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Early-Life Adversity, CRF Dysregulation, and Vulnerability to Mood and Anxiety Disorders

By Charles B. Nemeroff, MD, PhD

ABSTRACT ~ A large and growing literature suggests that traumatic experiences early in life increase the risk of mood and anxiety disorders in genetically predisposed persons. Findings from laboratory animal studies as well as studies of women with histories of early-life trauma demonstrate that long-lived alterations in the corticotropin-releasing factor (CRF) system and stress responses underlie this vulnerability. Women with histories of abuse plus current depression exhibit the greatest abnormalities in the hypothalamic-pituitary response to stress and may represent a unique cohort of patients. Studies in laboratory animals also suggest that persistent changes in the CRF system may be reversed by antidepressants or surrogate parenting, which underscores the urgent need for primary and secondary prevention studies in children who are living in adverse or dangerous environments. Psychopharmacology Bulletin. 2004;38(Suppl 1): 14-20.

INTRODUCTION

Child abuse is extraordinarily prevalent. The National Center of Child Abuse and Neglect estimates that nearly 1.5 million children are mistreated each year in the United States, of which approximately half involve sexual, physical, or emotional abuse.¹ However, because most states do not mandate the reporting of cases of child abuse, current rates are believed to be gross underestimates. These data do not capture other forms of early-life adversity, such as neglect, poverty, loss of a parent, serious childhood illnesses, or premature birth requiring prolonged hospital stays and multiple invasive procedures in neonatal intensive care units.

A robust literature on the long-term sequelae of child abuse and other forms of childhood adversity offers compelling evidence that traumatic experiences early in life predispose to mood disorders and suicidal behavior.²⁻⁷ The findings of one large, cross-sectional study of 1,931 women revealed that women with a history of physical or sexual abuse during childhood had significantly higher rates of depression,

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anxiety, alcohol/substance abuse, somatization, low self-esteem, and suicide attempts than controls.⁴ In another study of over 17,000 adult members of a health maintenance organization in which the relationship between the magnitude of adverse childhood experiences and suicidality in adulthood was assessed, the presence of any single form of adversity (eg, abuse, household dysfunction, domestic violence) increased suicide risk by two- to five-fold. However, adults who experienced multiple forms of adversity as children were 31 times more likely to attempt suicide compared with controls.³

As with depression, adults with a history of childhood adversity have a greatly increased risk of anxiety disorders.⁸⁻¹² Posttraumatic stress disorder (PTSD) in adults is an anxiety disorder that is very closely associated with child abuse.^{8,12} Panic disorder may also be a common consequence of childhood adversity. In one study, adults seeking treatment at an anxiety disorders clinic were queried about their history of child abuse. Persons with panic disorder were significantly more likely than individuals with either generalized anxiety disorder or social anxiety disorder to have experienced physical or sexual abuse as children.¹⁰ The close association between panic disorder and childhood abuse was also observed in an earlier study of 250 patients in which childhood sexual abuse was endorsed by 45% of women with anxiety disorders compared with 16% of control subjects.¹¹

CRF AND THE STRESS RESPONSE

Corticotropin-releasing factor (CRF) mediates behavioral, autonomic, endocrine, and immune function and is a pivotal component of the physiological stress response. It is widely distributed in the central nervous system, including the hypothalamus, amygdala, neocortex, and brain stem. There is considerable evidence that CRF is also involved in mediating behavioral and cognitive responses to stress.¹³

In preclinical models of anxiety, intraventricular administration of CRF results in anxious behaviors, such as fear conditioning and an increased startle response.¹⁴⁻¹⁶ Laboratory animal studies have shown that CRF antagonists blunt the symptoms of anxiety and depression that follow CNS administration of CRF.^{15,17} Increased concentrations of CRF have been reported in the cerebrospinal fluid (CSF) of patients with PTSD¹⁸⁻²⁰ or depression.^{21,22} In post-mortem tissue studies, depression is associated with increased CRF immunoreactivity and CRF mRNA expression in the paraventricular nucleus.^{23,24}

EARLY-LIFE ADVERSITY, CRF DYSREGULATION, AND VULNERABILITY TO DEPRESSION/ANXIETY

Persistent changes in the CRF systems that regulate the stress response in the brains of young children who are exposed to trauma or other untoward

events have been postulated as one of the key underlying variables in the relationship between early-life adversity and later development of mood and anxiety disorders.²⁵ This hypothesis has been extensively tested in animal models and studied in women with early-life trauma.

Preclinical Studies

Early-life adversity can be elicited in rats by briefly separating neonatal pups from their mothers. In a series of studies, adult rats that were maternally deprived as neonates exhibited symptoms of depression and anxiety compared with control animals, including anhedonia (eg, reduced consumption of sweetened solutions), decreased exploratory behaviors, and increased acoustic startle responses.²⁶⁻²⁹ Abnormalities in the CRF system also have been noted. Maternally-deprived adult rats exhibited increased ACTH and corticosterone responses to psychological stressors (eg, restraint, airpuff startle); increased expression of CRF mRNA in the hypothalamus, locus ceruleus, and amygdala; decreased CRF receptor binding in the pituitary; and elevated concentrations of CRF in the median eminence, hypophysial portal blood, and CSF, compared with controls.²⁸⁻³¹ Maternal separation also is associated with long-term abnormalities in the serotonin neurotransmitter system.^{32,33}

Taken in the aggregate, an animal model of early-life adversity demonstrates that maternally-deprived adult rats exhibit HPA axis abnormalities, serotonergic neurotransmitter dysfunction, extrahypothalamic CRF neuronal hyperactivity, and symptoms resembling mood and anxiety disorders.³⁴ While these changes appear to be long-lived, administration of a selective serotonin re-uptake inhibitor (SSRI) resulted in normalization of the behavioral changes and HPA axis abnormalities associated with exposure to early-life stress.³⁵ Discontinuation of the SSRI resulted in a return to pre-treatment status. In addition, increased extrahypothalamic and hypothalamic CRF receptor mRNA expression was reversed when maternally-deprived rat pups were provided with surrogate maternal care.³⁶

Clinical Studies

A number of clinical studies have followed on the heels of the rodent maternal-separation studies, and the results show that persons who experienced severe adversity as young children have persistent neurobiological abnormalities and increased risk of mood and anxiety disorders that persist into adulthood.^{4-7,37-40} Most studies have evaluated adults with histories of severe physical or sexual abuse during childhood.

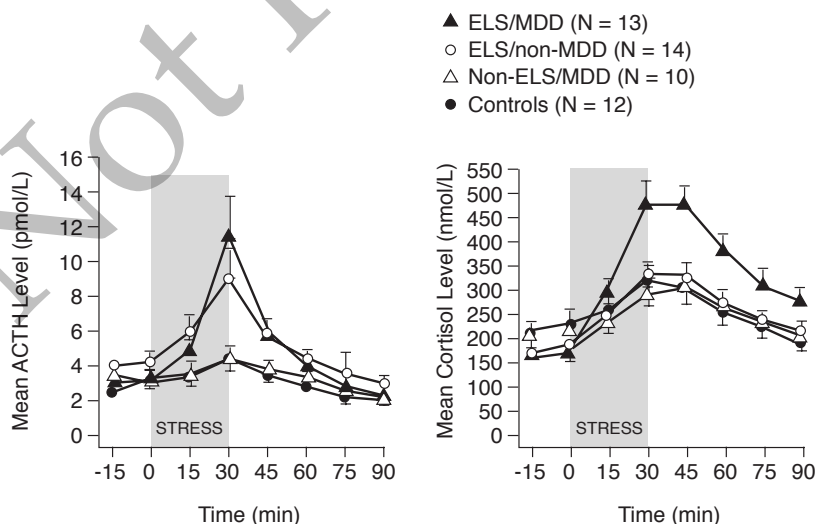
We conducted a series of studies that measured stress reactivity in women with and without current major depression, all of whom were severely sexually abused as children, and compared the results to a group

of normal, healthy volunteers. Women with histories of childhood abuse exhibited increased adrenocorticotropin hormone (ACTH) responses to a standardized social stress test compared with controls, with the most exaggerated responses occurring among women with current depression (Figure 1). Healthy controls and women with current depression but no history of abuse did not exhibit an increased ACTH response.^{37,38} Interestingly, the cortisol response was markedly elevated only in those women with both early-life trauma and current depression. Cortisol levels in depressed women without a history of abuse appeared similar to healthy controls and women with a history of childhood abuse, but without current depression (Figure 1).

In a subsequent analysis, endocrine challenge tests were administered to a similar group of women.³⁹ The women in this cohort who had depression and a history of childhood abuse were more likely to endorse current abuse and to fulfill diagnostic criteria for PTSD than were the women with childhood abuse but no depression. Depressed women, both with and without a history of childhood sexual abuse, exhibited a

FIGURE 1

ACTH AND PLASMA CORTISOL RESPONSES TO THE TRIER SOCIAL STRESS TEST IN HEALTHY WOMEN (CON), NON-DEPRESSED WOMEN WITH A HISTORY OF CHILDHOOD SEXUAL ABUSE (ELS/NON-MDD), DEPRESSED WOMEN WITH CHILDHOOD ABUSE (ELS/MDD), AND DEPRESSED WOMEN WITH NO HISTORY OF SEXUAL ABUSE (NON-ELS/MDD).



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blunted ACTH response to CRF administration, whereas non-depressed women who were abused as children had a blunted cortisol response to an ACTH1-24 stimulation test. These findings can be interpreted to mean that sensitization of the CRF neuronal circuits following childhood trauma may result in CRF hypersecretion, particularly in the context of current abuse in adulthood. Blunted ACTH responses to CRF in abused women with depression may reflect pituitary CRF receptor down-regulation due to chronic CRF hypersecretion in the face of recent life stress. Taken in the aggregate, these findings demonstrate that early-life adversity results in an aberrant stress response that persists into adulthood and likely increases the risk of mood and anxiety disorders in genetically predisposed persons.

CONCLUSIONS

Animal studies of early-life adversity have demonstrated that stressful experiences occurring during critical periods of brain development persistently and perhaps permanently change behavior and the response of the HPA axis to stress, thereby increasing vulnerability to mood and anxiety disorders later in life. The results of clinical studies of adults who were abused as children are concordant with the preclinical data. The laboratory animal study findings also suggest that the long-term changes in the CRF system may be reversed by antidepressants or surrogate parenting, which underscores the urgent need for primary and secondary prevention studies. ❀

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and the Heinz C. Prechter Fund for Manic Depression. Dr. Nemeroff has patents to methods and devices for transdermal delivery of lithium and methods to estimate serotonin and norepinephrine transporter occupancy after drug treatment using patient or animal serum.

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EARLY-LIFE ABUSE AND MOOD/ANXIETY DISORDERS

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