Glucocorticoids

Mood, Memory, and Mechanisms

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Elevated circulating levels of glucocorticoids are associated with psychiatric symptoms across several different conditions. It remains unknown if this hormonal abnormality is a cause or an effect of the psychiatric conditions. For example, the hypercortisolemia observed in a subset of patients with depression may have a direct impact on the symptoms of depression, but it is also possible that the hypercortisolemia merely reflects the stress associated with depression. Further, rather than causing depression, hypercortisolemia could represent a homeostatic attempt to overcome glucocorticoid resistance. Each of these possibilities will be considered, and correlational and causal evidence will be reviewed. This article will focus on the relationships between glucocorticoids and psychiatric symptoms in Cushing’s syndrome, major depression, and steroid psychosis/steroid dementia, as well as the effects of exogenously administered glucocorticoids in normal volunteers. Similarities and differences in the relationship of glucocorticoid hormones to psychiatric symptoms in these conditions will be reviewed. Possible mediators of glucocorticoid effects on the brain and behavior, as well as possible “pro-aging” effects of glucocorticoids in certain cells of the body, will be reviewed. The article concludes with a conceptual model of glucocorticoid actions in the brain that may lead to novel therapeutic opportunities.

Key words: cortisol; dexamethasone; prednisone; steroids; glucocorticoids; glucocorticoid resistance; glucocorticoid receptor; stress; depression; memory; psychosis; dementia; Cushing’s; hippocampus; cytokines; inflammation; oxidative stress; telomeres; telomerase; anti-glucocorticoid; mifepristone; RU-486; ketoconazole; metyrapone

Introduction

Glucocorticoids (GCs) are released during stress as well as diurnally throughout the day and have pleiotropic effects in the body. Depending upon the circumstances, they can promote life and successful adaptation to stress or can contribute to disease and premature death. Elevated circulating GC levels are often seen in association with psychiatric symptoms in depression, Cushing’s syndrome, and (exogenous) steroid psychosis. However, considerable variability exists in these effects, between studies, between individuals and even within individuals over time. The physiological significance of increased circulating GC levels remains unknown, but further clarification may lead to the development of novel classes of hormonally active medications for depression and other psychiatric disorders. In this review, we first consider correlational and causal evidence that GCs are involved in psychiatric symptoms, and we discuss similarities and differences between different syndromes of circulating GC excess. We then discuss...
putative mediators of GC effects on behavior and the brain. We conclude with a conceptual model for understanding certain GC effects on human behavior and the brain and discuss novel therapeutic approaches suggested by this model.

Correlational Evidence for Glucocorticoid Involvement in Psychiatric Symptoms

cushing's Syndrome

Symptom Profile

Among the most compelling lines of evidence supporting a role of hypercortisolemia in psychiatric symptoms is the behavioral presentation of patients with Cushing’s syndrome, a condition typically characterized by cortisol hypersecretion. In his first description of this disease, Harvey Cushing observed symptoms of insomnia, inability to concentrate, visual disturbances, and “fits of irritability (alternating) with periods of depression” (p. 137). Starkman and colleagues have documented a markedly increased rate of psychiatric symptoms, such as (in decreasing order of frequency, but all occurring in over 50% of patients) fatigue, decreased energy, irritability, impaired memory, depressed mood, decreased libido, insomnia (especially initial insomnia), anxiety, impaired concentration, crying, and restlessness. Psychosis is also prominent in some patients. The specific aspects of memory that are impaired suggest dysfunction of the neocortex and hippocampus, areas of the brain densely populated with glucocorticoid receptors (GRs). Alterations of electroencephalographic coherence in association with increasing hypercortisolism in Cushing’s syndrome have also been reported. The psychiatric presentation of Cushing’s syndrome partially resembles that of major depression. In one study, 83% of patients with Cushing’s syndrome met strict diagnostic criteria for an affective disorder, as defined by the Research Diagnostic Criteria; 67% met criteria for “endogenous depression” and 27% for mania or hypomania. Certain differences exist, however: the mood changes in Cushing’s syndrome are typically more labile than those in major depression, and the neurovegetative symptoms are predominantly “atypical.” Compared to some other endocrinopathies, such as Grave’s disease, psychiatric symptoms are significantly more common in Cushing’s syndrome patients, suggesting the psychiatric symptoms are not simply nonspecific responses to being ill.

The Relationship of Cortisol and Adrenocorticotropic Hormone Levels to Psychiatric Symptoms in Cushing’s Syndrome

Psychiatric disability in Cushing’s syndrome is directly correlated with cortisol concentrations, and depression ratings and cognitive function improve in direct relationship to treatment-associated resolution of the hypercortisolemia. The symptoms that most clearly improve with treatment of the hypercortisolemia are (in descending order): depression, concentration difficulties, insomnia, memory disturbance, and irritability. Psychiatric symptoms in Cushing’s syndrome are more closely related to elevated cortisol levels than to elevated adrenocorticotropic hormone (ACTH) levels, since depression is equally common in Cushing’s disease (characterized by hypercortisolemia in response to increased ACTH secretion) and in Cushing’s syndrome (in which ACTH levels are decreased).

Cortisol and the Hippocampus in Cushing’s Syndrome

Starkman et al. have also demonstrated decreased hippocampal volume in Cushing’s syndrome patients. In these studies, hippocampal volume was inversely correlated with circulating cortisol levels, and it at least partially normalized following treatment, in direct proportion to the therapeutic lowering of circulating cortisol concentrations.
Major Depression

Cortisol Abnormalities in Major Depression

Cortisol’s relationship to psychiatric illness has been most widely investigated in major depression. Often considered a nonspecific reflection of the stress accompanying depression, hypercortisolemia (and/or abnormalities in GR function) has increasingly been seen as directly affecting the depressive state. With over 4000 papers published on this topic, indices of hypothalamic-pituitary-adrenal (HPA) axis hyperactivation (e.g., increased serum, urinary, or cerebrospinal fluid (CSF) cortisol levels or nonsuppression of cortisol in response to dexamethasone administration (the dexamethasone suppression test (DST)) have been found in many studies of depression, particularly those studying inpatient samples and individuals with more severe, recurrent or psychotic depression. Yet, the nature of cortisol’s relationship with depression remains uncertain. First, HPA axis activation is neither a necessary nor sufficient condition for being depressed, as many hypercortisolemic individuals are not depressed, and many depressed individuals are not hypercortisolemic. This raises the possibility that depression is a biologically heterogeneous disorder or that some other vulnerability, sensitivity or “co-factor” is required for the cortisol-depression relationship to become manifest. Also, while hypercortisolemia is more prevalent than hypocortisolemia in depression, the latter is also commonly seen. Indeed, cortisol signaling may bear an “inverted U-shaped” relationship with mood, memory and mental functioning, with both high and low levels associated with depression and poorer function than more moderate levels. It has been suggested that hypercortisolemic and hypocortisolemic depression differ in their symptomatic presentation and may even represent distinct subtypes of depression, despite the fact that both may meet diagnostic criteria for major depression. For example, hypocortisolemic depression may be characterized by “atypical” symptoms of hypoarousal, hypersomnia, hyperphagia, lethargy, pain, fatigue, and relative apathy, whereas hypercortisolemic depression may be characterized by more “typical” depressive symptoms, such as hyperarousal, anxiety, insomnia, and loss of appetite. It remains unknown whether changes in cortisol dynamics cause depression (for example, initiating or perpetuating it or altering its presentation) or if they are merely epiphenomena. Regardless of how they arise, however, it would be surprising if chronic alterations in cortisol signaling did not, in some way, contribute to psychiatric symptoms, since cortisol freely crosses the blood–brain barrier and enters the brain, where cortisol receptors are densely located in the hippocampus, frontal cortex, and other areas. As reviewed below, biological actions in these and other sites could have significant effects on mood, memory and cell biology.

Is Hypercortisolemia an Endophenotype?

Another explanation for the heterogeneity of cortisol findings in depression is that cortisol activity may map onto specific psychiatric symptoms more closely than onto specific psychiatric diagnoses. The concept of endophenotypes is increasingly being applied to studies of psychiatric nosology, in recognition of the fact that genetic or biological markers may map more closely onto specific symptoms than onto traditional diagnoses. For example, in several studies, cortisol hypersecretion (or DST nonsuppression) in depression has been related to specific symptoms, of sleep disturbance (especially initial insomnia), decreased attention and memory, psychosis, psychomotor disturbance (agitation or retardation), and anxiety, more so than to global depression or to more “psychological” symptoms, such as guilt, worthless- ness, helplessness, or hopelessness (Table 1). Other symptoms that have been related to cortisol hyperactivity in depression, but less consistently so, include decreased energy,
TABLE 1. A Possible Endophenotype of Hypercortisolemia\(^a\)

<table>
<thead>
<tr>
<th>Overlapping symptoms in Cushing’s syndrome, hypercortisolemic depression and steroid psychosis and improving with anti-glucocorticoid treatment</th>
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</thead>
<tbody>
<tr>
<td>- Insomnia (initial)</td>
</tr>
<tr>
<td>- Memory and concentration impairment(^b)</td>
</tr>
<tr>
<td>- Psychosis</td>
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<tr>
<td>- Anxiety</td>
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<tr>
<td>- Psychomotor change(^c)</td>
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</tbody>
</table>

\(^a\)Other symptoms reported less uniformly across distinct states of elevated glucocorticoid levels include: depressed mood, irritability, suicidality, decreased libido, and lability (the latter in steroid psychosis and Cushing’s syndrome).

\(^b\)Memory impairment is consistent with hippocampal and prefrontal cortical dysfunction in each of these conditions.

\(^c\)Agitation or retardation.

suicidal thoughts and decreased libido. Capitalizing on the endophenotype model, Reus\(^61\) used response to the DST as the independent variable to assess correlations with specific symptoms across psychiatric diagnostic categories. He found that that DST non-suppressors showed evidence of increased anxiety, interpersonal sensitivity, suicidal ideation, and sleep disorder compared with suppressors. In subsequent sections, we will compare these specific symptoms to those seen in distinct clinical conditions of GC excess. From the perspective of treatment response, many of these same symptoms respond to anti-GC treatment (discussed below) with improved symptoms of depression, concentration difficulties, insomnia, memory disturbance and irritability (in Cushing’s syndrome)\(^22\); and mood, insomnia, anxiety, diurnal variation, paranoia, and obsessive-compulsiveness (in depression)\(^69\).

The Dexamethasone Suppression Test and Glucocorticoid Receptor Function in Depression

Two different aspects of hyperactivity of the HPA axis have been investigated in depression: increases in basal serum, urinary, or CSF levels of cortisol, and failure to suppress cortisol in response to the DST. The DST (and a later refinement, the “Dex/CRH test”)\(^70,71\) assesses the sensitivity of pituitary GRs to feedback inhibition by GCs.\(^72,73\) While meta-analyses have shown that the DST is not useful as a diagnostic test for depression,\(^74,75\) DST normalization more often precedes than follows clinical response,\(^76–78\) and persistent nonsuppression on the DST despite treatment predicts early relapse and poor outcome in treated depressed patients.\(^75,79\) These observations raise the possibility that normalization of GR sensitivity is an important condition for lasting clinical recovery. Consistent with this, many antidepressants, even those of differing mechanisms, increase GR signaling\(^34,72\) in a time course that parallels the time course of clinical antidepressant response.\(^80\) It is possible that, by increasing GR-mediated negative feedback, antidepressants normalize the pituitary’s response to circulating cortisol levels (viz., curtailing ACTH release, and hence, additional cortisol release in response to elevated cortisol levels), and that this lowering of cortisol levels may contribute to their antidepressant effects.\(^34\) Other interpretations are discussed in the next section.

Is Hypercortisolemia in Depression Evidence of Overactive or Underactive Glucocorticoid Signaling?

The association between circulating levels of cortisol and depression is more nuanced than previously thought, and there are two competing hypotheses for this association. Cortisol hypersecretion, rather than being part of the “problem” contributing to depression, may be the body’s attempt at a “solution” by trying to overcome a primary GC resistance caused by downregulated GRs.\(^81,82\) This model posits that it is not the absolute level of circulating cortisol that is most important to health, but instead the ability of cortisol to affect intracellular activities of the target tissue.\(^82\) According to this model, the chronically elevated levels of cortisol that often accompany depression may lead to, or be the result of, GC resistance at the level of the GR. In this model, net GC signaling (or “throughput”) in
depression is too low, which could lead to psychiatric symptoms associated with GC insufficiency. Antidepressant-induced up-regulation of GRs is then seen as a primary beneficial effect leading to increased, rather than decreased, GC signaling. This GC signaling insufficiency hypothesis is supported by findings that pro-inflammatory cytokine levels (e.g., tumor necrosis factor (TNF)-α, interleukin (IL)-1β and IL-6) tend to be increased in the serum of depressed patients, and that pro-inflammatory cytokines may contribute to depressive symptomatology. Since cortisol typically has anti-inflammatory actions and suppresses pro-inflammatory cytokines (except in certain acute stress situations and situations of acute neuronal necrotic injury), the co-existence of elevated cortisol and pro-inflammatory cytokine levels suggests an insensitivity to cortisol at the level of the lymphocyte GR. One difficulty in assessing the GC signaling insufficiency hypothesis is that the specific GRs typically assessed in studies of depression (e.g., in lymphocytes and in the pituitary) may be structurally different than those in various brain areas relevant to depression, such as the hippocampus, and thus may respond differently and show different degrees of GC resistance. For example, in one study, response to GCs in peripheral leukocytes was found to be unrelated to responses at the level of the HPA axis. Highlighting the importance of this distinction, cortisol can stimulate, rather than suppress pro-inflammatory cytokine release in the brain in some situations.

On the other hand, the GC signaling overactivity hypothesis is supported by phenotypic somatic and central features suggestive of cortisol excess and end-organ cortisol receptor overactivation in depression, e.g., osteoporosis, insulin resistance, type II diabetes, a relative hypokalemic alkalosis accompanied by neutrophilia and lymphocytosis, hypertension, metabolic syndrome, and visceral/intra-abdominal adiposity (but see Ref. 102). Further support of net GC activation in the brain is provided by evidence of altered expression of target genes, such as brain-derived neurotrophic factor (BDNF), which is under negative regulatory control by cortisol. There is a growing body of evidence showing that depressed patients exhibit reduced BDNF expression in limbic structures of the brain, whereas antidepressant treatment reverses this effect. Last, the presence of deficits in declarative memory function and working memory, as well as the increased incidence of psychosis in hypercortisolemic depressed patients, is consistent with net GC activation in the brains of these patients, since these have both been related to increased regional brain GC activity. Ultimately, the question of whether depression is associated with net increased or net decreased cortisol signaling hinges on whether the elevated cortisol levels seen in hypercortisolemic depression are sufficient to override the GC resistance. Currently, there is no definitive answer to this question, and, indeed, some patients may be characterized by one and some by the other.

**Cortisol and the Hippocampus in Depression**

Most, but not all, studies examining hippocampal volume in depression using high-resolution magnetic resonance imaging report decreased hippocampal volume, but this may depend upon factors, such as gender, length of time since onset of illness, and total length of untreated depression. Despite the lack of convincing evidence in depression, a longitudinal study in...
normal aging controls did suggest that chronic exposure to elevated cortisol levels (i.e., elevations in current cortisol levels as well as a history of increasing cortisol levels over time) is associated with smaller hippocampal volumes and with decreased hippocampally mediated memory function. The evidence reviewed so far regarding cortisol activity and psychiatric symptoms is correlational rather than causal in nature. According to the GC hyperactivity hypothesis of depression, treatments that directly increase or decrease GC activity should have detrimental or beneficial effects, respectively. This is examined in the following section.

Causal Evidence for Glucocorticoid Involvement in Psychiatric Symptoms

Anti-Cortisol Treatment Effects

Cushing’s Syndrome

Treatments aimed at lowering cortisol levels, or at correcting the source of elevated ACTH or cortisol levels, have been extensively utilized in the treatment of Cushing’s syndrome (e.g., tumor irradiation, surgery, or treatment with cortisol-biosynthesis inhibitors or cortisol receptor blockers). Cortisol biosynthesis inhibitors most often utilized for this purpose include ketoconazole, metyrapone and aminoglutethimide. The cortisol receptor blocker utilized is mifepristone (RU-486). The steroid biosynthetic pathway is diagrammed in Figure 1, showing the sites of enzymatic blockade of one particular cortisol-biosynthesis inhibitor, ketoconazole. It should be noted in Figure 1 that ketoconazole, as well as the other cortisol biosynthesis inhibitors, affect multiple steroids besides cortisol, limiting a mechanistic interpretation of the results in these studies. In a review of studies through 2005, at least 30 reports documented decreased depression, anxiety, irritability, psychosis, and cognitive impairment, even complete psychiatric remission, in patients with Cushing’s syndrome who received either tumor irradiation or surgical or medical (e.g., ketoconazole, metyrapone, aminoglutethimide, or RU-486) treatment aimed at lowering cortisol levels. The largest two case series documented a response rate of 70–73% of treated patients. However, in more recent reviews, psychiatric improvement was erratic, delayed or incomplete, and improvement varied greatly among patients, possibly secondary to irreversible changes in central nervous system function even after treatment was complete. Continued elevations of ACTH levels after treatment did not prevent improvement in depressed mood, suggesting an adrenocortical, rather than pituitary, locus of action. These observations are suggestive of an etiologic role of hypercortisolemia in psychiatric symptomatology in these patients.

Major Depression

Following the success of anti-cortisol treatment approaches in Cushing’s syndrome, several investigators began assessing the effects of pharmacologic lowering of cortisol levels, or of pharmacologic blockade of GRs, in patients with major depression. Across 11 studies reviewed up until 1999, 77% of the patients showed at least a partial antidepressant response, and 67% showed a full or clinically meaningful response, although the majority of these studies were open-label, single-blind, or small-scale. One open-label study suggested that psychotic depressed patients, compared to nonpsychotic ones, showed poorer antidepressant responses to biosynthesis inhibitors. In the largest double-blind trial to date, 3 weeks of metyrapone augmentation of serotonin-specific reuptake inhibitor (SSRI) treatment in depressed patients was associated with more rapid and more complete antidepressant response, compared to the SSRI alone; the benefit was maintained for at least 2 weeks after metyrapone augmentation was discontinued.

Several of these studies suggested that anti-cortisol treatment benefits were maintained
Figure 1. The Steroid Biosynthetic Pathway. Heavy bars indicate sites of enzymatic blockade by ketoconazole, one of the cortisol biosynthesis inhibitors discussed in the text. scc = side chain cleavage; HSD = hydroxysteroid dehydrogenase; SST = steroid sulfotransferase; arom = aromatase.

for extended periods after drug discontinuation.\textsuperscript{69,128–130} This argues against a pure “placebo effect” leading to the improvement and suggests that a “resetting” of the HPA axis (perhaps an upregulation of GR sensitivity in response to treatment-induced lowering of GC levels) may lead to persisting remissions.\textsuperscript{130} Consistent with this, Murphy and colleagues found that, of the treatment responders who were nonsuppressors on the DST prior to treatment, five of six had reverted to normal suppression when tested 1–2 weeks after cessation of therapy; the one patient who did not revert to normal suppression suffered an early relapse.\textsuperscript{131,132} Studies differ in whether baseline cortisol levels predict antidepressant response to anti-GCs and whether treatment-associated changes in cortisol levels parallel antidepressant responses.\textsuperscript{69,133,134} One difficulty interpreting these studies is that cortisol levels were often assessed using only single time point samples. In one small double-blind study, ketoconazole had significant antidepressant effects in hypercortisolemic but not eucortisolemic patients,\textsuperscript{135} and baseline serum cortisol levels were directly correlated with antidepressant responses ($r = 0.56$). Further, treatment-associated decreases in serum cortisol levels were directly correlated with decreases in Hamilton Depression Rating Scale (HDRS) ratings ($r = 0.45$), Cognitive Disturbance subscale ratings ($r = 0.50$), and Anxiety-Somatic subscale ratings ($r = 0.64$), although the correlations were not statistically significant, given the small sample size in that study. In another study by the same investigators, patients with schizophrenia or schizoaffective disorder, who were at least partially resistant to treatment with antipsychotics, antidepressants and/or mood stabilizing medications alone, showed ketoconazole-associated antidepressant responses (but not antipsychotic responses).\textsuperscript{136} The magnitude of the antidepressant response was directly correlated with baseline serum cortisol levels ($r = 0.63$), as was the case in ketoconazole treatment of patients with major depression.\textsuperscript{135}

In a different approach to curtailing GC activity, investigators have utilized the GR antagonist RU-486 in the treatment of psychotic major depression (PMD). PMD was chosen in these studies because PMD has the highest average cortisol levels (and rates of DST nonsuppression) among depressive subtypes, and because cortisol hyperactivity in PMD is theorized to drive the psychotic symptoms by increasing brain dopamine activity.\textsuperscript{32} Unmedicated patients with PMD received, in a
double-blind manner, RU-486 or placebo for 7–8 days, after which standard treatment could be administered for an additional 21 days. RU-486 had no significant antidepressant effect, but significantly more patients showed evidence of response on the Positive Symptom Subscale of the Brief Psychiatric Rating Scale, suggesting a beneficial effect on psychotic symptoms.\textsuperscript{137,138}

A recent Cochrane meta-analysis of nine double-blind, placebo-controlled anti-GC studies in major depression (involving 211 participants), using either RU-486, ketoconazole, metyrapone, or dehydroepiandrosterone (DHEA, which was considered an anti-GC in this meta-analysis [even though DHEA has multiple other physiological actions\textsuperscript{201}]), concluded that, in nonpsychotic depressed patients, those treated with anti-GCs (compared to placebo) had higher response rates and greater decreases in depression ratings.\textsuperscript{139} In patients with PMD, anti-GC treatment was not associated with a higher categorical response on the HDRS, but it was associated with numerical decreases in depression ratings and with improvement in positive psychotic symptoms. The review concluded that anti-GC treatments of depression appear promising in particular subsets of patients, but that, at this time, they remain at the “proof of concept” stage.\textsuperscript{139}

\textbf{Possible Mechanisms of Anti-Cortisol Drug Treatment Effects}

Several studies have attempted to clarify the mechanisms by which anti-GCs may alleviate depression in some patients. Thakore and Dinan treated eight depressed patients with ketoconazole for 4 weeks and noted significant antidepressant effects and significant decreases in serum cortisol levels.\textsuperscript{133} They had postulated that elevated cortisol activity provokes or maintains depressive symptoms by inducing subsensitivity of the serotonin system. This hypothesis was based on observations that, in depressed patients, baseline cortisol levels are inversely related to the magnitude of serum prolactin (PRL) responses to serotonin agonists, such as d-fenfluramine (a putative marker of serotonin system sensitivity). To test this hypothesis, they administered single doses of d-fenfluramine to their subjects at base line and after 4 weeks of ketoconazole treatment. Ketoconazole normalized the PRL response to d-fenfluramine (i.e., increased the PRL response relative to base line), and the increases in PRL responses were significantly correlated with reductions in depression ratings. These findings are consistent with anti-GC treatments lessening depression by increasing serotonin sensitivity. In another study, O’Dwyer \textit{et al.} treated eight depressed patients with metyrapone (plus replacement doses of hydrocortisone), or placebo, in a single-blind manner in a 2-week-per-arm crossover design and noted significant decreases in depression ratings and in serum cortisol levels during metyrapone treatment.\textsuperscript{129} Checkley \textit{et al.},\textsuperscript{140} commenting on the same group of subjects as O’Dwyer \textit{et al.},\textsuperscript{129} noted that, in addition to normalizing cortisol levels, metyrapone led to increased urinary levels of the neurally active steroids tetrahydro-11-deoxycortisol and tetrahydro-deoxycortisone. They suggested that either the decreases in cortisol levels or the increases in levels of these neurosteroids might have facilitated the antidepressant response. The efficacy of anti-GCs in depression accords well with the GC hyperactivity hypothesis of depression but could also be consistent with the GC insufficiency hypothesis. In the latter case, treatment-induced decreases in cortisol levels could “reset” the HPA axis, leading to upregulation of GR sensitivity, thereby improving net GC signaling.\textsuperscript{130} The possibility that anti-GCs improve depression via effects on steroids other than cortisol (e.g., neurosteroids) could be compatible with either the GC hyperactivity or insufficiency hypotheses. The GC insufficiency hypothesis could also be consistent with the antidepressant effect of anti-GCs being due to increases in neurosteroids, rather than to decreases in cortisol.\textsuperscript{140}
Glucocorticoid Treatment of Depression

In what seems a diametrically opposite approach to altering GC activity in depressed patients, several small-scale studies reported that administration of GCs, such as dexamethasone, prednisone, or hydrocortisone, is associated with antidepressant effects in some depressed patients.141–150 These findings could support the GC insufficiency hypothesis of depression by showing that increasing GC levels (and presumably signaling) lessens depressive symptoms, but the findings would still need to be reconciled with anti-GCs having similar effects. Several explanations are possible: (1) it is unknown if the antidepressant effects with GC treatment are true antidepressant effects or rather, short-term activational responses often seen with GCs even in nondepressed individuals144; (2) anti-GCs and dexamethasone administration could both have antidepressant effects by altering levels of other adrenal or neurosteroid hormones140,151; (3) since dexamethasone is actively excluded from the brain (but not from the pituitary), and therefore does not replace endogenous cortisol at hippocampal GRs,152 dexamethasone’s lowering of cortisol concentrations may actually lead to lowered GC signaling within the brain153; and (4) last, it is possible that GC administration versus GC antagonism benefit different subgroups of depressed patients, perhaps those with basally low or high cortisol levels, respectively.141,154

Exogenous Steroid Administration

In research studies, administration of GCs to nondepressed individuals, with prospective assessment of behavioral changes, may provide more direct evidence of GC effects on human behavior. However, several caveats limit extrapolation of such effects to those seen with endogenous hypercortisolemia: (1) GC administration often involves GCs with different receptor affinities and blood–brain barrier penetration than the endogenous GC, cortisol; (2) plasma GC levels and durations of GC exposure often differ; (3) most importantly, endogenous hypercortisolemia is often due to increased corticotropin-releasing hormone (CRH) and/or ACTH activity, whereas exogenous GCs suppress both of these.

Steroid Psychosis

The introduction of GCs into medical practice in 1949 was accompanied almost immediately by an awareness of behavioral side effects, occasionally profound, in some medically ill patients prescribed cortisone, dexamethasone, prednisone and other GCs.155–164 It has since become apparent that a majority of patients treated with moderate doses of GCs will develop some degree of behavioral symptoms, but these are generally mild and more subjectively than objectively apparent.165–173 These reactions are quite variable, both within and between individuals, but they are typically in the direction of short-lived mild euphoria, hyperarousal, or anxiety.169,174 Depressive reactions are less common than hypomanic or activated reactions initially, but they become more common with continued steroid treatment.166 Subtle changes in sleeping patterns, sensory processes and thought processes may also become apparent. Apart from these common mild side effects, some patients develop a much more serious reaction called “steroid psychosis,” which is characterized by a fluctuating and unpredictable constellation of symptoms, such as delirium, confusion, insomnia, emotional lability, depression, mania/hypomania, memory and attentional impairments, sensory flooding, psychosis, and even suicidality.156 The incidence of steroid psychosis is directly related to the dose of GC prescribed. It is estimated that less than 2% of patients administered <40 mg/day of prednisone will develop steroid psychosis, whereas approximately 18% of patients treated with doses of >80 mg/day will develop it.155 In addition to mood and thought changes, cognitive changes frequently characterize steroid psychosis. Rheumatoid arthritis patients treated with prednisone for >1 year
were compared to closely matched nonsteroid-treated medical patients and were found to exhibit poorer paragraph recall (a hippocampus-dependent task) but equivalent word stem priming (a nonhippocampus-dependent task). These and other results were interpreted as consistent with GC-induced hippocampal dysfunction.172,173,175

**Steroid Dementia**

Most behavioral side effects and cognitive impairments associated with GC treatment fully and quickly remit once the steroid is discontinued.176 Varney et al., however, called attention to the possibility of severe and persisting cognitive disturbances that may begin during, and persist for extended periods of time after, steroid treatment.177 In the patients they described, the symptoms superficially resembled early Alzheimer’s disease, and they termed the condition “steroid dementia.” The cognitive deficits were largely reversible, but not until 1–11 months after discontinuing steroid medication. Although it is impossible to know the incidence of steroid dementia, we estimate it to be between 0.4% and 1.25%.156,177,178 At least 14 cases of steroid dementia have been described in the medical literature (reviewed in Ref. 179).

The possibility that this is a true “syndrome” is supported by the phenomenological similarity of the cases (described more fully in Refs. 179 and 180). In the reported cases, the cognitive impairments were characterized by relatively intact immediate but impaired delayed verbal recall, with encoding deficits more pronounced with lengthier complex material and with interposed interference; each case also had decreased abstraction and analytic capabilities, difficulty with step-wise thinking requiring the recall of prior steps, difficulty distinguishing relevant points from less relevant ones and decreased IQ scores compared to estimates of prior functioning.177,179–183 These cases also had similar general subjective complaints, e.g., difficulty concentrating, difficulty recalling written material from one page to the next, difficulty remembering what they had already said in conversations, difficulty keeping track of serial questions, and difficulty with word finding. As was the case with the cognitive deficits in Cushing’s syndrome,14 the cognitive deficits in steroid dementia are likely related to dysfunctional hippocampal and frontal cortical neuroanatomic circuits.14,37,184–188 This is supported by in vivo human data suggesting that GC actions in the medial temporal lobe (especially the para-hippocampal gyrus) may be responsible for their effects on declarative memory processes.189,190

**Studies in Normal Volunteers**

Investigators have also administered GCs, in a double-blind manner, to medically and psychiatrically healthy volunteers to study changes in behavior and cognition that are not confounded by the medical conditions for which GCs are typically prescribed. Wolkowitz and colleagues administered 80 mg per day of prednisone versus placebo to 12 medically and psychiatrically healthy volunteers in a double-blind manner for a period of 5 days.41,171,191 Few consistent behavioral changes were observed across the group as a whole, with the exception of an impairment in aspects of declarative memory and an increase in sensory sharpness. However, nine (75%) of the individual volunteers reported mild and varied behavioral changes including depression, tearfulness, irritability, anger, insomnia, talkativeness and giddiness, increased appetite, mood elevation, increased energy, confusion, racing thoughts, and depersonalization.171,191 Subsequently, a similar study using a higher dose of prednisone (160 mg per day) in healthy volunteers found a predominance of negative emotions during treatment.192 The findings suggest that mild behavioral reactions to brief courses of exogenous GCs are common but idiosyncratic.

Newcomer and colleagues reported that stress-level doses of hydrocortisone (160 mg per day), administered to healthy volunteers, produced reversible decreases in verbal declarative memory after 4 days of treatment,
without effects on nonverbal memory, sustained or selective attention, or executive function.\textsuperscript{193} Kirschbaum and colleagues reported that hydrocortisone (10 mg p.o.), compared to placebo in a single-blind design, acutely impaired declarative memory (cued verbal recall) and spatial thinking (mental rotation) in healthy volunteers without impairing procedural memory (word stem priming).\textsuperscript{194} These data are consistent with deficiencies in hippocampus-dependent activity following steroid administration.\textsuperscript{194} Several studies additionally implicate impairments in prefrontal cortex processing following GC administration.\textsuperscript{40,107,186,187,195,196} 

**Summary of Conditions Characterized by Excess Circulating Glucocorticoid Levels**

The three conditions we have reviewed here (Cushing’s syndrome, major depression, and steroid psychosis/steroid dementia) have important differences but share important similarities. In Cushing’s syndrome, mood changes and neurovegetative symptoms are typically labile and are most commonly “atypical” in nature (a preponderance of lethargy, hyperphagia and hypersomnia), circulating cortisol levels are typically very high, and Cushingoid physical stigmata are usually present. In hypercortisolemic depression, on the other hand, depressive symptoms generally do not rapidly fluctuate and may either be “typical” or “atypical,” elevations in circulating cortisol levels are often less pronounced than in Cushing’s syndrome and physical stigmata are not generally grossly apparent. Indeed, downregulated GRs induce some degree of GC resistance in major depression. Last, steroid psychosis is characterized by idiosyncratic unpredictable labile behavioral symptoms that are often activated or manic/hypomanic in nature, are generally time-limited and self-resolving and are associated with decreased hypothalamic CRH and circulating ACTH levels. Yet, certain similarities exist among these three conditions. Examination of the reported symptom profiles of each condition reveals an area of overlap of certain specific symptoms, i.e., psychomotor disturbances (either activation or retardation), anxiety, insomnia (especially early insomnia), psychosis and memory/cognitive impairment (Table 1). The memory impairment in each condition is generally suggestive of hippocampal and frontal-cortex impairment. Finally, each condition (if of sufficient duration) is associated, to greater or lesser extents, with certain somatic sequellae of chronic cortisol exposure, e.g., metabolic syndrome, insulin resistance, visceral adiposity and osteoporosis.

**Mediators**

**The “Glucocorticoid Cascade” Hypothesis**

GC effects on the brain can be broadly divided into three categories: genomic, nongenomic, and neurotrophic versus neurotoxic. Classic genomic effects, occurring over the timeframe of minutes to hours or days, are exerted by altering gene expression, leading to altered protein synthesis. Such effects are responsible for the majority of GC effects and lead to alterations in the synthesis of various cellular components, enzymes responsible for synthesizing and metabolizing various neurotransmitters and neurotransmitter receptors, to name a few. In addition, steroid hormones can have nongenomic effects, occurring rapidly, over the timeframe of seconds to minutes, and are mediated by direct actions at cell surface receptors, such as the GABA-A, NMDA, and sigma receptors.\textsuperscript{7,28,29,51,171,197–201} Steroid hormones with these properties in the central nervous system are termed “neurosteroids” and include pregnenolone, pregnenolone sulfate, progesterone, DHEA, DHEA sulfate, tetrahydro-deoxycorticosterone, and allopregnanolone and others. Such neurosteroids may have important interactions with cortisol and may help determine overall cortisol...
effects. For example, DHEA and DHEA-S appear to have “anti-GC” properties, and DHEA itself appears to have antidepressant effects. The cortisol-to-DHEA ratio may correlate more closely with certain psychiatric symptoms than levels of either hormone alone.

GCs can also have neurotrophic, neuroendangering, or neurotoxic effects in the brain, depending on the concentration and duration of exposure. At low physiological levels, GCs permissively sustain the viability of cells in the dentate gyrus. At prolonged high-stress doses, however, GCs are able to decrease pyramidal cell dendritic branching and axonal sprouting, impairing recovery from damage and potentiating ischemic, convulsive, and other forms of neuronal damage. Atrophy of dendritic processes is reversible, while others steroid effects, such as death of hippocampal neurons, represent long-lasting or potentially permanent changes in neural circuitry. GCs can also decrease hippocampal glucose utilization, setting in motion a cascade of excitatory amino acid, calcium and free-radical neurotoxicity. This action may exacerbate the effects of ongoing or coincident metabolic insults (“neuroendangerment”) or may occur even in the absence of extraneous insults (“neurotoxicity”). Two endpoints of hippocampal damage elicited by such a steroid-excitatory amino acid-calcium synergism are proteolysis of the cytoskeletal protein spectrin and accumulation of the abnormally phosphorylated tau microtubule protein. Elevated GC levels also decrease hippocampal and neocortical expression of neurotrophic factors, such as basic fibroblast growth factor and BDNF, which can significantly diminish hippocampal and prefrontal cortical neurogenesis and impair the brain’s ability to recover from damage. Low brain levels of BDNF may contribute to the development of major depression and may represent an important link between cortisol, depression, the hippocampus, and the frontal cortex. Interestingly, RU-486, the GR antagonist being investigated as a treatment for depression and PMD, normalizes corticosterone and chronic stress-induced reduction of adult hippocampal neurogenesis in rats.

**Accelerated Cell Aging**

Hans Selye is quoted as saying, “Every stress leaves an indelible scar, and the organism pays for its survival after a stressful situation by becoming a little older.” New data affirm that chronic psychological stress and elevated GC levels can contribute to premature aging of certain cells in the body. One widely accepted measure of cellular aging is telomere length (TL). Telomeres are DNA-protein complexes that “cap” the ends of DNA, protecting the DNA from damage and end-to-end fusions. Telomerase is a ribonucleoprotein reverse transcriptase that can lengthen and restore TL. In mitotic cells (such as peripheral blood mononuclear cells (PBMCs), fibroblasts, cardiomyocytes and stem cells (including neurogenic stem cells in the subventricular zone and in the subgranular layer of the dentate gyrus in the hippocampus)), mitosis is associated with telomere shortening if there is insufficient telomerase activity. When the telomeres reach a critically short length, the cell dies. Even in postmitotic cells, such as mature neurons, telomeres may shorten as a function of cumulative exposure to genotoxic stressors, such as oxidative stress, and TL may provide a marker of cumulative exposure to such noxious stimuli. In several studies, telomere shortening has been associated with increased risk of atherosclerotic cardiovascular disease, dementia, stroke, diabetes, infectious disease, and early mortality. To examine whether chronic psychological stress affects TL and telomerase activities in humans, Epel et al. measured these parameters in stressed caregivers (mothers of chronically ill children) and found that greater duration of caregiving, as well as greater perceived levels of stress, were significantly correlated with shorter PBMC TL and lower telomerase activity.
negative mood was also associated with lowered telomerase activity. The magnitude of telomere shortening was nontrivial, as it was estimated to represent approximately 13 years of accelerated biological aging. Importantly, decreases in PBMC TL were associated with elevated nocturnal urinary cortisol excretion. The involvement of cortisol in decreasing TL is supported by a recent in vitro study, in which cortisol application to human T lymphocytes significantly decreased telomerase activity. Preliminary data suggest that PBMC telomeres are also shortened in depressed patients compared to controls, but this has not yet been examined in comparison to circulating cortisol levels.

**Theoretical Model and Novel Treatment Possibilities**

Based on the data reviewed here and elsewhere, we propose a model in which stress-induced HPA axis activation, or chronic exposure to elevated levels of GCs even in the absence of stress, sets in motion multiple pathways that ultimately endanger neurons or glial cells in the brain, may accelerate aging in certain cells in the brain and periphery and may contribute to various psychiatric symptoms (Fig. 2). First, elevated GC activity is associated with down-regulation of GRs, leading to some degree of GC resistance. The deficit in GR function may precede or result from the hypercortisolism. To the extent lymphocyte GRs become GC resistant, immune function is altered, and undesirable pro-inflammatory cytokine effects may occur. Changes in cortisol activity also result in multiple genomic changes, e.g., altered levels of certain neurotransmitters and other mediators (e.g., decreased serotonin and increased dopamine activity in certain brain regions, which might contribute to depressive or psychotic symptoms). To the extent that GC activity is excessive in certain brain regions, a cascade of events may follow, which is characterized by diminished insulin signaling, intraneuronal glucoprivation and diminished energy availability, defective clearance of intrasynaptic glutamate, excitotoxicity, intracellular buildup of calcium, generation of oxygen free radicals (oxidative stress), and cellular damage or death. Increased oxidative stress can damage telomerase and shorten telomeres, at least in certain cells in the body. In PBMCs, telomere shortening is associated with a host of physical illnesses and premature mortality, and possibly major depression. Chronic stress and/or excessive GC exposure may also be associated with underproduction of certain neurosteroid hormones, e.g., DHEA, DHEA sulfate, and allopregnanolone, which might contribute to unopposed cortisol activity, loss of neuroreparative activity, and anxiety and depression. Additionally, increased GC activity downregulates BDNF activity, which further diminishes neuroreparative activity and attenuates neurogenesis. To the extent this theoretical model is accurate, several potential treatment loci emerge, as diagramed in Figure 2: (1) traditional antidepressants upregulate GR function, increase allopregnanolone synthesis (certain SSRIs), and increase BDNF levels, (2) CRH antagonists, (3) stress reduction and other behavioral interventions, (4) anti-GCs, (5) energy supplementation or insulin receptor sensitizers, (6) glutamate antagonists, (7) calcium blockers, free radical scavengers, anti-oxidants, (8) DHEA, (9) 3-alpha-hydroxysteroid dehydrogenase stimulators (including SSRIs), (10) environmental enrichment, exercise, (11) small molecule BDNF analogs, (12) telomerase activation, and (13) anti-inflammatory drugs, TNF-α antagonists, etc. Already, preliminary studies are testing some of these strategies.

**Summary**

We have summarized evidence of a relationship between elevated GC levels and various psychiatric symptoms in three different conditions: Cushing’s syndrome, hypercortisolemic depression, and exogenous GC administration. Each of these conditions has unique
pathophysiological features, but some similarities in GC-associated symptom profiles may exist. In the case of Cushing’s syndrome and exogenous GC treatment, the excess GC signaling is clear-cut; in the case of major depression, however, there are conflicting views as to whether net GC signaling is increased or decreased. Nonetheless, anti-GC treatment strategies (and possibly treatments that increase GC levels too) appear helpful in at least some patients with depression. The continuing discovery of the mechanisms by which GCs (either excess or deficient) may affect psychopathology will doubtless give rise to new therapeutic modalities for conditions causally related to GC abnormalities.

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Conflicts of Interest

The authors declare no conflicts of interest.

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