Altered Pituitary-Adrenal Axis Responses to Provocative Challenge Tests in Adult Survivors of Childhood Abuse

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Objective: Early adverse life events may predispose individuals to the development of mood and anxiety disorders in adulthood, perhaps by inducing persistent changes in corticotropin-releasing factor (CRF) neuronal systems. The present study sought to evaluate pituitary-adrenal responses to standard hypothalamic-pituitary-adrenal axis challenge tests in adult female survivors of childhood abuse with and without major depressive disorder.

Method: Plasma ACTH and cortisol responses to the administration of 1 µg/kg ovine CRF and plasma cortisol responses to the administration of 250 µg $ACTH_{1–24}$ were measured in healthy women without early life stress (N=20), women with childhood abuse without major depressive disorder (N=20), women with childhood abuse and major depressive disorder (N=15), and women with major depression but no early life stress (N=11).

Results: Abused women without major depressive disorder exhibited greater than usual ACTH responses to CRF administration, whereas abused women with major depressive disorder and depressed women without early life stress demonstrated blunted ACTH responses. In the $ACTH_{1–24}$ stimulation test, abused women without major depressive disorder exhibited lower baseline and stimulated plasma cortisol concentrations. Abused women with comorbid depression more often suffered from posttraumatic stress disorder and reported more recent life stress than abused women without major depressive disorder.

Conclusions: These findings suggest sensitization of the anterior pituitary and counterregulatory adaptation of the adrenal cortex in abused women without major depressive disorder. On subsequent stress exposure, women with a history of childhood abuse may hypersecrete CRF, resulting in down-regulation of adenohypophyseal CRF receptors and symptoms of depression and anxiety.

Over the last three decades, compelling evidence has accrued indicating that adverse experiences early in life, such as childhood abuse and neglect as well as parental loss, result in a greater than usual risk for the development of mood and anxiety disorders in adulthood, including major depressive disorder and posttraumatic stress disorder (PTSD) (1–6). This higher stress vulnerability may be mediated by persistent alterations in neurobiological systems that are known to be stress-responsive. Central nervous system (CNS) corticotropin-releasing factor (CRF) systems are likely involved in mediating the effects of stress early in life on the development of certain psychiatric disorders in adulthood. First, the heterogeneous distribution of CRF neurons in cortical, limbic, and brainstem regions infers a role for CRF as a major regulator of the endocrine, autonomic, immune, and behavioral stress responses (7). Second, direct CNS application of CRF to laboratory animals produces many physiological and behavioral changes that parallel the cardinal symptoms of depression and anxiety (8). Third, higher than normal CRF concentrations have repeatedly been measured in the CSF of patients with major depressive disorder and PTSD (9–11). Fourth, findings from preclinical laboratory animal studies have provided evidence that stress early in life, i.e., maternal separation in rats or adverse rearing conditions in nonhuman primates, produces long-lived hyperactivity of CRF neuronal systems as well as greater reactivity of the hypothalamic-pituitary-adrenal (HPA) axis to stress in adulthood (11–14). The concatenation of these findings suggests that genetic vulnerability coupled with early stress in a critical and plastic period of development may result in persistent sensitization of CRF neuronal systems to even mild stressors in adulthood, forming the basis for the development of mood and anxiety disorders (15). In support of this hypothesis, we recently observed higher pituitary-adrenal and autonomic responses to a standardized psychosocial laboratory stressor in adult women with a history of childhood sexual and/or physical abuse (16). Sensitization of the stress response was particularly robust in abused women with symptoms of depression and anxiety, including PTSD symptoms.

To further explore the mechanisms of this biological vulnerability to stress in these women, we employed standard HPA axis challenge tests, including the CRF stimulation test and $ACTH_{1–24}$ stimulation test. The administration of synthetic CRF stimulates ACTH release from the

pituitary corticotrophs and, subsequently, cortisol release from the adrenal cortex. Thus, the CRF stimulation test allows an evaluation of the reactivity of the adenohypophysis to CRF. In contrast, a psychosocial stress test stimulates a stress response involving higher levels of cognitive and emotional processing mediated by several neurotransmitter systems. Changes in pituitary responsiveness to CRF stimulation may reflect CRF receptor changes on corticotrophs due to alterations in the activity of the paraventricular nucleus/median eminence CRF circuit. Similarly, the administration of high doses of biologically active $ACTH_{1-24}$ allows for the evaluation of the maximal response capacity of the adrenal cortex.

Method

Subjects

The study group was composed of women without a history of significant early life stress and no psychiatric disorders (comparison subjects, N=20), women with a history of childhood abuse without current major depressive disorder (N=20), women with a history of childhood abuse and current major depressive disorder (N=15), and women without a history of significant early life stress but with current major depressive disorder (N=11). All women were of reproductive age and had regular menstrual cycles. For assignment to the childhood abuse groups, women had to have experienced repeated moderate to severe sexual or physical abuse before their first menstrual period, defined as having been forced to touch another person's intimate parts; having been touched in intimate parts; having experienced attempted or completed intercourse; having been spanked, kicked, or choked in a way that left bruises or injuries; or having been attacked with a weapon or tied up or locked in a room or a closet. Assignment to the major depressive disorder groups required a diagnosis of current major depressive disorder according to DSM-IV criteria. For the assignment to groups without significant early life stress, women could not have experienced any stressful event, such as neglect, parental loss, separation from parents, adoption, accidents, severe illness, or natural disaster before the first menstrual period. General exclusion criteria were significant medical illness, past or current presence of psychotic symptoms or bipolar disorder, current presence of psychoactive substance abuse or dependency, or eating disorders. All patients and volunteers were free of hormonal (except oral contraceptives) and psychotropic medication. All subjects were recruited from responses to newspaper advertising and were paid for participation. After complete 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

For the diagnosis of major depressive disorder and other psychiatric disorders, the Structured Clinical Interview for DSM-IV (17) was given to patients and comparison subjects before study entry. Severity of symptoms of depression and PTSD were rated by using standard rating scales (18, 19). Stressful childhood experiences were assessed by using the Early Trauma Inventory (20). The Early Trauma Inventory is a semistructured interview that assesses different types of sexual and physical abuse, as well as emotional neglect and general trauma, and yields excellent test-retest reliability, internal consistency, and external validity. We additionally monitored recent major and minor stress experiences using the Life Experiences Survey (21) and the Daily Hassles Scale (22).

All patients and volunteers were admitted as inpatients to the General Clinical Research Center at Emory University Hospital for the entire study. On the day after admission, the CRF stimulation test was performed in the afternoon, when pituitary-adrenal activity is low (23). Catheters were inserted into a forearm vein at 12:00 noon and were kept patent by means of normal saline infusion. To obtain baseline hormonal measures, blood samples were collected from 1:30 p.m. (–150 minutes) to 4:00 p.m. (0 minutes) in half-hour intervals. At 4:00 p.m., 1 µg/kg ovine CRF was intravenously administered through the catheter. Blood samples were collected 5, 15, 30, 60, 90, and 120 minutes after administration of ovine CRF. Two days later, the $ACTH_{1-24}$ stimulation test was performed in the morning (24). Catheters were inserted into a forearm vein at 8:00 a.m. and were maintained as described. Blood samples for baseline hormone measures were collected at 8:30 a.m. and 9:00 a.m., and subsequently, 250 µg $ACTH_{1-24}$ (Cortrosyn, Organon, Oss, the Netherlands) was administered through the catheter. Blood samples were collected 30, 60, 90, 120, 150, and 180 minutes after $ACTH_{1-24}$ administration. Blood was collected in EDTA tubes, placed immediately on ice, and centrifuged at 4°C for 10 minutes at 3,000 rpm. Plasma was separated, coded, and stored at –80°C until assayed. Blood samples were assayed by using commercial radioimmunoassays (ACTH: Nichols, San Juan Capistrano, Calif.; cortisol: DiaSorin, Stillwater, Minn.).

Statistical Analyses

Demographic and clinical data were analyzed by using frequency tests for categorical data, Kruskal-Wallis analysis of variance for ranked data, and two-way analysis of variance (early life stress by major depressive disorder) for continuous data. Hormone data from endocrine challenge tests were analyzed by using three-way analysis of variance with repeated measurement (early life stress by major depressive disorder by time [repeated factor: 12 for ovine CRF and eight for $ACTH_{1-24}$ stimulation]) (25). Age, education, and race were entered as covariates, since the effects of demographic variables on pituitary-adrenal axis activity have been documented in the literature (26, 27). In the case of a significant three-way interaction effect, the structure of the interaction was identified by using nonorthogonal contrasts obtained by using Dunn's multiple comparison procedure (28). Contrasts were calculated by using pooled mean square errors of the repeated measurement analysis. Patient group means were contrasted against those of comparison subjects, resulting in 36 possible contrasts for the CRF stimulation test and 24 possible contrasts for the $ACTH_{1-24}$ stimulation test. All tests were two-tailed with the level of significance set at p<0.05.

Results

Description of the Study Groups

Table 1 presents the characteristics of the study groups. There were significant differences in groups with respect to age and racial distribution but not with respect to education. As expected, abused women attained higher numbers and magnitude scores on the Early Trauma Inventory than nonabused women. Depressed women had significantly higher mean Hamilton Depression Rating Scale scores than nondepressed women. Although it was perhaps not clinically significant, mean Hamilton depression scale scores were statistically higher in abused women without major depressive disorder than in comparison subjects. It is of interest that there was a significantly higher prevalence of PTSD in the group of abused women with current major depressive disorder than in the abused

TABLE 1. Characteristics of Healthy Comparison Subjects, Women With a History of Childhood Abuse With and Without Major Depression, and Women With Major Depression but No History of Early Life Stress

Variable	Comparison Subjects (N=20)		Women With Childhood Abuse Without Major Depression (N=20)		Women With Childhood Abuse and Major Depression (N=15)		Women With Major Depression but No History of Early Life Stress (N=11)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age (years)[a]	27.8	6.8	31.1	6.4	32.6	6.5	34.5	6.9
Education (mean rank)	36.2		35.3		25.2		36.7	
Number of early stressful events[b]	3.1	2.2	15.9	6.9	16.8	4.9	5.7	3.6
Early Trauma Inventory score[c]	83.2	95.8	731.8	827.3	985.3	561.9	139.0	194.5
Hamilton depression scale score[d]	1.9	1.8	6.6	5.4	18.3	5.8	21.4	2.7
Clinician-Administered PTSD Scale score[e]	—	—	19.7	14.1	52.3	16.4	—	—
Negative life events (as indicated by Life Experiences Survey) score[f]	3.5	2.5	6.1	4.8	14.6	9.4	9.3	3.9
Daily Hassles Scale intensity score[g]	1.1	0.1	1.5	0.3	1.8	0.3	1.8	0.5
	N	%	N	%	N	%	N	%
Race[h]								
Caucasian	15	75.0	9	45.0	13	86.7	9	81.8
Other	5	25.0	11	55.0	2	13.3	2	18.2
PTSD diagnosis[i]	—	—	4	20.0	14	93.3	—	—

[a] Significant main effect of major depression (ANOVA: $F=5.91$, $df=1, 62$, $p<0.05$).
[b] Significant main effect of childhood abuse (ANOVA: $F=92.12$, $df=1, 62$, $p<0.01$).
[c] Number of separate events multiplied by frequency and duration. Significant main effect of childhood abuse (ANOVA: $F=29.92$, $df=1, 62$, $p<0.01$).
[d] Significant main effect of major depression ($F=201.65$, $df=1, 62$, $p<0.01$) and significant interaction between childhood abuse and major depression ($F=12.06$, $df=1, 61$, $p<0.01$) (ANOVA). Post hoc comparisons with Tukey's honestly significant difference test showed significant differences ($p<0.01$) between the comparison subjects and each of the other groups and between the women with childhood abuse without major depression and each of the groups with major depression.
[e] Significant difference between groups ($t=-6.30$, $df=33$, $p<0.01$).
[f] Significant main effects of childhood abuse ($F=7.77$, $df=1, 61$, $p<0.01$) and major depression ($F=25.56$, $df=1, 61$, $p<0.01$) (ANOVA).
[g] Significant main effect of major depression (ANOVA: $F=39.19$, $df=1, 56$, $p<0.01$).
[h] Significant difference between groups ($\chi^2=8.85$, $df=3$, $p<0.05$).
[i] Significant difference between groups ($\chi^2=18.45$, $df=1$, $p<0.01$).

women without major depressive disorder. A history of childhood abuse as well as current major depressive disorder was associated with higher numbers of negative life events in the past year. Depressed women reported more intense daily hassles in the past month than nondepressed women. Abused women with major depressive disorder attained a significantly higher mean negative life events score ($t=3.12$, $df=17.68$, $p<0.01$) and Daily Hassles Scale score ($t=3.09$, $df=30$, $p<0.01$) than abused women without major depressive disorder.
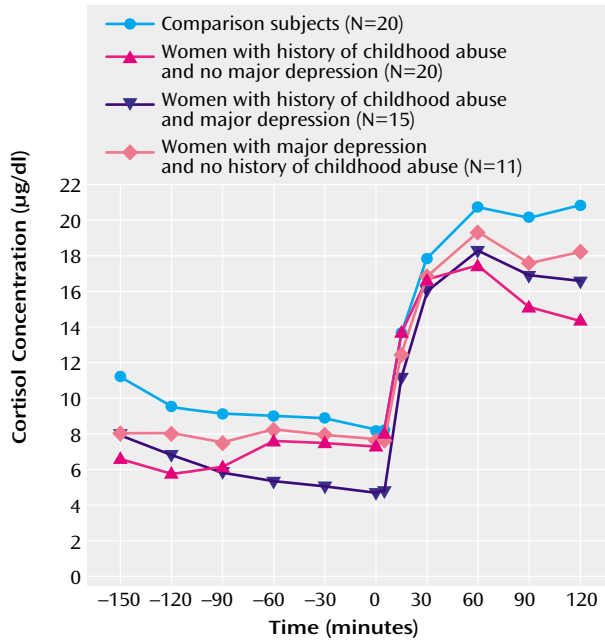
CRF Stimulation Test

Three-way analysis of covariance with repeated measurement revealed two significant main effects (time: $F=2.68$, $df=11, 649$, $p<0.01$; major depressive disorder: $F=21.76$, $df=1, 59$, $p<0.01$), a significant two-way interaction effect (time by major depressive disorder: $F=5.61$, $df=11, 649$, $p<0.01$), as well as a significant three-way interaction effect (early life stress by major depressive disorder by time: $F=1.87$, $df=11, 649$, $p<0.05$). Education and race had significant effects on mean ACTH concentrations (education: $F=6.24$, $df=1, 59$, $p<0.05$; race: $F=8.02$, $df=1, 59$, $p<0.01$) and response profiles (education by time: $F=3.72$, $df=11, 649$, $p<0.01$; race by time: $F=4.83$, $df=11, 649$, $p<0.01$). Dunn's multiple comparison procedure (critical values: tD[0.05/2; 36,649]=3.23; tD[0.01/2; 36,649]=3.66) revealed

FIGURE 1. Mean Plasma ACTH Concentrations During Corticotropin-Releasing Factor Stimulation in Healthy Comparison Subjects, Women With a History of Childhood Abuse With and Without Major Depression, and Women With Major Depression but No History of Early Life Stress[a]
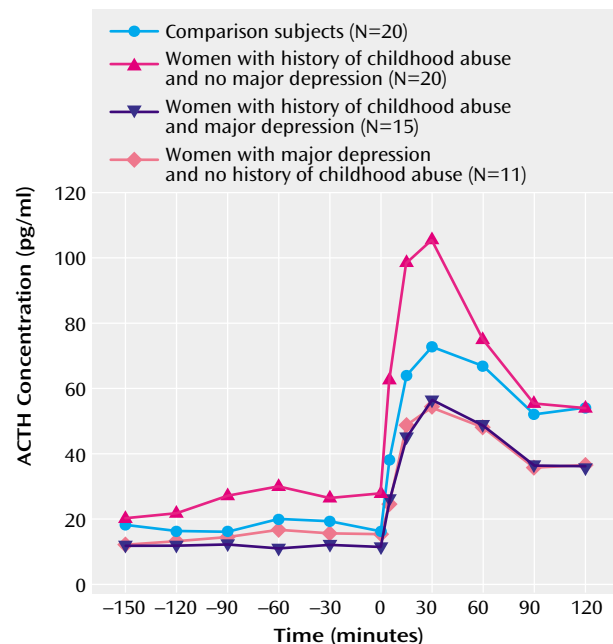
[a] Baseline: −150 to 0 minutes. Response: 5 to 120 minutes.

FIGURE 2. Mean Plasma Cortisol Concentrations During Corticotropin-Releasing Factor Stimulation in Healthy Comparison Subjects, Women With a History of Childhood Abuse With and Without Major Depression, and Women With Major Depression but No History of Early Life Stress[a]

FIGURE 3. Mean Plasma Cortisol Concentrations During ACTH$_{1-24}$ Stimulation in Healthy Comparison Subjects, Women With a History of Childhood Abuse With and Without Major Depression, and Women With Major Depression but No History of Early Life Stress[a]

[a] Baseline: −150 to 0 minutes. Response: 5 to 120 minutes.

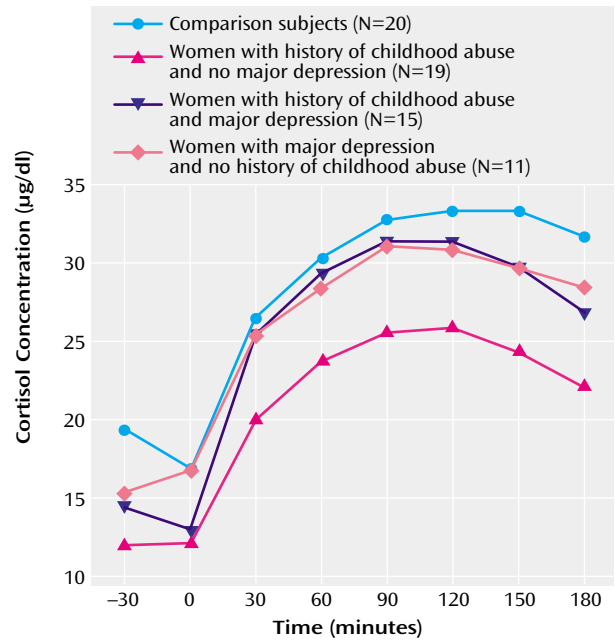[a] Baseline: −30 to 0 minutes. Response: 30 to 180 minutes.

that abused women without major depressive disorder demonstrated higher mean stimulated ACTH concentrations than comparison subjects at 5 (tD=5.08), 15 (tD=7.16), and 30 minutes (tD=6.79). Abused women with major depressive disorder (60 minutes: tD=3.34, 120 minutes: tD=3.42) and depressed women without a history of abuse (60 minutes: tD=3.26) exhibited lower stimulated ACTH concentrations than comparison subjects (Figure 1).

As for cortisol concentrations in the CRF stimulation test (Figure 2), three-way analysis of covariance with repeated measures revealed a significant main effect of time (F=7.86, df=11, 649, p<0.01) as well as a significant three-way interaction effect (early life stress by major depressive disorder by time: F=4.43, df=11, 649, p<0.01). Dunn's multiple comparison procedure (critical values: tD[0.05/2; 36,649]=3.23; tD[0.01/2; 36,649]=3.66) showed that abused women with major depressive disorder demonstrated lower baseline and stimulated cortisol levels than comparison subjects at −150 (tD=4.12), −90 (tD=3.83), −60 (tD=4.29), −30 (tD=4.55), 0 (tD=4.01), 5 (tD=4.05), 90 (tD=4.07), and 120 (tD=4.96) minutes. Abused women without major depressive disorder also demonstrated lower basal and stimulated cortisol concentrations at −150 (tD=5.51), −120 (tD=4.84), −90 (tD=3.82), 90 (tD=5.96), and 120 (tD=8.29) minutes.

ACTH$_{1-24}$ Stimulation Test

Results obtained by using three-way analysis of covariance with repeated measures (Figure 3) revealed a signifi-

cant main effect of time (F=5.15, df=7, 406, p<0.01) and a significant three-way interaction effect (early life stress by major depressive disorder by time: F=2.18, df=7, 406, p<0.05). Education had a significant main effect on cortisol concentrations (F=4.33, df=1, 58, p<0.05). Dunn's multiple comparison procedure (critical values: tD[0.05/2; 24,406]=3.02; tD[0.01/2; 24,406]=3.48) revealed that abused women who were not depressed exhibited lower basal and stimulated cortisol concentrations at −30 (tD=6.83), 0 (tD=4.38), 30 (tD=5.92), 60 (tD=6.01), 90 (tD=7.35), 120 (tD=7.43), 150 (tD=8.24), and 180 (tD=8.96) minutes than comparison subjects. Abused women with depression also showed lower basal cortisol levels at −30 (tD=4.14) and 0 (tD=3.37) minutes than comparison subjects.

Discussion

It is now well established that early adverse experiences constitute a major risk factor for the development of major depressive disorder and certain anxiety disorders, including PTSD. In adulthood, symptoms of depression and anxiety as well as posttraumatic stress symptoms often exacerbate in relationship to acute or chronic life stress (29, 30). We have, thus, hypothesized that stress early in development may alter the set point of the stress response system, rendering these individuals particularly vulnerable to stress and increasing their risk for stress-related diseases. This stress vulnerability may be mediated through persistent hyperactivity and/or sensitization of CNS CRF

systems. In support of this hypothesis, we recently demonstrated a marked increase in pituitary-adrenal and autonomic reactivity to psychosocial laboratory stress in adult women with a personal history of childhood sexual or physical abuse (16). We now present findings on pituitary-adrenal reactivity to standard endocrine provocative tests in these women. Adult women with a history of childhood abuse without major depressive disorder exhibit an exaggerated ACTH response to exogenous CRF. In women with a history of childhood abuse with major depressive disorder, the ACTH response is blunted and resembles that of depressed women without a history of childhood adversities. There also appears to be an altered adrenocortical function in abused women without depression, reflecting adrenocortical insufficiency. Although the two groups of abused women did not differ with respect to the magnitude of childhood abuse, abused women with current major depressive disorder suffered more often from comorbid PTSD and reported more recent chronic mild stress than abused women without major depressive disorder.

To the best of our knowledge, this is the first clinical study of pituitary-adrenal responses to CRF and $ACTH_{1–24}$ administration in adult survivors of childhood abuse. However, several studies have been published in which the CRF stimulation test was administered to abused children (31, 32). DeBellis et al. (31) reported that sexually abused girls exhibit a blunted ACTH and normal cortisol response in a standard CRF stimulation test. These findings are comparable to our findings in abused women with current major depressive disorder. The majority of the abused girls studied by DeBellis et al. suffered from dysthymia; unfortunately, PTSD was not systematically evaluated, and the abused girls were not subgrouped according to the presence or absence of psychiatric disorders. More recently, Kaufman et al. (32) reported that abused children with major depressive disorder demonstrate enhanced ACTH responses and normal cortisol responses when living under conditions of ongoing abuse. These subjects were also at high risk for comorbid PTSD. Taken together with our findings, one might posit that an initial sensitization of the stress response system evolves into a blunted pituitary responsiveness over time in the face of ongoing stress.

Several studies have measured pituitary-adrenal axis responses to CRF in patients with major depressive disorder or anxiety disorders, including combat-related PTSD. In general, blunted ACTH and normal cortisol responses have been reported (33–35). We further extend these findings by demonstrating a similar blunting of the ACTH response in abused women with current major depressive disorder and comorbid PTSD. In contrast, we did not observe basal hypercortisolemia or higher cortisol responses to $ACTH_{1–24}$ (24, 36) in our group of depressed women without a history of childhood abuse. It is unlikely that the latter finding is caused by ceiling effects, since other au-

thors have reported considerably higher $ACTH_{1–24}$-stimulated cortisol concentrations in depressed subjects, whereas those of comparison subjects were comparable to those in our study (24). Abused women, with and without depression, demonstrated low basal adrenocortical activity. Furthermore, abused women without major depressive disorder also exhibited decreased plasma cortisol concentrations after administration of $ACTH_{1–24}$. Lower basal adrenocortical activity is a prominent finding in patients with PTSD in the aftermath of other trauma experiences, such as combat exposure, Holocaust victimization, or earthquakes (37). However, the capacity of the adrenal gland to respond to ACTH has never been studied in patients with PTSD (38).

Animal models of early untoward stressful life events, e.g., maternal separation, have provided evidence for higher CNS CRF activity and higher ACTH responses to acute psychological stress in adulthood (12, 13). These findings are in accordance with our recent findings of higher pituitary reactivity to psychosocial stress in adult women with a history of childhood abuse (16). Unfortunately, comprehensive endocrine challenge studies in animal models of early abuse and depression have not been performed. This is of paramount importance because a stress exposure and a CRF stimulation test address different levels of the HPA axis; therefore, findings are not directly comparable. As shown by our findings, indeed, pituitary responses can be enhanced in response to a laboratory stressor and blunted in response to exogenous CRF stimulation. Most likely, CRF receptors are down-regulated because of chronic CRF hypersecretion from the hypothalamus in the face of greater exposure to recent stress in abused women with major depressive disorder. Indeed, reduction of pituitary CRF receptor numbers has been observed in adult rats who were maternally deprived in the postnatal period, despite an exaggerated ACTH response to stress (13). Thus, greater pituitary responses to acute stress may involve activation of corticolimbic pathways, resulting in higher endogenous CRF activation and/or other neuromodulators such as arginine vasopressin. Recent studies (39) have indicated that maternal separation also increases CRF neuronal activity in corticolimbic pathways and in the locus ceruleus, both of which have long been implicated in the pathogenesis of depression and anxiety (15). It is of interest that during chronic stress or after a single stress exposure, a shift in the ratio between hypothalamic arginine vasopressin and CRF expression occurs, resulting in greater arginine vasopressin-releasing activity as well as sensitization of pituitary arginine vasopressin receptors (40, 41). Such mechanisms may underlie the HPA axis dysfunction in adult survivors of childhood abuse and require further scrutiny.

Mechanisms of adrenocortical counterregulation are obscure. In some animal models of severe stress early in life, dissociation of central and adrenocortical (re)activity was noted (13, 14). In our study (13), rats who were mater-

nally deprived for 6 hours/day during the postnatal phase exhibited greater CNS CRF activity and greater basal and stress-induced ACTH concentrations along with unaltered basal and stress-induced corticosterone concentrations. Remarkably, we (14) found higher CSF CRF concentrations and lower CSF cortisol concentrations in nonhuman primates exposed to early adverse rearing conditions. Thus, there appears to be peripheral adaptation to CNS hyperactivity as a result of early stress. Similar findings have been obtained in patients with fibromyalgia and other related disorders known to be related to early life stress, trauma, and PTSD (38). Thus, first, alterations at the adrenal level may contribute to hypocortisolism in PTSD, and, second, a lack of the protective effects of cortisol may increase the risk for the development of immune-related disorders (38).

Taken together, we conclude that severe stress early in life is related to greater sensitivity of the HPA axis to stress in adulthood, which underlies greater vulnerability to major depression. Stress early in life may initially lead to sensitization of the anterior pituitary to CRF, possibly reflecting a biological vulnerability to the effects of stress. This vulnerability may result in relatively high CRF secretion whenever these women are stressed, which may eventually lead to pituitary receptor down-regulation and to depression and anxiety because of the behavioral effects of CRF at extrahypothalamic sites. Relative adrenal insufficiency may increase these women's risk for the development of immune-related disorders or pain syndromes. A lack of feedback may additionally drive central CRF release and symptoms of stress, depression, and anxiety. The seeming discrepancy between greater ACTH responses to psychosocial stress and blunted ACTH responses to CRF stimulation in abused women with major depression may reflect the involvement of corticolimbic pathways and enhanced hypothalamic releasing activity (CRF and other releasing factors), thus overriding receptor down-regulation.

Future studies should explore indices of extrahypothalamic CRF activity and other releasing factor activity, as well as mechanisms of adrenal dysfunction in adult survivors of childhood abuse. Finally, it should be determined whether this biological alteration, which may represent a risk factor for stress-related disorders, can be reversed by either pharmacological or psychological treatment in different stages of its development.

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