Neurobiological Consequences of Childhood Trauma

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There is considerable evidence to suggest that adverse early-life experiences have a profound effect on the developing brain. Neurobiological changes that occur in response to untoward early-life stress can lead to lifelong psychiatric sequelae. Children who are exposed to sexual or physical abuse or the death of a parent are at higher risk for development of depressive and anxiety disorders later in life. Preclinical and clinical studies have shown that repeated early-life stress leads to alterations in central neurobiological systems, particularly in the corticotropin-releasing factor system, leading to increased responsiveness to stress. Clearly, exposure to early-life stressors leads to neurobiological changes that increase the risk of psychopathology in both children and adults. Identification of the neurobiological substrates that are affected by adverse experiences in early life should lead to the development of more effective treatments for these disorders. The preclinical and clinical studies evaluating the consequences of early-life stress are reviewed.

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Abuse, parental loss, and other traumatic experiences of childhood are unfortunately quite prevalent in our society. Estimates from the National Center of Child Abuse and Neglect have revealed that nearly 1.5 million children are confirmed to be mistreated each year in the United States,[1] although most authorities consider this an underestimation. Of these cases, approximately 700,000 involved sexual, physical, or emotional abuse. Additionally, a larger percentage of children lose one or both parents or live with a parent who is not able to provide continuous care.[2,3]

A burgeoning database indicates that stress and traumatic experiences in early life predispose individuals to the development of both mood and anxiety disorders.[4,5] Childhood adversities, such as physical and sexual abuse, parental loss, and other traumatic experiences, increase the risk for development of psychiatric disorders in later life.[5] Children who experience the loss of a parent in early life are at increased risk for unipolar and bipolar depression, as well as anxiety disorders.[6–8] Clearly, there is a relationship between genetic vulnerability and early adverse experiences that exerts long-term effects on the developing brain and leads to biological modifications, changes in behavior, and the pathogenesis of mental disorders (Figure 1). Individuals who experience stress in early life appear to develop pathologic changes that increase vulnerability to stress in later life, predisposing them to development of psychiatric disorders. It is possible that these individuals possess a preexisting genetic vulnerability that is affected by early adverse experiences, increasing the risk for development of psychiatric sequelae in response to additional stress exposure.

A number of studies have shown that onset of mood disorders is undoubtedly impacted by stressful life events that occur in childhood.[10–13] In one community-based study of approximately 2000 women of various socioeconomic levels, those with a history of childhood physical or sexual abuse had increased symptoms of depression and anxiety ($p < .001$) and were more likely to have abused drugs or attempted suicide than women without such a history.[10] Women with a history of childhood abuse have a 4-fold increased risk for development of depression as adults compared with women with no history of abuse.[11] Similarly, individuals who experienced stressful events or abuse in childhood also appear to be predisposed to anxiety disorders, such as panic disorder, posttraumatic stress disorder (PTSD), and generalized anxiety disorder.[14–17] Individuals with a history of childhood abuse are at higher risk for developing PTSD, a disorder associated with symptoms of intrusion, avoidance, and increased arousal, in response to traumatic events in adulthood.[14,17]

As noted, there is a relationship between genetic predisposition to major psychiatric disorders and the impact of early traumatic experiences during critical phases of development. One theory underlying this relationship is that persistent changes occur in specific neurobiological

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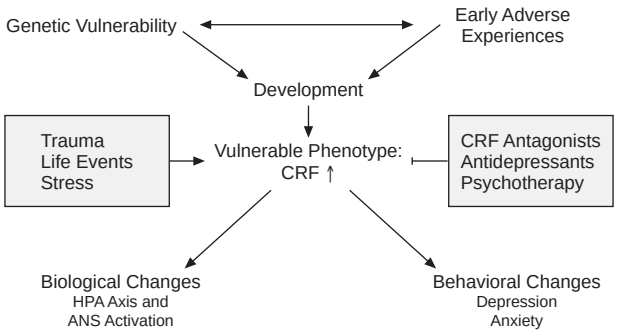
Figure 1. The Relation Between Early-Life Stress, Sensitization of Corticotropin-Releasing Factor (CRF) Neuronal Systems, and Development of Depression and Anxiety[a]



[a]Reprinted with permission from Heim and Nemeroff.[9]
Abbreviations: ANS = autonomic nervous system, HPA = hypothalamic-pituitary-adrenal. Symbol: ↑ = increase.

systems in response to early stress, which later mediate mood and anxiety symptoms. This article reviews the effects of stressful early-life events on the hypothalamic-pituitary-adrenal (HPA) axis, the corticotropin-releasing factor (CRF) system, and the subsequent development of mood and anxiety disorders in adulthood. Data derived from both preclinical animal model and clinical research are summarized to comprehensively describe the neurobiological consequences of early-life adverse events.

NEUROCIRCUITS AFFECTED BY STRESS: CORTICOTROPIN-RELEASING FACTOR

The association between childhood trauma and the development of mood and anxiety disorders may be mediated by changes in neurotransmitter systems that modulate the stress response.[18] In particular, CRF is a major mediator of the mammalian stress response and coordinates behavioral, autonomic, endocrine, and immune responses to stress. Elevated cerebrospinal fluid (CSF) CRF concentrations have been observed in combat veterans with PTSD,[19,20] and increased numbers of CRF immunoreactive neurons and CRF mRNA expression have been observed in the postmortem tissue of depressed patients.[21,22] In 1981, Vale and colleagues[23] characterized the 41-amino acid sequence of CRF, which was subsequently found to be heterogeneously distributed throughout the central nervous system (CNS).[24]

Corticotropin-releasing factor is found in high concentrations in the medial parvocellular region of the hypothalamic paraventricular nucleus, which is a fundamental component of the neuroendocrine stress-response system.[25] Following stimulation of the HPA axis, CRF is released into the hypothalamo-hypophysial portal circulation, where it stimulates adrenocorticotropin hormone (ACTH) release from the anterior pituitary. Once in the systemic circulation, ACTH stimulates the secretion of glucocorticoids from the adrenal cortex.[26] Neurons containing CRF are also found in abundance in cortical regions and may be involved in mediating behavioral and cognitive responses to stress. The central nucleus of the amygdala, which is involved in processing emotional responses, also contains a high density of CRF neurons. Thus, CRF may play a role in modulating affective stress responses.[27] Corticotropin-releasing factor neurons also have been located in the brain stem nuclei, which contain noradrenergic and serotonergic projections of the locus ceruleus and raphe nuclei, respectively. Consequently, CRF may be involved in the modulation of monoaminergic neurotransmitter systems that appear to be involved in the pathophysiology of mood and anxiety disorders, exerting both depressogenic and anxiogenic effects.

Two G protein–linked subtypes of CRF receptors, CRF_1 and CRF_2, have been described.[28,29] A high density of CRF_1 receptors is located in the anterior pituitary gland, as well as in a variety of subcortical and cortical brain regions. The CRF_2 receptors are predominantly expressed in heart, testes, and some brain regions (i.e., septum, ventromedial hypothalamus, dorsal raphe nuclei). Stress responses appear to be mediated through the CRF_1 receptor, whereas the CRF_2 receptor may diminish the stress responses, although it appears to also modulate appetitive behavior.[30]

Aside from its role as a hypothalamic hypophysiotropic hormone, there is evidence that CRF mediates immune, autonomic, and behavioral stress responses in its role as a CNS neurotransmitter (Figure 2). In laboratory animals, direct administration of CRF into the CNS leads to activation of the autonomic nervous system, elevation of peripheral catecholamines, modification of gastrointestinal activity, and increased heart rate and blood pressure. Behavioral alterations are also observed following CNS CRF administration, including diminished food intake, disturbed sleep patterns, facilitation of fear conditioning, and decreased reproductive behavior—behaviors that resemble depressive symptomatology.[24,31]

In humans, CSF CRF concentrations are elevated in depressed patients compared with controls.[32,33] Interestingly, direct CNS administration of CRF in nonhuman primates produced depressive symptoms, such as inactivity and huddling behavior.[34] In laboratory experiments, administration of CRF also leads to anxious behaviors in rats, such as fear conditioning and an enhanced startle response.[31] Agents that antagonize the effects of CRF can attenuate the anxiety and depressive symptoms mediated by CNS administration of CRF.[31,35] Antagonists of the CRF_1 receptor are being evaluated for drug development as novel anxiolytics or antidepressants.[36–39]

Increasing evidence suggests that endogenous CRF also mediates anxiety and may have a role in encoding

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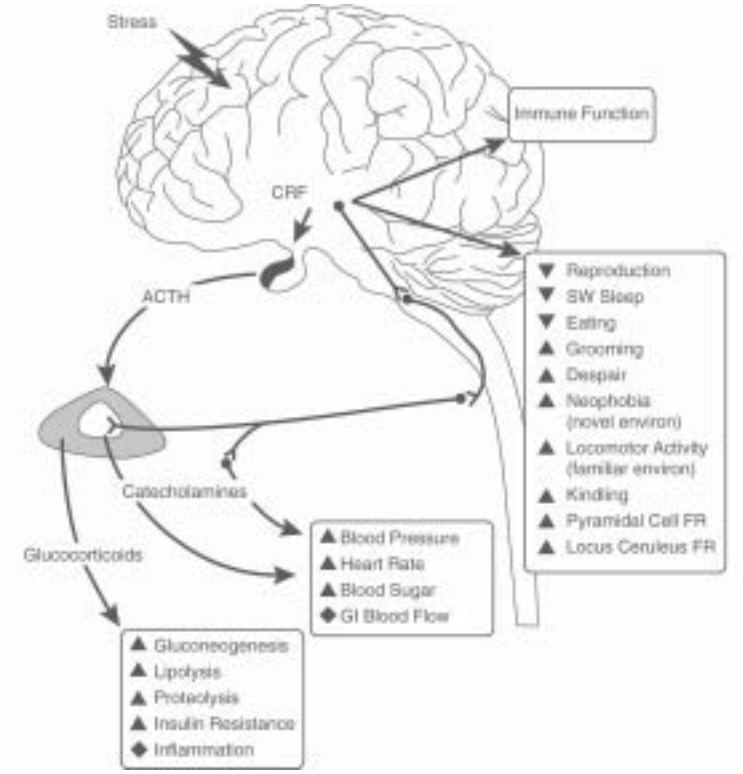
Figure 2. Effects of Central Corticotropin-Releasing Factor (CRF)[a]



[a]Reprinted with permission from Heim and Nemeroff.[9]
Abbreviations: ACTH = adrenocorticotropin hormone, FR = firing rate, GI = gastrointestinal, SW = slow-wave.
Symbols: ▼ = decrease, ▲ = increase, ◆ = bidirectional changes.

emotional memories.[30,40] In the presence of stress, CRF concentrations rise in the locus ceruleus and appear to augment tyrosine hydroxylase activity.[41,42] Patients with PTSD also exhibit increased central CRF activity.[43] Injection of CRF into the locus ceruleus induces anxious behaviors in a variety of animal models.[44,45] The anxiogenic effects of CRF may be attenuated by benzodiazepines or CRF_1-receptor antagonists,[46,47] and these effects are associated with a decrease in CRF concentrations in the locus ceruleus.

In summary, CRF is a key mediator of the stress response of mammals. Dysregulation of the CRF system may explain the symptomatology of increased vigilance and enhanced startle observed in patients with anxiety disorders, such as PTSD, and may in part explain the high incidence of comorbid mood and anxiety disorders.

PRECLINICAL FINDINGS IN EARLY-LIFE STRESS

Because of the limitations associated with conducting experiments in human subjects, animal models are invaluable in understanding the pathologic consequences of severe childhood adversity. A multitude of preclinical studies have demonstrated that early-life stressful experiences, such as maternal deprivation, affect both acute and long-term development of neuroendocrine, cognitive, and behavioral systems.[26] Early stress appears to produce persistent changes in CRF-containing neural circuits, increasing the risk for development of depression or anxiety disorders in adulthood.

Rodent Models

Much of neural development in the rat brain, including synaptogenesis and HPA axis development, occurs in the postnatal period.[48] During this stage, the neonatal rat is solely dependent on maternal care for survival. In the wild, maternal separation is common for brief periods (from 15 to 30 minutes) because rodent mothers forage for food.[49] In rats, early-life stress can be provoked by prolonged maternal separation (e.g., briefly removing pups from their mothers during the neonatal period), thereby eliciting behavioral changes resembling depression and anxiety.[50] Prolonged maternal separation is highly stressful for rat pups and leads to increased vulnerability to stress in adulthood.[51] As adults, maternally separated rats exhibit behavioral abnormalities, such as anhedonia,

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which is defined as reduced consumption of sweetened fluids and changes in feeding behavior. These animals also demonstrate numerous anxious behaviors, including increased startle response (P. M. Plotsky, Ph.D., unpublished data).

A number of models have been developed to study the effects of maternal separation in rodents, including removing the pups for 3 to 24 hours between postnatal days 1 and 21.[48] Depending on the study, pups may be completely isolated or kept together as a litter during the period of separation. In some of these studies, on postnatal day 2, pups are randomized to different rearing conditions from postnatal days 2 through 14. In the animal-facility rearing (AFR) group, pups are briefly handled twice weekly beginning on postnatal day 5 with no other handling or separation. In the second group, pups are removed from their home cage for 15 minutes each day (i.e., 15 minutes of maternal separation) (handled and maternally separated [HMS] 15). In the final group, pups are removed from their cage for 180 minutes each day (HMS 180). After the specified period of separation, litters are returned to their dams in the home cage.[26]

At adulthood (postnatal day > 60), maternally deprived rats exhibited differences in HPA axis response to stressors when compared with AFR rats. In these studies, the HMS 180 rats exhibited more anxious behaviors than AFR or HMS 15 animals.[52–54] Rats in the HMS 180 group also developed several behavioral abnormalities, such as reduced consumption of sweetened solutions, decreased exploratory behaviors, and increased acoustic startle responses,[53,55] which are associated with increased indices of CRF neurotransmission. Of interest, the AFR and HMS 15 rats appeared to be less stressed compared with nonhandled animals,[54] suggesting that brief handling in early life may decrease the stress response in adulthood, whereas prolonged separation increases stress responses in adulthood.

Maternally deprived rats (HMS 180) exhibit a number of alterations of the CRF system as adults. When stress hormones were measured, HMS 180 rats exhibited enhanced ACTH and corticosterone responses to psychological stressors (e.g., airpuff startle, novel environment, restraint),[56] although this effect was not noted in response to physical stress (e.g., controlled hemorrhage, temperature extremes).[53] These animals also exhibited increased CRF mRNA expression in the hypothalamus, decreased pituitary CRF receptor binding, and increased CRF concentrations in the median eminence, portal blood, and CSF compared with rats reared under normal conditions.[51,53] Increased CRF_1 receptor mRNA expression in the paraventricular nucleus of the hypothalamus and the locus ceruleus was also observed in these animals (P. M. Plotsky, Ph.D., unpublished data). These findings suggest that maternal deprivation resulted in both hypersecretion of CRF and an increase in CRF signal transduction. In addition to changes in the HPA axis, changes in extrahypothalamic sites occurred as a result of maternal deprivation. In the HMS 180 rats during periods of stress, CRF mRNA expression was elevated in the amygdala and in the bed nucleus of the stria terminalis,[48] pathways by which CRF most likely activates noradrenergic neurons in the locus ceruleus.[57] In support of this, Liu and colleagues[58] recently showed that maternally deprived rats exhibited greater noradrenergic responses and increased ACTH release in response to stress compared with handled animals.

Increased CRF receptor binding also has been observed in the raphe nuclei,[52] the site of origin of serotonergic projections to the forebrain. Adult HMS 180 rats also exhibited decreased firing of the raphe nuclei neurons following increasing doses of the selective serotonin reuptake inhibitor (SSRI) citalopram,[59] suggesting that long-term alterations occur in the serotonin neurotransmitter system in response to the stress of maternal separation. These findings indicate that serotonergic dysfunction in response to early-life trauma may contribute to subsequent increases in the stress response.

Taken as a whole, longer periods of maternal separation induce the development of symptoms that resemble mood and anxiety disorders. Interestingly, cross-fostering maternally separated rats or treatment with an SSRI partially or completely reversed many, if not most, of these changes.[60,61] Newport and colleagues[61] indicated that the effects of maternal separation on CRF_2 receptor mRNA expression in the hypothalamus could be reversed by providing surrogate maternal care. Huot and associates[62] reported that following 21 days of treatment with paroxetine, HMS 180 rats showed a reversal in some of the behavioral changes induced by maternal deprivation compared with AFR or HMS 15 animals. In the elevated maze test, HMS 180 rats treated with paroxetine spent significantly more time in the open arms compared with nontreated HMS 180 comparators ($p < .01$), indicative of an anxiolytic effect of the antidepressant. In the airpuff startle test used to assess HPA axis responsivity, paroxetine-treated HMS 180 rats had normalized ACTH and cortisol responses. Similar changes were not observed in the HMS 15 rats after paroxetine treatment.

Interestingly, separation of rat pups from their dams also altered maternal behavior.[63,64] Dams from which rat pups were removed for 15 minutes daily showed improved maternal caregiving as evidenced by increased licking, grooming, and nursing of their pups after the period of separation. These behaviors were correlated with decreased CRF mRNA expression in the hypothalamus and other neurobiological responses that appeared to lessen fearful response and stress in the pups.[63,64] Thus, maternal response has an obvious effect on stress response in offspring.

The concatenation of preclinical data suggests that maternal deprivation during the period of rapid CNS de-

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velopment in rodents produces profound and long-lasting neurobiological changes. The results of these studies suggest that there are specific developmental "windows" in which maternal separation leads to differential effects on the CNS.[65] Recent studies indicate that some of the neurochemical and behavioral changes induced by the stress of prolonged maternal deprivation may be reversed by providing surrogate care or treatment with SSRIs.

Nonhuman Primate Models

The neurobiological consequences of early-life stress have also been evaluated in nonhuman primate models. When a social deprivation model is utilized, monkeys that are raised with no attachment object or an inanimate surrogate develop depressive symptoms and lower CNS norepinephrine concentrations during later periods of separation.[66] In an earlier study, rhesus monkeys that were totally isolated from their mothers during a 24-hour period exhibited increased plasma cortisol concentrations when compared with monkeys who remained with their mothers or monkeys who were separated but were able to see their mothers.[67] During the first 6 months of life, rhesus monkeys that have been deprived of maternal contact during infancy demonstrate increased distress and passive behaviors when separated from their peers when compared with maternally raised primates.[68] Monkeys who are raised with peers in the absence of a mother during the first 6 months of life have increased cortisol responses to social separation and a diminished ability to handle stressful events and exhibit numerous exaggerated behaviors compared with monkeys reared by their mothers.[69,70]

In a study using magnetic resonance imaging in nonhuman primates, the volume of the posterior corpus callosum was decreased in animals that were raised in social isolation from 2 months to 1 year of age compared with those reared in a social environment.[71] This study suggested that neurobiological changes occur in the brain in response to early stress and may result in long-term maladaptive behaviors.

In another primate model, dyads of mother-infant macaques were exposed to 3 different foraging demands during a 12-week period[72]: low foraging demand, during which food was available with no effort, constantly high foraging demand, during which food was available after completion of a daily task, and variable foraging demand, during which food was variably available or not available (i.e., food supply was unpredictable). The variable foraging demand mothers had decreased perception of security, which was reflected in reduced maternal care of their offspring. Subsequently, offspring who were reared by variable foraging demand mothers were more anxious and depressed as adults and had significantly elevated CRF concentrations in the CNS compared with the other 2 groups.[72] These animals also exhibit dysfunctional responses in both noradrenergic and serotonergic systems as adults,[73] indicating that early stress resulted in long-term neurobiological consequences.

Although the data extrapolated from animal studies to patients with psychiatric disorders must be interpreted with some caution, preclinical findings suggest that there is a critical period during development when the consequences of stress lead to long-term neurobiological changes, most prominently alterations in CRF neural circuits, that increase vulnerability for development of mood and anxiety disorders in response to subsequent stressor exposure in later life.

CLINICAL FINDINGS IN EARLY-LIFE STRESS

Compared with the number of studies that have characterized the effects of early-life stress in rodents and nonhuman primates, studies evaluating the consequences of early-life trauma in human subjects are relatively limited. However, there is a burgeoning database suggesting that individuals who are exposed to traumatic experiences or stressors early in life are predisposed to mood and anxiety disorders as adults,[7,10–13,74–76] indicating that childhood trauma impacts response to stress in adulthood.

Data from the field of developmental neuroscience suggest that the developing CNS is characterized by considerable plasticity, which is influenced by personal experience.[77] This theory postulates that the CNS is more "plastic" early in development and may be more profoundly influenced by events and experiences during this period. As evidenced by the maternal-deprivation studies conducted in rodents and nonhuman primates, when young animals are deprived of maternal care during a critical postnatal period, neurobiological changes occur that lead to increased vulnerability to stress in adulthood. Although animal models are useful for comparison and parallel findings are expected, it is not known to what extent animal data can be extrapolated to humans to explain the effects of early-life stress. Most likely, the period of plasticity in brain regions differs between species. Undoubtedly, early-life stress is much more complicated in humans and would be affected by the age when the experience occurred, type of stress, environmental variations, frequency, severity of the stressor, and the nature and magnitude of resilience. Because of the multitude of factors that may influence human response to early-life stress, the importance of conducting clinical trials to study the neurobiological effects of childhood trauma is paramount. Currently, most clinical studies evaluating childhood trauma have been conducted in adults or children who have a history of physical or sexual abuse.

In several studies, children who have experienced various types of early-life trauma exhibited alterations in HPA axis activity.[78–81] However, different results have been found in these studies, indicating that the effects of early-life stress may be variable and influenced by numerous

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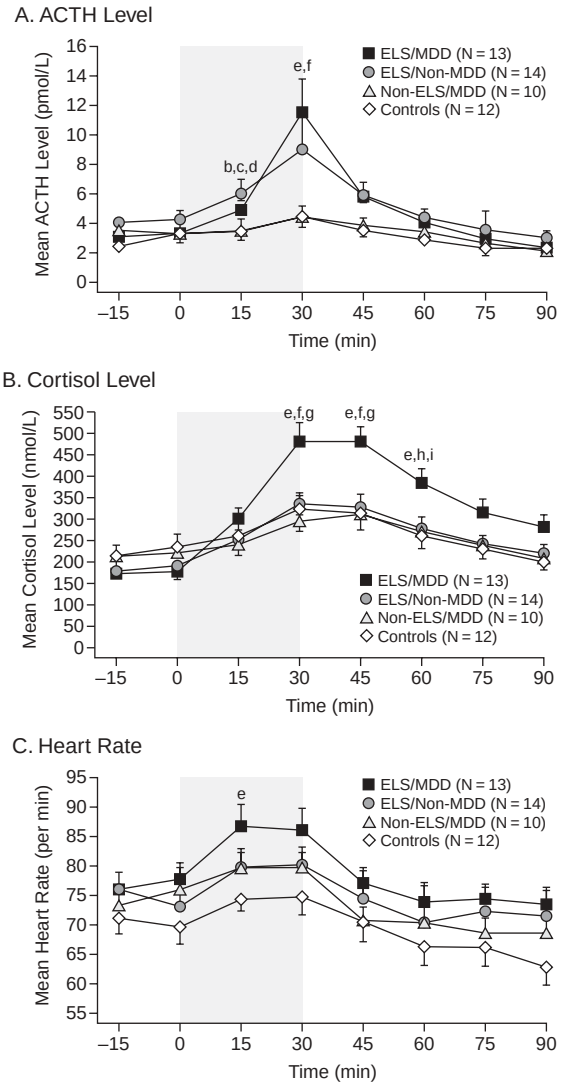
factors. A study conducted in sexually abused girls found a blunted ACTH response to CRF stimulation testing in comparison with control subjects.[82] Another study found that depressed, abused children exhibited increased ACTH and normal cortisol responses to CRF stimulation testing when compared with nonabused, depressed children or control subjects.[83] In abused children who developed PTSD, elevated urinary norepinephrine, epinephrine, and dopamine excretion has been observed, along with increased heart rate and blood pressure.[84,85] Sensitization of serotonin receptors in response to early-life stress has also been reported in abused children.[86,87]

Retrospective studies have been conducted to evaluate the long-term consequences of childhood trauma in adults. In one study, increased 24-hour urinary cortisol excretion was noted in women with PTSD who had a history of childhood sexual abuse.[88] Our first study (described in detail below) revealed that these women had increased ACTH responses to a standardized laboratory stressor when compared with healthy subjects without a history of early stress.[74,75] The largest ACTH responses were noted in the group with a history of childhood abuse who currently had depression; these women also exhibited greater cortisol levels in response to psychosocial stress. Women with current depression and a history of abuse in childhood also had higher rates of comorbid PTSD compared with women without current depression who had a history of abuse in childhood. Similarly, adults who lost a parent as children and who had a lifetime psychiatric diagnosis were found to have increased plasma cortisol concentrations.[89] Another study in adults with early parental loss showed that cortisol levels increased while giving a speech in front of a video camera, whereas levels decreased in controls.[90] These findings indicate that early-life stress is associated with long-term sensitization of stress responsiveness.

There is evidence that following early-life stress, the set-point of HPA activity in response to stress is permanently altered so that subsequent responses to stressful situations are affected. Our group evaluated women with or without depression who had a history of physical or sexual abuse in childhood to determine whether early-life stress affected pituitary-adrenal and autonomic responses to mild stress in adulthood.[75] In a prospective controlled study, 49 women were recruited into 4 study groups: those with no history of childhood abuse or psychiatric disorders (controls; N = 12), those with diagnosis of current major depression who were abused as children (N = 13), those without current major depression who were abused as children (N = 14), and those with a diagnosis of current major depression and no history of childhood abuse (N = 10). The women were subjected to mild psychosocial stress (public speaking and mental arithmetic test in front of an audience), and ACTH and cortisol levels were measured. Increased plasma ACTH and cortisol responses were noted in the women with childhood abuse history but not in controls or depressed women without a history of abuse (Figure 3). In response to stress, the women who were currently depressed and had a history of childhood abuse demonstrated a 6-fold greater ACTH response compared with controls ($p < .001$). The largest increase in heart rate in response to stress was observed in the women who were depressed and had a history of early-life abuse.

Figure 3. Pituitary-Adrenal and Autonomic Reactivity to a Standardized Laboratory Stressor in Women After Childhood Sexual or Physical Abuse[a]



[a]Reprinted with permission from Heim et al.[75] Bars indicate standard error of the mean.
[b]Controls vs. ELS/non-MDD, $p < .05$.
[c]Controls vs. ELS/MDD, $p < .05$.
[d]ELS/non-MDD, $p < .05$.
[e]ELS/non-MDD vs. ELS/MDD, $p < .05$.
[f]ELS/MDD vs. non-ELS/MDD, $p < .05$.
[g]Controls vs. ELS/MDD, $p < .01$.
[h]ELS/MDD vs. non-ELS/MDD, $p < .01$.
[i]ELS/non-MDD vs. ELS/MDD, $p < .01$.
Abbreviations: ACTH = adrenocorticotropin hormone, ELS = early-life stress, MDD = major depressive disorder.

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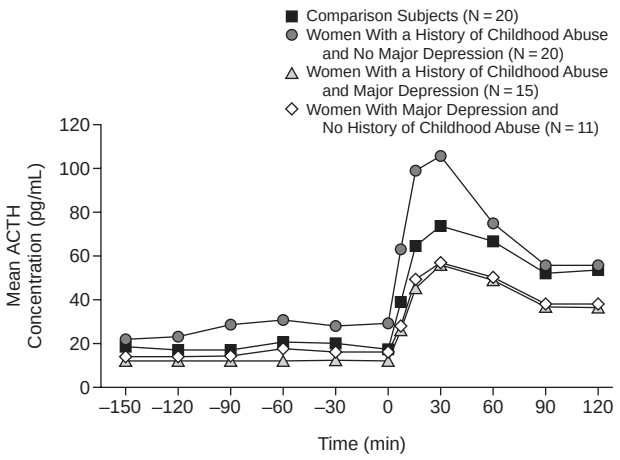
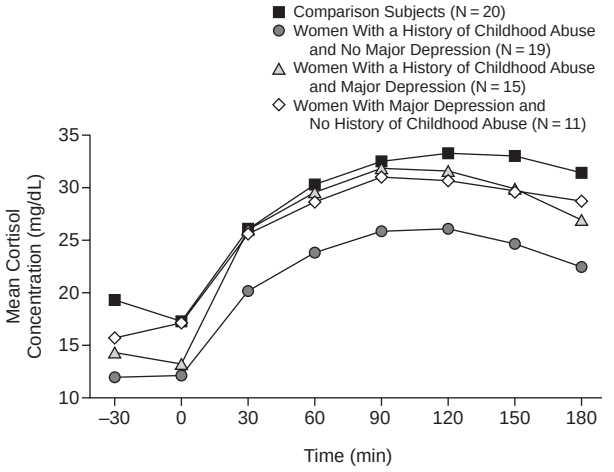
Figure 4. Plasma Adrenocorticotropin Hormone (ACTH) Concentrations During Corticotropin-Releasing Factor Stimulation in Healthy Comparison Subjects, Women With a History of Childhood Abuse With and Without Major Depression, and Women With Major Depression but No History of Early-Life Stress[a]



[a]Reprinted with permission from Heim et al.[76] Baseline: –150 to 0 minutes, response: 5 to 20 minutes.

Figure 5. 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]Reprinted with permission from Heim et al.[76] Baseline: –30 to 0 minutes, response: 30 to 180 minutes.
Abbreviation: ACTH = adrenocorticotropin hormone.

Notably, 85% of depressed women with a history of early-life trauma met the criteria for PTSD compared with 36% of women with early-life trauma who were not depressed. This study suggests that early-life stress is related to persistent sensitization of pituitary-adrenal and autonomic stress response, most likely caused by CRF hypersecretion, and may increase risk for psychopathology during adulthood. In some individuals, the manifestation of depression or anxiety disorders may depend on additive factors, such as more recent life stress.

In another analysis, standard provocative HPA axis tests were administered in healthy women without early-life stress (N = 20), women with a history of childhood abuse without major depressive disorder (N = 20), women with a history of childhood abuse and major depressive disorder (N = 15), and women with major depression but no early-life stress (N = 11) to evaluate pituitary-adrenal axis response.[76] Depressed women who were abused as children and depressed women who did not experience early-life stress both demonstrated a blunted ACTH response to exogenous CRF administration (1 μg/kg); in contrast, abused women who were not depressed had increased ACTH responses to CRF administration (Figure 4). In response to the $ACTH_{1-24}$ stimulation test, abused women who were not depressed had lower plasma cortisol levels at baseline and after administration of 250 μg of ACTH (Figure 5). Notably, depressed women who had a history of abuse were more likely to report recent life stress and to suffer from PTSD than abused women who were not depressed. This study showed that sensitization of the CRF neuronal circuits in response to childhood trauma may result in CRF hypersecretion when other stressful situations occur. Blunted ACTH responses to CRF in abused women with depression may reflect pituitary CRF receptor down-regulation as a result of chronic CRF hypersecretion in the face of recent life stress. There appears to be a counterregulatory adaptation of the adrenal cortex to central hyperactivity in abused women without depression.

Recent advances in neuroimaging techniques have allowed the measurement of CNS structural changes, integrating psychological and neurobiological processes. Hippocampal atrophy has been observed in women who developed PTSD following sexual or physical abuse and had a history of childhood trauma.[91–93] Hippocampal volume is also reduced in patients with depression.[94] Some researchers believe that reductions in hippocampal volume may be the long-term effect of increased glucocorticoid exposure.[95] Other neuroimaging studies have noted alterations in the prefrontal cortex in patients with depression or PTSD and structural changes in the amygdala in depressed individuals.[94,96] Recent data suggest that CRF hypersecretion itself may be one causative factor in these structural alterations.[97] In our analysis of hippocampal size in the 4 groups of subjects described above, only the depressed women with early-life trauma exhibited a reduction in hippocampal size,[98] suggesting that the changes in hippocampal size reported in depression previously might solely be the result of early-life trauma.

Collectively, these findings suggest that sensitization of the stress hormone system in response to early-life stress

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renders an individual vulnerable to subsequent development of depressive and anxiety disorders. As evidenced by clinical trials, early adverse experiences mediate both acute and long-term biological changes, including persistent sensitization of CRF neurocircuits. Studies are evaluating whether pharmacologic therapy can reverse or even prevent the damage caused by early-life stress in children and adults. Numerous trials have shown that the SSRIs are effective in the treatment of several psychiatric disorders, including PTSD and depression, that are manifested in individuals with a history of childhood trauma.[99–101] In light of these promising findings, additional studies of the SSRIs are needed to substantiate the benefit of these agents in the prevention or reversal of psychiatric disorders in patients exposed to early-life stressors. Other agents, such as the serotonin/norepinephrine inhibitors or benzodiazepines, may also be beneficial.[102,103] Although none of the CRF_1-receptor antagonists have been approved for clinical use to date, these agents, as well as novel antidepressants and anxiolytics, will most likely be useful in the future as potential preventive therapy for individuals exposed to early-life stress. Finally, intriguing data showing that cross-fostering of rodent pups and environmental enrichment may reverse some of the neurobiological consequences of early-life stress indicate that similar results may be achieved in human children.[60,104,105]

SUMMARY

Unfortunately, a large number of children are exposed to early adverse experiences that increase their risk for development of psychiatric disorders. Based on preclinical and retrospective studies, it is clear that a strong relationship exists between childhood adversities and the subsequent development in adulthood of major psychiatric disorders, particularly depressive and anxiety disorders. Neuroendocrine studies have shown that early stress appears to induce long-term changes in various neurotransmitter systems, and CRF activity is increased in patients who have depressive or anxiety disorders. Preclinical analysis of rodent and nonhuman primates also indicates that stressful events during a critical period in development may lead to persistently increased CRF activity and sensitization of the HPA axis in response to stress. Similar findings in adult survivors of childhood abuse further support this hypothesis and indicate that individuals exposed to childhood trauma are increasingly vulnerable even in response to mildly stressful events in adulthood, which increases their risk for development of mood and anxiety disorders. Recent studies suggest that stress vulnerability may be reversed with the use of antidepressants. Additional studies are needed to further elucidate the impact of childhood trauma, the pathogenesis of the stress response, and potential for treatments to prevent or minimize the impact of anxiety and depressive disorders in these individuals. Furthermore, clinicians should take into account the role of early adverse experiences when diagnosing and treating adults with psychiatric disorders, because childhood trauma clearly exerts long-lasting effects.

Drug names: citalopram (Celexa), paroxetine (Paxil).

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Questions and Answers

Question: Are you suggesting that in the future, when outcome studies are being conducted, it is important to routinely ask about early trauma? Is this something that should be standardized in the methodology of study protocols?

Dr. Nemeroff: Unfortunately, in the early studies that we conducted, we did not collect any data on early trauma, so now we can't even determine whether early trauma was a confound in the outcomes of those studies. Clearly, this information would be important to obtain in future studies because early traumatic experiences appear to exert long-lasting effects.

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Question: What would happen if you just eliminated the maternal response to rat pups without using the separation model? Could the dams be made nonresponsive and still remain with the pups?

Dr. Nemeroff: In the past, dams have been anesthetized so that they become unresponsive to the pups, but remain in the cage. However, the problem is that the anesthetic agent passes to the pups in the breast milk, so it is difficult to rule out any pharmacologic effects of the anesthetic.

Question: After pups are subjected to the 14-day period of separation, can you intervene to prevent the development of symptoms? For example, if you intervene within 1 week or 1 month, can you prevent symptomatology?

Dr. Nemeroff: I don't fully know the answer to this question because in most of our studies, we have allowed the pups to mature after the separation period. Our studies have also shown that treatment with paroxetine, reboxetine, or mirtazapine can reverse many of the long-term consequences of early trauma in these animals and appears to normalize corticotropin-releasing factor mRNA expression [*P. M. Plotsky, Ph.D.; C.B.N., unpublished data*]. The whole idea of intervening early in life is intriguing and worthy of further study. ❑

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