The Neurobiology of Depression: Inroads to Treatment and New Drug Discovery

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The underlying causes of most mood and anxiety disorders remain unknown. There is a strong heritable component to psychiatric illnesses that, when coupled with environmental influences, results in increased vulnerability. Intensive research efforts have been expended to better characterize the genetic underpinnings of mental illness. However, most psychiatric disorders, including mood and anxiety disorders, are polygenetic in nature rather than determined by traditional autosomal-dominant Mendelian genetics. Recent technological advances, including the completion of the human genome inventory, chromosome mapping, high throughput DNA sequencing, and others, offer the promise of someday identifying the genetic basis of mental illnesses. In parallel, tremendous inroads have been made into understanding the neurobiological basis of mood and anxiety disorders and the influence of life events on risk and resilience. Evidence from preclinical, epidemiologic, and clinical studies has converged to convincingly demonstrate that stressful or traumatic events occurring in early life significantly increase the risk for depression and other psychiatric illnesses in adulthood. Neural circuits containing corticotropin-releasing factor (CRF) have been identified as an important mediator of the stress response. Early-life adversity, such as physical or sexual abuse during childhood, results in long-lasting changes in the CRF-mediated stress response and a greatly increased risk of depression in genetically predisposed persons. Identification and cloning of CRF receptors and characterization of their role in the stress response have enabled a better understanding of maladaptive responses to early-life adversity. In addition, studies of the CRF system have suggested molecular targets for new drug development, biological risk factors, and predictors of treatment response.

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Despite intensive and multidisciplinary research efforts over the past 4 decades, the causes of mood and anxiety disorders continue to be obscure. Depression is believed to occur as a result of environmental influences in genetically predisposed persons. Although depression is clearly transmitted in families, specific genetic loci associated with syndromal disorders have yet to be determined. Epidemiologic and clinical studies have repeatedly uncovered a relationship between depression and adverse life events in childhood. The burgeoning field of clinical neuroscience has identified many different neuroanatomical, endocrine, and neurochemical abnormalities that occur in depression and are also associated with initiation and regulation of the stress response. These divergent findings offer a compelling argument that the interaction between a permissive genetic diathesis and early-life adversity may represent the underpinnings of risk for depression.

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GENETICS AND DEPRESSION VULNERABILITY

Heritability is a variable in affective disorders in approximately 40% of cases,[1] and a family history of affective disorder is among the strongest predictors of vulnerability to depression.[2] Though current and past life experiences clearly contribute to the development of depression in genetically predisposed individuals, it is not yet fully understood how environmental factors influence genetic tendency.[3] Major achievements in the field of genetics, most notably completion of the human genome inventory, promise to significantly advance the understanding of depression and other heritable mental illnesses. However, technological advances in genomics have outpaced our appreciation of the etiology of psychiatric illnesses. The human genome project offers the benefits of rapid identification of genetic polymorphisms, accelerated analysis and comparison of human genes, and the capacity to express and manipulate genes in animal

models of clinical disease. Other new genetic tools, such as chromosome mapping, high throughput DNA sequencing, whole genome microarray scanning, and others, promise to provide a great deal of additional information.[4–7]

The underlying biology of depression and other complex psychiatric disorders is not influenced by traditional autosomal-dominant Mendelian genetics. Rather, polygenetic heritability (i.e., multiple genes), epigenetic factors, such as early-life experiences, and other factors most likely converge to result in expression of the phenotype.[3,4] Thus, at least in the immediate future, the human genome project is not expected to produce significant inroads with regard to the identification of a "depression" gene. A better understanding of depression etiology, risk and resilience, and treatment response will be achieved through studies of the underlying neurobiology of the illness.

Indeed, significant discoveries have contributed to progress toward understanding the neurobiology of mood disorders. One such important finding was the discovery of a polymorphism in the serotonin (5-HT) transporter (SERT) allele that may represent a form of genetic vulnerability to mood and anxiety disorders.[8] The short form variant of the SERT results in a reduction in 5-HT expression and uptake,[9] which has been confirmed in brain imaging studies.[10] Persons with the short form of the SERT allele have been observed to exhibit greater novelty seeking and harm avoidance behaviors.[11] The short form of the SERT has also been associated with neuroticism in personality disorder[12,13] and depression in Parkinson's disease,[14] but not with bipolar disorder[15] or panic disorder.[16] Of particular relevance to this review are the recent landmark findings that the short form of the SERT confers considerably greater vulnerability to depression in children, young adolescents,[17] and young adults[18] who are exposed to adverse events, such as sexual or physical abuse, in early life. Additional studies of this putative vulnerability factor may someday enable diagnosis of mood disorders, determination of suicide risk, and prediction of treatment response.

THE CORTICOTROPIN-RELEASING FACTOR SYSTEM AND EARLY-LIFE ADVERSITY

A large body of preclinical and clinical evidence confirms that there is a relationship between genetic vulnerability to mood and anxiety disorders and adverse life events that occur during critical phases of brain development. One rational and increasingly accepted explanation for this relationship is that stressful or traumatic experiences occurring in childhood result in persistent changes in hypothalamic neuroendocrine circuits and extra-hypothalamic pathways, which subsequently increase the vulnerability to mood and anxiety disorders later in life. Evidence points to the hypothalamic-pituitary-adrenal (HPA) axis and the corticotropin-releasing factor (CRF) system as important mediators of the acute and long-term response to stress and later development of psychiatric illness.

History of CRF and the Stress Response

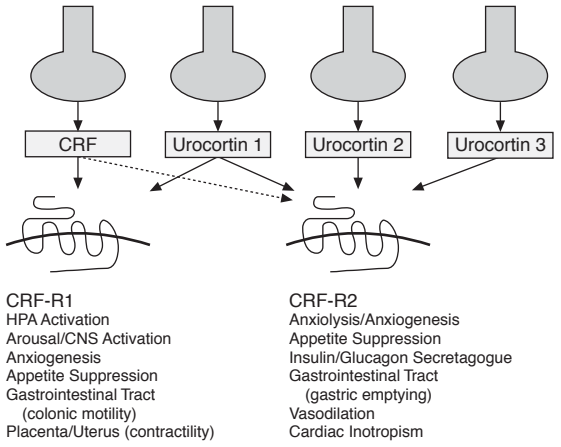
Corticotropin-releasing factor is a 41-amino acid peptide that stimulates adenohypophysial production and release of adrenocorticotropic hormone (ACTH) and is the principal mediator in the activation of the HPA axis response to stress. Following a physical or psychological threat, CRF is released from nerve terminals in the parvicellular portion of the paraventricular nucleus of the hypothalamus and transported humorally to the hypothalamus-hypophysial portal vessels to activate CRF receptors on the anterior pituitary, resulting in release of ACTH into the general circulation. In response to systemic ACTH, the adrenal glands increase synthesis and release of cortisol, which feeds back to the hypothalamus, hippocampus, and anterior pituitary to inhibit ACTH release and to suppress further release of CRF.[19,20]

Corticotropin-releasing factor was isolated from ovine hypothalamic fragments and characterized in 1981.[21] Intensive research efforts have since focused on exploring the anatomical, physiologic, and pathophysiologic roles of this peptide in the central nervous system (CNS). In the brain, CRF-containing neurons and CRF receptors are found in the hypothalamus, amygdala, cerebral cortex, septum, bed nucleus of the stria terminalis, cerebellum, brain stem nuclei, and spinal cord. Much progress has been made in identifying the neuroendocrine, behavioral, and autonomic effects of CRF and understanding its role in a wide variety of illnesses, including mood and anxiety disorders.[22]

Since the isolation of CRF over 20 years ago, a number of related ligands and receptors have been identified (Figure 1). Ligands that are included in the CRF family include urocortin 1, urocortin 2, and urocortin 3 (i.e., stresscopin), all of which play roles in the stress response and in regulating other functions. Corticotropin-releasing factor and its family of ligands exert their effects by binding to G protein-coupled, membrane-bound receptors, which signal through the cyclic adenosine monophosphate, mitogen-activated protein kinase, and additional pathways. Target tissues for the CRF family of ligands extend beyond the brain to the gastrointestinal, cardiovascular, reproductive, endocrine, and immune systems. Subsequent technological advances enabled a CRF receptor to be cloned initially from a human Cushing corticotropic cell tumor in 1993.[23] To date, 2 CRF receptors, CRF-R1 and CRF-R2, have been identified and cloned from mammalian DNA. The CRF receptors are members of the class B, 7-transmembrane domain receptor family that includes receptors for calcitonin, vasoactive intestinal peptide, secretin, and growth hormone-releasing factor.[22,24]

Although the CRF receptors are chemically similar and are approximately 70% identical, their ligand binding

Figure 1. Ligands and Receptors of the Corticotropin-Releasing Factor (CRF) Signaling Network and Their Putative Roles



Abbreviation: HPA = hypothalamic-pituitary-adrenal.

properties and anatomical distribution differ considerably.[22,24] Corticotropin-releasing factor has high affinity for CRF-R1, but is less tightly bound to CRF-R2. In contrast, urocortin binds tightly to both CRF-R1 and CRF-R2.[25] Relatively recently, urocortin 2 and urocortin 3 were identified in the human and rodent genomes and shown to be highly selective ligands for the CRF-R2 receptor,[26–28] with urocortin 2 displaying a higher affinity for the receptor than urocortin 3.[27] However, both peptides are quite selective and are active in a variety of biological models. Thus, urocortin and, to a lesser degree, CRF are nonselective ligands for the CRF receptors, and urocortins 2 and 3 bind exclusively to the CRF-R2 receptor. The CRF-R1 receptor is widely distributed in the CNS and less so in peripheral tissues. Expression of CRF-R2 also occurs in the CNS, but this receptor is largely distributed throughout the periphery in the cardiovascular system, gastrointestinal tract, and skeletal muscle.[24]

The behavioral effects associated with stimulation or antagonism of the CRF receptor subtypes are not fully understood. Available evidence suggests that CRF-R1 is anxiogenic and primarily involved in the initiation of the stress response. In contrast, the interaction of urocortin 3 with CRF-R2 has been associated with anxiolytic behavior in murine models of anxiety.[29] This and other ligands working through CRF-R2 may therefore be responsible for dampening the stress response.[22] However, several studies involving delivery of agonists of CRF-R2 to specific brain regions have revealed anxiogenic effects of CRF-R2 stimulation as well. Adding to these findings are the observations that benzodiazepine dependence in rats dampened CRF and CRF-R1 function and increased measures of urocortin 1 and CRF-R2, effects that were reversed upon spontaneous withdrawal of the benzodiazepine.[30]

The behavioral properties associated with the CRF receptors have been investigated using several different animal models. The use of mice bred to be deficient in the gene that encodes for CRF receptors (i.e., knockout or null mice) has proved to be a useful paradigm for measuring the effects of this system. Mice that are deficient in CRF-R1 demonstrate an impaired hormonal stress response and blunted anxiety-like behaviors.[31,32] In contrast, CRF-R2–deficient mice exhibit exaggerated anxiety behaviors (Figure 2) and are hypersensitive to stress compared with control animals.[19,33] These findings suggest that CRF-R1 is the principal CRF receptor in the stress response and that CRF-R2 may play a role in modulating the effect of CRF-R1.[34]

Risk Factors for Depression

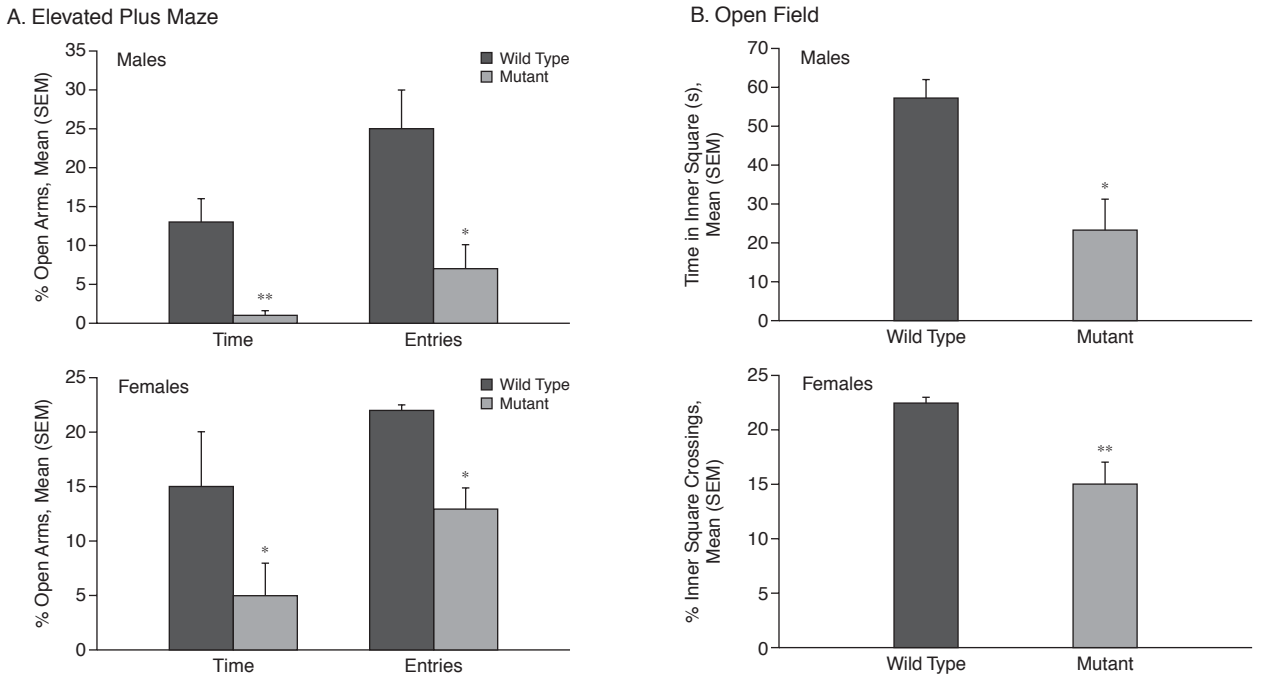
As the behavioral and neuroendocrine effects of CRF and the role of its receptors in regulating the HPA axis became apparent, research efforts focused on examining the relationship between dysregulation of the stress response and psychiatric illness. Vulnerability to mood or anxiety disorders in genetically predisposed individuals is believed to be related to heightened stress sensitivity. Dysregulation of stress-coping mechanisms appears to involve regulatory mechanisms of the CRF system and the HPA axis.[22] Clinical and laboratory evidence shows that affective disorders are associated with hyperactivity of the HPA axis and the stress hormone system. Indeed, the relationship between major depressive disorder and alterations in the CRF system has been recognized for more than 2 decades. Depression is associated with increased concentrations of CRF in cerebrospinal fluid (CSF), increased CRF immunoreactivity and CRF mRNA expression in the hypothalamic paraventricular nucleus, and down-regulation of CRF-R1, but not CRF-R2, receptors in the cerebral cortex.[35–38]

Early-Life Adversity and Adaptation of the CRF System

Recognition of the relationship between a hyperactive stress response and vulnerability to mood and anxiety disorders led to a search for causal events or factors. A number of different lines of research support the hypothesis that traumatic events during childhood permanently alter the stress response and increase the risk for psychopathology later in life. In a seminal study of twin pairs, Kendler and associates[39] identified genetic and environmental factors, including early parental loss, lack of perceived parental warmth, and poor social support, as key influences in childhood that predispose to the development of major depression in adults. Later epidemiologic studies have built on Kendler's findings by showing that physical or sexual abuse during childhood is associated with a significantly increased risk of depression, suicide, anxiety disorders, and alcohol/drug abuse in adulthood.[40–43]

The possibility that lasting changes in the CRF system underlie psychopathology in persons who had suffered early-life adversity has been the impetus for a broad re-

Figure 2. Anxiety-Like Behaviors of CRF-R2–Null Mice and Wild-Type Controls as Measured in the Elevated Plus Maze and Open-Field Tests[a]



[a]Adapted with permission from Bale et al.[19]
*p < .05.
**p < .01.

search effort. Rodent and nonhuman primate models[44] and clinical studies[45,46] have tested the hypothesis that a chronic increase in CRF availability and persistent change in CRF-containing neural circuitry results in the neuroendocrine consequences (e.g., pituitary and adrenal hyperactivity) and extra-hypothalamic alterations that contribute to the phenomenology of depressive and anxiety disorders.

Preclinical studies. Animal models have been used to reproduce the effects of early adverse life events in humans during the neonatal period on behavior and on the HPA axis response. In one neonatal rat model, prolonged maternal deprivation elicited behavioral changes that resembled depression (e.g., decreased preference for sucrose) and anxiety (e.g., exaggerated startle response).[47] Another model consists of removal of neonatal rat pups from their dams for random 3-hour intervals over the course of approximately 2 weeks after which the pups are returned to the home cage.[44] When tested at postnatal day 60 or later, the adult animals are examined for neuroendocrine, neurobiological, and behavioral changes caused by the early stress of maternal separation.[44]

Maternal separation of rodents early in life, which is often viewed as a model of human parental neglect, is associated with a myriad of neurobiological sequelae in the rat. In the model studied by Plotsky and associates,[48] the air puff startle test elicited a markedly exaggerated stress response in adult rats that were maternally separated during the neonatal period as measured by 10-fold increases in plasma ACTH and corticosterone concentrations compared with control animals. Maternal deprivation in these animals also resulted in increased CRF mRNA expression and CRF concentrations in the hypothalamus, locus ceruleus, and amygdala; decreased CRF receptor binding in the pituitary; and increased CRF concentrations in the median eminence, portal blood, and CSF compared with controls.[48–50] There is a narrow window of time in the rat during which maternal deprivation produces these persistent neuroendocrine and neurobiological effects. Maternal deprivation in rats 10 to 15 days or older does not result in an increased stress response in adulthood (P. M. Plotsky, Ph.D., C.B.N., unpublished observations, 2003). As noted below, these preclinical data are congruent with clinical findings which show that prepubertal, but not postpubertal, abuse is associated with the same persistent HPA axis hyperactivity in women.

The CRF system is not the only CNS circuit that is altered by early maternal deprivation. Other neurobiological effects that have been observed in adult rats separated from their dams during the neonatal period include a reduction in 5-HT_{1B} receptor expression,[51] reduced expression of $GABA_A$ receptors,[52] and impaired dopamine trans-

porter expression.[53] Early-life maternal separation has also been shown to be associated with impaired mossy fiber development[54] and a lower rate of neurogenesis in the hippocampus of adult rats.[55]

Not surprisingly, maternal separation during early life in rodents is associated with behavioral alterations that are similar to the signs and symptoms of depression and anxiety in humans. For example, adult rats that were deprived of normal maternal care exhibited decreased consumption of sucrose and saccharine, indicative of anhedonia.[56] Maternally separated adult rats spent less time than control animals in the open arm of the elevated plus maze,[56] which is a validated measure of anxiety. In another model of anxiety, a significantly increased acoustic startle response was observed in maternally deprived adult rats (C.B.N., P. M. Plotsky, Ph.D., unpublished observations). Maternally deprived adult rats also exhibit a marked preference for ethanol[56] and cocaine,[57] suggesting that early-life adversity may be a risk factor for substance abuse and dependence later in life.

The neuroendocrine and behavioral effects of early-life stress appear to be permanent. However, interventions, such as foster care, enriched environments, and antidepressant administration, have been demonstrated to attenuate or reverse these changes. Maternal deprivation results in lasting changes in the stress response and in the neurocircuitry that mediates the fear response.[58] Such altered maternal behavior could serve as a model for a disrupted child-parent relationship.[59] Cross-fostering experiments in which the pups were removed from their nest and placed with a surrogate dam demonstrated that good foster care attenuates the adverse consequences of early maternal separation.[60] Maternally deprived rats that were housed in enriched conditions (e.g., cages linked by burrows with access to toys) during the peripubertal period demonstrated a normalization of plasma corticosterone concentrations and fearful responses to stress compared with maternally deprived animals housed in standard laboratory cages. However, enriched environmental conditions had no effect on CRF mRNA expression in the hypothalamus, which suggests the presence of a compensatory mechanism rather than permanent reversal of the neuroendocrine sequelae of early-life stress.[61]

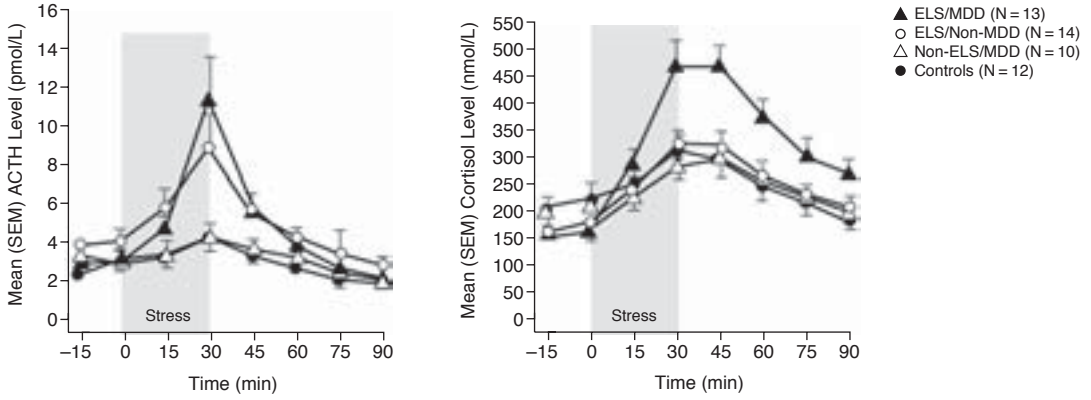
Administration of certain antidepressants also attenuates the effect of early rearing conditions on the CRF system and other biological responses. When the selective serotonin reuptake inhibitor (SSRI) paroxetine was chronically administered to adult rats maternally deprived as neonates, serum ACTH and corticosterone concentrations and CRF mRNA expression approached levels found in control animals, and anxiety-like behaviors were reversed.[56] The antidepressant also restored the animals' preference for sucrose and reversed their preference for ethanol. Of note, the salutary effects of the antidepressant on the neurobiological and behavioral changes caused by early-life maternal deprivation all returned to pretreatment baseline levels following withdrawal of the antidepressant.[56]

Clinical studies. The neurobiological changes observed in rodent models of early-life maternal separation are in many respects parallel to the findings in patients with major depressive disorder. Similarities between the animal model and depressed patients include increases in plasma and CSF concentrations of cortisol, elevated CSF CRF concentrations, increased number of CRF-expressing hypothalamic neurons, increased CRF mRNA expression, and down-regulation of CRF receptors in frontal cortex or anterior pituitary.[20] Recognition of these similarities calls into question many of the established theories about the neurobiology of depression and suggests that some of the findings in previously published studies of depression may have been confounded by the presence of undetected early-life trauma. The variability in treatment response and high placebo response rates seen in antidepressant and psychotherapy trials[62] may be associated with the fact that biologically distinct populations of depressed patients with and without early-life trauma are enrolled in clinical trials.

Many clinical studies have been conducted to identify risk factors for psychiatric illness. A large database has generated a strong association of childhood adversity and abuse with depression and suicidality in adulthood.[41–43,45,46,63,64] Most studies assessed patients with severe childhood sexual or physical abuse. The concatenation of findings of these studies demonstrates that traumatic events occurring in childhood result in persistent neurobiological changes and a markedly increased risk for mood and anxiety disorders later in life.

Nemeroff and associates[45,46,65] at Emory University (Atlanta, Ga.) have conducted a series of studies supported by the NIMH Conte Center in adult women who were sexually and/or physically abused as children. In one of these studies,[46] women underwent a psychosocial stress test (i.e., the Trier Social Stress Test) that reliably induces activation of the HPA axis and is roughly considered the human equivalent of the air puff startle test in rats. After an overnight stay in the National Institutes of Health–funded General Clinical Research Center, subjects were asked to deliver a public speech in front of 3 trained observers and to perform a difficult mental arithmetic task. Plasma ACTH and cortisol concentrations were measured at baseline, during the stress challenge, and for 1 hour thereafter. Study participants consisted of 12 healthy female controls, 14 nondepressed women with a history of childhood abuse, 13 women with childhood abuse and current major depression, and 10 women with major depression without a history of childhood abuse. Compared with healthy control subjects and the women without a history of early-life abuse, women who were abused as children exhibited significantly greater ACTH responses,

Figure 3. ACTH and Plasma Cortisol Responses to the Trier Social Stress Test in Healthy Women (Controls), Nondepressed 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)[a]



[a]Adapted with permission from Heim et al.[46]
Abbreviation: ACTH = adrenocorticotropic hormone.

and the depressed women who were abused as children exhibited a markedly exaggerated cortisol response. It was also of great interest that the endocrine stress response in women with major depression without childhood abuse was virtually identical to that of healthy controls.[46] These findings suggest that the increased HPA axis activity repeatedly reported in depressed patients may, in fact, not be due to depression per se, but rather to the persistent effects of early-life trauma (Figure 3).

In a subsequent analysis, a similar cohort of women underwent provocative HPA axis challenge tests.[45] Current, ongoing abuse and syndromal posttraumatic stress disorder (PTSD) were more common among the women with both depression and a history of childhood abuse than among women with a history of childhood abuse without depression. The ACTH response to an intravenous CRF challenge (a standardized CRF stimulation test) was blunted in depressed women with and without childhood abuse, and nondepressed women who were abused as children had a blunted cortisol response in the $ACTH_{1\text{-}24}$ stimulation test.[45] These observations are supported by the findings of a study of drug-free women with major depression and matched, healthy controls which showed that a history of early-life adverse experiences was a more powerful predictor of elevated CSF concentrations of CRF than adversity during adolescence or a diagnosis of major depression.[66]

Of considerable interest are the findings of structural neuroimaging studies that were conducted in our cohort of patients.[67] Reduction in hippocampal volume has been observed in patients with major depression[68] and in women with PTSD plus a history of childhood trauma[69,70]; this reduction may be related to chronic hypercortisolemia[71] or CRF hypersecretion.[72] In the population studied by Vythilingam and associates,[67] volumetric magnetic resonance imaging revealed smaller hippocampal volumes only in the women with both depression and childhood abuse.

Taken together, the findings of CRF circuit alterations and HPA axis responses and the results of CSF and neuroimaging studies in adult victims of childhood abuse describe a pathophysiology that is remarkably similar to rodent models of maternal separation. Sensitization or increase in number of CRF secretory cells of the CRF neuronal circuits following childhood trauma are associated with CRF hypersecretion, which may be even greater in those who are currently victims of ongoing abuse. The blunted ACTH responses to CRF in abused women with depression may reflect pituitary CRF receptor down-regulation in response to chronic CRF hypersecretion and/or a further increase in CRF activity in the face of recent life stress. More recently, Kilts and colleagues,[73] using positron emission tomography (PET) to assess regional cerebral blood flow as a measure of regional brain activity, studied a similar cohort of women. Subjects showed marked differences in their regional CNS responses to 4 visual stimuli—positive, negative, interesting, and neutral. Compared with women who were abused as children but had no history of depression, the women with depression and childhood trauma exhibited a more negative response psychologically and markedly increased brain activation in limbic and cortical regions.

Clinical Implications

With the convergence of basic and clinical research relevant to the putative role of the CRF system in the pathogenesis of depression, a multidisciplinary group of investigators has formed that has fostered a fresh look at

the interpretation of existing depression treatment studies, the design of future studies, and the approach to new drug discovery.

Differential response to depression treatments. Trauma history has rarely been assessed in depression treatment studies. In an effort to assess the relationship between early-life trauma and clinical response to treatment, a reexamination of a large dataset of patients with chronic depression was conducted. In a double-blind, randomized, 3-arm study, 681 adults with chronic, nonpsychotic depression were randomly assigned to receive a 3-month course of nefazodone, cognitive behavioral-analysis system of psychotherapy (CBASP), or the combination of nefazodone and CBASP.[74] Overall response, which was defined as either remission (Hamilton Rating Scale for Depression [HAM-D] total score ≤ 8) or satisfactory response (50% or greater reduction in baseline HAM-D score with endpoint total score < 15), was similar for both the nefazodone and CBASP groups (approximately 48%). In contrast, the mean overall response rate for the combination therapy group was 73% ($p < .001$).

A subsequent analysis stratified this population according to history of childhood trauma.[75] Of the 681 patients with chronic depression in the original cohort, more than two thirds had a history of early-life trauma (e.g., early parental loss, physical or sexual abuse, neglect) that began in most cases before the age of 10. Among those patients with early-life trauma, CBASP alone was significantly more effective than antidepressant monotherapy and only slightly less effective than the combination of psychotherapy and antidepressant, which suggests that psychotherapy should be considered for depressed patients with a history of childhood trauma. These findings have important implications for treatment strategies and for the design of clinical trials and interpretation of clinical trial data. A better understanding of the treatment response in major depressive disorder awaits the findings of randomized, controlled clinical trials that prospectively measure early-life and current trauma as part of the baseline demographic assessments and determine if there is indeed a differential clinical response in patients with and without early-life adversity.

New drug discovery. In theory, drug therapy is based on the correlation between the actions of a drug and the etiology of the disease being treated. Rational therapeutics, such as dopamine replacement therapy in Parkinson's disease or digitalis in congestive heart failure, requires insight into the biological basis of disease. The field of psychiatry, in contrast, has historically been advanced by serendipitous discoveries; most notably relevant to this discussion is the observation that the antituberculosis drug iproniazid both elevated mood and inhibited monoamine oxidase. As a result, the contemporary psychopharmacologic armamentarium consists largely of drugs that are reasonably effective in the treatment of illnesses for which the biological underpinnings are just beginning to be recognized. Indeed, some of the more revealing neurobiological findings, such as the polymorphism in the gene that encodes for the serotonin transporter, have come about through efforts to better understand antidepressant mechanisms of action.

Virtually all of the drugs in the existing psychopharmacologic armamentarium act by enhancing or inhibiting the action of neurotransmitters, the existence of which has been known for decades. Until relatively recently, new drug development in psychiatry focused primarily on altering existing compounds in an effort to increase efficacy and decrease side effects. Data demonstrating the neuroendocrine regulation of the HPA axis suggest that dampening the CRF response to stress may be of therapeutic utility in mood and anxiety disorders. The CRF receptors, particularly CRF-R1, are therefore logical targets for antidepressant and anxiolytic drug development.

Preclinical studies of CRF-R1 antagonists demonstrate positive behavioral effects with little or no compromise of HPA axis function.[76] In the first published clinical study, Zobel and colleagues[77] administered the selective CRF-R1 antagonist R121919 to 24 patients with major depression. This was an open-label, forced dose-escalation study in which patients received either low (i.e., 5–40 mg) or moderate daily doses (i.e., 40–80 mg) for 1 month. Significant and dose-related improvements in baseline depression and anxiety rating scale scores were observed, and HPA axis function was not significantly altered. However, development of R121919 is no longer being pursued because of concerns about hepatotoxicity.

Another CRF-R1 antagonist, NBI 34041, has been studied in phase 1 multidose clinical trials in patients with mood and anxiety disorders, but further development of this compound has been halted. The compounds CP-154,526 and its analog antalarmin are selective, nonpeptide CRF-R1 antagonists that have been studied in animal models of psychiatric illnesses.[78–80] CP-154,526 exerts antidepressant, anxiolytic, and drug-seeking attenuation effects in rodent models. Clinical studies of CP-154,526 are ongoing, but results have not yet been published.[79,81,82] Overall, the efficacy signal for CRF receptor antagonists is encouraging. Several pharmaceutical companies have active CRF antagonist clinical trial programs in phase 1 and early phase 2 trials.

CONCLUSIONS

Technological advances, such as completion of the sequencing of the human genome and the opportunities this achievement affords, offer the hope of eventual identification of genetic subtypes of psychiatric disorders, with their own unique treatment requirements. Until these inroads become available, efforts continue to better understand the neurobiology of depression and the role of childhood

trauma and maladaptive stress responses in its pathophysiology. Early-life adversity results in sensitization of the pituitary-adrenal and autonomic stress response that persists into adulthood and is at least in part mediated by CRF hypersecretion. Neuroimaging studies have demonstrated that reduced hippocampal size, previously interpreted as associated with depression or PTSD, may instead be largely due to undetected childhood trauma. The neurobiological changes associated with childhood adversity, including persistent hyperactivity and sensitization of CRF circuits, most likely increase the risk of mood and anxiety disorders in genetically predisposed individuals. Clearly, this work contributes to the identification of subpopulations of neurobiologically distinct forms of depression, which will likely lead to prediction of treatment response, reduced heterogeneity of study populations in clinical trials, and identification of a novel class or classes of antidepressants and anxiolytics. This is necessary because current rates of response (55% to 65%) and remission (35% to 50%) after 8 to 10 weeks of treatment with SSRIs or related antidepressants[83] are unacceptably low.

Drug names: nefazodone (Serzone and others), paroxetine (Paxil, Pexeva, and others).

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