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Glucocorticoid Sensitivity in Mood Disorders

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Key Words

Glucocorticoid sensitivity · Glucocorticoid receptor · Mineralocorticoid receptor · Cortisol-releasing hormone receptor-1 · Polymorphisms · Mood disorders · Cortisol awakening rise · Scalp hairs · Childhood adversity

Abstract

In this review, we provide an overview of recent literature on glucocorticoid (GC) sensitivity in mood disorders. Assessing GC sensitivity is often performed by measuring the cortisol awakening rise (CAR), by challenging the hypothalamic-pituitary–adrenal (HPA) axis using a dexamethasone suppression test (DST) or a dexamethasone/cortisol-releasing hormone test (DEX/CRH); more recently by measuring cortisol as a retrospective calendar in scalp hair. The main findings in mood disorders are higher mean cortisol levels in hair samples and a higher CAR, showing a hyperactivity of the HPA axis. This is in line with the mild resistance for GCs previously observed in challenge tests during mood episodes. GC sensitivity is partly determined by polymorphisms in the genes encoding receptors and other proteins involved in the regulation of the HPA axis. We shortly discuss the glucocorticoid receptor, as well as the mineralocorticoid receptor, the cortisol-releasing hormone receptor-1, and the glucocorticoid receptor co-chaperone FKBP5. Data clearly indicate genetic changes, along with epigenetic changes which influence the set-point and regulation of the HPA axis. Early trauma, as well as influences in utero, appears to be important. Future research is necessary to further clarify the biological background and consequences of an individual's cortisol exposure in relation to mood.

Introduction

During daily life, mood is known to be largely influenced by circadian rhythms and stress. An individual's risk to develop a mood disorder can depend on one or a combination of factors including vulnerability, defined by genetics, early life stress, and consequences of life events. The biological stress response has an important function in coping with life events, and differs between individuals with a genetically and epigenetically determined set-point during youth. The key systems in the stress response are regulated by fast adrenergic neurotransmitters (the sympathetic nervous system) and slower glucocorticoid hormones (the hypothalamic-pituitary–adrenal (HPA) axis), of which cortisol is the main hormone in humans. It is complex to properly measure and assess the functioning of the HPA axis in humans. However, it is important to evaluate the role of the stress response and hence the flexibility of the individual to cope with physical and mental changes in life in order to identify risk factors defining health and disease. In addition, an individual's level of chronic cortisol exposure in brain areas related to affection and cognition may be very important in mood disorders. Aside from the stress system reactivity, it is also important to mention the consequences of absolute high and low cortisol levels. The consequences of absolute high cortisol levels are best observed in the clinically well-known Cushing's syndrome, where cortisol levels are usually extremely high due to exogenous or endogenous causes. These symptoms can vary between physical symptoms, for example weight gain, increase abdominal fat, hyperhidrosis and hirsut-

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ism, and psychiatric symptoms, for example manic and depressive episodes, psychosis and anxiety. Also hypocortisolism as seen in morbus Addison can have serious consequences on mental health, making patients vulnerable to mood disorders and anxiety.

Cortisol is known to exert its effect through two receptors: the glucocorticoid receptor (GR) and the mineralocorticoid receptor (MR). Both receptors are also present in the brain. The GR is found throughout the brain, with a very high density in the hippocampus, the prefrontal cortex (PFC), the paraventricular nucleus of the hypothalamus, the amygdala and the dentate gyrus. The MR is predominantly found in the hippocampus, the PFC and the amygdala [1]. The GR is known to be an important regulator during the acute stress response, while both GR and MR are active under basal conditions. Both corticosteroid receptors are co-expressed in the limbic system, and it seems obvious that both receptor systems have a balanced function in regulating the stress response [2]. FKBP5, a co-chaperone of the GR, also influences GR activity [3]. Finally, the cortisol-releasing hormone receptor-1 (CRHR1) is important in initiating the stress response.

Assessment of Glucocorticoid Sensitivity in Relation to Mood

Functional evaluation of the HPA axis is complex. The HPA axis is characterized by daily rhythms, seasonal rhythms, and pulsation leading to varying cortisol levels in blood and saliva. The two most common approaches to evaluate HPA axis functioning are the measurement of basal cortisol levels in response to awakening, as a model for an endogenous stress response; and the measurement of the HPA axis functioning during challenging conditions, which gives an impression about the reactivity of the stress response itself. This measurement is characterized by negative feedback at the pituitary level on the production of adrenocorticotropic hormone (ACTH), and hence by diminished stimulation of the cortisol production in the adrenal glands.

The Cortisol Awakening Rise

It is best to collect samples immediately upon waking to evaluate the cortisol awakening rise (CAR), which reflects the natural response to awakening with an increase in cortisol levels of 50–75% within half an hour after awakening [4]. Several influences on the CAR are defined by Vreeburg et al. [5], including sleep patterns (duration, awakening time), season of sampling, activities (working day, physical activity) and health indicators (smoking, cardiovascular disease, physical activity). Also psychosocial stressors and job stress have been found to result in higher CARs, whereas exhaustion and burnout resulted in lower CARs [6].

In patients with mood disorders, a higher CAR was observed in both remitted (n = 579) and currently depressed (n = 701) patients [7]. In acutely depressed outpatients, cortisol levels were 25% higher compared with healthy controls [8]. In addition to this finding, a study among 230 late adolescents revealed that a higher CAR was predictive for developing a major depressive disorder (MDD) within a year after sampling [9]. In addition, subjects without a history of depression but with parents diagnosed with MDD had higher CARs, which were equal to the subjects with a current depression [10]. It seems that these findings reflect higher basal cortisol levels as a trait phenomenon irrespective of current status.

Challenging the HPA axis

The dexamethasone suppression test (DST) is a neuroendocrine test measuring GR-mediated negative feedback. This test consists of a low-dose administration (1 mg or 0.25 mg) of dexamethasone, a synthetic glucocorticoid hormone, at 11 p.m. and the measurement of cortisol levels the following morning. Due to the negative feedback action at the pituitary and hypothalamic levels, subsequent cortisol levels are suppressed the next day. Nonsuppression of cortisol levels after dexamethasone indicates GR resistance. The strength of cortisol suppression reflects the negative feedback mechanism, which is largely variable between but rather stable within individuals [11]. The test is very easy; however, an important restriction to consider for use in psychiatry is the limited sensitivity in studying MDD [12]. Particularly in outpatients, the sensitivity is low. It was reported that only 12% of outpatients with nonmelancholic depression showed nonsuppression in the DST, while 64% patients with psychotic depression showed nonsuppression [12]. Low percentages of nonsuppression after 1–2 mg dexamethasone in moderately depressed patients (44%) were found, in contrast with severely depressed psychotic patients and bipolar patients (67–78%) [13]. Heuser et al. [14] developed the combined DEX/Cortisol Releasing Hormone test (DEX/CRH test) as a refinement of the DST. This challenge test consists of administration of 1.5 mg dexamethasone at 11:00 p.m. followed by administration of 100 μg CRH at 3 p.m. on the next day. Cortisol and ACTH levels are sampled every 15 min from 2 p.m. until 6 p.m.

This test was found to be more sensitive for MDD (about 80%), and is even above 90% when the cohort was stratified for age.

However, the DEX/CRH test is more intrusive for patients, which limits the use in research among large cohorts of outpatients. Zobel et al. [15] found that in a cohort of 74 remitted patients, the DEX/CRH test was able to predict relapse of depression within 6 months. In patients with a relapse within 6 months after discharge, there was a 4- to 6-fold increased cortisol response in the DEX/CRH test just before discharge. Appelhof et al. [16] found in a sample of 45 outpatients with remitted major depression that higher cortisol levels in the DEX/CRH test were associated with relapse, which was confirmed by Ising et al. [17]. Rybakowski's group [84] also stressed that the number of episodes was associated with more non-suppression. Bipolar patients in the same study were found to have most non-suppression when compared with healthy controls and unipolar depressed patients in remission. Watson et al. [18] confirmed that in bipolar patients, cortisol levels in response to the DEX/CRH test are increased, with no difference between a current depressive episode and remission.

The issue whether this is a state or trait phenomenon is not yet solved. The studies including healthy family members suggest that hyperactivity of the HPA axis is not only a reflection of current mood state [19]. A new approach to this problem is the scar theory [20], describing long-lasting changes in the function of the brain (cognition, biological) following depression, increasing the risk for developing future depressive episodes. The premorbid regulated 'set-point' of the HPA axis is thought to be changed through depression by, for example, epigenetic changes in DNA methylation in depressed suicide victims [21] and children of mothers who were depressed during pregnancy [22]. This scarring process is possibly a structural phenomenon developed during life. Later, we will briefly discuss the influence of early life trauma on epigenetic phenomena.

Cortisol in Scalp Hairs

A novel and noninvasive parameter is measuring cortisol in scalp hair. Hair grows with an average of 1 cm per month, and it has been shown that cortisol can be reliably measured in hair [23–25]. The use of hair provides the opportunity to measure long-term cortisol levels (reflecting mean levels of the past months) in an easy way without limitations caused by the pulsatility and circadian rhythm of cortisol or acute circumstances. Strong correlations of hair cortisol have been observed with tissue effects of cortisol in healthy individuals (e.g. waist circumference), as well as with cortisol exposure in patients with hyper- or hypocortisolism [25]. This method has only preliminary been applied in psychiatry. Steudte et al. [26] found a decreased cortisol level in patients with generalized anxiety disorder. Our group recently found that cortisol levels were increased in patients with BD when having a co-morbid psychiatric diagnosis [27]. Interestingly, hair cortisol levels were decreased when patients with BD were also diagnosed with panic disorder. Moreover, we found an association of higher hair cortisol levels with adult onset (older than 30 years) of BD, and impaired executive functioning, compared to patients with puberty onset, normal executive functioning and normal cortisol levels [28].

Genetics of HPA Axis: Consequences for Physical and Mental Health

GR Polymorphisms: Physical Health

There are several known genetic variations in the GR Gene *NR3C1* with consequences for cortisol sensitivity [29]. Subtle changes in cortisol signaling leading to relative resistance or hypersensitivity for glucocorticoids (GCs) can have long-term consequences. It is known that these changes can affect metabolic and inflammatory status and body composition. Cognitive performance and mental health can also be influenced by altered HPA axis regulation.

Haplotype 4 (*TthIII*I + 9β) and haplotype 5 (*TthIII*I + 9β + ER22/23EK) are both associated with a relative resistance for GCs [30–33]. The ER22/23EK polymorphism is associated with a healthy metabolic and inflammatory profile, characterized by lower total cholesterol and low-density lipoprotein cholesterol levels as well as lower fasting insulin concentrations, a better insulin sensitivity and lower C-reactive protein levels [31, 34]. This GR variant is also associated with a beneficial body composition, shown by young male ER22/23EK carriers (taller, stronger and more muscle mass than noncarriers) and female ER22/23EK carriers (tendencies for smaller waist and hip circumferences, lower body weight [35], and protective effect on weight gain during pregnancy [32, 36]). These associations of the ER22/23EK polymorphism are in line with a mild GR resistance. The clinical data are supported by in vitro experiments showing reduction of transactivating capacity in transfection experiments and in peripheral blood mononuclear lymphocytes of carriers of this polymorphism [37]. In addition, the underlying molecular mechanism of the GR gene variant has been revealed [38].

The 9β-polymorphism seems to increase the stability of mRNA of GR-β, an alternative splice variant of the GR gene [30]. GR-β is thought to exert a dominant negative effect on the active GR-α. The association of the 9β polymorphism and the immune system has been shown by the higher risk of developing rheumatoid arthritis in carriers [30, 39]. Patients with multiple sclerosis have been found to have a more aggressive course of disease when they carry at least one allele of haplotype 5 (*TthIII*I + 9β + ER22/23EK), which is possibly related with an altered inflammatory state due to GC resistance [40]. Interestingly, in 2008 van den Akker et al. [41] reported that the 9β polymorphism is related to a more active proinflammatory system, and subsequently associated with the risk of cardiovascular disease. In line with these findings, the Heart and Soul Study showed that the 9β SNP is associated with reduced heart function, partly mediated by low-grade inflammation [42].

Haplotype 2 (*Bcl*I), haplotype 3 (*TthIII*I + *Bcl*I) and haplotype 6 (N363S) have all been associated with a relative hypersensitivity to GCs and clinical signs of hypersensitivity to cortisol in various tissues [43]. Carriers of N363S have in addition to increased cortisol suppression also an increased insulin response in the DST, a tendency towards lower bone mineral density, and increased BMI [32]. Although other studies have reported associations with increased BMI, as expected as a result of glucocorticoid hypersensitivity, these findings have not been consistently confirmed [29, 44]. The *Bcl*I polymorphism has been found to be associated with abdominal obesity [32], lower bone mineral density [45] and unhealthy body composition in young boys [46].

GR Polymorphisms: Mental Health

Recently, we reviewed the GR and MR SNPs in relation to mood disorders [47]. The most important findings will be summarized and supplemented by recent progress in this area of research. The ER22/23EK polymorphism has repeatedly been associated with a higher risk on developing a depressive episode [48–50], and a faster response after antidepressant treatment [48]. In the study of Bet et al. [50], an association to this polymorphism and clinically relevant depressive symptoms in an elderly population was only found in combination with childhood adversity, indicating a gene-environment interaction. Recently, attention has been directed to the 9β SNP in relation to mood. In a sample of 245 bipolar patients, we found an association between the 9β polymorphism and reduced risk of (hypo)mania. In the aforementioned study of Bet et al., a relationship between this SNP and clinically relevant depressive symptoms, in combination with childhood adversity, was found [50]. Recently, in a sample of 173 patients with bipolar I depressive episodes, the response to lamotrigine (anti-epileptic medication used in treatment of bipolar depression) in a subgroup of 88 patients was associated with the GR polymorphisms rs258747 and rs6198 (9β) [52]. Finally, in a group of 526 outpatients with coronary heart disease, the prevalence of depression was increased with an allele-dosage effect (from 24.4% of the noncarriers to 52.9% of the homozygous 9β carriers) [53]. The *Bcl*I polymorphism is also associated with an increased risk on developing a depressive episode [48, 54–56], as well as with a reduced response after antidepressant treatment [54], which was not confirmed by Lee et al. [56]. Remarkably, in the latter study, it was found that in the Korean population there were no carriers of ER22/23EK and N363S. This is consistent with other reports in Asian populations [57].

MR Polymorphisms

Two SNPs in the MR gene are known to have clinical consequences. The V allele in the MRI180V SNP is associated with higher cortisol levels in saliva and plasma in healthy subjects performing the Trier Social Stress Test (a validated psychological procedure inducing acute stress under laboratory circumstances, allowing evaluation of biological measurements of differences in stress levels between individuals). In vitro testing, using transactivational assays, this I180V variant was shown to have a slight loss of function using cortisol as a ligand [58]. This SNP was associated with higher frequency of depressive symptoms in an elderly cohort (participants aged >85 years) [59] and with neuroticism in depressed patients [60]. Another MR SNP, the -2G/C variant, also affects the transactivational capacity of the MR in vitro in response to cortisol. Both SNPs modified cortisol suppression in a DST (0.25 mg DEX) in a sex-specific manner [61].

FKBP5 and CRH-R1 Polymorphisms

An important co-chaperone protein functionally interacting with the GR is FK506 binding protein 5, better known as FKBP5, a member of the immunophilin protein family. Genetic variations in the FKBP5 gene lead to increased intracellular FKBP5 protein expression, which in turn leads to adaptation of the GR function. Healthy subjects carrying these SNPs show GR resistance and diminished negative feedback of the HPA axis. Carriers of these variations have been found to be overrepresented in patients with mood disorders (MDD and BD) and posttraumatic stress disorder [62], as well as respond faster to

antidepressant treatment [63]. Another gene, which is a key factor in the HPA axis, is the CRH1-receptor (CRH-R1). This receptor has been considered as a mediator in initiating the stress response. The CRH-R1 is located in the paraventricular nucleus (PVN) of the hypothalamus, the hippocampus as well as widely distributed beyond the hypothalamus. It interacts with a wide range of neurotransmitters, for example, influences the activity of the 5-$HT_{2A/C}$ receptor [64, 65]. Several SNPs in the CRH-R1 gene have been recently identified and explored in relation with mood disorders. Liu et al. found an overrepresentation of rs242939 in patients with major depression compared to healthy controls [66]. They also found that rs242941 carriers with major depression and high levels of anxiety responded faster after treatment with fluoxetine in 127 Han Chinese patients [67]. This was not confirmed by Dong et al. [68] in a population of 536 unrelated Mexican Americans from Los Angeles. In male suicide attempters, a relation between illness severity and a haplotype of the CRHR1 has been found [69], as well as in their offspring with CRH-R1 haplotypes, who were found to score higher on the Beck Depression Inventory, which was found in the same study.

Interestingly, these SNPs in the CRHR1 gene are also studied in relation with the environment and with other genes. Experiencing childhood abuse leads to a higher risk for developing a lifetime depressive episode specifically in carriers of polymorphisms of the CRH-R1 in combination with the short serotonin transporter gene 5-HTTLPR [70]. In parallel, Bradley et al. [71] found an interaction between SNPS in the CRHR1 gene and childhood abuse as predictor for depressive episodes. In one cohort of more than 1,000 female participants, Polanczyk et al. [72] found that carriers of a haplotype formed by rs7209436, rs110402, and rs242924 who were abused during childhood as measured by the Childhood Trauma Questionnaire (CTQ), are protected against depression in adulthood. This was not replicated in another cohort described in the same study, where childhood abuse was not measured by the CTQ.

A recent review by Binder and Nemeroff [64] extensively summarized the relation between genetics of the CRH system in relation with psychopathology.

Epigenetics of the HPA Axis: Adversity in Childhood

The influence of genetic variations in the DNA sequences of HPA axis related genes on mood disorders is clear, but may only be one brick in the building of our understanding of mood disorders. Of all other influences, it is important to mention epigenetic changes in regulating the 'set-point' of the HPA axis. Epigenetic changes comprise changes in gene expression which remain stable during cell divisions, but do not affect the DNA sequence itself. Epigenetic changes are heritable and could be caused by changes such as those found in DNA methylation, the modeling of chromatin and the de-acetylation of histones in the DNA.

Several circumstances can lead to epigenetic changes, for example intra-uterine influences and changes in early youth due to childhood adversity. A well-known example of intrauterine effects on health in adulthood is the Dutch Famine Birth Cohort study. Children of the women who were pregnant during the famine in World-War II scored lower in mental health, and this effect was repeated in their children's children, suggesting an epigenetic effect [73]. However, there was no relation found with changes in HPA axis regulation [74]. Other studies emphasize the importance of regulation of the HPA axis in utero. Raised GC concentrations during pregnancy are associated with lower birth weight and later during childhood and adulthood with an increased cortisol response during HPA axis activation [75]. As a consequence, these patients are at higher risk to develop obesity and/or diabetes. Yehuda et al. [76] reported that women who were pregnant during the World Trade Center attack and developed posttraumatic stress disorder had lower salivary cortisol levels than did their 1-year-old offspring, suggesting they had already developed a risk factor for posttraumatic stress disorder in later life. Animal studies show that prenatal stressed offspring developed hyperactivation of the HPA axis through epigenetic programming, and develop high anxiety levels and depression-like behavior [77, 78].

In early childhood, the regulation of the HPA axis is further developed. Early life trauma could have devastating consequences for the HPA axis 'set-point'. In a recent review, the relation between early life trauma and the HPA axis is characterized by hypocortisolism and an attenuated cortisol response during acute stress [79], which suggests a dysregulation of the negative feedback mechanism in the HPA axis. This diminished stress response is continued throughout life and tends to worsen with aging [80]. Animal studies have shown that mouse pups that have been separated for several days from their mothers have an increased GR expression in frontal cortical and hippocampal areas during the separation. After the separation they showed a diminished GR expression [81]. In humans, this was recently confirmed

by McGowan et al. [82], showing that suicide victims with a history of childhood abuse had decreased GR mRNA levels in the hippocampus, as well as increased cytosine methylation of the GR. Secure attachment is a central theme in the work of Bowlby and Ainsworth. The 'strange situation' is a classic test, comprising a short separation between mother and child. After reunion the response of the child towards the mother is categorized in attachment styles, reflecting the involvement or neglect/abuse of the mother for her child [83]. Neglect by the mother is devastating for the development of a secure attachment style of the child, with definite changes (e.g. alterations of methylation pattern of the GR) for the rest of its life.

Conclusive Remarks

In conclusion, while accumulating evidence indicates that alterations in the HPA axis are important biological factors in mood disorders, the exact pathophysiological mechanisms are at present not completely understood. This is partly due to the difficulties in assessing the HPA axis. One of the promising future techniques could be the assessment of the long-term cortisol levels through analysis of scalp hairs. The 'set-point' of the HPA axis is influenced by genetic changes in the GR gene, MR gene, CRH-R1 gene and FKBP5 gene, as well as polymorphisms in other genes involved in cortisol signaling. These changes have been associated with mood disturbances. During life this set-point is further defined by epigenetic changes due to intrauterine influences and/or childhood adversity. Finally, during life this set-point could be influenced by mood episodes. As a result, hyperactivity of the HPA axis may increase the vulnerability for future mood episodes.

Future research should focus on new tools in order to obtain a clear indication of an individual's cortisol status. This may provide better opportunities to understand possible causal relationships between cortisol exposure (in the brain) and mood disorders which may yield new treatment strategies.

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