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Depression and stress: is there an endophenotype?

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Abstract

Objective—To review the new findings about stress, hypothalamic-pituitary-adrenal axis and depression trying to explain a possible endophenotype prone to depression.

Method—Nonsystematic review of the literature based on the endophenotype hypothesis.

Results—Depression is linked to hypercortisolemia in many patients, but not all patients present these hypothalamic-pituitary-adrenal axis dysfunction. The dexamethasone suppression test is not the most accurate test to measure the hypothalamic-pituitary-adrenal axis function, and its use in the first studies published probably jeopardized the results. Hypercortisolemia frequently occurs in patients with severe depression, melancholic, either psychotic or nonpsychotic type; it is linked to the presence of a polymorphism in the promoter of the serotonin transporter gene, with a history of childhood abuse or neglect, or other significant stressful experiences like the loss of a parent during childhood and temperament leading to alterations in the response to stress.

Conclusions—The alterations of the hypothalamic-pituitary-adrenal axis depend on many factors like severity and type of depression, genotype, history of exposure to stress, temperament, and probably resilience. All these factors together result in an endophenotype thought to be prone to depression.

Descriptors

Depression; Corticotropin releasing hormone; Hypothalamus-hypophyseal system; Pituitary-adrenal system; Stress

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Introduction

Hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis in major depression is one of the most consistent findings in psychiatry. A significant percentage of patients with major depression have been shown to exhibit increased concentrations of cortisol (the endogenous glucocorticoid in humans) in the plasma, urine and cerebrospinal fluid (CSF); an exaggerated cortisol response to adrenocorticotropic hormone (ACTH); and an enlargement of both the pituitary and adrenal glands.[1] In the last several years, many studies about the HPA axis in depressed patients have been published, and it seems that there is a new perspective for these old finding of hypercortisolemia. The knowledge about it is converging to some directions, hypercortisolemia is apparently linked to some specific cases of depression and it depends on the type and severity of the illness, genotype, history of stress during childhood, and probably resilience, leading us to believe that there is an endophenotype prone to depression. We intend to summarize in this article some of the findings that support this hypothesis.

Background

The first studies about hypercortisolemia in depressed patients were published in the seventies, back then Carroll et al. have found that severely depressed patients had non suppression in the dexamethasone suppression test (DST).[2] The DST showed that a high proportion of patients with various affective disorders had elevated cortisol levels, thus escaping the suppressive effect of dexamethasone. Unfortunately, dexamethasone has pharmacodynamic and pharmacokinetic features that are very distinct from those of the human endogenous glucocorticoid, cortisol. These features, together with the low (40–50%) sensitivity of the DST in detecting patients with major depression, have strongly limited the use of this test in routine clinical and research practice.[3] The use of the DST resulted in conflicting findings that were not widely replicated and the studies about the HPA axis function in depression were left apart for some time.

Besides the limitation of the DST, many factors work as confounders biasing the results of stress tests able to measure the HPA axis function. Most of the studies have included mixed populations with diagnosis of both posttraumatic stress disorder (PTSD) and depression with patients with different severity degrees of illness and with and without a history of early life stress that made the results nonreplicable.

Nearly ten years after the development of the DST, Holsboer et al. have developed a more sensitive neuroendocrine function test to detect HPA axis dysregulation. It combines the DST and the corticotrophin releasing hormone (CRH) stimulation test and its called the DEX/CRH challenge test.[4–5] The test involves oral administration of a single dose of dexamethasone (DEX) 1.5 mg at 11 pm, followed the next day at 3 pm by an intravenous bolus of CRH 100 μg. Since then, Holsboer et al. have been publishing interesting results about hypercortisolemia and depression.

Recently, Watson et al. have examined if the DEX/CRH test unveils subtle HPA axis disturbance not detected by the DST in patients with mood disorders and controls.[6] They have found a close correlation between the cortisol responses on the two tests. The

sensitivity of DEX/CRH was 61.9%, and the specificity was 71.4%. The sensitivity of DST was 66.6%, and the specificity was 47.6%. This suggests that the two tests measure common pathology, but that the DEX/CRH test has better diagnostic utility.

Zobel et al. have described a cohort of patients receiving the DEX/CRH test on two different moments: after starting the first antidepressant treatment; secondly, a few days before the discharge.[7] The authors have found that those patients who had an increase in cortisol levels after the DEX/CRH test between admission and discharge tended to relapse during the follow-up period, whilst those who showed a decrease in the post DEX/CRH cortisol levels tended to remain clinically stable in the follow-up period. In general, HPA axis changes appear to be state dependent, tending to improve upon resolution of the depressive syndrome.[8]

Recently, a suppressive test using another synthetic glucocorticoid, prednisolone has been developed by Pariante et al., such test has a higher affinity for the mineralocorticoid receptor (MR) and, therefore, should probe both receptors.[9] Glucocorticoids mediate their actions, including feedback regulation of the HPA axis, through two distinct intracellular corticosteroid receptor subtypes referred to as the type I or mineralocorticoid receptor, and the type II or glucocorticoid receptor (GR), see Figure 1. In contrast to the MR, the GR has a high affinity for dexamethasone and a lower affinity for endogenous corticosteroids. However, most of the literature in this field has examined the GR. The first results with the prednisolone test in depressed patients seem to confirm the notion that MR-mediated negative feedback in depression is intact in depressed patients.[10]

Although different tests have been used and conflicting results have been published, there are some converging results in the specific case of depression. Hypercortisolemia frequently occurs in patients with severe depression, melancholic, either psychotic or nonpsychotic type, it is linked to the presence of a polymorphism in the promoter of the serotonin transporter gene, with a history of childhood abuse or neglect, or other significant stressful experiences like the loss of a parent during childhood and temperament leading to alterations in the response to stress.[12] All these factors together result in an endophenotype thought to be prone to depression.

Another group of states is characterized by hypoactivation of the stress system, rather than sustained activation, in which chronically reduced secretion of CRH may result in pathological hypoarousal and an enhanced HPA negative feedback. Patients with atypical and seasonal depression fall in this category[13] although in this article we will not emphasize this last group of patients.

Severity and type of depression

A hyperfunction of the HPA axis, characterized by a CRH hyperdrive, reduced negative feedback and hypercortisolism, has been a consistent research finding in major depression. Classically, the abnormalities have been observed in patients with unipolar disorder (one or recurrent major depressions), but they can also be present in the depressive phase, the manic phase and the remission phase of patients with bipolar affective disorder (recurrent episodes of both major depression and mania or hypomania).[14–15] In one study, Young et al. have

found that anxiety disorders occur in approximately 30% of patients with major depressive disorder and have concluded that depressed patients with comorbid anxiety disorders show even greater impairment of the negative feedback on the HPA axis than that observed in depressive patients without comorbid anxiety disorders.[16]

In the last decades, several studies have reported that psychotic major depression (PMD) has unique characteristics including neuroendocrine differences from nonpsychotic major depression. Many studies found hyperactivity of the HPA axis in PMD patients.[17–19]

More recently, Gomez et al. have examined 29 patients with PMD, 24 nonpsychotic major depressive patient (NPMD) and 26 healthy control subjects who were recruited at Stanford University Medical Center.[20] Psychiatric ratings, cortisol levels from 6 pm-9 am, and neuropsychological test data were obtained. The results showed that PMDs had elevated mean cortisol levels from 6 pm to 1 am.

Contreras et al. have also studied 40 inpatients meeting DSM-III-R criteria for major depressive episode with melancholia (21 nonpsychotic and 19 psychotic). DST, TSH-TRF and GH-GRF tests were undertaken by all patients. The results for disturbances of the HPA axis showed up to 80% alterations in melancholic depressive patients (whether psychotic or nonpsychotic), and that these disturbances may relate more to the presence of psychotic symptoms. The importance of HPA axis dysfunction in melancholia is clearly suggested. Only 20% of the whole sample (23.9% in nonpsychotic and 15.8% in psychotic depression) had no disturbance in any hormonal axis.[21]

Keller et al. have studied patients with depression with psychotic symptoms (PMD) and without (NPMD) and healthy control subjects using rating scales of depression and psychosis and measures of HPA activity, including overnight cortisol and adrenocorticotropin levels.[22] Thirty-seven PMD and 32 NPMD participated in the study. The results showed that PMDs had higher cortisol during the evening hours than did NPMDs or control subjects, who did not differ from one another. Regression analyses suggest that depression and the combination of depressive and psychotic symptoms were important contributors to the variance in evening cortisol levels. PMD is associated with increased cortisol levels during the quiescent hours. Enhanced cortisol activity, particularly a higher nadir, was related to depression severity and the interaction of depressive and psychotic symptoms. This increase suggests a defect in the action of the circadian timing system and HPA axis, creating a hormonal milieu similarly to that seen in early Cushing's syndrome and potentially an (im)balance of mineralocorticoid and glucocorticoid receptor activity.

Genetics

There are conflicting evidence concerning the relationship between a polymorphism in the promoter of the serotonin transporter gene (SLC6A4) and risk for depression.[23] After the publication of the study by Caspi et al. in 2003,[24] many studies replicated the results found and some did not. Caspi's research team found that childhood maltreatment predicted adult diagnosed depression among individuals carrying at least one copy of the short allele. This polymorphism of the serotonin transporter gene (5-HTTLPR) consists of a 20–23 base pair

sequence that is repeated either 14 (short) or 16 (long) times, with the presence of the short(s) allele putatively conferring greater risk for depression, particularly for people who have experienced stress recently or early in life. They also found that people with one or more s alleles who were exposed to adult stressful life events were more likely to develop depression than those homozygous for the long (l) allele. Many studies have replicated these data.[25–28]

Wilhelm et al. have examined 127 subjects, associations were investigated between the 5-HTTLPR genotype, positive and adverse life events and the gene X environment interaction.[29] The results showed that adverse life events had a significantly greater impact on the onset of depression for individuals with the s/s genotype than for the s/l or l/l, concluding that the 5-HTTLPR genotype is a significant predictor of onset of major depression following multiple adverse events.

Zalsman et al. have examined the relationship of a triallelic 5-HTTLPR polymorphism to stressful life events, severity of major depression, and suicidality.[30] One hundred and ninety-one (191) mood disorders subjects were compared to 125 healthy volunteers; all subjects were genotyped for the triallelic 5-HTTLPR polymorphism and underwent structured clinical interviews to determine DSM-IV diagnosis, ratings of psychopathology, stressful life events, developmental history, and suicidal behavior. The results showed that lower expressing alleles (L_G, S) independently predicted greater depression severity and predicted greater severity of major depression with moderate to severe life events compared with the higher expressing L_A allele. The research group concluded that lower expressing transporter alleles, directly and by increasing the impact of stressful life events on severity, explain 31% of the variance in major depression severity

However, Surtees et al. have reported that adversity in childhood and adulthood was associated with major depressive disorder, defined by DSM-IV diagnostic criteria, but these relations did not interact with the 5-HTTLPR genotype.[31] Gillespie et al. have also reported no replication of the pattern identified by Caspi.[32]

Stress during childhood

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.[33]

Increasing evidence indicates that childhood neglect and abuse are risk factors for both adolescent- and adult- onset depression.[34–36] Since the HPA axis is activated in response to stressors, early life stressful events may also have an etiologically significant role in the HPA axis abnormalities found in depression.[37]

Cortisol dysregulation and deficient glucocorticoid feedback regulation have been repeatedly identified as biological correlates of adult depression and anxiety disorders[38–39] and early life adversity is consistently associated with these disorders in epidemiological studies.[40] A large body of clinical literature has characterized major depressive disorder (MDD) as a condition associated with excessive basal cortisol secretion and inadequate inhibitory feedback regulation of the HPA axis constituents.[41] Childhood maltreatment is another example of a risk factor for depression that has been examined in nonclinical samples. In a study by Heim et al., women with a history of sexual or physical abuse demonstrated increased ACTH but normal cortisol responses to the TSST when compared with female control subjects without abuse histories.[42]

Moskvina et al. have studied the relationship of childhood trauma (CT) to age of onset (AO) of depression, personality traits, and expression of symptom dimensions in 324 adults with recurrent unipolar depression.[43] Subjects received structured psychiatric interviews and completed CT, depressive symptom, and personality rating questionnaires. Experience of at least one type of trauma was reported by 79.9% of subjects, and the most common forms of trauma were physical neglect, emotional abuse, and emotional neglect. There was an earlier AO of depression in the groups that reported CT compared to those that reported none, with earliest AO occurring in those who had experienced the highest levels of CT. The effect of CT on individuals with an underlying genetic vulnerability to depression may result in differences in depressive phenotype characterized by earlier AO of depression and the expression of specific depressive symptom dimensions.

Recent studies have shown that depressed patients with a history of childhood trauma and chronic forms of major depression are more likely to show hyperactivity of the HPA axis and to present symptoms that are resistant to standard antidepressants, but instead benefit from adjuvant treatment with psychotherapy.[44] It has been concluded from these studies that child maltreatment may lead to disruptions in HPA axis functioning, and that factors such as age of maltreatment, parental responsiveness, subsequent exposure to stressors, type of maltreatment, and type of psychopathology or behavioral disturbance displayed may influence the degree and pattern of HPA disturbance. However, results from studies examining the relationship between child maltreatment, psychopathology and the HPA axis do vary. While most studies report HPA axis dysregulation, inconsistencies have been noted. Furthermore, results should be analyzed by gender and by type of stressor for maximum consistency, as the effects on the HPA axis may vary due to these factors.

Temperament

Temperament and personality characteristics such as behavioral inhibition and neuroticism have been linked to mood and anxiety disorders. For example, prospective studies of nondepressed individuals have shown that neuroticism, which can be characterized by the tendency to experience negative affect, is a risk factor for the subsequent development of depression.[40,45–46] Moreover, findings from behavioral and molecular genetics studies indicate that neuroticism and major depression share common genetic risk factors.[47–48]

Behavioral inhibition is another temperament factor that has been found predictive of anxiety disorders and depression.[49] This trait, defined as the tendency to withdraw and avoid novel situations, demonstrates stability over time in both non-human primates[50] and children. Behavioral inhibition has been linked to anxiety disorders in family studies and in prospective longitudinal studies of young children who have been followed through childhood and into adolescence.[51–53]

Stressful life experiences also play a prominent role in the development of major depression,[54–55] several lines of research suggest the possibility that personality or temperament may account for some of the association between stress, depression, and HPA axis hyperactivity. There is evidence that personality can influence the likelihood of exposure to stressors. In addition to altering exposure, personality or temperament may confer sensitivity to stressors and conversely, a temperament-based tendency to experience negative affect or to be socially inhibited may in part result from psychological or physiological sensitivity to stressors.[40,56–57]

Our research group reported lower levels of Novelty Seeking predicting higher cortisol concentrations in response to the DEX/CRH test in healthy adults. The findings of this study support the hypothesis that personality factors, which may reflect increased sensitivity to stimuli, are predictive of enhanced activation of the HPA axis. Low levels of Novelty Seeking, which reflect an introverted, rigid temperament, were predictive of greater cortisol responses to the DEX/CRH test.[58]

Discussion

Could the HPA axis dysfunction be seen as the primary biological cause of major depression, or is it a secondary phenomenon? There are several indications in our data and in the literature that the HPA axis has a primary role in the predisposition and the onset of major depression. The HPA axis is a major element of the stress system and both acute and chronic stress can elicit major depression.[59] Interestingly, early-life stress leads to persistent neurobiological adaptations that resemble the findings in depression. There is a correlation between stress, HPA axis (responsible for the stress response) and the development of depression that is becoming clearer.

Holsboer et al. have found that the HPA feedback impairment observed among patients with depression was also present in otherwise healthy individuals who are at risk because they have a first-degree relative with an affective illness.[60] Moreover, this disturbance was shown to be stable over a four-year period.[61] These data suggest that some individuals have a genetically determined vulnerability to develop a chronic HPA axis hyperdrive and possibly major depression. There is also a link between genetics, the HPA axis function and vulnerability to depression.

To better understand the development of depression we can make a correlation between many factors, starting from genotype that includes heritability, childhood environment that includes possible traumas, temperament that gives to the individual the capacity to deal with the environment, and the resilience of some subjects that can explain different types of

response to the same stressful events. The HPA axis is one of the most important systems to be studied to elucidate the etiology of depression, but many other factors also need to receive attention.

The knowledge in this area of interest is becoming more consistent, we know more about the limitations of the stress tests and about confounding factors in this research field. The endophenotype hypothesis linking many findings about gene versus environment is not only being studied in the case of depression, but in many others illnesses; it is the tendency for the present.

Conclusions

The above observations are suggestive of an etiological role of the HPA axis in major depression; however, it is important to keep in mind that major depression is a complex and heterogeneous disorder. Whereas some subtypes of major depression, such as psychotic major depression, are associated with high rates of HPA axis hyperactivity, some depressed patients do not exhibit any disturbance of HPA axis at all. For a better understanding the complex interplay between nature and nurture in the development of depression in adults, future studies should ideally consider as many factors as possible trying to create a complete Environment versus Gene interaction. Such kind of research ideally connects psychosocial and genetics, psychological and biological approaches for better understanding mental illnesses.

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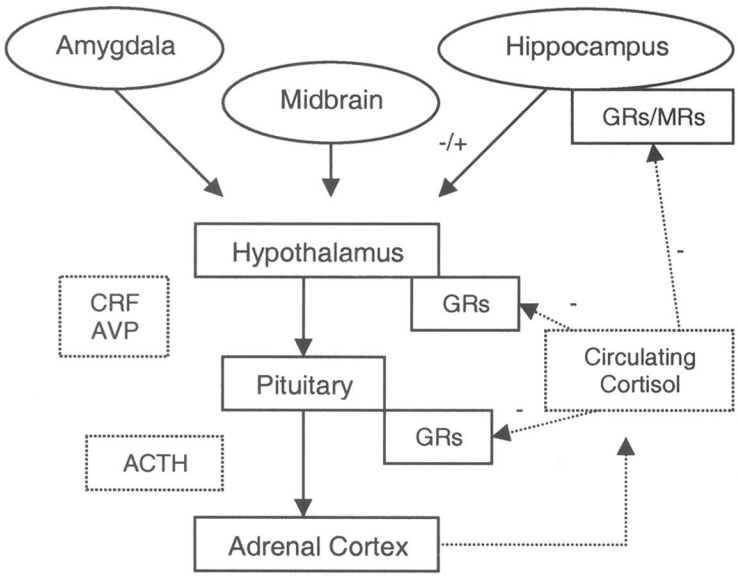

Figure 1.

Schematic diagram of Hypothalamic-Pituitary-Adrenal (HPA) axis, describing regulation and negative feedback (−) of Cortisol via glucocorticoid receptors (GR) and mineralocorticoid receptors (MR)[11]