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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 PTSD[18-20] 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

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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, hypophysical 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

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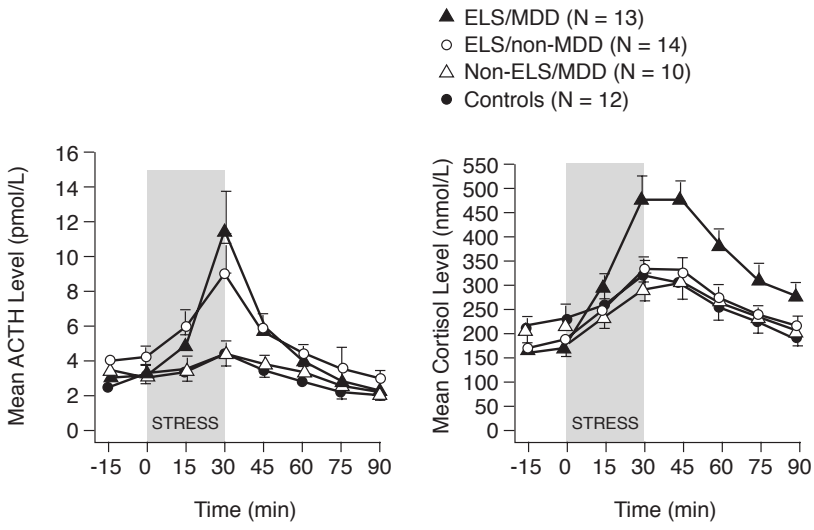
of normal, healthy volunteers. Women with histories of childhood abuse exhibited increased adrenocorticotropin hormone (ACTH) responses to a standardized social stress test compared with controls, with the most exaggerated responses occurring among women with current depression (Figure 1). Healthy controls 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.

REFERENCES

1. Sedlack AJ, Broadhurst DD. *Third National Incidence Study of Child Abuse and Neglect*. The National Clearinghouse on Child Abuse and Neglect Information. Washington, DC: September, 1996.
2. Dube SR, Felitti VJ, Dong M, Giles WH, Anda RF. The impact of adverse childhood experiences on health problems: evidence from four birth cohorts dating back to 1900. *Prev Med*. 2003;37:268-277.
3. Dube SR, Anda RF, Felitti VJ, Chapman DP, Williamson DF, Giles WH. Childhood abuse, household dysfunction, and the risk of attempted suicide throughout the life span: findings from the Adverse Childhood Experiences study. *JAMA*. 2001;286:3089-3096.
4. McCauley J, Kern DE, Kolodner K, et al. Clinical characteristics of women with a history of childhood abuse: unhealed wounds. *JAMA*. 1997;277:1362-1368.
5. Mullen PE, Martin JL, Anderson JC, Romans SE, Herbison GP. The long-term impact of the physical, emotional, and sexual abuse of children: a community study. *Child Abuse Negl*. 1996;20:7-21.
6. Young EA, Abelson JL, Curtis GC, Nesse RM. Childhood adversity and vulnerability to mood and anxiety disorders. *Depression Anx*. 1997;5:66-72.
7. Zlotnick C, Ryan CE, Miller IW, Keitner GI. Childhood abuse and recovery from major depression. *Child Abuse Negl*. 1995;19:1513-1516.
8. Bremner JD, Southwich SM, Johnson DR, Yehuda R, Charney DS. Childhood physical abuse and combat-related posttraumatic stress disorder in Vietnam veterans. *Am J Psychiatry*. 1993;150:235-239.
9. Portegijs PJM, Jeuken FMH, van der Horst FG, Kraan HF, Knottnerus JA. A troubled youth: relations with somatization, depression and anxiety in adulthood. *Fam Pract*. 1996;13:1-11.
10. Safren SA, Gershuny BS, Marzol P, Otto MW, Pollack MH. History of childhood abuse in panic disorder, social phobia, and generalized anxiety disorder. *J Nerv Ment Dis*. 2002;190:453-456.
11. Stein MB, Walker JR, Anderson G, et al. Childhood physical and sexual abuse in patients with anxiety disorders in a community sample. *Am J Psychiatry*. 1996;153:275-277.
12. Zaidi LY, Foy DW. Childhood abuse experiences and combat related PTSD. *J Trauma Stress*. 1993;7:33-42.
13. LeDoux JE. Emotion circuits in the brain. *Ann Rev Neurosci*. 2000;23:155-182.
14. Butler PD, Weiss JM, Stout JC, Nemeroff CB. Corticotropin-releasing factor produces fear-enhancing and behavioral activating effects following infusion into the locus coeruleus. *J Neurosci*. 1990;10:176-183.
15. Dunn AJ, Berridge CW. Physiological and Behavioural responses to corticotropin-releasing factor administration: is CRF a mediator of anxiety or stress responses? *Brain Res Rev*. 1990;15:71-100.
16. Weiss JM, Stout JC, Aaron M, Owens MJ, Nemeroff CB. Experimental studies of anxiety and depression: locus ceruleus and corticotropin-releasing factor. *Brain Res Bull*. 1994;35:561-572.
17. Skutella T, Montkowski A, Stohr T, et al. Corticotropin-releasing hormone (CRH) antisense oligodeoxynucleotide treatment attenuates social-defeat induced anxiety in rats. *Cell Mol Neurobiol*. 1994;14:579-588.
18. Baker DG, West SA, Nicholson WE, et al. Serial CSF corticotropin-releasing hormone levels and adrenocortical activity in combat veterans with posttraumatic stress disorder. *Am J Psychiatry*. 1999;156:585-588.
19. Bremner JD, Licinio J, Darnell A, et al. Elevated CSF corticotropin-releasing factor concentrations in posttraumatic stress disorder. *Am J Psychiatry*. 1997;154:624-629.
20. Yehuda R. Biology of posttraumatic stress disorder. *J Clin Psychiatry*. 2000;61(suppl):14-21.
21. Nemeroff CB, Widerlov E, Bissette G, et al. Elevated concentrations of CSF corticotropin-releasing factor-like immunoreactivity in depressed patients. *Science*. 1984;226:1342-1344.
22. Wong ML, Kling MA, Munson PJ, et al. Pronounced and sustained central hypernoradrenergic function in major depression with melancholic features: relation to hypercortisolism and corticotropin-releasing hormone. *Proc Natl Acad Sci USA*. 2000;97:325-330.
23. Purba JS, Raadsheer FC, Hofman MA, et al. Increased number of corticotropin-releasing hormone expressing neurons in the hypothalamic paraventricular nucleus of patients with multiple sclerosis. *Neuroendocrinol*. 1995;62:62-70.
24. Raadsheer FC, Hoogendijk WJG, Stam FC, Tilders FJH, Swaab DF. Increased numbers of corticotropin-releasing hormone expressing neurons in the hypothalamic paraventricular nucleus of depressed patients. *Neuroendocrinol*. 1994;60:436-444.
25. Nemeroff CB. The preeminent role of early untoward experience on vulnerability to major psychiatric disorders: the nature-nurture controversy revised and soon to be resolved. *Mol Psychiatry*. 1999;4:106-108.

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26. Caldji C, Francis D, Sharma S, Plotsky PM, Meaney MJ. The effects of early rearing environment on the development of GABA-A and central benzodiazepine receptor levels and novelty-induced fearfulness in the rat. *Neuropsychopharmacol*. 2000;22:219-229.
27. Finamore T, Port R. Developmental stress disrupts habituation but spares prepulse inhibition in young rats. *Physiol Behav*. 2000;69:527-530.
28. Ladd CO, Huot RL, Thrivikraman KV, Nemeroff CB, Meaney MJ, Plotsky PM. Long-term behavioral and neuroendocrine adaptations to adverse early experience. *Progr Brain Res*. 2000;122:81-103.
29. Plotsky PM, Meaney MJ. Early postnatal experience alters hypothalamic corticotropin-releasing factor (CRF) mRNA, median eminence CRF content and stress-induced release in adult rats. *Mol Brain Res*. 1993;18:195-200.
30. Engelmann M, Thrivikraman KV, Su Y, et al. Endocrine and behavioral effects of airpuff startle in rats. *Psychoneuroendocrinol*. 1996;21:391-400.
31. Huot R, Ladd CO, Plotsky PM. Maternal deprivation. In: *Encyclopedia of Stress*. New York: Academic Press; 2000:699-707.
32. Arborelius L, Plotksy PM, Nemeroff CB, Owens MJ. Increased 5-HT cell firing responsiveness to citalopram in adult rats previously subjected to maternal separation. *Soc Neurosci Abstr*. 2000;26:867-917.
33. Ladd CO, Owens MJ, Nemeroff CB. Persistant changes in corticotropin-releasing factor neuronal systems induced by maternal deprivation. *Endocrinol*. 1996;137:1212-1218.
34. Heim C, Nemeroff CB. Neurobiology of early life stress: clinical studies. *Semin Clin Neuropsychiatry*. 2002;7:147-159.
35. Huot R, Thrivikraman KV, Meaney MJ, Plotsky PM. Development of adult ethanol preference and anxiety as a consequence of neonatal maternal separation in Long Evans rats and reversal with antidepressant treatment. *Psychopharmacol*. 2001;158:366-373.
36. Newport DJ, Stowe ZN, Nemeroff CB. Parental depression: animal models of an adverse life event. *Am J Psychiatry*. 2002;159:1265-1283.
37. Heim C, Graham YP, Heit Sc, Bonsall R, Miller AH, Nemeroff CB. Increased sensitivity of the hypothalamic-pituitary-adrenal axis to psychosocial stress in adult survivors of childhood abuse. *Soc Neurosci Abst*. 1998;28:201-212.
38. Heim C, Newport DJ, Heit S, et al. Pituitary-adrenal and autonomic responses to stress in women after sexual and physical abuse in childhood. *JAMA*. 2000;284:592-597.
39. Heim C, Newport DJ, Bonsall R, Miller AH, Nemeroff CB. Altered pituitary-adrenal axis responses to provocative challenge tests in adult survivors of childhood trauma. *Am J Psychiatry*. 2001;158:575-581.
40. Kendler KS, Neale MC, Kessler RC, Heath AC, Eaves LJ. Childhood parental loss and adult psychopathology in women: a twin study perspective. *Arch Gen Psychiatry*. 1992;49:109-116.