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Review

Glucocorticoid antagonists in neuropsychotic disorders

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Abstract

Neuropsychiatric disorders often involve considerable psychological stress and elevated cortisol activity. Glucocorticoid receptors have relatively low affinity for cortisol and are found distributed throughout the brain, particularly in the frontal cortex and hippocampus. In recent years, glucocorticoid receptors antagonists have been actively studied in both animal models of several disorders as well as a potential treatment in specific types of neuropsychiatric patients. Data from these various studies are reviewed with an emphasis on seven clinical disorders or problems: major depression with psychotic features, bipolar disorder, schizophrenia, cognitive disorders, (e.g., Alzheimer's disease and mild cognitive impairment), cognitive side effects of electroconvulsive therapy, and weight gain with atypical antipsychotic agents. Potential benefits and limitations are discussed.

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Keywords: Cortisol; Stress psychotic major depression; Glucocorticoid receptors; Mineralocorticoid receptors; Mifepristone

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1. Introduction

In recent years, considerable attention has been paid to the possible use of glucocorticoid receptor antagonists to

* Corresponding author. *E-mail address:* afschatz@stanford.edu (A.F. Schatzberg). treat neuropsychiatric disorders. These drugs are characterized by their greater affinity for the glucocorticoid (Type 2 cortisol) receptor than for the mineralocorticoid receptor. Glucocorticoid receptors are widely distributed both in the brain and throughout the body and could serve as important pharmacologic targets for treating a variety of stress-related disorders. The rationale for developing these agents for neuropsychiatry is discussed below and recent preclinical and clinical data on this class of agents are reviewed.

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2. Hypothalamic Pituitary Adrenal axis activity and receptor pharmacology

The Hypothalamic Pituitary Adrenal axis controls the production and release of cortisol, a key stress hormone secreted by the adrenal gland. The hypothalamus releases corticotropin releasing hormone — a peptide that stimulates the pituitary to release adrenocorticotropin hormone which in turn stimulates the adrenal. Cortisol feeds back at the level of the pituitary and the hypothalamus to inhibit adrenocorticotropin hormone and corticotropin releasing hormone secretion, respectively. There is a diurnal rhythm to cortisol with levels being highest in the morning and at a nadir at about midnight. There are two forms of receptors that bind to cortisol. Glucocorticoid receptors are cytosolic receptors that bind to the nucleus receptors when bound with ligand. They have relatively lower affinity for cortisol, and are activated particularly under high degrees of stress or during the time of the diurnal rhythm cycle when cortisol levels are highest — e.g., in the early morning. They are not particularly activated at the nadir. In contrast, mineralocorticoid receptors are occupied much of the time and are most active functionally at night relative to glucocorticoid receptors. The hippocampus appears to contain a greater concentration of mineralocorticoid receptors than glucocorticoid receptors; the reverse is true for the cortex (Patel et al., 2000). Feedback inhibition can be tested by administering a dose of a synthetic steroid - dexamethasone which normally suppresses the release of both adrenocorticotropin hormone and cortisol for 24 h (Carroll et al., 1981). Conversely, the Axis can be stimulated via administering either corticotropin releasing hormone or adrenocorticotropin hormone. Corticotropin releasing hormone administration results in a release of adrenocorticotropin hormone and in turn cortisol. Blunted adrenocorticotropin hormone responses to ovine (o)-corticotropin releasing hormone have been reported in groups of patients with depression, suggesting overactivity of the corticotropin releasing hormone peptide in brain in depression (Heuser et al., 1994). An alternative strategy has been to pretreat with dexamethasone to potentiate the corticotropin releasing hormone effect and this provides more dramatic increases in adrenocorticotropin hormone (Ising et al., 2005). Adrenocorticotropin hormone stimulates the adrenal to release cortisol and adrenal responses to adrenocorticotropin hormone have been reported as increased in some subtypes of depression (Amsterdam et al., 1989).

Mineralocorticoid receptor is activated in the kidney by aldosterone, and can be blocked by the drug spiranolactone. Synthetic mineralocorticoid receptor agonists – e.g., fludrocortisone – can increase blood pressure and are used to treat orthostatic hypotension; in contrast the antagonist, spiranolactone, is used to treat hypertension. Glucocorticoid receptors can be activated by administering high doses of cortisol or dexamethasone and blocked by a number of agents — e.g., mifepristone, ORG 34157, etc. To date, these compounds all have a steroidal chemical structure. Unfortunately, there is great homology between cortisol and progesterone as well as between the progesterone receptor and glucocorticoid receptors, such that all the currently available agents are potent progesterone antagonists and thus are capable of inducing abortions in pregnant women and in causing amenorrhea in pre-menopausal females.

The Hypothalamic Pituitary Adrenal axis plays important roles in glucose metabolism, blood pressure regulation, immune function, cognition and other key homeostatic functions. It is activated during acute stress in the so-called flight or fight response that helps the body mobilize glucose and epinephrine. In man, increased activity at the extreme is seen with tumors of the pituitary (Cushing's Disease) that result in excessive adrenocorticotropin hormone and cortisol release and considerable physical and psychiatric morbidity. In normative states, feedback inhibition of the Axis decreases with age and higher levels of cortisol are observed post-dexamethasone in elderly than in younger subjects (Rosenbaum et al., 1984).

Psychiatric disorders often involve a major stress component and understandably the Hypothalamic Pituitary Adrenal axis has been well studied in these disorders, with particular emphasis on depressive and anxiety disorders. Major depression has frequently been characterized by hypercortisolemia; although, many studies have failed to observe elevated cortisol activity in nonpsychotic depressives (Keller et al., 2006). For a while, it was thought that testing of feedback using dexamethasone could be used as a test for melancholia (Carroll et al., 1981). Unfortunately, this was not the case. The test was neither sufficiently specific nor sensitive to be adapted as a screen for nonpsychotic depression (Arana et al., 1985) and it was virtually discarded not long after its introduction.

We and others reported over two decades ago that patients with major depression with psychotic features who are generally amongst the most severely ill of patients do demonstrate very high post-dexamethasone cortisol levels pointing to marked Hypothalamic Pituitary Adrenal axis overactivity in the disorder (Schatzberg et al., 1983; Evans et al., 1983). Two major meta- or pooled analyses (Arana et al., 1985; Nelson and Davis, 1997) have confirmed that the test can best be used for assessing patients with this disorder. This consistent overactivity suggests this subtype might be amenable relatively to an antiglucocorticoid intervention. Attempts to treat refractory depression with glucocorticoid receptors antagonists proved generally unsuccessful in the early 1990s (Murphy et al., 1993). These trials employed relatively low doses of the glucocorticoid receptors antagonist mifepristone in nondelusional patients.

3. Psychotic major depression

Psychotic major depression is relatively common accounting for some 15–19% of depressives (Ohayon and Schatzberg, 2002). Current prevalence rates are approximately 0.3–0.8% (Ohayon and Schatzberg, 2002; Perälä et al., 2007). The disorder is characterized predominantly by delusions involving thoughts of nihilism, deserved punishment or paranoia, or somatic percepts (Schatzberg and Rothschild, 1992). Approximately a third of the patients experience hallucinations primarily auditory in nature. The disorder is found in equal numbers of men and women and bipolar patients are more likely to demonstrate delusions than are unipolar depressives. Classically psychotic major depression was thought to be more common in the elderly but this is largely a misperception. Patients with the disorder demonstrate significant elevations in cortisol activity much more commonly than do nondelusionally depressed patients. This was seen particularly in the early observations of high rates of dexamethasone non-supression as well as in the very high post-dexamethasone cortisol levels (Schatzberg et al., 1983; Evans et al., 1983). However, the increased cortisol activity is not limited to dexamethasone nonsuppression. These patients demonstrate elevated urinary free cortisol levels (Anton, 1987), elevated nocturnal plasma cortisol levels (Keller et al., 2006), and elevated plasma adrenocorticotropin hormone levels (Posener et al., 2000).

Two decades ago we hypothesized that the elevated cortisol activity in psychotic major depression was not an epiphenomenon but could lead to cognitive disturbance such as psychotic thinking. At that time, the putative mechanism was thought to be an increase in dopamine activity in the nucleus accumbens secondary to an increase in cortisol. Over the years our thinking has changed somewhat about possible mechanisms. The original hypothesis was based on the findings that dexamethasone administered at 11PM to healthy controls resulting in increased levels of dopamine activity and its metabolite homovanillic acid, in the periphery the next afternoon as well as that administration of dexamethasone to rats increased brain dopamine activity metabolite levels 4 h later (Rothschild et al., 1984, 1985; Langlais et al., 1984). Subsequent studies in man by our group also point to corticotropin releasing hormone and adrenocorticotropin increasing dopamine metabolites, particularly the next day (Posener et al., 1994, 1995, 1999). Others point to metyrapone - a cortisol synthesis blocker - increasing dopamine turnover in man (Lupien et al., 1995) suggesting that corticotropin releasing hormone overactivity also drives the dopamine activity. Thus the original observations of dexamethasone induced increases in dopamine activity several hours after dexamethasone has probably cleared the body might be better explained by a corticotropin releasing hormone rebound effect. Conversely, Duval et al. (2006) administered a central dopamine activity challenge using apomorphine and followed cortisol responses in healthy controls and psychotic major depression patients. The latter demonstrate a significantly blunted response to apomorphine. Of interest nonpsychotic depressives do not. Taken together these data suggest that the effects of the hypothalamic pituitary adrenal axis on dopamine are complex and may differ acutely or chronically.

At the time of our original hypothesis we emphasized the increased activity of dopamine activity in the nucleus accumbens — a part of the mesolimbic circuit that was thought to be involved in the production of psychotic symptoms. In recent years, increasing attention has been paid to the reciprocal relationship in schizophrenics between increased dopamine activity in the nucleus accumbens and decreased activity in the prefrontal cortex as a mechanism in schizophrenia. This relationship has been used to explain both the positive psychotic symptoms and the executive function deficits in schizophrenia. Our own preclinical work in the rat (Lindley et al., 2002) points to corticosterone causing a decrease in prefrontal dopamine activity turnover, consistent with the cognitive effects seen with steroids — see below.

Cortisol plays key roles in modulating cognition. This can be tested by administering cortisol or dexamethasone to controls or by studying the relationship of cortisol activity to neuropsychological performance in patients and controls. Prolonged surges in cortisol via exogenous administration or stress or disease can be often associated with cognitive impairment in multiple domains and we have reviewed this extensive literature elsewhere (Belanoff et al., 2001a). The relationship of cortisol to working memory appears to be U-shaped with very low and very high levels being associated with poor performance (Lupien et al., 2002). In psychotic major depression, patients demonstrate deficits in attention, executive function and verbal memory and these are functions that can be negatively affected by cortisol (Belanoff et al., 2001a,b; Schatzberg et al., 2000; Fleming et al., 2004; Gomez et al., 2006). We have recently reported on negative correlations between nocturnal cortisol and cognitive measures (Gomez et al., 2006).

We hypothesized in the 1980s that reducing cortisol activity could relieve the psychosis of psychotic major depression (Schatzberg et al., 1985). In 1991, Lamberts' group had reported that mifepristone at high doses rapidly - within a few days - reversed psychotic and depressive symptoms in patients with intractable Cushing's disease (van der Lely, 1991). We decided to employ this strategy and in a series of 5 patients treated under double-blind, placebo controlled crossover conditions, Belanoff et al. (2001c) reported several years ago that 600 mg/day of mifepristone appeared to rapidly ameliorate the psychotic symptoms in 5 psychotic major depression patients treated under double-blind, crossover conditions. Several open label and double-blind reports supported these early observations of clinical efficacy with this strategy, although, some have disagreed with the interpretations (Carroll and Rubin, 2006).

In the first study, we observed a mean 31% decrease in the Brief Psychiatric Rating Scale score after 4 days in contrast to 1% for placebo. Clinically these patients did not appear to lose their response with cessation of drug treatment. In a second study of 30 patients (Belanoff et al., 2002a) treated under open label conditions for 7 days with 50 mg, 300 mg or 600 mg/day of the drug, 67% of the patients on the higher 2 doses demonstrated a 50% reduction in psychotic symptoms with one week of treatment. Again, the response did not appear to be transient, although formal follow-up at one month was not incorporated into the design. Simpson's group in another open label study of 20 patients (Simpson et al., 2005) reported high rates of response at 4 and 8 weeks after only 6 days of treatment with 600 mg/day. Here formal open label follow-up was included and patients were kept off other medications after the 6 day trial until 8 weeks. Patients continued to respond between week one and week 4 and maintained their response until at least 8 weeks. The effect sizes observed in these studies were above 0.9 - pointing to considerable effect.

Two double-blind studies using 600 mg/day have recently been published. In one, Flores et al. (2006) reported that 45% of the 15 psychotic major depression patients met the response criterion of a 50% reduction in the Brief Psychiatric Rating Scale — Positive Symptom Subscale at 1 week in contrast to 14% of the 15 patients treated with placebo. The effect size was 0.9. In the other study of over 200 patients, DeBattista et al. (2006) reported a significantly higher response rate in reduction of the Brief Psychiatric Rating Scale — Positive Symptom Subscale with drug over placebo at weeks one and 4. Continued improvement was reported to 8 weeks in a subgroup followed for an additional month.

However, the recently completed, Phase III trials conducted by Corcept Therapeutics failed to significantly separate drug from placebo although the drug was numerically superior on reduction of the Brief Psychiatric Rating Scale — Positive Symptom Subscale (Corcept Therapeutics Press Release, March 29, 2007). Follow on analysis of one trial of 600 mg/day of mifepristone for 7 days revealed a relationship between trough plasma level of drug and clinical response. These data point to levels of approximately 1400 mcg/dl being associated with response. The level was confirmed in a subsequent trial that employed 300 mg, 600 mg, and 1200 mg/day doses for 7 days. This is approximately 10 fold higher on a nanomolar basis than is the level of cortisol and the difference in levels appears to be much greater than the relative affinities for glucocorticoid receptors. This level is best attained at 1200 mg/day and this dose was well tolerated.

One possible explanation for the relatively high dose rests with the observation that mifepristone serves as a potent antagonist for the p-glycoprotein pump that controls the efflux of cortisol from brain. In rats, administration of mifepristone results in a three fold higher concentration of cortisol centrally and this may then require an even higher dose and level of mifepristone than one might have expected (Karssen et al., 2003). Studies of mifepristone effects on cerebrospinal fluid cortisol and mifepristone are needed.

The drug appears well tolerated in clinical trials to date with the major side effect being a diffuse skin rash that frequently appears after the drug is stopped. Rashes respond to diphenhydramine administration. Nausea rates have been low and appear not to differ from placebo.

The clinical effects seen with short-term administration are not short-lived, suggesting that there may be carry-over effects from the drug. Mifepristone's half-life is 1–2 days and a continued response (after one week of therapy) to 8 weeks suggests some lasting physiological alteration such as a possible resetting of regulation of the Hypothalamic Pituitary Adrenal axis to a more normal state. The plasma levels of cortisol seen after administration are high and the effect on the P-GP protein point to even higher levels of cortisol in brain. With the drug resulting in blockade of glucocorticoid receptors, it is conceivable that cortisol floods mineralocorticoid receptor which is then re-regulated and cortisol rhythm is normalized. Mineralocorticoid receptor dysfunction has been postulated to underlie depressive symptoms. Study of this hypothesis is currently underway in our laboratory.

4. Bipolar depression

Two lines of evidence suggest that patients with bipolar depression may be helped by mifepristone. For one, Young's group has demonstrated elegantly that bipolar depression is characterized by overactivity of the Hypothalamic Pituitary Adrenal axis (Watson et al., 2004). Others have reported on a number of cognitive deficits in bipolar disorder similar to those reported in delusional depression (Clark et al., 2001). These include decrements in attention and verbal and visual memory. Young's group has reported (Young et al., 2004) in 20 bipolar depressives that one week of treatment with 600 mg/day of mifepristone was associated with improved cognition 2 weeks after cessation of the drug, particularly in visual memory that is negatively affected by cortisol administration (Porter et al., 2002). Increases in cortisol levels with drug were correlated significantly with improvement in spatial memory error rate. Depressed mood was improved by one week but this effect was not sustained, indicating further that the cognitive effect is independent of a mood effect. A large multi-center trial is currently underway in bipolar depression.

5. Schizophrenia

Elevated cortisol activity is seen in a subgroup of schizophrenic patients, although, we failed to observe elevated dexamethasone non-suppression rates or post administration cortisol levels in our schizophrenia inpatient studies in contrast to our paralleled psychotic major depression studies (Rothschild et al., 1982). Young's group has conducted a pilot study of mifepristone in 20 schizophrenic patients, using the same design as in bipolar depression (Gallagher et al., 2005). They failed to observe significantly greater effects of drug over placebo on schizophrenic or depressive symptoms or on cognition. Drug produced significant improvement over baseline in Brief Psychiatric Rating Scale total scores as well as in depression scale scores 2 weeks after drug cessation — limiting somewhat what one can conclude re potential efficacy. Higher doses of drug have not been tried.

6. Cognitive disorders

In the elderly, cortisol levels are higher than in younger subjects. In elderly subjects who maintain relatively elevated cortisol levels over time or whose cortisol levels increase over time, poorer cognitive performance has been reported (Lupien et al., 1998). These data fit the previously mentioned data pointing to negative relationships between elevated cortisol activity and cognitive performance taking place out of the task's context or occurring over a considerable period of time. A number of neurobiological mechanisms may help to explain this. For one, stress affects long term potentiation in nucleus accumbens dopaminergic neurons. For another, stress and cortisol administration both suppress neurogenesis in the hippocampus. Mifepristone blocks all of these effects in rats (Saal et al., 2003; Mayer et al., 2006; Krugers et al., 2006) and thus could be used to improve cognition (Belanoff et al., 2002b). Elevated cortisol levels have been reported to be associated with APOE-4 status in Alzheimer's disease and with cognitive impairment, further suggesting a glucocorticoid receptors antagonist can be useful in the disorder (Peskind et al., 2001). There is one report of a double-blind comparison of 200 mg/day of 6 weeks of mifepristone versus placebo in 9 subjects with Alzheimer's disease (Pomara et al., 2003). The Alzheimer's disease Assessment Scale-Cognitive subscale improved by 2.7 points on the drug group and worsened by 1.7 on placebo but the difference did not attain significance in this small sample. There was a trend for more improvement on Alzheimer's disease Assessment Scale-Cognitive subscale scores as well. Further studies are required at multiple fixed doses to assess efficacy and side effects. The drug appeared well tolerated in the elderly with one patient demonstrating a rash. Whether mifepristone or glucocorticoid receptors antagonists will be helpful in Alzheimer's disease is not clear since cognitive decline and neuronal loss might be too advanced to be reversible with a glucocorticoid receptors antagonist. In contrast, earlier and milder cognitive disorders in the elderly – e.g. mild cognitive impairment – could prove to be a better target.

7. Cognitive side effects of electroconvulsive therapy

Electroconvulsive therapy is perhaps the most effective of antidepressant treatments; however, it can produce considerable memory impairment (Sackeim et al., 2007). This is more commonly observed with bilateral administration and recent reports point to higher rates of memory impairment and more severe loss than had previously been reported in the scientific literature (Sackeim et al., 2007). The effect is usually most pronounced for contextual memory often of a personally important nature. One clinical study reported that patients with higher pretreatment salivary cortisol levels were most likely to experience memory effects with electroconvulsive therapy (Neylan et al., 2001). Recently, a study in rats reported that mifepristone administration blocks electroconvulsive therapy-induced memory loss (Nagaraja et al., 2007). At least one trial of a glucocorticoid receptors antagonist to block the untoward memory effects of the disorder is currently underway.

8. Weight gain with atypical antipsychotic agents

The development of atypical antipsychotic agents revolutionized the treatment of schizophrenia. These agents appeared to provide more benefit on the positive symptoms of schizophrenia, the deficit or negative symptoms; as well as cognitive performance than did first generation antipsychotic medications. However, the degree of true advantage has been brought into question by several recent large-scale effectiveness trials (Lieberman, 2006). Still these drugs have become the dominant method of treatment of patients with schizophrenia. Unfortunately these agents are frequently associated with weight gain, insulin resistance and potentially diabetes, all of which carry great medical consequence (Newcomer and Lieberman, 2007).

Elevations in cortisol are associated with changes in body fat and insulin resistance. Several years ago we reported that mifepristone was a highly effective treatment for multiple medical complications in a patient with Cushing's disease whose illness had not responded to surgery and radiation (Chu et al., 2001). The glucocorticoid receptors antagonist reversed the insulin dependent diabetes and the patient was able to stop insulin within a month. In addition, the mifepristone reversed his severe cardiomyopathy. These data suggest that a glucocorticoid receptors antagonist could be useful for blocking and reversing the insulin resistance and weight changes seen in some patients treated with atypical antipsychotic agents. To this end, Beebe et al. (2006) have reported that mifepristone in rats blocked olanzapine-induced weight gain and increases in abdominal fat. Moreover, mifepristone reversed the weight gain in animals that had already occurred while taking olanzapine. Very recently, Corcept Therapeutics (Corcept Therapeutics Press Release June 21, 2007) announced that in a 2 week study 600 mg/day of mifepristone reduced olanzapine-induced weight gain in 57 nonoverweight healthy males with Body Mass Index's less than 25. Thus, glucocorticoid receptors antagonism could prove a useful mechanism to target in treating psychotic patients with atypical antipsychotic agents. The effect of mifepristone on insulin resistance is also under investigation. One strategy could be to develop a formulation that would combine an atypical antipsychotic agent with a glucocorticoid receptors antagonist. Ultimately, multiple fixed doses would need to be tested in combination with the various atypical agents.

Glucocorticoid receptors antagonism represents an interesting mechanism of action that could provide relief for patients with various psychiatric or cognitive disorders or for blocking side effects associated with electroconvulsive therapy or atypical antipsychotic agents. Both peripheral and central effects may be brought into play in these uses. The exact biological effects that underlie possible clinical improvements need to be studied and optimal doses for specific disorders need to be established along with efficacy. This area would also be benefited by the development of agents that did not produce anti-progesterone effects. This would allow for safer long term administration to pre-menopausal women as long term progesterone without worry of irregular blockade creates a de facto state of unopposed estrogen. Such agents are currently being developed by at least one pharmaceutical company and we are likely to see clinical trials in specific disorders or conditions in the next few years.

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Dr. Schatzberg consults to Eli Lilly and is a co-founder of Corcept Therapeutics, a biotechnology company developing glucocorticoid antagonists.

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