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GLUCOCORTICOID INHIBITION IN THE TREATMENT OF DEPRESSION: CAN WE THINK OUTSIDE THE ENDOCRINE HYPOTHALAMUS?

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Abstract

Background—Major depressive disorder affects a substantial percentage of the U.S. population, and can be highly debilitating. Selective serotonin reuptake inhibitors are commonly prescribed to treat depression, but may not be as effective for more severe or persistent depression.

Methods—The authors review data concerning the effects of corticosteroid synthesis inhibitors (CSIs) in the management of depressive disorders, present a hypothesis as to their possible mechanisms of action based on recent data suggesting synergistic effects of glucocorticoids on extrahypothalamic corticotropin-releasing hormone (CRH), and consider alternative hypotheses. Published reports evaluating the efficacy of CSIs in treating depression are reviewed and presented in light of recent findings regarding actions of glucocorticoids on the central CRH system.

Results—Results from open label and double-blind studies by several groups have indicated that CSIs may be efficacious or of adjunctive value in some patients with depression, including those refractory to other agents; however, there is a need for more controlled studies. Several lines of data suggest that the mechanism of action of these agents may not be solely a function of inhibition of adrenal cortisol production.

Conclusions—The authors propose that CSIs may be efficacious in part by reducing glucocorticoid enhancement of CRH action in neurons of the central nucleus of the amygdala and other structures outside the endocrine hypothalamus. Possible effects of systemically administered CSIs on glucocorticoid receptor regulation, neuroactive steroids, and classical monoamine systems are also discussed. We conclude that available clinical data suggest a potential role for CSIs in the management of depressive disorders, especially major depression with psychotic features.

Keywords

antiglucocorticoids; depression; mifepristone; ketoconazole; CRH; cortisol; glucocorticoid inhibition

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INTRODUCTION

Major depressive disorder (MDD) is a common,usually recurrent, and debilitating condition that affects about 121 million people worldwide and is the leading cause of disability worldwide.[1] Episodes of MDD are characterized by a period of at least 2 weeks during which there is either depressed mood or the loss of interest or pleasure in almost all activities.[2] Significant distress or impaired functioning must be present to qualify for a diagnosis of MDD. There is evidence that MDD with psychotic features (i.e., "psychotic depression") is a relatively distinct subtype of MDD that is more severe and is characterized by a greater degree of anxiety and psychomotor agitation than is usually seen in depression without psychotic features. Psychotic depression affects roughly 20% of hospitalized patients with major depression.[3] Significant differences between MDD and psychotic depression have been noted in presenting features, neurocognitive features, biological features, familial transmission, course and outcome, and response to treatment.[4,5] Given the variability in treatment response for psychotic depression and the knowledge that treatment strategies for depression in general may take weeks or months to take effect, researchers have turned their focus to antiglucocorticoids as a possible treatment approach. Hypercortisolism is one of the most consistent and reproducible biological abnormalities seen in patients with major depression[6,7]; thus, the overlap between symptoms associated with depressive episodes and those occurring during acute stress has led to a closer examination of the association between this depression and elevated levels of glucocorticoids, which are among the most consistent and important effectors of stress responses.[8-12] There are reports that patients with psychotic depression have specific abnormalities in the hypothalamic–pituitary–adrenal (HPA) axis activity, tend to have the highest rates of nonsuppression on the dexamethasone suppression test among clinically defined subtypes, and have markedly elevated postdexamethasone cortisol levels.[13,14] This study will focus on reviewing the literature pertaining to the hypercortisolism associated with depression (MDD) and psychotic depression, the efficacy of antiglucocorticoid drugs to treat it, and suggest that extrahypothalamic corticotropin-releasing hormone (CRH) may be implicated in this type of treatment.

HYPERCORTISOLISM IN DEPRESSION

For many years, researchers have noted that about 40–60% of all severely depressed people have raised levels of cortisol.[12] As depressive symptoms are a frequent concomitant of the hypercortisolism seen in patients with Cushing's syndrome[7,15-17] and in patients undergoing sustained treatment with corticosteroid anti-inflammatory agents,[18] a hypothesis that interfering with cortisol secretion and/or actions may be beneficial to patients with major depression was developed.[19,20] This hypothesis is based on the proposition that depressive symptomatology is at least in part a consequence of excess cortisol.[21,22] However, it is now known that there are distinct differences in the pathophysiology of hypercortisolism between major depression and Cushing's disease, the most common form of endogenous Cushing's syndrome and perhaps the most extensively studied in terms of pathophysiology. Thus, researchers[23-25] have advanced evidence suggesting that the hypercortisolism of major depression is associated with a defect at or above the level of the hypothalamus resulting in the hypersecretion of CRH. Studies have shown that the initial recovery of the HPA axis during the treatment of depression with fluoxetine is mediated via restoration in part of glucocorticoid negative feedback on adrenocorticotropic hormone (ACTH) levels.[26] Despite the differences in clinical presentation and pathophysiology between depression and Cushing's disease, several recent reports have suggested that inhibitors of corticosteroid synthesis may be of benefit in some patients with major depression.[27] People who are not depressed tend to have secretions of

cortisol at certain times of the day.[7] Cortisol levels are highest at approximately 8:00 a.m. and lowest during the night. This normal cycling of cortisol levels does not occur in some people who are depressed. For instance, they might have a consistent level of cortisol all the time or highest amounts in the middle of the night. Data from Young and colleagues[28] examining circadian variation in the response to the administration of metyrapone, a compound that blocks cortisol synthesis, revealed increased central/pituitary drive in the evening compared to the morning in patients with depression, supporting alterations in circadian-driven HPA axis secretion.[29,30] A study examining cortisol circadian rhythm alterations in psychotic major depression specifically found that individuals with psychotic depression also had higher cortisol during the evening hours than did control subjects or individuals with nonpsychotic depression.[31]

Due to the implication of elevated cortisol in depression, many researchers began to examine the possibility of treating depression with antiglucocorticoids, though the mechanisms on which antiglucocorticoids are working remain unclear.

ANTIGLUCOCORTICOIDS IN THE TREATMENT OF DEPRESSION

Several antiglucocorticoid drugs have been studied in depressed patients: metyrapone, aminoglutethimide, and ketoconazole, all cortisol-synthesis inhibitors, and mifepristone (RU 486), a glucocorticoid receptor antagonist. The results are encouraging, but not consistent across psychotic and nonpsychotic depressed patients.[27] Ravaris et al.[32] reported on a 38-year-old female who had a history of depression with onset at menarche, premenstrual exacerbation of depressive symptoms, and recurrent postpartum depressions. At age 33 she was diagnosed with Cushing's disease. Major depression with psychotic features later recurred with increased serum and urinary-free cortisols. Although psychotic symptoms and anxiety were reported to be ameliorated by haloperidol and lorazepam, symptoms of depression persisted. Treatment with ketoconazole resulted in a rapid reduction in cortisol production. The severity of the depressive symptoms decreased, and the patient became euthymic by the end of the 14-day treatment period. Discontinuation of ketoconazole resulted in an increase of urine cortisol and a return of depressive symptoms with delusions after 7 days of being medication free. Haloperidol and ketoconazole were restarted, and urinary-free cortisol decreased. She experienced complete remission even after the cessation of haloperidol treatment. Follow-up at 6 years showed persistence of euthymia with continued ketoconazole treatment.

Murphy et al.[19] reported on a series of 10 patients with major depression who had failed to respond to standard antidepressive agents. Hydrocortisone was given daily, and patients were treated openly with steroid suppressive agents for 2 months and followed for an additional 2 months. Plasma cortisol, ACTH, and dehydroepiandrosterone sulfate were obtained prior to and at intervals during and after treatment. Six of the eight patients who completed the protocol were classified as responders by a decrease of 50% in Hamilton Depression (HAM-D) scores from pretreatment scores. The other two completers were classified as partial responders, meaning observable behavioral improvement and better coping skills with a drop of 20–50% on the HAM-D. A trend toward more rapid and complete improvement appeared among those lacking psychotic features. In a subsequent study by Murphy et al.,[33] a glucocorticoid receptor antagonist (RU 486, 200 mg/kg per day) was given to four patients for up to 8 weeks with a diminution of reported depressive symptoms.

Additionally, Ghadirian et al.[34] reported results from eight psychotic and nine depressed patients treated again with corticosteroid-synthesis inhibitors (CSIs). As in the previous

report, patients without psychotic features were found to respond better to the antiglucocorticoid treatment than those with psychosis.

Wolkowitz and colleagues,[20,35] following a review of the evidence implicating cortisol excess in the pathophysiology and symptomatology of major depression, also indicated positive results with ketoconazole administration in patients with major depression.

Amsterdam et al.[36] treated six hypercortisolemic outpatients having treatment refractory depression with ketoconazole on an open-label basis, either alone or in combination with other antidepressants. Two patients had a “partial” response, one had a modest response, and three had no discernible response. None of these patients achieved a complete remission with ketoconazole. One of the patients, although showing no response to ketoconazole at doses that reduced urinary-free cortisol excretion by 450% to within the normal range, did respond dramatically to the addition of tranylcypromine. However, all medications had to be discontinued due to a substantial elevation of liver enzymes.

Thakore and Dinan[37] examined the effects of open ketoconazole administration on symptoms of depression as well as on prolactin responses to oral D-fenfluramine administration before and after 4 weeks of treatment in eight patients with major depression. Five of these patients showed clinical improvement in depression as defined by a two-third reduction in HAM-D scores from pretreatment values; the remaining three patients showed decreases in HAM-D scores of <50%. None of the patients developed “significant” alterations in electrolytes or liver enzymes during treatment. A negative correlation was found between the changes in HAM-D scores and prolactin responses To *d*-fenfluramine with treatment in these patients, as well as the expected drop in basal morning plasma cortisol levels following ketoconazole treatment.

Anand et al.[38] reported on a patient with psychotic depression who showed a significant clinical response to a 4-week trial of ketoconazole administered under double-blind conditions given concomitantly with evening doses of cortisol (20mg/day). Although the patient continued to respond over a subsequent 14-week period of open ketoconazole administration at doses of 800–1,000 mg/day, treatment was discontinued due to aggravation of hyperbilirubinemia associated with the patient’s known Gilbert’s disease at these doses, whereas lower doses were ineffective for relieving depressive symptoms. In two small studies the results were inconsistent with one another: in one study with metyrapone there was a reported reduction of depressive symptoms in eight subjects[39] and with ketoconazole administration only two of eight patients demonstrated any therapeutic efficacy in refractory major depression.[40]

Many earlier reports on antiglucocorticoid treatment of depression were open label and based on a small number of subjects.[41] More recent data also tout the effectiveness of antiglucocorticoids in the treatment of severe mood disorders, with several published studies having the benefit of a double-blind design.[27] One study[42] tested whether the addition of metyrapone to standard antidepressants induced a more rapid, more efficacious, and sustained treatment response in patients with major depression. They utilized a doubleblind, randomized, placebo-controlled design in a hospital setting. The study participants were 63 inpatients with major depression and a baseline score 18 points or higher on the HAM-D. Participants were randomly allocated to two treatment groups receiving either placebo or metyrapone for the first 3 weeks during a 5-week treatment with standard serotonergic antidepressants (i.e., nefazodone or fluvoxamine). Results showed that a higher proportion of patients receiving metyrapone showed a positive treatment response at days 21 and 35 compared with placebo patients. The clinical course of patients treated with metyrapone showed an earlier onset of action beginning in the first week. The plasma concentrations of

corticotropin and deoxycortisol were significantly higher during metyrapone treatment, whereas cortisol remained largely unchanged. The authors reported no serious adverse side effects associated with metyrapone treatment, and concluded that it is an effective adjunct in the treatment of major depression and leads to a better treatment outcome than the standard treatment. Reus and Wolkowitz[41] reported metyrapone's side effects to include nausea, headache, sedation, rash, acne, and hypertension.

Another study[28] examined the effects of corticosteroid receptor antagonists on mood and neurocognitive functioning in bipolar disorder. The authors conducted a double-blind study in which 20 bipolar patients were treated with 600 mg/day of mifepristone (RU 486) or placebo for 1 week. Over the 6 weeks of the study, neurocognitive and neuroendocrine functions were evaluated at baseline, days 21, and 42. Following mifepristone treatment, selective improvement in neurocognitive functioning was observed. HAM-D scores were significantly reduced compared to baseline, as were Montgomery–Asberg Depression Rating Scale scores. Spatial working memory performance, verbal fluency, and spatial recognition memory were also significantly improved compared to placebo. No significant changes occurred with the placebo.

Belanoff et al.[13] conducted a small blinded study of mifepristone as a treatment for psychotic major depression. Five patients with psychotic major depression participated in a 4-day, double-blind, placebo-controlled crossover study using 600 mg of mifepristone as monotherapy for psychotic major depression. In these patients, Brief Psychiatric Rating Scale (BPRS) scores declined by 34% while they were receiving mifepristone but rose 0.4% while receiving placebo. Similarly, scores on the HAM-D declined by 26% during mifepristone administration versus 6% during placebo administration. The decrease in BPRS and HAM-D scores in the mifepristone condition was statistically significant when compared to score changes during placebo administration.

A follow-up study by Belanoff et al. in 2002[5] indicated that in the higher dose groups (600 and 1,200 mg), nearly two thirds of the subjects showed significant reductions in their psychosis in a week or less. It is noteworthy that more than 40% of the subjects taking higher doses of mifepristone had a greater than 50% reduction in their depression scale scores. In a clinical case report, Stowell and colleagues[43] also reported therapeutic efficacy in a psychotic patient treated with antiglucocorticoid therapy.

Flores et al.[3] conducted a randomized double-blind study examining the effects of mifepristone on patients diagnosed with psychotic major depression. Thirty patients with this diagnosis were treated with either 600 mg/day mifepristone or placebo for 8 days. The HAM-D and the BPRS were administered at baseline and again after 8 days of treatment. Cortisol and ACTH were measured hourly at baseline and after 8 days of treatment. More patients in the mifepristone group showed a 50% or greater decline on the BPRS positive symptoms subscale as compared to the placebo group. Patients who received mifepristone had lower HAM-D and BPRS scores at study completion compared to those who received placebo, but these differences were not statistically significant. The authors concluded that short-term use of mifepristone may be effective in the treatment of psychotic major depression and may regulate the HPA axis. These results are inconsistent with the results from Murphy et al.[19] and Ghadirian et al.[34] in which patients did better without the psychotic features;severity of patient symptoms might be one factor. Preliminary data from all of these investigators indicate that corticosteroid-synthesis inhibition may be an effective form of treatment for some patients with major depression, either alone or in combination with more conventional antidepressant therapy. Though the data are not overall consistent as of yet, they are suggestive of therapeutic efficacy. Clearly, however, additional double-blind controlled trials are needed to more definitively establish the efficacy of these agents and to

identify potential predictors of responsiveness to them.[27] Available data, albeit limited, suggest that these agents may be effective even in patients who do not manifest hypercortisolism, and despite apparent partial compensation by the HPA axis for this synthesis blockade. These observations suggest that inhibition of cortisol secretion alone may not fully account for their therapeutic effects. One hypothesis in the literature posits that impairment of glucocorticoid receptor expression in the brain may be indicated, and that normal glucocorticoid receptor function may be restored with glucocorticoid antagonists. [44,45] Another possibility implicates central neuropeptides and their regulation (CRH), [10,46] to which we now turn.

EFFECTS OF CORTICOSTEROID SYNTHESIS INHIBITION ON CENTRAL CRH SYSTEMS

There are three lines of thought regarding the involved brain mechanisms in corticosteroid-synthesis inhibition. The first is that antiglucocorticoids impact the HPA axis, the second is that they normalize hyperactivity of the amygdala, and the third involves the regulation of a dysregulated frontal cortex. These theories are not mutually exclusive, and it is important to recognize the possibility of multi-system involvement in corticosteroid-synthesis inhibition. Many lines of data suggest that hormones of the HPA axis are dysregulated in patients with major depression.[10,12,41] It has been reported that HPA axis hyperactivity at baseline increases the odds of eventual suicide 14-fold, independently of clinical or historical variables.[41] Patients with major depression, in contrast to patients with Cushing's disease, have normal glucocorticoid negative feedback at the pituitary rather than at the hypothalamus.[9] As a consequence of intact negative feedback at the pituitary, as plasma cortisol rises, plasma corticotropin (ACTH) levels fall in response to glucocorticoid negative feedback, followed by a fall in plasma cortisol. As cortisol falls, there is less glucocorticoid negative feedback at the pituitary and ACTH rises once again. This phenomenon could lead to an underestimation of the rate of hypercortisolism in depression.

HPA activity has been understood to be regulated by the central nervous system since the 1950s, with the principal driving force emanating from the hypothalamus in the form of CRH. In response to a stressful situation, the hypothalamus increases the release of CRH, which stimulates the pituitary to secrete ACTH. ACTH travels through the circulation to the adrenal glands causing them to secrete cortisol and cortisol initiates changes in the body, which prepare it to deal with the imposed duress with appetite decreased and energy reserves are shunted to the muscles. Anorexia, insomnia, reduced libido, and increased sympathetic activity, all of which are observed in patients with psychotic depression, can be produced in experimental animals by the intracerebroventricular administration of CRH. [47,48]

Peripherally secreted glucocorticoids are known to exert negative feedback effects at both pituitary (by suppression of ACTH) and hypothalamic (by suppression of CRH) levels.[49] Therefore, blockade of cortisol synthesis is expected to be accompanied by a feedback increase in hypothalamic secretion of CRH in an attempt to restore cortisol levels to normal. Mifepristone in vivo is a competitive inhibitor of glucocorticoid receptors but is inactive at mineralocorticoid receptors. By blocking glucocorticoid receptors, mifepristone immediately raises circulating cortisol by blocking cortisol's feedback mechanism. Hence, Flores et al.[3] hypothesized that one major effect of mifepristone may be to block glucocorticoid receptors that are found in key brain regions. Reus and Wolkowitz[41] offer evidence that HPA axis dysregulation is the primary mechanism connecting hypercortisolism and depression through their report of normalization of HPA axis function with successful drug treatment and observations that continued HPA dysfunction represents a strong indicator of risk of therapeutic relapse.

The above evidence reflects the prevailing view, largely in the clinical research community, that the endocrine hypothalamus is the sole locus at which glucocorticoids influence CRH, and that the effect of glucocorticoids is to exert feedback inhibition on CRH. Clearly, this locus is most relevant to the regulation of peripheral ACTH and cortisol secretion. However, it is now apparent from studies in experimental animals that glucocorticoids can influence CRH in other brain loci beyond the medial paraventricular nucleus, and with qualitatively different effects. However, there are alternatives to this view. Levels of cortisol in depressed patients have also been shown to be correlated with enhanced amygdala activation and frontal cortex dysregulation.[50] The overactivation of CRH and cortisol occurs in conjunction with the overactivation of the amygdala and the right frontal cortex in depressed and anxious people.[51]

How, then, do we account for the efficacy of CSIs in some patients with depression? A distinct possibility is that the hypothalamic CRH system is not the principal target system for these agents, and thus that the drugs are acting on other neurobiological substrates.[52,53] We can begin to approach the resolution of this dilemma by considering the basic physiology of central CRH systems and their relationship with peripheral pituitary–adrenal function. The medial paraventricular nucleus-median eminence CRH pathway can be thought of as a “motor neuron” system[54] whose principal action is to regulate peripheral cortisol secretion. As such, this hypothalamic–pituitary CRH pathway, although likely to be involved in the mechanism of increased peripheral cortisol secretion in depression, may not necessarily be the pathway responsible for symptoms of this illness, which may be attributable to CRH hypersecretion. Such symptoms, if at all related to central CRH activity, are more likely to result from increased activity of CRH localized in brain areas outside this neurosecretory pathway, such as other areas of the hypothalamus (e.g., the dorsal paraventricular nucleus that projects to spinal cord nuclei regulating sympathetic outflow), the amygdala, bed nucleus of the stria terminalis (BNST), central autonomic nuclei, and the cerebral cortex.[55,56]

Data may help to reconcile some of these apparent discrepancies between theoretical considerations and empirical observations. Thus, the amygdala and related components of the limbic system have received considerable attention as brain structures that may play a role in the clinical and physiological manifestations of depression, particularly those associated with symptoms of anxiety.[57,58] In addition, a large body of evidence suggests that the amygdala plays a role in the generation of fear and anxiety in response to threatening stimuli.[59,60] Schulkin et al.[61] postulated that enhanced release of CRH in the amygdala following repeated stress was cortisol-dependent by unblocking the increased CRH release with the glucocorticoid antagonist mifepristone. They suggested that CRH is actually released in the amygdala during fear-related events.

Given the clinical findings, it is possible that the three theories presented above are all valid explanations for hypercortisolism in depression. In other words, a dysregulated HPA axis, a hyperactive amygdala, and a hypoactive frontal cortex may all be present and respondent to antiglucocorticoid treatment. Peripherally derived glucocorticoids can increase the synthesis and functional effects of CRH in the amygdala and related structures. Hence, Makino et al.[62] have shown that repeated administration of 5mg of corticosterone daily to adrenally intact rats over several days significantly elevates the expression of CRH mRNA in the central nucleus of the amygdala (CeA). Similar results were found by Swanson and Simmons[56] and Watts and Sanchez-Watts[63] in adrenalectomized rats. Data have also shown enhancement by glucocorticoids of cocaine-induced kindling,[64] conditioned freezing,[65] and startle responses,[66] all of which have been suggested to involve CRH in the amygdala. In addition to the CeA, peripherally derived glucocorticoids have been shown to increase CRH mRNA expression in the BNST.[62,63] The BNST, which shows close

anatomic and functional relations with the amygdala,[67,68] nevertheless has been suggested to play a different role in conditioned fear from that of the CeA.[59] The CeA appears to participate in the development of fear associated with specific cues in classical conditioning models, whereas the BNST has been implicated in the conditioning of fear by contextual factors, which are less precisely defined. Context-dependent fear may be more relevant than cue-elicited fear to disorders characterized by anxiety.[59]

The ability of glucocorticoids to sustain conditioned fear was demonstrated by Thompson et al.[69] They found that repeated corticosterone injections increased the retention of contextual fear learning. In addition, glucocorticoid antagonists such as mifepristone cross the blood brain barrier.[70] Moreover, injections of a glucocorticoid receptor antagonist both systemically given or injected into the basolateral amygdala decreased fear-related behaviors,[71] perhaps again by altering CRH gene expression in the CeA. This study showed, in part, that chronic heightened levels of glucocorticoids facilitated CRH-induced fear-related behaviors, but did not localize the effects to a particular brain region.

Shepard et al.[72,73] demonstrated that corticosterone implanted directly into the CeA increased CRH expression in the CeA and the BNST and reduced exploratory behavior in rodents. Myers and colleagues[74] also showed that implants of corticosterone into the CeA reduced the exploration of an elevated plus maze and increased the physiological distress. Moreover, they found that antalarmin, a CRH type-I receptor antagonist, eliminated the behavioral and endocrine responses. Cook,[75] using microdialysis to measure the release of CRH, found a significant relationship between cortisol and CRH in the amygdala of sheep in response to acute and repeated predator stress. With a single exposure to a dog, sheep demonstrated a biphasic CRH response in the amygdala. There was an initial rapid increase in CRH levels that decreased quickly and was a direct response to the dog. This was followed by a slower rising cortisol response that was paralleled by a second CRH peak, smaller and more prolonged than the first. The first CRH response is cortisol-independent and is part of the initial fear response to a stressor, whereas the second response is a cortisol-dependent elevation of CRH, which perhaps sustains the fear state and related behavior through and beyond the presence of the threat. The second response was mimicked by administration of cortisol in nonstressed animals. These studies demonstrate that the prolonged release of CRH is cortisol-dependent and that this CRH response is sensitized by repeated stress in a cortisol-dependent manner. Cook[75] also showed that CRH is actually released in the amygdala during fear-related events.

Because glucocorticoids appear to positively modulate CRH expression and actions in CeA and BNST, in contrast to their negative regulation of hypophysial-portal CRH secretion, corticosteroid synthesis inhibition would be expected to decrease the CRH expression in these regions. Therefore, symptoms mediated by CRH release induced by the activation of CeA and/or BNST CRH-containing neurons (e.g., fear, anxiety), as well as the sympathetic activation that might accompany CRH activation in dpPVN neurons, might be expected to be ameliorated by the reduction of circulating cortisol levels. The limited clinical information to date does not permit conclusions as to whether prominent symptoms of anxiety and/or fear, which have been termed “dysphoric hyperarousal,”[47] or signs of sympathetic activation, can predict a favorable clinical response to CSIs. This prediction can be addressed in future controlled trials of these agents. It would also be of interest to examine whether those with abnormalities of functional cerebral activity in the amygdala are more likely to respond to CSIs than those without such abnormalities.

CONCLUSION

MDD is the leading cause of disability worldwide,[1] taking a significant toll on the body and manifesting in both biological and psychological disturbances. Hypercortisolism is one of the most consistent biological abnormalities seen in depressed individuals.[27] Given the implication of elevated cortisol in MDD, antiglucocorticoids were initially examined as a potential treatment method. Several studies, conducted over the last 20 years, indicate that antiglucocorticoids have been effective with both psychotic and nonpsychotic depression, though perhaps more so with nonpsychotic depression as the data are still not entirely consistent with regard to the efficacy of therapeutic antiglucocorticoids on patients with psychotic depression.[27] Positive findings have been replicated even in depressed individuals found not to be hypercortisolemic, which points to the possibility that inhibition of cortisol may not fully account for the therapeutic effects of antiglucocorticoids and suggests that perhaps changes in glucocorticoid receptor (GR) function may also be a factor.[45]

We have integrated both empirical observations regarding the potential therapeutic efficacy of CSI with theoretical considerations regarding the respective involvement of glucocorticoids and CRH in the pathophysiology of severe mood disorders by proposing mechanisms by which these agents may exert their putative therapeutic effects. The reports cited here suggest that these agents may ultimately have a place in the acute management of depressive disorders; however, further replication is necessary.

We propose that CSIs exert their putative therapeutic effects, at least in part, by reducing the release of CRH at terminals of neurons with cell bodies in brain sites outside the endocrine hypothalamus, particularly the CeA (leading to decreased fear and anxiety). We further recognize that other mechanisms may be involved (including, but not necessarily limited to, GR receptors, neurosteroids acting through GABA-A and perhaps serotonin, and dopamine). In addition, these considerations suggest that CSIs may be of adjunctive value in patients who are refractory to antidepressant treatments by reducing CRH in projections of the CeA and other relevant cell groups. The hypotheses raised here lead to specific predictions that can be tested through further research.

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