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Review Article

What Should Psychiatrists Know About HPA Axis Dysfunction and Altered Cortisol Levels in Major Depression?

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Abstract

An innate or acquired dysfunctional (mainly hyperactive) Hypothalamic-Pituitary-Adrenal (HPA) axis and altered cortisol levels are the mainstays of the proposed hypothesis for the pathophysiology of Major Depressive Disorder (MDD). The hypothesis has a strong theoretical basis and is supported by the animal studies, but it encounters difficulties when applied to humans. The current hypothesis explains structural and functional brain pathologies and symptoms of the disease *via* high cortisol levels. However, only about half of MDD patients have high cortisol levels, which are mostly observed in specific subgroups. Depressive patients with melancholic and psychotic features have higher cortisol levels than other depressive patients, but patients with atypical features have normal or even lower cortisol levels. HPA axis and cortisol abnormalities in a high-risk population for depression (e.g., healthy daughters of depressed mothers) suggest that genetic factors might underlie the HPA axis dysfunction. In clinical trials antiglucocorticoid treatments have not been promising, and there is no currently available antiglucocorticoid treatment for depression. In this paper we briefly summarize the current status of the evidence and discuss whether the hypothesis of a dysfunctional HPA axis and an abnormal cortisol level is well-founded for depression.

Keywords: Major depressive disorder; Cortisol; Hypothalamic Pituitary Adrenal (HPA) axis; Pathophysiology

Abbreviations

MDD: Major Depressive Disorder; HPA: Hypothalamic Pituitary Adrenal; DSM: Diagnostic and Statistical Manual of Mental Disorders; CRH: Corticotrophin-Releasing Hormone; VP: Vasopressin; ACTH: Adrenocorticotrophic Hormone; GC: Glucocorticoids; MR: Mineralocorticoid (Type I) Receptors; GR: Glucocorticoid (Type II) Receptors; DEX: Dexamethasone; DST: Dexamethasone Suppression Test; TCA: Tricyclic Antidepressant; SSRI: Selective Serotonine Reuptake Inhibitor; ANS: Autonomic Nervous System; APA: American Psychiatric Association; PTSD: Post-traumatic Stress Disorder; CA: Cornu Ammonis; DG: Dentate Gyrus; CSF: Cerebrospinal Fluid; DHEA: Dehydroepiandrosterone

Introduction

Major Depressive Disorder (MDD) is one of the most common psychiatric diseases. The World Health Organization estimates that it will be the second most prevalent disabling disease by 2020 [1]. Half a century of significant efforts at understanding the etiology of MDD has led to few evidence-based hypotheses and models to explain the pathophysiology of the disease. One of the best known is that depressed patients have a dysfunctional HPA axis resulting in abnormal plasma cortisol levels, which in turn are associated with depressive symptoms. In this review, we will briefly summarize the current state of the evidence and consider whether this hypothesis is sufficiently well-founded to explain the pathophysiology of the disease. We note that many books and articles written for a general non-medical readership present the hypothesis as proven theory and many clinicians accept the hypothesis without realizing its weaknesses. This review seeks to clarify the strong and weak points of the hypothesis for clinicians who are not experts in the field.

First, an explanation of the terminology used in this review. As discussed below, some researchers have found evidence for a hyperactive HPA axis and high cortisol levels in MDD, while others have reported reduced HPA axis activity and normal or reduced plasma cortisol levels [2]. Many authors assume that abnormal cortisol levels are sufficient evidence of HPA axis dysfunction, but the HPA axis is not the only regulatory system determining plasma cortisol levels. Many other systems such as the sympathoadrenal and immune systems, which are important in MDD etiology, also influence plasma cortisol levels significantly. Past researchers may have underestimated these other systems in their attribution of cortisol levels solely to the HPA axis [3]. Therefore, we prefer the term "cortisol abnormality" if there is no specific observation of HPA axis pathology. On the other hand, we use the term "HPA dysfunction" if there is specific evidence of HPA pathology.

Depression and Cortisol

Since its first definition by Hippocrates as melancholia, both physicians and patients have described stress-provoking events before the onset of clinical depression. Up to 70% of depressed patients report at least one stressful event in the previous year [4]. In a large epidemiological study, subjects carrying susceptibility

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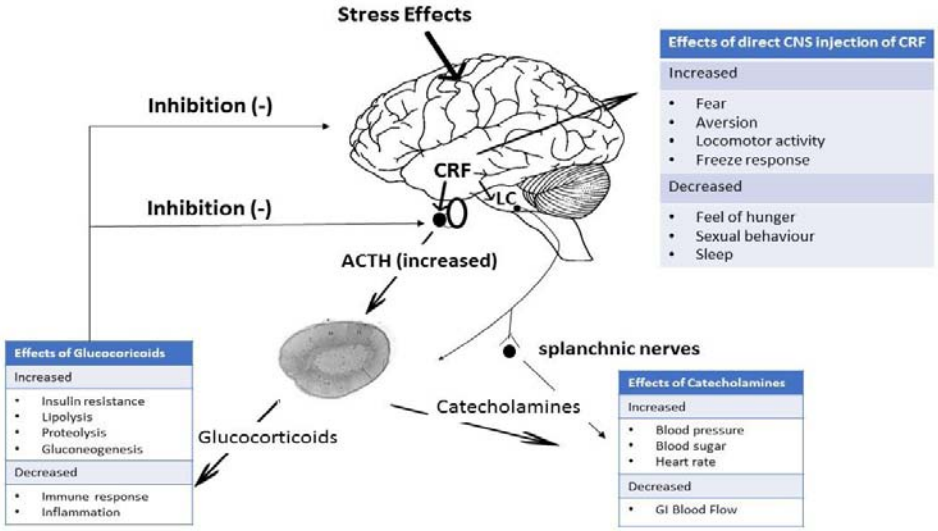

Figure 1: The HPA axis and interaction with other systems.

Box 1

The prolonged stress response varies according to the type of stress. For example chronic exposure to repeated stress such as restraint is associated with increased HPA activity in the first few days but cortisol and ACTH levels gradually normalize with down-regulation of limbic GC receptors. On the other hand, ongoing chronic stress induces amygdala hypertrophy, dendritic remodeling and reduction in hippocampal cell production. Another form of chronic stress such as chronic inflammation is associated with high ACTH and cortisol levels, which lasts as long as inflammation persists. The reduction of parvocellular CRF expression and release whereas the increment of AVP expression and release suggests that AVP plays the primary role for the high ACTH and cortisol during chronic stress.

Box 1:

genes had higher odds for depression if they had a high number of past stressful events compared to those who had a low number [5]. Although the commonly used Diagnostic and Statistical Manual of Mental Disorders (DSM) does not require adverse life events as a criterion preceding the onset of a depressive episode, it recognizes stressful experiences and childhood trauma as risk factors by stating that "Stressful life events are well recognized as precipitants of major depressive episodes, but the presence or absence of adverse life events near the onset of episodes does not appear to provide a useful guide to prognosis or treatment selection" [6]. We strongly suspect that the stress-depression association is an important research area for a more complete understanding of the pathophysiology of depression.

The basic function of the stress response is preserving homoeostasis. The homeostatic threat may range from small everyday annoyances to serious trauma. The brain and body have a reciprocal relationship during the stress response *via* chemical and hormonal feedback loops. The best known stress system consists of the HPA axis, which is activated by neurons located in the dorsomedial parvocellular subdivision of the hypothalamus [7] (Figure 1). These neurons synthesize Corticotrophin-Releasing Hormone (CRH) as well as Vasopressin (VP), which are released into portal circulation. CRH reaches the anterior pituitary gland where it stimulates the secretion of Adrenocorticotrophic Hormone (ACTH) into peripheral circulation. The primary target of ACTH is the zona fasciculata of the adrenal gland, where it stimulates the production and secretion of Glucocorticoids (GC) (cortisol in humans, corticosterone in rats). Glucocorticoids influence metabolic and immune systems, especially during stress. Cortisol adaptively enhances gluconeogenesis and increased vascular tone during the acute stress response, but a prolonged stress response increases the risk of disease states like diabetes or hypertension [8,9]. In the case of prolonged stress, adaptations (e.g. target organ desensitization) take place to reduce deleterious long-term cortisol effects (Box 1).

The brain's stress response is similar to that of other organs in that a temporary cortisol surge is helpful for metabolic adaptation and augments cognitive functions like memory and alertness during the acute stress response [10]. On the other hand, prolonged high cortisol levels in chronic stress apparently cause neuronal atrophy and decreased neurogenesis in the hippocampal formation and other brain regions, resulting in impaired cognitive functions. Therefore, the fine-tuning of cortisol levels is not only essential for optimum functioning under stress but also for prevention of neuronal damage in the long-term. The fine-tuning of cortisol secretion depends on free (unbound) cortisol, which has a regulatory effect on HPA axis, as well as the axis itself. Stimulation of cortisol receptors in the pituitary, hypothalamus and many areas of the limbic system (i.e. hippocampal

Box 2

There are two kinds of GC receptors. c have a high affinity for endogenous corticosteroids compared to Glucocorticoid (Type II) Receptors (GR). The high-affinity MR are typically saturated under resting conditions, and the pulsatile cortisol secretions mainly stimulate GR. Therefore, it is believed that GR receptors are more important for regulation of HPA axis. GR receptors also show high affinity for dexamethasone whereas MR receptors do not.

Box 2:

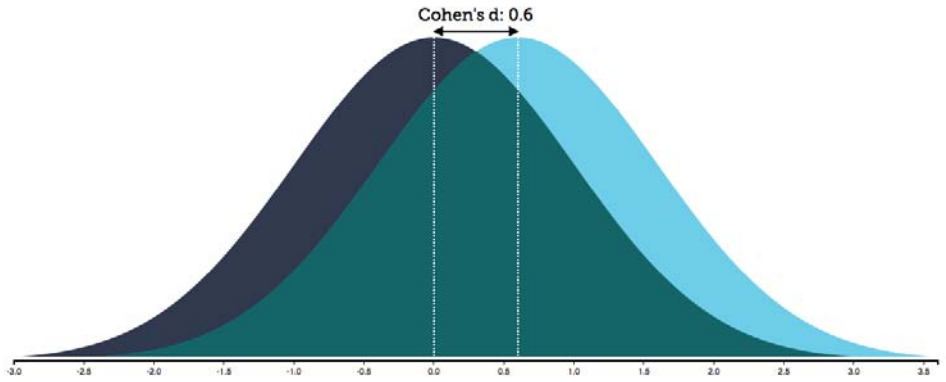

Figure 2: Hypothetical Gaussian Curves for the cortisol levels of healthy subjects and depressed patients. Black curve represents healthy subjects and blue curve represents patients. Although there is a large overlap (76%) among the groups, 73% of depressed subjects' values are above the mean of the healthy subjects. X axis represents standard deviations.

formation, amygdala) can reduce cortisol levels following the reduction of ACTH levels (Box 2).

Although cortisol and its secretion are generally studied under challenging conditions, cortisol is an essential hormone that is needed to meet everyday life challenges. Cortisol follows a circadian rhythm reaching its peak around sunrise and its lowest value around midnight [7] under the control of pulsatile secretion of CRH.

Based on the idea that depression is associated with stress, pioneer researchers measured the cortisol levels of depressed patients. Initial studies found increased cortisol secretion or loss of daily rhythm (i.e. normal cortisol levels in the morning with higher cortisol values in the evening) [11-13]. However, those studies most commonly recruited small samples of patients with severe depression such as hospitalized melancholic patients and patients with psychotic features. Subsequent studies with larger but heterogeneous sample groups confirmed the higher cortisol values in depressed patients, with a medium effect size (Cohen's d=0.6) [14]. It is important to consider this number carefully because it implies that up to 76% of the cortisol values of depressed patients and healthy subjects overlap but 73% of depressed subjects' values are above the mean of the healthy subjects (Figure 2). There is a 66% chance that a person picked at random from the depressed group will have higher cortisol levels than a person picked at random from the healthy group (probability of superiority).

Long-term high cortisol secretion in depressed patients suggests that the regulatory HPA feedback mechanism involving cortisol is not functioning, as it should. One way to test the cortisol feedback system is to stimulate GC receptors at different levels of the HPA axis. Under normal conditions, stimulation of cortisol receptors would reduce HPA axis activity. Dexamethasone is a synthetic cortisol, which has a capability of inhibiting the pituitary-adrenal segment of the HPA axis but cannot reach the hypothalamus or other brain areas because of the presence of the P-glycoprotein blood brain barrier. During a Dexamethasone Suppression Test (DST) [15], low dose dexamethasone (i.e. 1 mg) administration in the evening stimulates only the GC receptors at the pituitary and decreases cortisol secretion *via* reducing ACTH levels. It is generally assumed that non-suppression of cortisol represents GC receptor resistance [16]. Up to 45% of depressed patients have higher post-dexamethasone cortisol levels than healthy controls [14]. The reduced sensitivity of GC receptors to dexamethasone is generally accepted as evidence for GC resistance to cortisol during depression, and depressed patients with high daily cortisol level also show DST non-suppression [17]. Further support for the idea of reduced GC receptor sensitivity in depression comes from treatment studies finding that Tricyclic Antidepressants (TCAs) increase the sensitivity of GC receptors leading to cortisol reduction [18]. (There are mixed results for Selective Serotonin Reuptake Inhibitors (SSRIs)). Reduced cortisol sensitivity of GC receptors leads to reduced physiological activity of cortisol in the body generally. Thus, high plasma cortisol levels might not produce the expected effects in specific target organs [19]. This might be a reason why we do not observe Cushing-like symptoms (increasing abdominal fat, round face, dermal stretch marks) among the primary depressive symptoms.

One problem with hyperactive HPA axis theory is that ACTH levels, which regulate cortisol levels at the adrenal cortex, do not show a parallel increase in depression: only 20% (Cohen's d=0.28) of depressed patients have increased ACTH levels compared to controls

[14]. This finding suggests that other factors affecting the adrenal gland might influence cortisol secretion. The sensitivity of ACTH receptors, sex hormones, immune system activation, and direct stimulation of the sympathetic system *via* the splenic nerve (sympathetic-adrenal-medullary axis) are examples of factors that modulate cortisol levels [20]. Altered functioning of the immune system (increase in TNF-α and IL-6) and the Autonomic Nervous System (ANS) are well-known findings in depression [21,22]. Removal of splenic nerve input to the adrenal glands increases cortisol secretion by augmenting adrenal responsiveness to ACTH [23]. During metabolic challenges, cortisol hyper secretion is dependent on ACTH sensitization [24]. Thus, cortisol levels of depressed patients do not depend solely on pituitary-adrenal axis function, and other factors that have a direct effect on cortisol secretion should be considered.

Depression subgroups

Although it is widely accepted that cortisol levels are high in depression, the literature suggests that only about 2/3 of depressed patients have higher cortisol levels than the average healthy subject. Why do some patients have abnormally high cortisol levels while the others do not? Can symptom heterogeneity and diagnostic problems underlie the low validity of cortisol findings?

For the last century clinicians have tried to define subgroups of depression with better symptom clustering. Based on those efforts, American Psychiatric Association (APA) recognized several subtypes and included them in the DSM system. Different subtypes of depression might be associated with different cortisol levels. Depressive patients with melancholic or psychotic features have higher cortisol levels than other depressive patients [14,25]. Although melancholic or psychotic features are generally associated with the severity of depression, the severity and the features of a depressive episode have independent associations with cortisol levels [14]. Furthermore dexamethasone non-suppression rates are higher in patients manifesting psychotic depression (64%) compared to those of non-psychotic patients (45%) [26]. In contrast, depressed patients with atypical features have normal or even low cortisol levels [27]. However, sub typing only partially explains the large variation in cortisol levels of depressed patients because more than 50% of depressed patients cannot be classified as one of those subtypes. Furthermore, in the long-term, patients often show differing symptom profiles in successive depressive episodes. Almost half of depressed patients have varying degrees of melancholia with atypical symptoms [28] and young patients with psychotic features have a higher incidence of mania in the forthcoming years [29]. Bipolar patients also show HPA dysfunction and recent meta-analyses suggested that HPA dysfunction rates are higher than those of unipolar depressed patients [30,31].

In recent years the generality of high cortisol levels in depression has been challenged further by findings of reduced cortisol levels in outpatient populations, not necessarily associated with atypical features [32]. These unexpected low cortisol findings were initially linked to comorbidity [33] because patients with comorbid anxiety disorders such as PTSD were reported to have lower cortisol levels than those suffering from depression alone [34]. However, more recent studies have found anxiety levels in depression to be associated with higher rather than lower cortisol levels [35]. But the finding of low rather than high cortisol levels in depressed patients without significant comorbidity has persisted [32,36].

Is HPA Dysfunction a State or Trait Factor?

It has long been questioned whether cortisol alteration is a state or a trait factor for depression. Trait factors should be present before the onset of the disease and also should be present between episodes. Moreover, trait factors may be present in the relatives of patients as endophenotypes. Endophenotypes are genetically transmitted and may be closely related to the etiopathogeneis of the disease. On the other hand, state factors are present only during a specific time window when the disease symptoms are present. The answer to the question of whether cortisol alterations in depressed patients are a trait or state factor is crucial for understanding the role of the HPA axis in the etiopathogeneis of the disease. So far there is no clear answer. Depression patients in remission show large variations in cortisol values. With some studies reporting state-like normalization of cortisol values while others show continued trait-like altered values. Recent studies further suggest that a hypoactive HPA axis is not an exceptional finding among remitted patients [32,36]. It is interesting that cortisol levels during the disease state also predict the cortisol levels in after treatment and more than half of the patients (56%) have similar cortisol levels before and after treatment regardless of symptomatic improvement [37].

Some confounding factor such as comorbidity discussed above might be responsible for the inconsistencies [38-40]. Another important confounding factor may be the proximity of future relapse. Both high [41,42] and low cortisol levels have been found to predict relapses [43-46]. Yet another confounding factor is being on antidepressant treatment. Antidepressants may have direct and indirect effects on the HPA axis *via* cortisol receptors or other mechanisms (e.g. antidepressants may decrease the amygdala's response to negative stimuli, reducing HPA activity). Antidepressants may exert a bidirectional normalizing effect on HPA axis activity and cortisol secretion in depressed patients [47]. Perhaps all one can say at this point is that HPA axis dysfunction and cortisol level alteration are present during remission in a majority of patients, though the details are unclear.

Supporting the view of altered cortisol levels or HPA axis dysfunction as a trait factor, investigators have reported abnormal (increased or decreased) morning cortisol levels in the healthy high-risk children of depressed patients [48,49]. Cortisol patterns during the day or after a Dex/CRH test are highly similar between such high-risk children and their depressive parents [36,50]. Cortisol values are similar and stable among discordant monozygotic twins, although the individuals with a history of MDD showed slightly higher cortisol than their discordant siblings [51]. These findings are important evidence that cortisol alterations in depression might be traits related to genetic mechanisms and present before the symptom onset.

Because cortisol secretion is a dynamic process and levels change in response to everyday stressors, researchers investigated the interaction between multiple cortisol measurement and daily events (Box 3). Depressed patients show blunted HPA axis responses to negative daily events and mood changes [52], and LeMoult et al. found further evidence for cortisol alterations in subjects before the disease onset [50]. Traumatic life events predicted depression in girls

Box 3

One of the important developments in the methodology is salivary cortisol measurement**.** Itenables the sampling of large numbers of subjects in ecologically valid conditions. It appears that salivary cortisol has time sensitivity and the gap between patients and controls is more prominent after 30 minutes of awakening whereas at 60 minutes the gap diminishes. Despite the fact that salivary measurement represents free (unbound) cortisol levels**,** while plasma measurements represent total cortisol levels (both bound and unbound); there is a strong correlation between salivary cortisol and post-dexamethasone cortisol [15]. One meta-analysis showed that morning salivary cortisol levels are higher in depressed patients, but there are high intra-assay coefficients of variations in cortisol kits [88]. Therefore, we need standardization of kits for measuring salivary cortisol.

Box 3:

with high cumulative cortisol secretion through the day but not in girls with low cortisol secretion.

Beyond the genes, epigenetic mechanisms might also influence the HPA axis and cortisol secretions. The childhood trauma is one of the best-known environmental factor affecting epigenetic mechanisms. Animal and human data suggest that early adversities increase HPA axis sensitivity to stress, producing abnormal cortisol levels during the stress response [53]. It seems that this effect is independent of having depressed parents.

One other well-known pre-disease vulnerability factor for depression is neuroticism. This trait-like vulnerability factor increases the odds of depression when it is associated with high morning cortisol levels in youths [54].

In conclusion, the present data suggest that trait-like cortisol level abnormalities (high or low) are present in high-risk subjects, both those with depressed parents and those with traumatic childhoods. During inter-episode periods, abnormal cortisol levels also constitute a risk factor for relapse. The presence of altered cortisol levels before the disease onset in high-risk groups and during the inter-episode periods of patients suggest that altered cortisol levels should be accepted as trait factor for depression for some groups of patients. However, we are still well short of defining the precise characteristics of such patient groups.

Does Cortisol Alter Brain Structures in the Depressed Patients?

A substantial literature exists examining the effects of cortisol on neural structures and functions. Acutely increased cortisol improves attention and memory functions, but chronically high cortisol has detrimental effects on both cognitive functions and neuronal structures [55]. Cortisol changes the energy metabolism of neurons and in the long-term leads to neuronal atrophy and cell death [56]. The reduction of new cell formation from stem cells is associated with depressive symptoms [57]. The hippocampal formation, which is intimately involved in memory, spatial orientation, and HPA regulation, comprises the neurons most sensitive to hypoxia and metabolic alteration. Whether cellular changes secondary to increased cortisol result in frank hippocampal formation atrophy is unclear, but 8-12% smaller hippocampi have been reported among depressed patients relative to healthy controls [58]. Furthermore, hippocampal formation volume is negatively correlated with the duration of depression, supporting the idea that high cortisol levels might impair new cell formation and lead to atrophy of the existing cells [59]. However, other studies did not show a clear relationship between duration of illness and hippocampal formation volume [60]. This may be because hippocampal atrophy as a function of illness duration appears to be influenced by the chromosome 11 codon 66 genotype, being present in Val66Val homozygotes but absent among Val66Met heterozygotes [61]. The val66met allele codes for brain derived neurotrophic factor which exerts a protective effect on hippocampal neurons [62]. Long-term follow-up studies (6 months to 11 years) do not show a further reduction in total hippocampal formation volume, but subjects with a smaller hippocampal formation have higher odds for relapse [63-67]. Age might have significant moderating effect. Elderly but not adolescent depressed patients had hippocampal formation volume loss in a long-term follow-up [66,67] and depression is a risk factor for dementia among the elderly [68].

In recent years, with the help of advanced imaging techniques, subfields of the hippocampal formation have been measured *in vivo*, and regional changes (rather than total volume) have been reported during long follow-up periods [65]. The hippocampal formation consists of three histologically identified subfields: the hippocampus proper or Cornu Ammonis (CA) with its areas CA1-4; the Dentate Gyrus (DG) with its superficial layer the hilus; and the subiculum. Among those regions, the DG is where stem cells replicate and differentiate into neurons. Preclinical studies have proposed that neurogenesis in this region is helpful for clinical recovery [69]. However, rather than the DG, the subiculum has been the most commonly reported region for structural alteration in depressed patients [65,70]. This is perhaps not surprising as the subiculum is the formation's major output structure projecting to frontal, parieto-occipital, and temporal cortex.

A few studies have shown a relationship between cortisol levels and hippocampal formation volume [71-73], and the correlations have been mostly negative, but concern remains that single cortisol levels might not be sufficient to assess HPA axis dysfunction. With new brain imaging and cortisol rhythm measurement techniques, future studies are awaited to show the relationship between cortisol levels and hippocampal formation structure, especially in specific regions.

Beyond the hippocampal formation, meta-analyses have suggested that other limbic regions (cingulate cortex, insula) and frontal cortex

are smaller in depressed patients [74]. Post-mortem investigations indicate that a loss of glial cells and neuronal atrophy might underlie the smaller brain regions [75]. The effects of cortisol on those regions are speculative and still under investigation [Arnsten, 2009].

Antiglucocorticoid Drugs for Treating Depression

Currently available antidepressants produce their efficacy *via* monoamine transmitters. Most of them inhibit serotonin and/or noradrenaline reuptake and increase monoamine concentration in the synaptic cleft. Those drugs, particularly the tricyclics, also increase the sensitivity of cortisol receptors and decrease HPA activity. On the other hand, there are only a few available drugs that inhibit cortisol synthesis and none has been approved for depression treatment alone or as an adjunct to ongoing antidepressant treatment. Among those drugs, metyrapone, which decreases cortisol synthesis by inhibiting the final step enzyme (11 beta-hydroxylase), was tested as an adjunct or augmentation treatment in depressed patients. In the first placebo-controlled study with 63 patients, metyrapone was superior to placebo as an adjunct therapy to SSRIs, accelerating the onset of antidepressant action and producing a better treatment outcome (more patients responded to treatment) [76]. But a second placebo-controlled study which enrolled 165 treatment resistant patients, fond no difference [77]. In both studies measured cortisol levels were unchanged with metyrapone treatment, perhaps reflecting HPA axis dysfunction in depression.

Ketoconazole, which similarly decreases cortisol synthesis by inhibiting a number of enzymes in the production chain, also acts as a GC receptor blocker. It is used primarily as a fungicidal drug at lower doses and may cause significant side effects at the higher doses required for antiglucocorticoid activity. Initial case reports suggested that ketoconazole might be a promising drug. However, two blind studies did not yield the expected results. In one, improvements of depressive symptoms were observed only in hypercortisolemic patients [78], and in the other no improvement was seen [79].

Although *in vivo* human studies have yielded conflicting results on Cerebrospinal Fluid (CSF) or blood CRH levels in depressed patients, animal studies have shown that high CRH secretion or exogenous CRH injection causes depressive and anxiety symptoms [7]. Furthermore, antidepressant or anxiolytic effects of CRH antagonists were found in animal models. However, clinical trials have not been promising [80,81].

Vasopressin is a peptide, which is released with CRH from the hypothalamus. It potentiates the action of CRH on ACTH. Vasopressin levels are increased in depressed patients and decreased with antidepressant treatment [82]. Vasopressin alone has a capacity for maintaining the basal ACTH secretion and HPA system activity in mice deficient for the CRH receptor. However, clinical trials with the vasopressin receptor antagonist SS149415 showed no superiority over placebo in depressed patients.

As a high cortisol level is accepted by many investigators as evidence of HPA dysfunction in depression, administrating glucocorticoid receptor blockers might directly reduce the detrimental effects of high cortisol and indirectly lead to up-regulation of the glucocorticoid receptor numbers, further enhancing cortisol's negative feedback on the HPA axis after removal of the blockers. Mifepristone is an antagonist with a high affinity for both progesterone and glucocorticoid receptors, increasing ACTH and cortisol in both patients and healthy subjects. Two controlled studies suggest that mifepristone is effective in decreasing psychotic symptoms in depression but not core depressive symptoms [83,84].

Among the antiglucocorticoid treatments, the most promising results have come from Dehydroepiandrosterone (DHEA) trials. Like cortisol, DHEA is secreted by the adrenal cortex and may interfere with cortisol *via* multiple mechanisms including decreasing cortisol activity at the receptor level. In open-label and double-blind studies, an antidepressant effect of DHEA has been reported [85-87].

Conclusions

After 50 years of investigating the HPA axis and cortisol in depressed patients it is hard to say we have reached strong conclusions. On the other hand, with each study, we increase our knowledge about the stress response, factors affecting the HPA axis and the neurobiology of depression.

1. During the depressed state abnormal cortisol levels are seen in nearly 50% of patients, and this proportion is higher in specific subgroups such as those with psychotic and melancholic features. With recent developments in cortisol measurements (e.g. repeated salivary cortisol measurement during the day in real life situations) [88], it will be possible to study acute cortisol abnormalities that we cannot presently detect, and the percentage of depressed patients showing cortisol abnormalities is likely to increase.

2. Most of the patients who manifest cortisol abnormalities during depression show similar abnormalities between the episodes. Furthermore, high-risk groups such as the patients' children and other relatives also show evidence of cortisol abnormality and/or HPA dysfunction. Thus, cortisol alteration and/or HPA dysfunction are strong candidates for trait-like endophenotypic features of depression susceptibility.

3. During remission the low cortisol levels found in some high-risk patient groups may be related to a pituitary CRH receptor down-regulation following a long period of stress-induced hypothalamic CRH secretion during depressive episodes [89]. This also may be a trait marker for a specific group of patients.

4. Cortisol is an end product of HPA axis activity, but the HPA axis is not the only system that controls cortisol secretion. Other factors (immune system, sex hormones, ANS) that are also involved in the pathophysiology depression might influence cortisol levels and have not been well studied in that context.

5. There is no currently available antiglucocorticoid treatment for depression. However, there is some evidence that antiglucocorticoids might be effective in ameliorating psychotic symptoms in psychotic depression.

6. It is well known that chronically high cortisol has deleterious effects on neurons and glial cells. However, it is unclear whether observable structural changes in the hippocampal formation and other brain regions in depression are caused by high cortisol levels. Advanced neuroimaging studies are needed to show the details of cortisol's effect on the brain.

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