

Pituitary-Adrenal and Autonomic Responses to Stress in Women After Sexual and Physical Abuse in Childhood

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THE RELATIVE CONTRIBUTION OF genetic and environmental factors in the etiology of psychiatric disorders has long been a hotly debated area of investigation. Considerable evidence from a variety of studies suggests a preeminent role of early adverse experiences in the development of mood and anxiety disorders. One study¹ composed of almost 2000 women revealed that those with a history of childhood sexual or physical abuse exhibited more symptoms of depression and anxiety and had more frequently attempted suicide than women without a history of childhood abuse. Women who have been abused in childhood are 4 times more likely to develop syndromal major depression in adulthood than women who have not been abused, and the magnitude of the abuse is correlated with the severity of depression.²

Early parental loss predominantly due to parental separation has also been found to increase the risk for major depression in case-control and epidemiological studies.³⁻⁸ Twin studies^{9,10} have provided concordant findings. Child-

Context Evidence suggests that early adverse experiences play a preeminent role in development of mood and anxiety disorders and that corticotropin-releasing factor (CRF) systems may mediate this association.

Objective To determine whether early-life stress results in a persistent sensitization of the hypothalamic-pituitary-adrenal axis to mild stress in adulthood, thereby contributing to vulnerability to psychopathological conditions.

Design and Setting Prospective controlled study conducted from May 1997 to July 1999 at the General Clinical Research Center of Emory University Hospital, Atlanta, Ga.

Participants Forty-nine healthy women aged 18 to 45 years with regular menses, with no history of mania or psychosis, with no active substance abuse or eating disorder within 6 months, and who were free of hormonal and psychotropic medications were recruited into 4 study groups (n = 12 with no history of childhood abuse or psychiatric disorder [controls]; n = 13 with diagnosis of current major depression who were sexually or physically abused as children; n = 14 without current major depression who were sexually or physically abused as children; and n = 10 with diagnosis of current major depression and no history of childhood abuse).

Main Outcome Measures Adrenocorticotrophic hormone (ACTH) and cortisol levels and heart rate responses to a standardized psychosocial laboratory stressor compared among the 4 study groups.

Results Women with a history of childhood abuse exhibited increased pituitary-adrenal and autonomic responses to stress compared with controls. This effect was particularly robust in women with current symptoms of depression and anxiety. Women with a history of childhood abuse and a current major depression diagnosis exhibited a more than 6-fold greater ACTH response to stress than age-matched controls (net peak of 9.0 pmol/L [41.0 pg/mL]; 95% confidence interval [CI], 4.7-13.3 pmol/L [21.6-60.4 pg/mL]; vs net peak of 1.4 pmol/L [6.19 pg/mL]; 95% CI, 0.2-2.5 pmol/L [1.0-11.4 pg/mL]; difference, 8.6 pmol/L [38.9 pg/mL]; 95% CI, 4.6-12.6 pmol/L [20.8-57.1 pg/mL]; $P < .001$).

Conclusions Our findings suggest that hypothalamic-pituitary-adrenal axis and autonomic nervous system hyperreactivity, presumably due to CRF hypersecretion, is a persistent consequence of childhood abuse that may contribute to the diathesis for adulthood psychopathological conditions. Furthermore, these results imply a role for CRF receptor antagonists in the prevention and treatment of psychopathological conditions related to early-life stress.

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hood abuse also predisposes to the development of anxiety disorders in adulthood, including panic disorder and generalized anxiety disorder.^{11,12} In addition, posttraumatic stress disorder (PTSD) may be a direct consequence of childhood abuse, and, moreover, such trauma early in life also appears to increase an individual's risk of developing PTSD in response to other traumas in adulthood.¹³ Depression and anxiety disorders, including PTSD, are often comorbid in individuals with a history of diverse early adversities.¹⁴

There is evidence that central nervous system (CNS) corticotropin-releasing factor (CRF) systems are likely to mediate the association between early-life stress and the development of mood and anxiety disorders in adulthood. Corticotropin-releasing factor neurons are found not only in the hypothalamus, but also in the neocortex and the central nucleus of the amygdala, which are believed to be involved in cognitive and emotional processing and in brainstem nuclei that contain the bulk of the noradrenergic and serotonergic perikarya that project to the forebrain.

These CNS CRF systems have also been strongly implicated in the pathophysiology of both depression and anxiety disorders.¹⁵ Thus, when administered directly into the CNS of laboratory animals, CRF produces many physiological and behavioral changes that closely parallel symptoms of depression and anxiety, such as elevations of peripheral adrenocorticotrophic hormone (ACTH), corticosterone, and catecholamine concentrations, increases in heart rate and mean arterial pressure, changes in gastrointestinal activity, decreased reproductive behavior, decreased appetite, disruption of sleep, increased grooming behavior, increased locomotor activity in a familiar environment, suppression of exploratory behavior in a novel environment, potentiation of acoustic startle responses, facilitation of fear conditioning, and enhancement of shock-induced freezing and fighting behavior.¹⁶⁻²⁰

Enhanced release of CRF from 1 or more CNS circuits may, thus, account for many of the symptoms of depression and anxiety and for the frequent comorbidity between these disorders.^{21,22} Indeed, our group and others have repeatedly measured increased CRF-like immunoreactivity in cerebrospinal fluid (CSF) of untreated depressed patients compared with healthy controls and patients with other psychiatric disorders.²³⁻²⁶ Moreover, increased numbers of CRF-positive neurons and increased CRF messenger RNA (mRNA) expression have recently been measured in the paraventricular nucleus (PVN) in postmortem hypothalamic tissue of untreated depressed patients.^{27,28} Similar to findings in depression, increased CSF CRF concentrations have been reported in patients with PTSD and obsessive-compulsive disorder.²⁹⁻³¹

Of particular relevance to the current study is evidence from preclinical studies that suggests that increased activity of CRF circuits may be the persisting neurobiological consequence of stress early in development. Adult rats repeatedly separated from their dams for 180 min/d on postnatal days 2 to 14 demonstrate increased CRF concentrations in the median eminence, hypothalamohypophysial portal blood, and CSF and increased CRF mRNA expression in the hypothalamic PVN under resting conditions. In response to a variety of stressors, these maternally separated rats exhibit increased CRF mRNA expression in the hypothalamic PVN and increased ACTH and corticosterone responses.^{32,33} Similarly, nonhuman primates reared as neonates with their mothers in a variable foraging demand condition for 12 weeks demonstrate significantly elevated CSF CRF concentrations along with stable traits of anxiety as adults.^{34,35} We hypothesize that stress early in life results in a persistent sensitization or hyperactivity of CNS CRF systems to even mild stress in adulthood, contributing to the development of mood and anxiety disorders. This study sought to test this hypothesis in human subjects.

METHODS

Subjects

A total of 49 subjects, ages 18 to 45 years, distributed into 4 groups participated in the study. Presuming a moderate effect size (10%) according to Cohen,³⁶ the power to detect a significant interaction effect among 4 groups and a time series of 8 repeated measurements at the .05 level of significance is 0.98.³⁷

We recruited women without a history of significant early-life stress and no psychiatric disorder (controls: $n=12$; mean age, 29 years; 95% confidence interval [CI], 24-34 years), women with a history of childhood sexual and/or physical abuse (repeated abuse, once a month or more for at least 1 year; sexual abuse, having been forced to touch another person's intimate parts, having been touched in intimate parts, attempted or completed vaginal, oral, or anal intercourse; physical abuse, 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; or both sexual and physical abuse, before the first menstrual period) without a *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)*³⁸ diagnosis of current major depression ($n=14$; mean age, 30 years; 95% CI, 27-33 years), women with a history of childhood sexual and/or physical abuse and a *DSM-IV* diagnosis of current major depression ($n=13$; mean age, 32 years; 95% CI, 27-36 years), and women with a *DSM-IV* diagnosis of current major depression but without a history of significant early-life stress ($n=10$; mean age, 34.6 years; 95% CI, 28.59-40.60 years).

All participants were recruited via newspaper advertising from the general population and were remunerated for the time required for participation. Exclusion criteria for the study were irregular menses, significant medical illness, past or current presence of psychotic symptoms or bipolar disorder, and current presence of substance abuse or dependency or eating

disorders. All subjects were free of hormonal (except for oral contraceptives) or psychotropic medication and were admitted as inpatients to the General Clinical Research Center of Emory University Hospital, Atlanta, Ga, after providing written informed consent. The study was approved by the Institutional Review Board (Human Investigation Committee) of Emory University School of Medicine and was conducted from May 1997 to July 1999.

Early Trauma Inventory

The presence or absence of childhood trauma was assessed using the Early Trauma Inventory (ETI).³⁹ The ETI is a structured interview that assesses the number, frequency, duration, and subjective impact of different types of traumatic experiences (physical, sexual, emotional abuse and general traumas). The ETI scale ranges from 0 to 524 for physical abuse and from 0 to 1017 for sexual abuse. High test-retest reliability, internal consistency, and external validity have been reported for the ETI.³⁹ We additionally made an effort to obtain independent validation of the abuse from court, social service, or medical records and from family or friends, although not all subjects included in the study were able to provide such validation. For the diagnosis of depression and other psychiatric disorders, the Structured Clinical Interview for *DSM-IV*⁴⁰ was used.

Cohort Characteristics

There were no significant differences in age, educational status, or ethnicity among the 4 comparison groups; however, there was a trend for fewer African Americans in the group of abused women with current major depression compared with the group of abused women without major depression (Fisher exact test $P=.08$). The 4 comparison groups did not differ with respect to the distribution of women using oral contraceptives (4 of 49) or women withdrawn from therapy with psychotropic medication (11 of 49). The magnitude of the abuse did not differ between abused women without ma-

jor depression (mean ETI sexual abuse score, 131.71; 95% CI, 20.97 to 284.39; mean ETI physical abuse score, 199.36; 95% CI, 37.07-361.64) and abused women with major depression (mean ETI sexual abuse score, 70.84; 95% CI, 7.53-140.94; mean ETI physical abuse score, 173.84; 95% CI, 88.86-258.83).

The mean severity of the depression was in the moderate range for abused women with major depression (mean Hamilton Depression Rating Scale⁴¹ [range, 0-38] score, 19.0; 95% CI, 15.56-22.44) and nonabused women with major depression (mean Hamilton Depression Rating Scale score, 21.1; 95% CI, 19.30-22.89). There were no significant differences with respect to the prevalence of past major depression among women with a history of childhood abuse without current major depression (8 of 14), women with a history of childhood abuse with current major depression (9 of 13), and nonabused women with current major depression (8 of 10). Only 5 of 14 abused women without current depression met *DSM-IV* criteria for PTSD, whereas 11 of 13 abused women with current depression fulfilled a *DSM-IV* diagnosis of PTSD ($\chi^2_1=6.68$, $P=.01$).

For the induction of stress, we used a standardized psychosocial stress protocol that has been shown to reliably induce activation of the hypothalamic-pituitary-adrenal axis and the autonomic nervous system.⁴² The test mainly consists of a 10-minute anticipation and preparation phase and a subsequent 10-minute public speaking and mental arithmetic task in front of an audience. In 6 independent validation studies, this protocol was shown to induce endocrine and autonomic changes reminiscent of stress, which significantly differ from placebo conditions.⁴² The magnitude of endocrine and autonomic responses is generally interpreted as reflecting biological stress reactivity.⁴²

The psychosocial stress test was performed between 1:30 and 4:00 PM as described elsewhere.⁴² Blood samples from indwelling catheters and heart rate measurements were obtained in 15-

minute intervals before (15 and 0 minutes), during (15 minutes), and after (30, 45, 60, 75, and 90 minutes) the stress exposure. Blood was collected in EDTA tubes, placed immediately on ice, and centrifuged at 4°C for 10 minutes at 3000 rpm. Plasma was separated, coded, stored at -80°C, and assayed for ACTH and cortisol concentrations by members of the research team blinded to group assignment and sample sequence using commercial radioimmunoassays (ACTH: Nichols, San Juan Capistrano, Calif; cortisol: DiaSorin, Stillwater, Minn).

Data Analysis

Hormone and heart rate data were analyzed using 2-way analysis of covariance (ANCOVA) with repeated measurement (first factor was group, second repeated factor was time, and covariate was ethnicity). In the case of significant effects, between-subjects comparisons were performed for single time points followed by a priori defined contrasts to compare individual group means. In addition, maximum levels of hormone concentrations and heart rates were computed and compared among groups using ANCOVA (factor was group and covariate was ethnicity) followed by a priori defined contrasts. Homogeneity of variance was tested using the Levene test.⁴³ In the case of unequal variance, raw data were logarithm transformed, and all analyses were repeated. All analyses were 2-tailed, with the level of significance set at $P<.05$.

RESULTS

Results obtained by 2-way ANCOVA with repeated measures indicated that the stress test induced significant increases in mean ACTH (main effect for the time factor [T]: $F_7=26.56$, $P<.001$), cortisol (T: $F_7=54.92$, $P<.001$), and heart rate levels (T: $F_7=26.62$, $P<.001$) across all groups. With respect to ACTH concentrations, there was a significant main effect for the group factor (G) ($F_3=3.81$, $P=.02$) and a significant group by time interaction effect ($G \times T$) ($F_{21}=3.81$, $P<.001$). Ethnicity (catego-

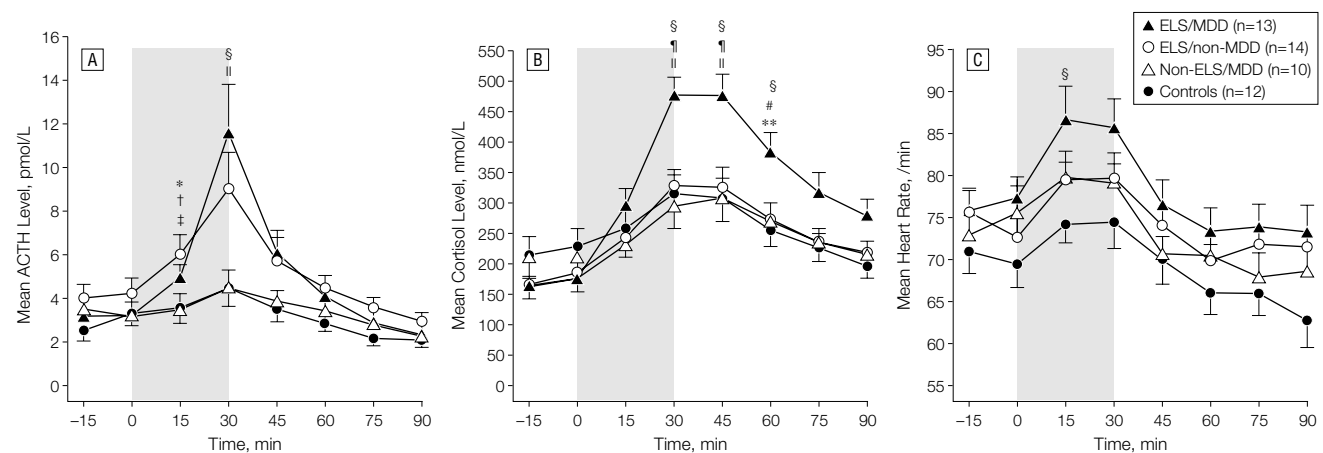
ries: African American, white; determined by self-report) had a significant effect on plasma ACTH concentrations ($F_1=6.68$, $P=.01$). Between-subjects comparisons showed that mean ACTH levels of the 4 groups significantly differed at 15 minutes (G : $F_3=3.40$, $P=.03$; regression [ethnicity]: $F_1=5.88$, $P=.02$) and 30 minutes (G : $F_3=5.85$, $P=.002$) after the start of stress induction. Abused women with and without current major depression exhibited increased ACTH concentrations compared with controls and nonabused depressed women (FIGURE, A). Comparison groups also differed with respect to

maximum ACTH concentrations (TABLE). Maximum ACTH responses minus baseline were more than 6-fold higher in abused women with depression (net peak, 9.0 pmol/L [41.0 pg/mL]; 95% CI, 4.7-13.3 pmol/L [21.6-60.4 pg/mL]) than in controls (net peak, 1.4 pmol/L [6.19 pg/mL]; 95% CI, 0.2-2.5 pmol/L [1.0-11.4 pg/mL]; difference, 8.6 pmol/L [38.9 pg/mL]; 95% CI, 4.6-12.6 pmol/L [20.8-57.1 pg/mL]; $P<.001$). Because of heterogeneity of variance of mean ACTH concentrations (Levene test[†] $P<.01$), logarithm-transformed ACTH values were additionally computed, and all statistical

effects for ACTH were confirmed (data not shown).

Comparison groups also differed with respect to profiles of cortisol responses ($G \times T$: $F_{21}=5.64$, $P<.001$; regression (ethnicity): $F_1=1.01$, $P=.32$). Between-subjects comparisons revealed that the comparison groups differed at 30 (G : $F_3=7.06$, $P=.001$), 45 (G : $F_3=5.24$, $P=.004$), and 60 (G : $F_3=3.47$, $P=.02$) minutes after the start of stress induction, with abused women with current depression exhibiting higher cortisol responses than all other groups (Figure, B). The 4 comparison groups also differed with regard to maximum

Figure. Pituitary-Adrenal and Autonomic Reactivity to a Standardized Laboratory Stressor in Women After Childhood Sexual or Physical Abuse



Mean plasma adrenocorticotropin (ACTH) (A) and cortisol (B) concentrations and mean heart rates (HR) (C) (\pm SEMs) before, during (shaded area), and after psychosocial stress induction in women without a history of significant early-life stress and no psychiatric disorder (controls, $n=12$), women with a history of childhood sexual or physical abuse without major depression (early-life stress and no major depression [ELS/non-MDD], $n=14$), women with a history of childhood sexual or physical abuse and current major depression (early-life stress and major depression [ELS/MDD], $n=13$), and women without a history of significant early-life stress and a current major depression (no early-life stress and major depression [non-ELS/MDD], $n=10$). To convert ACTH from pmol/L to pg/mL, divide by 0.22. To convert cortisol from nmol/L to mg/dL, divide by 27.59. Asterisk indicates $P<.05$ for controls vs ELS/non-MDD; †, $P<.05$ for controls vs ELS/MDD; ‡, $P<.05$ for ELS/non-MDD vs non-ELS/MDD; §, $P<.01$ for controls vs ELS/MDD; ||, $P<.01$ for ELS/MDD vs non-ELS/MDD; ¶, $P<.01$ for ELS/non-MDD vs ELS/MDD; #, $P<.05$ for ELS/non-MDD vs ELS/MDD; and **, $P<.05$ for ELS/MDD vs non-ELS/MDD.

Table. Comparison of Mean (95% Confidence Interval) Maximum Plasma Adrenocorticotropin (ACTH), Plasma Cortisol, and Heart Rate Responses to a Standardized Psychosocial Laboratory Stressor in Study Subjects*

| Variable | Controls (n = 12) | ELS/Non-MDD (n = 14) | ELS/MDD (n = 13) | Non-ELS/MDD (n = 10) | ANCOVA† |
|----------------------------|----------------------|-------------------------|---------------------|-------------------------|---------------------------|
| ACTH peak, pmol/L | 4.7 (3.1-6.3) | 9.3 (5.6-13.0)‡ | 12.1 (5.5-16.6)§ | 5.3 (3.6-7.1)¶ | $F_3 = 6.31$, $P = .001$ |
| Cortisol peak, nmol/L | 339 (281-395) | 359 (290-425) | 527 (455-596)§ | 337 (248-422)¶ | $F_3 = 7.56$, $P < .001$ |
| Heart rate peak, beats/min | 78.4 (72.4-84.3) | 82.2 (78.4-85.9) | 89.7 (81.8-97.5)§ | 83.8 (76.8-90.7) | $F_3 = 3.08$, $P = .04$ |

*Study subjects include women without a history of significant early-life stress and no psychiatric disorder (controls), women with a history of childhood sexual or physical abuse without major depression (early-life stress and no major depression [ELS/non-MDD]), women with a history of childhood sexual or physical abuse and current major depression (early-life stress and major depression [ELS/MDD]), and women without a history of significant early-life stress and a current major depression (no early-life stress and major depression [non-ELS/MDD]). To convert ACTH to pg/mL and cortisol to mg/dL, see conversion equations in Figure legend.

†Analysis of covariance (ANCOVA) (factor was group, and covariate was ethnicity). For ACTH, regression (ethnicity): $F_1 = 4.69$, $P = .04$; for cortisol, regression (ethnicity): $F_1 = 1.01$, $P = .32$; for heart rate: regression (ethnicity): $F_1 = .00$, $P = .95$.

‡ $P<.05$ for controls vs ELS/non-MDD.

§ $P<.01$ for controls vs ELS/MDD.

¶ $P<.01$ for ELS/non-MDD vs ELS/MDD.

|| $P<.01$ for ELS/MDD vs non-ELS/MDD.

cortisol concentrations. Abused women with current depression demonstrated increased maximum levels vs all other groups (Table).

There was a trend of a group effect with respect to the mean heart rates ($F_3=2.24$, $P=.09$; regression (ethnicity): $F_1=.00$, $P=.95$) across all time points. Significant differences between subjects were found at 15 minutes (G : $F_3=2.94$, $P=.04$) after the start of stress induction. Abused women with current major depression exhibited significantly higher heart rate responses at this time compared with controls (Figure, C). Comparison groups also differed with respect to maximum heart rate levels. Abused women with depression demonstrated higher mean maximum heart rates than did controls (Table).

COMMENT

Severe stress early in life is associated with persistent sensitization of the pituitary-adrenal and autonomic stress response, which, in turn, is likely related to an increased risk for adulthood psychopathological conditions. This is the first human study to report persistent changes in stress reactivity in adult survivors of early trauma. The findings are remarkably consistent with findings from laboratory animal studies.^{32,33}

Increased pituitary reactivity to stress in some women with a history of early-life stress without psychiatric disorder may reflect a biological vulnerability for the development of stress-related psychiatric disorders. In these women, there appears to exist a counterregulatory adaptation of the adrenal cortex as reflected by increased ACTH concentrations but normal cortisol responses, which also has been observed in some animal models of severe early stress.^{34,44} The manifestation of affective or anxiety disorders in adulthood may depend on additive factors, including genetic vulnerability and recent life stress. These factors, taken together, may result in relatively high CRF neuronal activity whenever these women are exposed to stress, ultimately resulting in symptoms of depression and anxiety.

Depressed subjects without early stress experiences showed normal stress reactivity, suggesting differential pathophysiology in subtypes of depression. Increased stress sensitivity may be related to a mixed state of depression and anxiety, including PTSD symptoms, which develops after early trauma. Recently, our group has shown that in rats many of the neurobiological consequences of maternal separation, including CRF hypersecretion, are reversed by treatment with antidepressants, including paroxetine and reboxetine (P.M. Plotsky, PhD; C.O. Ladd, BS; R.L. Huot, BS; et al, unpublished data, 2000).

Future studies in survivors of childhood abuse should separate the effects of different kinds of abuse at different developmental stages and should explore potential reversibility of this biological stress vulnerability after psychotherapeutic and psychopharmacological intervention. Such findings may have important implications for the prevention and treatment of mood and anxiety disorders in survivors of early trauma. Much effort has recently been directed toward the development of CRF receptor antagonists for the treatment of depression and anxiety.⁴⁵ The utility of CRF receptor antagonists in depression is currently being evaluated in an open-label clinical trial.⁴⁶ Our findings suggest potential utility of such compounds for the prevention and treatment of psychopathological conditions related to early-life stress.

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It is sad that man is not intelligent enough to solve problems without killing. . . . The present world crisis can be solved only by a general human revolution against outdated concepts. . . . Man is not a blood-thirsty animal, and war is only due to the greed and lust for power of relatively small groups, the conspiracy of the few against the many.

—Albert Szent-Györgyi (1893-1986)