Update on stress and depression: the role of the hypothalamic-pituitary-adrenal (HPA) axis

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Abstract
Over the past 50 years, relationships between stress and the neurobiological changes seen in psychiatric disorders have been well-documented. A major focus of investigations in this area has been the role of the hypothalamic-pituitary-adrenal (HPA) axis, both as a marker of stress response and as a mediator of additional downstream pathophysiologic changes. This review examines the emerging literature concerning the relationship between stress, HPA axis function, and depression, as well as the role of early life stress as an important risk factor for HPA axis dysregulation. The more recent studies reviewed suggest that the prominence of HPA axis hyperactivity in adults with depressive and anxiety disorders may constitute a link between the occurrence of adversity in childhood and the development of adult psychopathology.

Keywords

Resumo
Nos últimos cinqüenta anos, as relações entre estresse e mudanças neurológicas nas doenças psiquiátricas foram bastante documentadas. Um dos maiores focos de investigação nesta área tem sido o eixo hipotálamo-hipofisário-adrenal (HHA), tanto como marcador da resposta ao estresse, quanto como um mediador das mudanças fisiopatológicas em resposta ao estresse. Esta revisão examina a literatura emergente no que concerne às relações entre estresse, eixo HHA e depressão, assim como o papel do estresse precoce como fator de risco para a disfunção do eixo HHA. Os estudos mais recentes sugerem um papel de destaque para a hiperatividade deste eixo em adultos com depressão e transtornos de ansiedade. Esta hiperatividade pode se constituir na ligação entre ocorrência de adversidades na infância e o desenvolvimento da psicopatologia no adulto.

Descritores

Introduction
Stress is defined as ‘a mentally or emotionally disruptive or upsetting condition occurring in response to adverse external influences’, as well as ‘a stimulus or circumstance causing such a condition’. Hans Selye coined the term ‘stressor’ in 1950 to differentiate the condition of stress from the stimuli which evoke it, but the dual connotation of ‘stress’ has persisted. Beginning in the ‘30s, Selye initiated a pioneering program of studies on the adaptive physiology of stress which ultimately came to constitute the foundation for modern biological research in this area. By the end of the 20th century, relationships between stress and the neurobiological changes seen in psychiatric disorders had been well-documented.

A major focus of investigation in this area has been the role of the hypothalamic-pituitary-adrenal (HPA) axis, both as a marker of the stress response and as a mediator of additional downstream pathophysiologic changes. The HPA axis functions in close concert with the locus coeruleus-norepinephrine (LC-NE) system, which is involved in extensive reciprocal innervation of regions throughout the central nervous system (CNS). Stressors detected via the primary sensory organs generate signals which pass through mediating systems located in...
the amygdala, limbic system, and prefrontal cortex. These regions serve to process and evaluate stress-related information and in turn generate responses through regulation of HPA and LC-NE activity and other effector systems.

For clinical psychiatrists, a keen awareness of the complex interplay of stressors, stress, and illness is obviously a sine qua non of routine practice. However, in order to gain a deeper understanding on the pathogenic and compensatory neurobiological mechanisms underlying these clinical phenomena, laboratory studies are essential. Preclinical research using animal models has historically provided crucial insights into the stress response in humans. In recent years, more sophisticated animal models have been developed in order to more closely mimic clinically relevant processes. Because of the prominence of HPA axis dysfunction in certain psychiatric syndromes, this system has been a major focus of attention. This coincides with a period of dramatic growth in our understanding on the molecular underpinnings and basic neurophysiology of the HPA axis. Efforts are now underway to ‘back-translate’ findings from these novel animal models to human laboratory and clinical paradigms.

Following a brief summary of current conceptualizations of the HPA axis as a component of the stress response system, this review will examine the emerging literature concerning the relationship between stress, HPA axis function, and depression. Detailed consideration will be given to preclinical and clinical studies on the role of early life stress as a risk factor for the development of HPA axis dysregulation and depression in adulthood.

Discussion

The stress response system and the HPA axis

The core stress response system consists of the corticotropin releasing hormone (CRH) and LC-NE systems and their respective peripheral components, the HPA axis and the sympathetic nervous system (SNS). CRH and NE are the main central regulators of the HPA axis and LC-NE systems, respectively, being responsible for the stimulation of brain regions, peripheral organs, and physiological functions downstream from their central release. Activation of this core stress response system stimulates behavioral arousal, increases cardiovascular and metabolic activity, and interferes with routine neurovegetative functions (Figure). The CRH and LC-NE systems are themselves closely linked, stimulating each other’s activity.

Activation of the LC-NE system operates as an emergency or alarm system. It diminishes engagement in restitutive, neurovegetative functions (e.g., grooming, eating, and sleeping), while promoting an increase in autonomic outflow in the periphery. The LC-NE system is not contiguous with the SNS, but the activity of the two systems is fairly closely coupled. Activation of the SNS increases blood pressure, heart rate, and the availability of glucose (which suppresses insulin secretion). These two systems also interact multidirectionally with neural substrates such as the amygdala, mesolimbic dopaminergic system, and medial prefrontal cortex. In this regard, it is important to note that the amygdala mediates fear, anxiety and emotional memory; the mesolimbic dopamine system mediates reward and pleasure; and the medial prefrontal cortex modulates complex executive behavior and affective flexibility.

During stress, the HPA axis becomes critically engaged through its role in activating the release of glucocorticoids, with consequent increases in heart rate, blood pressure, and metabolism. CRH is expressed by parvocellular neurons located in the paraventricular nucleus of the hypothalamus. Following secretion from nerve terminals in the median eminence, CRH traverses the hypophysial portal circulation to bind at specific receptors in the anterior pituitary, resulting in the secretion of adrenocorticotropic hormone (ACTH). There are two types of CRH receptors in the brain. CRH type 1 receptors are widely distributed and appear to transduce the effects of CRH during stress. Consistent with this, CRH type 1 receptor knockout mice, which have been genetically altered to eliminate the expression of this receptor, show decreased anxiety. In contrast, CRH type 2 receptor knockout mice show increased arousal and anxiety, suggesting that CRH type 2 receptors counterregulate type 1 receptors. Type 2 receptors also mediate diminished food intake. Arginine vasopressin (AVP) is also expressed in parvocellular CRH neurons. Alone, it is a weak ACTH secretagogue, but in synergy with CRH, AVP potentiates ACTH release from the pituitary.
tuitary.\(^7\) ACTH itself binds to receptors in the adrenal cortex to stimulate the production and release of cortisol.

Cortisol has both central and peripheral effects, mediated via at least two specialized glucocorticoid receptor subtypes, the high-affinity type 1 receptor (or MR ['mineralocorticoid receptor']) and the low-affinity type 2 receptor (or GR ['glucocorticoid receptor']).\(^8\) The high-affinity MRs putatively respond to low, basal levels of circulating cortisol, while the lower-affinity GRs come into play during circadian and stress-related peaks in cortisol secretion. The binding of cortisol to glucocorticoid receptors in the hypothalamus and hippocampus, as well as in other upstream components of the HPA axis, acts as a potent inhibitory regulator of HPA axis activity.\(^9\)

CRH-mediated glucocorticoid secretion has both adaptive and adverse effects. Acute release of cortisol during stress is responsible for the enhancement of cardiovascular function, mobilization of fuel, and inhibition of growth and reproductive functions, as well as some immunological responses. However, the adaptive advantages of glucocorticoid secretion during stress are limited to its acute rather than chronic release. Chronic elevation of cortisol is almost always deleterious, resulting in insulin resistance, visceral fat deposition, osteopenia and osteoporosis, inhibition of T helper-1 directed cellular immunity, and chronic suppression of the mesolimbic dopaminergic reward system; in animal models, it is associated with excessive fear.\(^7\) There is evidence from studies in rats and non-human primates that chronic mobilization of the stress response, resulting in exposure to excessive glucocorticoids, has pronounced adverse effects on the hippocampus. These include inducing the regression of dendritic processes, inhibiting neurogenesis, impairing the ability of neurons to survive coincident insults (e.g., increasing the neurotoxicity of seizure, hypoxia/ischemia, metabolic poisons, hypoglycemia, and oxygen free-radical generators), and promoting neurotoxicity even in the absence of additional insult.\(^10,11\) Recent clinical studies using structural magnetic resonance imaging (MRI) show evidence of hippocampal atrophy in patients with severe recurrent depression;\(^12\) while the mechanisms responsible for this atrophy are still unclear, some findings suggest that hypercortisolism is involved in the process.

**Stress, corticotrophin releasing hormone (CRH), and depression**

Early clinical observations and several decades of systematic studies overwhelmingly document a prominent role for psychosocial stressors and untoward life events in the pathogenesis of psychiatric illnesses. Psychological stress, as determined by self-report of negative life events, frequently precedes the onset of affective episodes,\(^13-15\) predicts depression severity\(^16\) and depression relapse,\(^17\) and is related to inferior antidepressant response.\(^18\) Stress in the form of childhood physical and sexual abuse is a well established risk factor for the development of depression in all age groups.\(^19-22\)

There are marked similarities between the cardinal features of major depression in humans and the behavioral and neuroendocrine responses to stress observed in laboratory animals. Numerous studies of basal and provoked measurements of plasma HPA axis hormone concentrations, imaging of pituitary and adrenal gland volume, cerebrospinal fluid (CSF) levels of CRH, and post-mortem measures of brain CRH receptor binding and CRH messenger ribonucleic acid (mRNA) levels, all point to hyperactivity of the HPA axis as a state marker for major depression.\(^23,24\) Hyperactive CRH neurons, manifested as CRH hypersecretion, and impaired efficacy of glucocorticoid-mediated feedback, are considered reliable hallmarks of disturbed neuroendocrine regulation associated with, and perhaps causally related to, depressive disorders.\(^23\)

CRH receptors are widespread throughout the CNS, and CRH regulates and modulates multiple neurochemical systems. Not surprisingly, alterations in CRH influence other neurotransmitter systems, including NE and serotonin (5-hydroxytryptamine [5-HT]), which are strongly implicated in the regulation of mood and emotional behavior. By means of its effects on the limbic system and brainstem autonomic nuclei, CRH may represent one of the links between factors capable of causing depression, such as psychological trauma in genetically predisposed individuals, and clinical symptomatology, which might be more directly mediated through biogenic amines.\(^25\)

Heim & Nemeroff,\(^26\) among others, have suggested an interactional model to explain the relationship between stress, HPA axis dysfunction, and the development of depression. According to this model, early adverse experiences may shape a pre-existing genetic vulnerability to stress and disease, which results in a phenotype vulnerable to the development of depression later in life, particularly following exposure to subsequent stressors. In this kind of model, the ‘dosage’ of subsequent stressors required to precipitate an episode of illness may vary widely depending upon the degree of vulnerability, reflecting the broad disparities clinically observed in the relationship between acute stress and depression. CRH responsiveness, as a product of predisposing genetic and early experiential factors, is poised to be the ‘transducer’ of adult stressors into the neurobiological derangements which characterise the depressed state.

**Studies of early life stress in laboratory animals**

Because of limitations inherent to research on humans, studies of the effects of stress on the developing brain using animal models have been particularly informative. A growing body of preclinical research demonstrates that stressful experiences during perinatal and early infant life result in profound and irreversible effects on the mature organism’s behavioral and neuroendocrine response to stress. Long-term consequences of the experimental disruption of usual mother-infant contact and interaction have been investigated in several important studies during the past decade. At the same time, factors which can mitigate the deleterious effects of such disruptions are also receiving increased attention.

For example, it has long been observed that postnatal human handling of laboratory rat pups produced salutary changes in the animals, which are manifested as permanent modifications in the their neuroendocrine (HPA), neurochemical, and behavioral responses to stressful stimuli when mature.\(^27-29\)
signed to better elucidate the mechanisms underlying the effects of handling and neonatal environmental factors on HPA axis development. Plotsky and Meany\textsuperscript{30} exposed rat pups to one of three conditions during the first two weeks of life. The pups were either left undisturbed, underwent daily handling with very brief (15 minutes) separation from their mothers, or underwent prolonged (180 minutes) daily maternal separation. All animals were subsequently weaned, housed with same-sex peers, and maintained under standardized conditions until adulthood. Compared with the undisturbed controls, significantly increased levels of hypothalamic CRH and CRH mRNA were found in the brains of rats which had been exposed to the prolonged maternal separation, while significantly lower levels were seen in the group which had been handled. After a 20-minute restraint stress, hypothalamic CRH content was depleted and plasma corticosterone was increased in all groups, but significantly less in this way in the handled group than in the other two groups. These findings demonstrate both the deleterious effects of maternal separation on the HPA axis (and specifically the hypothalamic CRH system) and the beneficial effects of nonaversive environmental stimulation in the neonatal period.

Employing a similar paradigm, Ladd et al\textsuperscript{31} studied adult rats which had been isolated in an incubator for six hours per day during the first 20 days after birth. This manipulation subjected the animals to standardized maternal deprivation before they were weaned, but without alteration in body temperature as a consequence of disrupted bodily contact with the mother. After weaning, all animals were housed and reared with same-sex peers under standard laboratory conditions. Compared with a cohort of rats which did not undergo isolation, the maternally deprived rats had significantly higher basal levels of plasma ACTH, a 125% increase in immunoreactive CRH concentrations in the median eminence, significantly reduced density of CRH receptor binding in the anterior pituitary, and increases in CRH receptor binding sites and CRH concentrations in extrahypothalamic CRH systems (raphe and parabrachial nuclei). These findings were consistent with those of Plotsky and Meany. A subset of the adult rats was subjected to a mild foot shock stress. Following the exposure to foot shock stress, the rats that had experienced early maternal deprivation exhibited augmented plasma ACTH release.

Nemeroff et al\textsuperscript{32} described a similar experiment investigating changes in CRH receptor density in the brains of 12-day-old rats that had been maternally deprived for only 24 hours before death. Again, when compared with nondeprived controls, the rats exposed to early stress in the form of relatively brief separation from their mothers exhibited heightened levels of basal- and stress-induced ACTH, as well as altered CRH receptor density in brain regions thought to be involved in the pathophysiology of depression and anxiety. Taken together, these findings suggest that even relatively brief perinatal maternal deprivation in rat pups produces a pattern of chronic hypersecretion of CRH in the median eminence, with associated CRH receptor down-regulation and diminished sensitivity of the glucocorticoid negative feedback regulatory mechanisms, which persists into adulthood.

Continued work by Meany and colleagues has teased out critical qualities of maternal care during the first 10 days of life which serve to ‘program’ the development of neural systems mediating the expression of fearfulness and anxiety in the adult rat.\textsuperscript{33} Mother rats were rated and grouped according to the degree to which they performed characteristic nurturing contact with their infants in the postnatal period. The rat pups were unmanipulated and allowed to mature into adulthood under standard laboratory conditions. The grown offspring of those mothers who demonstrated frequent licking/grooming and arched-back nursing of their babies (high LG-ABN) were compared with grown offspring from mothers who demonstrated low levels of that maternal behavior (low LC-ABN) during the postnatal 10-day period. As adults, the offspring were examined with regard to fear in the presence of novelty. High LG-ABN offspring exhibited substantially reduced behavioral fearfulness as compared with low LG-ABN offspring. More importantly, a number of biological findings suggested correlates of those differential behavioral responses between the two offspring groups: adult rats who were postnatal recipients of more maternal attention and contact in the form of licking/grooming and arched-back nursing demonstrated increased central benzodiazepine receptor density in the amygdala and locus coeruleus, increased α-2 adrenergic receptor density in the locus coeruleus, and increased CRH receptor density in the locus coeruleus. These neurotransmitter systems and brain structures are thought to be intimately involved in the expression of fear and anxiety in both animals and humans. With regard to HPA axis functioning, every measure of stress responsivity correlated with the frequency of maternal licking and grooming, and the high- vs. low-LG-ABN offspring groups were consistently significantly different from each other. Compared with the low-LG-ABN offspring, offspring of high-LG-ABN mothers showed reduced levels of plasma ACTH and corticosterone in response to stress, increased expression of hippocampal glucocorticoid receptor mRNA, enhanced glucocorticoid feedback sensitivity, and diminished levels of hypothalamic CRH mRNA.\textsuperscript{34}

An important parallel step in current research on stress and developmental neurobiology has been undertaken by Coplan et al.\textsuperscript{35} These investigators utilized a population of nonhuman primates to explore the effects of disrupted infant-mother interaction on cerebrospinal fluid (CSF) concentrations of CRH. Coplan and colleagues randomly assigned pairs of mother/infant monkeys to varying levels of environmental unpredictability in order to experimentally manipulate the quality and quantity of mother-infant interaction. One group of animals was exposed to conditions of variable foraging demand (VFD), while the other two groups were subjected to consistent availability of food: abundantly available and easily attainable in the low foraging demand group (LFD) or consistently available but limited in quantity and difficult to obtain in the high foraging demand (HFD) group. The monkey pairs were assigned to these conditions when the infants were around 17 weeks old. The physical configuration of this experiment permitted the full range of mother-infant behavioral patterns, yet the infants had ad lib access to food and water in an area that was inaccessible to the mothers. The rear-
ing behavior exhibited by VFD mothers is anxious, inconsistent, erratic, and sometimes frankly neglectful, presumably creating a psychological stressor for the infant by virtue of the perception of ‘insecure’ attachment with the mother. As adults, the grown monkeys underwent a standardized procedure for sampling of cisternal CSF for measurement of CRH and cortisol. Results indicated that CSF CRH concentrations were significantly elevated in VFD subjects in comparison with both HFD and LFD groups, while CSF cortisol concentrations were significantly lower in the VFD monkeys. The two groups (HFD and LFD) exposed to consistent foraging conditions (and hence less maternal neglect) were indistinguishable from one another. These findings constitute evidence for persistent hyperactivity of CRH-releasing neurons in the CNS of adult nonhuman primates which, as infants, were exposed to adverse experiences disrupting the usual mother-infant attachment behaviors.

Subsequent analyses of CSF from these same monkey groups showed that VFD animals had significantly elevated levels of somatostatin, 5-HT, and dopamine metabolites as compared with non-VFD subjects. Behaviorally, monkeys exposed to VFD stress were more readily frightened by novelty and less independent of their mothers in the first year of life, and continued to be more timid, less social, and more subordinate than LFD offspring as young adults. When exposed to a single oral dose of the alpha-2 adrenergic antagonist yohimbine, adult VFD offspring showed significant decreases in self-protection behaviors, increases in behavioral inhibition, and increases in feeding behaviors, while LFD animals (thought to represent ‘normal’ controls) did not. Additionally, an array of behavioral responses noted to occur in LFD animals in response to the 5-HT agonist m-chloro-phenyl-piperazine (mCPP) were suppressed in VFD animals. These data were interpreted as suggesting that VFD animals showed a shift away from adaptive external monitoring of the social environment, reflected in decreased self-protective/tension behavior, and toward distress patterns involving greater internal monitoring, as reflected in increased inhibition/enervation behavior. The types of behaviors assessed in these studies are felt to be reflective of affective distress and to constitute an anxiety syndrome in animals which is relevant to human mood and anxiety states. The data thus support the view that aspects of early infant-mother relationship have long-term effects on psychological functioning, particularly with regard to the development of acute anxiety. Such effects appear to be associated with enduring alterations in both noradrenergic and serotonergic neurotransmission, as well as the HPA axis, underscoring the complexity and persistence of the effects of early adversity on a range of neuromodulatory systems relevant to emotional regulation.

**Effects of early life stress in humans**

The results of the preclinical investigations described above have the potential to markedly enhance our understanding of the etiology of affective and other psychiatric disorders. However, translational research which tests hypotheses generated from the animal laboratory in clinical populations has been limited to date, and extrapolations from the infant animal experiences of maternal separation/handling, variable foraging, and frequency of maternal licking-grooming to the human aspects of early mother-infant interaction are inherently inadequate. There is no way to know if the laboratory animal’s aberrant responses to restraint, foot shock, or novelty translate into effects that are meaningful in terms of how humans feel and function in the face of new stressors.

An extensive literature, dating back to the work of Freud, describes observations and theories regarding the importance of early maternal attachment in, and the impact of maternal deprivation on, the development of adult psychological health. Much descriptive work has been published on the relationship between adult psychopathology and early adversities such as parental loss in childhood, inadequate parental care, divorce, ‘affectionless’ or dysfunctional parenting, childhood physical and sexual abuse, and other childhood traumas. These studies have consistently found early life stressors to be associated with increased risk for mood and anxiety disorders and personality pathology in adulthood.

Nemeroff et al. have conducted a series of studies examining the complex interactions of early life experiences, depression, and laboratory-based stress, as reflected in HPA axis function. Preliminary findings on stress responsiveness in adult survivors of childhood abuse with and without depression were reported by Heim et al. In that study, women with a history of child abuse with major depression showed significantly increased cortisol responses to psychological stress as compared with healthy control subjects and abused women without depression. The ACTH and cortisol responses were positively correlated with the degree of childhood abuse and the severity of depression and post-traumatic stress disorder (PTSD). Women with a history of childhood abuse and current depression suffered more often from comorbid PTSD and had been exposed to more recent life stress when compared with women having a history of childhood abuse without depression. In CRH stimulation tests of these women, those with a history of childhood abuse without depression exhibited increased ACTH responses along with normal to decreased cortisol responses. In contrast, women with a history of childhood abuse with comorbid major depression exhibited blunted ACTH responses, likely due to chronic overexposure of the pituitary to CRH. These findings suggest that there may be an initial sensitization of the stress hormone system during early life adversity, representing a biological vulnerability for the development of depression and anxiety disorders in later life.

In another study, these same investigators examined 66 women divided into four groups: 1) healthy without early life stress (H); 2) history of childhood abuse without major depression (CA); 3) history of childhood abuse and current major depressive disorder (CAMDD); 4) current major depressive disorder but no early life stress (MDD). Plasma ACTH and cortisol responses to ovine CRH 1 µg/kg and plasma cortisol responses to ACTH250 µg were measured. In comparison with the H group, CA subjects exhibited enhanced ACTH responses to CRH administration, whereas the CAMDD and MDD groups demonstrated blunted ACTH responses; cortisol responses to...
CRH were blunted in the CAMDD and CA groups relative to the H group. In the ACTH stimulation test, the CA group exhibited lower baseline and stimulated plasma cortisol concentrations than the H subjects, whereas the CAMDD group showed lower baseline cortisol levels only. The results of this study are consistent with the earlier hypothesis that there is sensitization of the anterior pituitary and counterregulatory adaptation of the adrenal cortex in abused women with major depression. These findings also support the etiological hypothesis that depression and anxiety in these women are related to stress exposure later in life resulting in hypersecretion of CRH and down-regulation of adrenocortical CRH receptors.

Late HPA axis sequelae of early life stress have also recently been demonstrated in an at-risk population by Meyer et al., who conducted a long-term follow-up study of children whose mothers had been diagnosed with unipolar depression, bipolar I or II disorder, or no psychiatric illness. At adolescence, 63 of these children underwent a CRH challenge. Adolescents whose mothers had displayed a highly angry or irritable parenting style were more likely to exhibit exaggerated ACTH activation in response to CRH than subjects who were not exposed to such parenting. Again, the possibility that pituitary sensitization of this type could contribute to the increased vulnerability of these adolescents for the development of major affective disorder in adulthood is highly intriguing.

Holsboer et al. have advocated the use of the dexamethasone/CRH test as a more sensitive and informative means of evaluating HPA dysregulation in human subjects. The test involves oral administration of a single dose of dexamethasone 1.5 mg at 11:00 p.m., followed the next day at 3:00 p.m. by an intravenous bolus of CRH 100 µg. Whereas previous studies using the CRH stimulus alone had found blunted ACTH responses in depressed patients, use of the dexamethasone/CRH test results in exaggerated ACTH responses in depressed patients compared with healthy controls. Similarly, the cortisol response after the dexamethasone/CRH test is much greater than following a challenge with CRH alone. These findings are hypothesized to reflect the preferential action of dexamethasone at the pituitary to suppress ACTH, resulting in decreased cortisol levels and failure of the pituitary to compensate for this, in turn resulting in increased release of CRH and vasopressin more centrally in an effort to enhance ACTH secretion.

Certainly, use of a variety of investigative approaches has yielded complementary insights into the relationship between HPA axis dysfunction and depressive illness. For example, studies using serial administration of the standard dexamethasone suppression test (DST) have shown that, in patients with cortisol nonsuppression, normalization of HPA axis function is necessary for clinical remission to become manifest during antidepressant treatment. Similarly, CSF studies have demonstrated elevated levels of CRH in depressed patients compared with control subjects, with clinical remission during antidepressant treatment associated with a decrease in CSF CRH down to the levels seen in controls. The combined dexamethasone/CRH test has proven particularly useful as a predictor of increased risk for relapse. For example, Zobel et al evaluated a sample of 74 depressed patients in a follow-up study six months after hospital discharge, of whom 61 remained stable and 13 relapsed. The dexamethasone/CRH test had been administered at admission and at discharge, in order to determine whether test results could predict clinical outcome. On admission, relapers and non-relapers did not differ on their maximal cortisol or ACTH responses, but prior to discharge the maximal cortisol and ACTH responses were significantly higher in the patients who subsequently relapsed at follow-up. The relative risk for relapse in the group with a high cortisol response at discharge was 4.32, i.e., a four-fold risk than in patients with a normal cortisol response to dexamethasone/CRH.

**Conclusion**

Early investigators believed that the HPA axis hyperactivity of depression was little more than a manifestation of the classic stress response. Subsequent authorities viewed this phenomenon as a somewhat unique, but state-dependent, feature of the illness itself. In contrast, the more recent studies reviewed here suggest that the prominence of HPA axis hyperactivity in adults with depressive and anxiety disorders may constitute a link between the occurrence of adversity in childhood and the development of adult psychopathology. The prognostic significance of continued HPA axis dysregulation in the face of adequate treatment suggests that this phenomenon may well represent a fairly central pathophysiological, and perhaps etiological, process in depression.

Taken together, these findings in laboratory animals and humans suggest that early life trauma may result in long-term, if not permanent, hyperactivity of the HPA system. Other studies suggest that such hyperactivity may engender neurotoxic effects in the hippocampus that lead to measurable decreases in hippocampal volume. These changes appear to represent sensitization of the CRH circuits to even mild stress in adulthood, leading to an exaggerated stress response. Upon exposure to persistent or repetitive stress in adulthood, these already sensitive stress pathways become markedly hyperactive, leading to persistent increases in CRH and cortisol secretion. This, in turn, could cause alterations in glucocorticoid receptors and thereby contribute to the pathogenesis of mood and anxiety disorders.

The nature and timing of early adverse events that will have long-term sequelae has been well-delineated in some animal models, but comparable parameters in humans are not known. Similarly, the range of sequelae that might be expected from specific traumas in humans is unclear. There is little data concerning what kinds of psychosocial or neurobiological interventions might mitigate or prevent the deleterious effects of early adversity. Finally, the compelling possibility that pharmacologic treatment targeted at HPA axis hyperactivity may have antidepressant or anxiolytic properties is only now being evaluated, and the prophylactic potential of such agents has yet to be considered. Notwithstanding these caveats, progress in understanding the role of the HPA axis in mediating stress in depression is highly promising for the development of novel approaches to treatment and prevention.
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