variability was 6% for ACTH, 6.7% for cortisol, and 5.5% for dexamethasone. Inter-assay variability was 7.3% for ACTH, 7.1% for cortisol, and 5.7% for dexamethasone.

Data Analysis

Demographic and clinical data were analyzed with frequency tests for categorical data, Kruskal-Wallis analysis of variance (ANOVA) for ranked data, and ANOVA for continuous data. For the analysis of hormone data, we computed response indexes, including total maximum ($Peak_{tot}$), baseline-corrected increase ($Peak_{inc}$), total area under the curve (AUC_{tot}), and baseline-corrected AUC (AUC_{inc}) with the trapezoidal rule (41). Concentrations at 3:00 PM were used as baselines. Response indexes

Table 1. Demographic and Clinical Features of Normal Control Subjects, ELS/Non-MDD, ELS/MDD, and Non-ELS/MDD

	Control Subjects (n = 14)	ELS/Non-MDD (n = 14)	ELS/ MDD (n = 15)	Non-ELS/ MDD (n = 6)	Statistic
Age (mean, SD)	29.1 (9.0)	31.4 (8.0)	32.3 (8.7)	30.0 (9.5)	$F(3,48) = .36$, ns
BMI (mean, SD)	24.7 (2.8)	26.2 (5.1)	26.3 (7.5)	25.7 (4.4)	$F(3,48) = .24$, ns
Race (n, %)					$\chi^2(3) = .51$, ns
Caucasian	6 (43)	7 (50)	7 (47)	2 (33)	
Other	8 (57)	7 (50)	8 (53)	4 (66)	
ETI Total (mean, SD)	38.8 (31.2)	237.6 (146.6)	409.0 (187.8)	93.1 (57.7)	$F(3,48) = 20.5$, $p < .001$
General trauma	7.5 (9.7)	41.9 (30.0)	56.4 (51.7)	10.8 (13.6)	$F(3,48) = 6.27$, $p = .001$
Physical abuse	18.5 (17.0)	52.5 (49.7)	110.1 (59.0)	26.8 (19.9)	$F(3,48) = 11.9$, $p < .001$
Sexual abuse	0.1 (0.3)	33.0 (27.0)	52.3 (43.0)	3.0 (7.3)	$F(3,48) = 9.93$, $p < .001$
Emotional abuse	12.8 (14.2)	110.1 (81.7)	190.1 (120.1)	52.5 (47.9)	$F(3,48) = 12.1$, $p < .001$
HRSD21 score (mean, SD)	4.3 (3.0)	7.7 (5.2)	21.8 (3.6)	22.7 (4.4)	$F(3,48) = 62.5$, $p < .001$
Episode Duration[a] (mean, SD)	—	—	6.9 (5.2)	4.8 (1.6)	$F(1,16) = .77$, ns
Past MDD (N, %)	0 (0)	8 (57.1)	14 (93.3)	5 (83.3)	$\chi^2(3) = 28.0$, $p < .001$
No. of Episodes (N, %)					$\chi^2(2) = 3.82$, ns
0	—	6 (42.9)	1 (6.7)	1 (16.7)	
1–5	—	2 (14.3)	3 (20.0)	2 (33.3)	
6–10	—	2 (14.3)	3 (20.0)	0 (0)	
>10	—	4 (28.6)	8 (53.3)	3 (50.0)	
PTSD (n, %)	0 (0)	7 (58)	5 (42)	0 (0)	$\chi^2(3) = 12.1$, $p = .007$
CAPS score (mean, SD)	—	24.9 (14.4)	41.9 (16.5)	—	$F(1,28) = 8.61$, $p = .007$
Anxiety Disorder (n, %)	0 (0)	2 (14.2)	8 (53.3)	3 (50.0)	$\chi^2(3) = 13.4$, $p = .004$
Past Substance Abuse (n, %)	0 (0)	7 (50.0)	11 (73.3)	1 (16.6)	$\chi^2(3) = 14.8$, $p = .002$
Life Event Score (mean, SD)					
Positive	8.2 (8.1)	10.9 (10.2)	7.0 (7.3)	4.3 (4.5)	$F(3,48) = 1.05$, ns
Negative	6.3 (6.4)	15.1 (16.0)	27.9 (18.7)	19.3 (10.5)	$F(3,48) = 5.58$, $p = .002$
Adulthood Trauma (mean, SD)	1.7 (1.5)	2.8 (1.7)	2.4 (1.9)	2.0 (1.7)	$F(3,48) = .81$, ns
Dexamethasone (pg/mL)	1690 (897)	1617 (855)	1234 (608)	1531 (494)	$F(3,48) = 1.00$, ns

ELS/non-MDD, men with childhood abuse history without major depression; ELS/MDD, men with childhood abuse history and MDD; non-ELS/MDD, men with no childhood abuse history but MDD; BMI, body mass index; ETI, Early Trauma Inventory; HRSD21, Hamilton Rating Scale for Depression 21 Items Version; PTSD, posttraumatic stress disorder; CAPS, Clinician Administered PTSD Scale.

[a]in months.

were normally distributed according to the Kolmogorov-Smirnov Z test. Response indexes were compared between groups with one-way analysis of covariance (ANCOVA) with age, PTSD, and dexamethasone levels entered as covariates. Bonferroni post hoc test was used to contrast group means. In the case of significant effects, we assessed response profiles with two-way ANCOVA with repeated measurement (1st factor: Group, 2nd factor: Time; covariates: age, PTSD, dexamethasone levels). In the case of a significant interaction effect, group means were contrasted at each time point. Analyses were repeated controlling for anxiety disorders, past substance abuse, past MDD, number of episodes, or negative life events. Additional analyses were conducted to describe effects of past MDD and PTSD. Pearson's correlations were computed between ETI scores and response indexes. Because of small group sizes, we confirmed significant effects with nonparametric tests. Analyses were two-tailed with the level of significance set at .05.

Initial power analysis was based on the presumption of a medium effect size according to Cohen (42). With 49 subjects distributed across four groups tested at nine time points, the power to detect an interaction effect between group and time factors at the .05 level of significance is 98% (43). We also conducted post hoc power analysis (43). For the one-way ANCOVA comparing mean cortisol $Peak_{tot}$ with a calculated effect size of .529 and an α of .05, four groups, and a sample size of 49, we achieved a power of 86%. For the two-way ANCOVA comparing cortisol concentrations with a calculated effect size of .448 and an α of .05, four groups, nine repetitions, and a sample size of 49, we achieved a power of 77%.

Results

Demographic and clinical data are summarized in Table 1. There were no differences between study groups in age, body mass index (BMI), or racial distribution. By definition, men with a history of childhood abuse had higher mean ETI scores than the non-abused groups [$F(3,48) = 20.47$, $p < .001$]. Not surprisingly, men with MDD had significantly higher HRSD21 scores than men without MDD [$F(3,48) = 62.52$, $p < .001$]. There was no difference in current episode duration between the MDD groups. There was no difference in past MDD or number of episodes among ELS/non-MDD, ELS/MDD, and non-ELS/MDD groups. Abused men more frequently suffered from PTSD [$\chi^2(3) = 12.05$, $p = .007$] and had higher CAPS scores [$F(3,48) = 12.46$, $p < .001$] compared with control subjects and depressed men without childhood trauma. Depressed men more frequently had comorbid anxiety disorders (i.e., specific phobias, generalized anxiety, and obsessive-compulsive disorder) [$\chi^2(3) = 13.4$, $p = .004$]. Abused men more frequently had past substance abuse disorders [$\chi^2(3) = 14.8$, $p = .002$]. There were no differences between groups regarding positive life events or adulthood traumas. Abused men with MDD reported more negative life events than control subjects [$F(3,48) = 5.579$, $p = .002$].

Plasma cortisol concentrations of the four groups in the dexamethasone/CRF test are illustrated in Figure 1. When com-

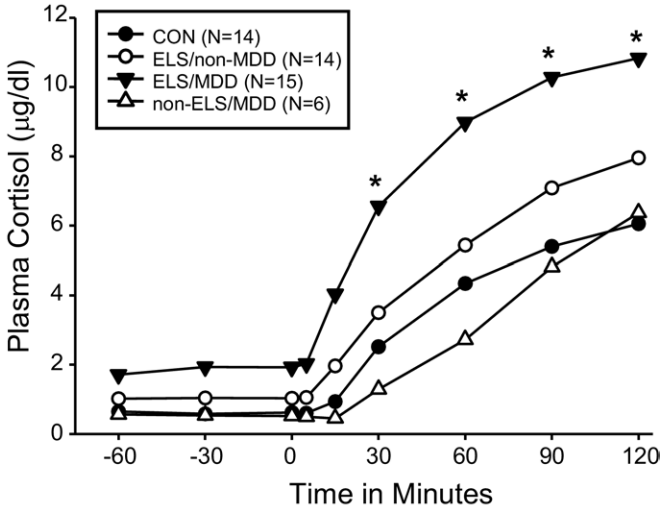

Figure 1. Mean plasma cortisol concentrations in the dexamethasone/ corticotropin-releasing factor (CRF) test in men without a history of significant early life stress (ELS) and no psychiatric disorder (CON; $n = 14$), men with a history of childhood sexual or physical abuse without major depression (ELS/non-MDD; $n = 14$), men with a history of childhood sexual or physical abuse and current major depression (ELS/ MDD; $n = 15$), and men without a history of significant early life stress and current major depression (non-ELS/ MDD; $n = 6$). For statistical information, see text. *ELS/MDD versus control subjects and non-ELS/MDD: $p < .05$.

paring abused versus non-abused men regardless of depression, abused men had significantly greater cortisol response indexes than non-abused men [$Peak_{tot}$: $F(1,48) = 6.83$, $p = .012$; $Peak_{inc}$: $F(1,48) = 4.98$, $p = .031$; AUC_{tot}: $F(1,48) = 7.06$, $p = .011$; AUC_{inc}: $F(1,48) = 6.64$, $p = .013$]. When comparing depressed versus non-depressed men, there was a significant difference for $Peak_{tot}$ [$F(1,48) = 4.42$, $p = .041$], whereas there were only trends for the other response indexes. When comparing the four groups stratified by ELS and MDD, abused men with MDD had significantly greater cortisol response according to most indexes compared with control subjects and depressed men without abuse (Table 2). Accordingly, two-way ANCOVA revealed a significant main effect for Group [$F(3,42) = 4.06$, $p = .013$] and a Group × Time interaction [$F(24,336) = 2.84$, $p < .001$], with abused men with current depression demonstrating higher plasma cortisol concentrations from 30 through 120 min after CRF injection compared with healthy volunteers and depressed men without childhood abuse histories (all $p < .05$). Age or a diagnosis of PTSD had no significant effects on cortisol concentrations. Plasma dexamethasone concentrations were inversely associated with cortisol response indexes, mean plasma cortisol concentrations across all time points, and cortisol response profile (all $p < .05$). Results remained similar when controlling for anxiety disorders, past substance abuse, past MDD, depressive episodes, or negative life events. When subdividing the ELS/non-MDD group into those with and without past MDD, there were no differences between these subgroups in terms of cortisol response. Significant group differences were confirmed with Kruskal-Wallis ANOVA (data not shown).

Plasma ACTH responses in the dexamethasone/CRF test are illustrated in Figure 2. When comparing all abused men versus all non-abused men regardless of depression, abused men had significantly greater ACTH response indexes than non-abused men [$Peak_{tot}$: $F(1,48) = 8.28$, $p = .006$; $Peak_{inc}$: $F(1,48) = 9.27$, $p = .004$; AUC_{tot}: $F(1,48) = 5.36$, $p = .025$; AUC_{inc}: $F(1,48) = 5.95$, $p = .019$]. When comparing depressed versus non-depressed men, there were no differences in ACTH response indexes. When comparing the four groups stratified by ELS and MDD, abused men with MDD had significantly greater ACTH response indexes compared with control subjects and depressed men without abuse histories (Table 2). Accordingly, two-way ANCOVA revealed a significant main effect for Group [$F(3,42 = 3.34$, $p = .028$] and a Group × Time interaction [$F(24,336) = 1.96$, $p = .005$], with abused men with current MDD demonstrating higher plasma ACTH concentrations from 5 through 120 min after CRF injection (all $p < .05$). Abused men with MDD also had elevated ACTH concentrations at −60 and −30 min, suggesting decreased sensitivity to dexamethasone suppression alone. Depressed men with no childhood abuse histories had somewhat lower plasma ACTH concentrations than control subjects, although this difference was not significant. Plasma dexamethasone concentrations were inversely correlated with ACTH response indexes, mean plasma ACTH concentrations across all time points, and ACTH response profile (all $p < .001$). Moreover, PTSD diagnosis impacted on ACTH response indexes, mean plasma ACTH concentrations across all time points, and ACTH response profile (all $p < .05$). Two-way ANOVA showed that abused men with PTSD had significantly smaller ACTH re-

Table 2. Mean (SE) Computed Indexes of Cortisol and ACTH Response in the Dexamethasone/CRF Test in Normal Control Subjects, ELS/Non-MDD, ELS/ MDD, and Non-ELS/MDD

	Control Subjects ($n = 14$)	ELS/ Non-MDD ($n = 14$)	ELS/ MDD ($n = 15$)	Non-ELS/ MDD ($n = 6$)	Statistic
Cortisol (µg/dl)					
$Peak_{tot}$	6.26 (1.1)	8.05 (1.1)	11.17 (1.0)[a]	6.34 (1.6)	$F(3,42) = 3.90$, $p = .015$
$Peak_{inc}$	5.64 (.96)	7.02 (.95)	9.23 (.89)	5.82 (1.4)	$F(3,42) = 2.70$, $p = .058$
AUC_{tot}	476 (123)	640 (122)	1015 (115)[a]	378 (180)[b]	$F(3,42) = 4.35$, $p = .009$
AUC_{inc}	384 (83.5)	485 (82.5)	728 (77.6)[a]	299 (122)[b]	$F(3,42) = 4.09$, $p = .012$
ACTH (pg/mL)					
$Peak_{tot}$	25.4 (6.8)	36.0 (7.7)	55.0 (6.3)[a]	16.8 (9.8)[b]	$F(3,42) = 4.61$, $p = .007$
$Peak_{inc}$	21.9 (5.2)	31.3 (5.2)	45.6 (4.9)[a]	15.6 (7.6)[b]	$F(3,42) = 4.87$, $p = .005$
AUC_{tot}	2383 (686)	3012 (678)	4731 (638)[a]	1290 (996)[b]	$F(3,42) = 3.38$, $p = .027$
AUC_{inc}	1869 (431)	2327 (426)	3363 (401)	1100 (625)[b]	$F(3,42) = 3.57$, $p = .022$

For statistics see text. Dexamethasone levels had significant effects on all indexes (all $p < .01$). Posttraumatic stress disorder (PTSD) had significant effects on adrenocorticotropin (ACTH) indexes (all $p < .05$). CRF, corticotropin-releasing factor; other abbreviations as in Table 1.

[a] $p < .05$ versus control subjects.

[b] $p < .05$ versus ELS/MDD.

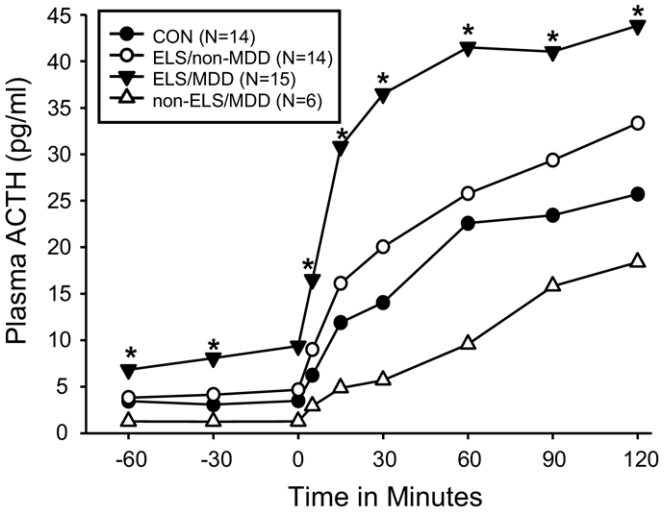

Figure 2. Mean plasma adrenocorticotropin (ACTH) concentrations in the dexamethasone/CRF test in men without a history of significant ELS and no psychiatric disorder (CON; $n = 14$), men with a history of childhood sexual or physical abuse without major depression (ELS/non-MDD; $n = 14$), men with a history of childhood sexual or physical abuse and current major depression (ELS/ MDD; $n = 15$), and men without a history of significant early life stress and current major depression (non-ELS/ MDD; $n = 6$). For statistical information, see text. *ELS/MDD versus control subjects and non-ELS/MDD: $p < .05$. Abbreviations as in Figure 1.

sponses than abused men without PTSD [$F(8,200) = 3.025$, $p = .003$; Figure 3]. Results remained similar when controlling for anxiety disorders, past substance abuse, past MDD, depressive episodes, or negative life events. When subdividing the ELS/non-MDD group into those with and without past MDD, there were no differences between these subgroups in terms of ACTH response. Significant group differences were confirmed with Kruskal-Wallis ANOVA (data not shown).

There were significant correlations between cortisol response

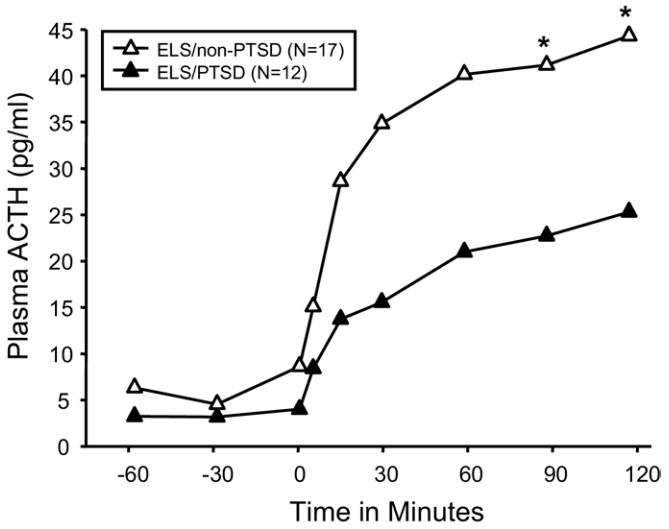

Figure 3. Mean plasma ACTH concentrations in the dexamethasone/CRF test in men with a history of childhood sexual or physical abuse without current posttraumatic stress disorder (ELS/non-PTSD; $n = 17$) and men with a history of childhood sexual or physical abuse and current PTSD (ELS/PTSD; $n = 12$). For statistical information, see text. *ELS/PTSD versus ELS/non-PTSD: $p < .05$. Abbreviations as in Figures 1 and 2.

Table 3. Pearson's Correlation Coefficients for Associations Between Cortisol Response Indexes in the Dexamethasone/CRF Test and Early Trauma Inventory Scores ($n = 49$)

	$Peak_{tot}$	$Peak_{inc}$	AUC_{tot}	AUC_{inc}
Physical Abuse				
Events	.466[a]	.402[a]	.497[b]	.453[a]
Yrs	.469[a]	.477[a]	.404[a]	.447[a]
Score	.389[a]	.402[a]	.316[c]	.356[c]
Sexual Abuse				
Events	.401[a]	.385[a]	.386[a]	.399[a]
Yrs	.398[a]	.432[a]	.336[c]	.416[a]
Score	.330[a]	.359[c]	.254	.313[c]

CRF, corticotropin-releasing factor; $Peak_{tot}$, total maximum; $Peak_{inc}$, baseline-corrected increase; AUC_{tot}, total area under the curve; AUC_{inc}, baseline-corrected AUC.

[a] $p < .01$.
[b] $p < .001$.
[c] $p < .05$.

indexes and ETI abuse scores, including number of events, years of exposure, and severity score (Table 3). There were also significant correlations between the number of emotional abuse events and cortisol $Peak_{tot}$ ($r = .308$, $p = .031$) or AUC_{tot} ($r = .313$, $p = .028$). Age at onset of physical abuse was inversely associated with cortisol $Peak_{tot}$ ($r = -.314$, $p = .028$), $Peak_{inc}$ ($r = -.363$, $p = .010$), and AUC_{inc} ($-.333$, $p = .019$), indicating that earlier abuse was associated with greater escape. Similar associations were found for ACTH response indexes. Significant correlations were confirmed with Spearman's rank correlation (data not shown).

Discussion

The combined dexamethasone/CRF test is generally considered to be the most sensitive measure of HPA axis activity, especially well studied in depressed patients (16–22). Furthermore, the test has served to demonstrate familial or genetic depression risk, clinical course, and treatment response or relapse (17–25). Because stress, especially early in life, is a major risk factor for MDD that profoundly impacts HPA axis activity (32), we sought to determine in the present study the effects of childhood trauma on dexamethasone/CRF test results in depressed patients. Our results suggest that childhood trauma has a marked influence on dexamethasone/CRF test results in MDD. Men with a history of childhood abuse exhibited increased HPA axis activity compared with non-abused men. Within the sample of depressed men, however, only those men with histories of childhood trauma exhibited increased HPA axis activity compared with normal comparison subjects. Increased HPA axis response in the dexamethasone/CRF test was associated with exposure to both sexual and physical abuse and correlated with the severity, duration, and age at onset of the abuse. These effects were not due to the presence of comorbid PTSD, other anxiety disorders, past substance abuse, past MDD, or recent life events.

Our findings are concordant with previous findings that childhood trauma influences neuroendocrine and autonomic stress reactivity in adulthood as well as reductions in hippocampal volume in MDD (32,44,45). Our findings suggest that childhood trauma is also associated with impaired glucocorticoid-mediated negative feedback inhibition of the pituitary under stimulated conditions. Similar findings have been reported for women with borderline personality disorder (46). As noted

previously, early adversity in rodent models induces reduced expression of central GR at the epigenomic level, by inducing DNA methylation at a promoter site of the GR gene (31). Escape in the dexamethasone/CRF test also occurs with increased hypothalamic vasopressin drive, which enhances the effects of CRF (47). The precise mechanisms contributing to increased HPA axis activity in the dexamethasone/CRF test after ELS in humans remain obscure.

Our results have several implications. First, they suggest that the combined dexamethasone/CRF test not only detects familial or genetic depression risk but also depression risk secondary to early-life adversity. In fact, an adverse early family environment might well have contributed to findings of increased dexamethasone/CRF responsiveness in never-depressed persons with a positive family history of MDD (23,24). Second, our results provide further support for the existence of biologically distinct types of MDD, as a function of ELS exposure, with only patients who suffer from depression in association with ELS demonstrating changes in stress response systems (32). Of note, this has also been reported for children with MDD (48). Previous studies using the dexamethasone/CRF test in patients with MDD did not consider the contributions of childhood trauma. Consideration of ELS histories could significantly enhance our understanding of factors contributing to altered neuroendocrine status in depressed patients. In fact, previous study results might have been influenced by the incidental frequency of childhood trauma in patient and control groups. Given the high sensitivity of the dexamethasone/CRF test in detecting HPA axis abnormalities in depression, it might be surprising that there were no changes in depressed men without abuse histories. It should be noted, however, that this finding is not necessarily incompatible with previous results. Note that we have artificially stratified MDD and control groups to create extremes of high versus no ELS. These groups per definition are not representative of the general depressed population in terms of ELS exposure. When we combined the depressed groups regardless of ELS, we did find escape of cortisol relative to the combined non-depressed groups. Recruitment on the basis of presence or absence of MDD in previous studies likely resulted in representative distribution of ELS in MDD (more ELS) and control subjects (less ELS) that then plausibly could have contributed to escape in the MDD group. By artificially stratifying groups, we could demonstrate that a previously not considered risk factor, ELS, contributes to escape. This does not hamper the validity of findings that depressed patients (with natural distribution of ELS) exhibit escape. Indeed, our findings suggest that ELS and MDD interact in producing escape. Thus, subjects with ELS who went on to develop MDD demonstrated escape, and this might represent involvement of factors that influence the relationship between ELS and MDD (i.e., genetic factors). For example, in non-human primates, HPA axis hyperactivity after early deprivation is linked to the serotonin transporter polymorphism 5HTTLPR (49), which is known to mediate depression risk versus resilience after childhood adversity (50–52).

It should be noted that previous studies using the dexamethasone/CRF test do not uniformly report or control for plasma dexamethasone concentrations. In the present study, the magnitude of the HPA axis response was highly correlated with dexamethasone availability 30 min before CRF administration. Because case and control groups might differ in dexamethasone metabolism, it seems important that future studies employ measures of plasma dexamethasone concentrations at various time points to increase insight into the role and time course of metabolic effects contributing to dexamethasone/CRF test results in depression. Measuring plasma dexamethasone is also useful as a method to verify oral intake of the drug.

In addition, PTSD not only did not contribute to increased cortisol responsiveness in our study but was associated with a reduced ACTH response in the dexamethasone/CRF test. Thus, subjects with ELS and PTSD had lower ACTH responses than subjects with ELS but no PTSD. The same finding was reported by Rinne *et al.* (46) in abused women with borderline personality disorder. It should be noted that these groups comprised depressed subjects. Future studies should recruit ELS groups stratified by both MDD and PTSD and their comorbidity, in order to fully understand the effects of these different disorders on the HPA axis. Nevertheless, our observation supports previous work by Yehuda *et al.* (53), suggesting that PTSD is characterized by increased negative feedback inhibition of the HPA axis. Studies using the dexamethasone/CRF test in depression research should consider effects of PTSD, particularly when patients with trauma experiences are included.

Several limitations of the current study should be addressed. First, the sample size was relatively small, particularly the group of depressed men without childhood trauma. This was due to the inherent difficulty of finding men with current MDD who do not report any major childhood stressor. Our finding of normal response in depressed men without abuse histories should therefore be interpreted with caution and must be replicated. A second limitation is reliance on retrospective self-reports of childhood experiences, which are subject to simple forgetting, non-awareness, non-disclosure, and reporting biases due to mood state (54). However, a recent meta-analysis of studies using external corroboration of self-reports suggested that use of validated psychometric instruments and focus on moderate–severe early trauma increased validity of self-reports (54). A third limitation concerns our focus on sexual and physical abuse, without the inclusion of other types of adversity, such as neglect or loss. It is plausible that different types of early trauma result in different biological consequences. Fourth, a methodological limitation concerns the absolute hormone levels in response to 1 μg/kg ovine CRF in our study that are not comparable to those from studies that used 100 μg hCRF. However, the key issue is that the same form of CRF is used for the entire study sample, allowing for identifying and interpreting group differences. Fifth, the study was limited to men. Because there are well-known gender differences in HPA axis function (55) as well as in the long-term consequences of childhood trauma (56), our results might not be generalized to women. Future studies should scrutinize gender differences in the effects of childhood trauma on HPA axis function and their relationship to psychiatric outcome. Finally, we did not consider effects of genotype, personality traits, and family history, all of which might impact dexamethasone/CRF test results.

In conclusion, our study provides further evidence that early adverse experience contributes to the neurobiology of depression. Consideration of the neurobiological effects of the various genetic, developmental, and psychosocial contributors to depression in the future will result in a more precise understanding of the pathophysiology of depression and the identification of specific depression endophenotypes. Ultimately, such studies will allow for differential strategies for the prevention and treatment of this debilitating disorder.

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