Monthly Focus: Central & Peripheral Nervous Systems

Antiglucocorticoid drugs in the treatment of depression

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A confluence of evidence indicates that prolonged elevation in glucocorticoid level may result in disturbances of mood and cognition. In Cushing's syndrome, hypersecretion of cortisol is associated with a high incidence of depression, impairment in memory and hippocampal atrophy. Pharmacological usage of glucocorticoids is similarly productive of mood change and memory deficit. In patients with endogenous depression, hypercortisolaemia is associated with cognitive dysfunction and possibly a decrease in hippocampal volume. In each of these conditions, reduction of glucocorticoid level, either through discontinuation of steroid treatment or through usage of agents that block glucocorticoid synthesis, ameliorates the adverse behavioural effects. Traditional antidepressant agents may, in addition, stabilise mood through actions on the hypothalamic-pituitary adrenocortical (HPA) system. Although clinical usage of the currently available antiglucocorticoid drugs is limited by significant adverse side effect profiles, development of drugs specifically targeting the glucocorticoid receptor may lead to innovative strategies in the treatment of mood disorders.

Keywords: allostasis, antidepressant, cortisol, glucocorticoid, ketoconazole, metyrapone

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1. Behavioural effects of glucocorticoids

The observation that excessive adrenal secretions could be productive of change in behaviour and cognition, as well as in body habitus, was first put forward by Harvey Cushing in the original case series descriptions of the syndrome that now bears his name. In the years since, numerous investigators have demonstrated that Cushing's syndrome (hypercortisolaemia secondary to an adrenal or pituitary adenoma or an ectopic tumour) is associated with a high incidence of fatigue, impaired memory and attention, decreased libido, insomnia and anxiety and a rate of depression that approaches 70% [1,2]. Neuropsychiatric symptoms in Cushing's syndrome patients are directly correlated with circulating cortisol levels and typically resolve with effective treatment of the hypercortisolaemia. Over thirty published reports have documented that either surgical or pharmacological (e.g., ketoconazole, metyrapone, aminoglutethimide, RU-486) intervention to lower cortisol level or block glucocorticoid effect results in behavioural and cognitive improvement and, in some cases, complete psychiatric remission, along with normalisation of blood pressure, hyperglycaemia, hypokalaemia and fat distribution [3].

In a manner parallel to endogenous dysfunction, exogenous alteration of corticosteroid level through the usage of corticosteroid medications can also result in significant changes in behaviour.

Initial treatment with synthetic steroids, such as cortisone, prednisone and dexamethasone, is most commonly associated with signs of mild activation in psychomotor function but more sustained and higher dosage treatment can cause profound mood lability and depression, memory and attentional impairment, sensory flooding and, rarely, psychosis [4]. Behavioural abnormalities usually resolve quickly with

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discontinuation of the corticosteroid but a small percentage of individuals may continue to experience a long lasting memory impairment ('steroid dementia syndrome'), even after drug cessation [4]. The mechanism for such an effect remains unknown but recent evidence has shown that some steroid-treated patients show signs of hippocampal neuronal apoptosis, as well as heat shock protein 70 staining (a correlate of oxidative damage and cellular stress), at autopsy [5]. In the cited study rare, but apparently convincing, apoptosis was observed in entorhinal cortex, subiculum, dentate gyrus, CA1 and CA4 in 11 of 15 depressed patients and in three steroid treated patients. The magnitude of cell loss, however, was minimal, making it unlikely that this effect contributes in any significant way to the hippocampal volume changes that have been independently described.

2. Basic mechanisms of corticosteroid action

Regulation of glucocorticoid level is dependent on hypothalamic release of corticotropin releasing hormone (CRH), and subsequent adrenal stimulation mediated through pituitary release of adrenocorticotropin (ACTH) and an autoregulatory negative feedback system of glucocorticoid receptors located in the hippocampus, hypothalamus and pituitary. Cells in the paraventricular nucleus (PVN) of the hypothalamus secrete CRH in response to neuronal inputs from a number of brain regions, including amygdala, hippocampus, midbrain and cortex and in response to modulation by neuropeptides such as substance P, neurophysin and cholecystokinin. Subsequent release of ACTH is markedly amplified by conjoint release of arginine vasopressin. Glucocorticoid negative feedback is mediated through binding at two different types of receptor. The Type I mineralocorticoid receptor (MR) is found predominantly in the hippocampus and has high affinity and low capacity, making it central to control of resting and basal levels of cortisol, while the Type II glucocorticoid receptor (GR) is more broadly localised across brain regions and is more directly involved in circadian and stress induced peaks in cortisol level as a result of its lower affinity.

Corticosteroids may affect brain function and behaviour through one of three general mechanisms:

- Action on the genome
- Direct activity on cell membranes and membrane receptors
- Morphological changes, neuroendangerment of vulnerable neurones

Corticosteroids freely cross neuronal cell membranes and, after binding to a specific cytosolic receptor, translocate to the nucleus where the receptor dimerises and the complex binds to a six nucleotide sequence, the glucocorticoid response element (GRE) and either enhances or inhibits gene transcription. Such actions have been implicated in the regulation of enzymes such as tyrosine hydroxylase, tryptophan hydroxylase, monoamine oxidase, dopamine beta-hydroxylase and phenylethanolamine *N*-methyl-transferase (PNMT), which control the activity of biogenic amines and other neurotransmitters, as well as the production of neuropeptides, such as CRH, somatostatin, ACTH and beta-endorphin, G-proteins and cytokines IL-6 and IL-8, which promote B-cell maturation and leukocyte stimulation [3,6]. Corticosteroids have also been shown to affect receptor synthesis, most specifically, the α_2 and β_2 adrenergic receptors and the 5-HT_{1A} and 5-HT_{1B} receptors [6,7]. Glucocorticoid effects on serotonergic function are complex but there is empirical evidence that stress levels of corticosteroids increase the excitability of CA1 hippocampal pyramidal cells through the 5-HT_{1A} receptor and that metyrapone, a glucocorticoid synthesis inhibitor, can exhibit antidepressant effects that are correlated with change in 5-HT_{1A} activity [8-12].

In addition to these genomically mediated effects, corticosteroids may act directly with neuronal cell membranes and neuronal receptors and cause rapid changes in neural function through modulation of ion channels or second messenger systems, or through receptor mediated protein-protein interactions [13].

Lastly, a confluence of evidence indicates that corticosteroids may, if sustained for a long enough period at a high enough level, result in neuroendangerment or neuronal death in specific brain areas (e.g., hippocampus CA3), although trophic effects have been observed at other sites, such as the hippocampal dentate gyrus, with lesser degrees of activation [14-17]. Repeated glucocorticoid exposure results in a shortening and debranching of dentrites in CA3 and a suppression of neurogenesis of dentate gyrus granule neurones, possibly by impairing glutamate removal from the synapse and calcium extrusion from the cytoplasm, as well as NMDA receptor activation. Both RU-486 (mifepristone), a glucocorticoid receptor blocker and ORG 2766, a non-steroidogenic ACTH 4-9 analogue, prolonged survival of CA1 neurones following ischaemia [17].

3. Role of glucocorticoids in the neurobiology of stress

Secretion of glucocorticoids represents the prototypical stress response, although it remains unclear whether the myriad of metabolic and physiological changes induced by glucocorticoids represent a mediation and prolongation of the response itself or an adaptation to it. The term 'allostasis' has recently been put forward to describe the fact that in a successful adaptation to stress, an organism must adeptly respond to the energetic and metabolic demands of a provocative stimulus but also be able to inhibit that same response when the acute stress subsides [18]. To explain the varying effects of glucocorticoids, the adaptive acute response to stress has been divided into separate classes of action that have differing time domains. Permissive actions, regulated by Type I receptors at lower basal levels of cortisol, predominate prior to the onset of stress and are tonically involved in the mediation of the initial response, while stimulatory and suppressive actions, mediated

by Type II receptors, either enhance or inhibit the effects of the initial change in stress responsive hormones. Preparative actions are those that alter the physiological response of the organism to a subsequent presentation of a stressor [19]. Such a nosology has proven useful in understanding the cost to the organism of constant and recurrent attempts to elicit a stress response, or 'allostatic load' [20]. From the specific perspective of glucocorticoid function, increasing allostatic load may be reflected in higher degrees of hyperglycaemia, increased visceral fat, elevated blood pressure, decreased bone density, hyperlipidaemia and subtle alterations in electrolyte function and immune response [15]. To the extent that these variables in turn affect morbidity and mortality, judicious usage of antiglucocorticoid agents may prove to be therapeutic in reducing allostatic load and in restoring a proper ratio of anabolic to catabolic metabolic activity.

4. Glucocorticoid dysregulation in depression

Dysregulation of the HPA axis in depression is the most consistently replicated finding in biological psychiatry [21]. Approximately half of all patients with major depression have increased levels of cortisol in plasma, urine and cerebrospinal fluid (CSF), an increased cortisol response to ACTH, a dampening of circadian rhythmicity and an impairment of suppression of cortisol release following administration of a synthetic glucocorticoid, dexamethasone. These changes appear to be state-dependent and become less prominent with remission. Increases in adrenal and pituitary mass have also been reported, as have an alteration of 'fast' feedback response of ACTH to infused hydrocortisone and increased pulsatility [22] Some but not all studies, have also documented an increase in CRH concentrations in the CSF, a blunted ACTH response to CRH alone and a loss of inhibition of ACTH response to CRH following dexamethasone pre-treatment. A decrease in CRH binding sites in the frontal cortex has also been observed in individuals who committed suicide and an increased number of CRH and arginine vasopressin (AVP) expressing neurones in the PVN of depressed patients overall [23]. It has also been reported that HPA axis hyperactivity at baseline increases the odds of eventual suicide 14-fold, independently of clinical or historical variables [24]. Taken in sum, these data suggest that evidence of HPA dysregulation may represent an endophenotypic marker that identifies an aetiologically more homogenous subgroup of the overall population of depressed individuals. Depressed patients lacking such findings may develop their syndrome through alternative pathways or simply fail to show HPA perturbations as a result of being sampled at a different phase of illness and/or treatment.

In light of the evidence for impaired glucocorticoid negative feedback, investigators have concentrated on the expression and function of the GR. Although a few studies have found a reduction in GR number in depression, most have been unable to detect a difference between depressed patients and normal controls and none have found an alteration in affinity for ligand in lymphocyte GR, or alteration in GR in mRNA in post-mortem brain tissue [25]. Studies exploring GR function have been more informative [26]. Using either lymphocyte proliferation in response to a GR agonist or GR binding in response to steroid manipulation, a consistent lack of response is observable in depressed patients, particularly those that had a predetermined collateral abnormality in HPA function. Such GR resistance may be localised, given evidence for preserved GR sensitivity to elevated glucocorticoid levels and clinical findings of increased abdominal fat distribution and decreased bone density in hypercortisolaemic patients. The mechanism for GR resistance remains unknown but may involve a transmitted genetic variant in the GR gene or an alteration in a regulatory pathway other than that dictated by changes in glucocorticoid level. Possible candidates include the cAMP/PKA cascade and pro-inflammatory cytokines, each of which has been independently found to be disrupted in major depression.

Although the emphasis thus far has been on the role of the GR in depression, evidence indicates that MR alteration may be implicated as well. Blockade of the MR increases GR mRNA and protein in CA1 and the dentate gyrus [27] and increases post-dexamethasone and post-CRH administration cortisol levels in healthy female volunteers [28], suggesting that the interactions between MR and GR in the hippocampus may be more relevant to understanding the regulation of stress response in depression than just focusing on GR alone [29-34].

5. Effect of antidepressants on glucocorticoid receptor expression

The traditional explanation of the mechanism of antidepressant drug action, the monoamine hypothesis, has been of heuristic utility but has failed to account for the time course of treatment response or explain the efficacy of novel agents that increase rather than inhibit monoamine uptake, such as tianeptine. Recently, two alternative and complimentary hypotheses of antidepressant drug action have been promulgated [35]. The first, articulated by Duman [36], emphasises activation of the cAMP cascade and subsequent induction of CREB (cAMP response element binding protein) and hippocampal brain derived neurotrophic factor (BDNF). Decreased levels of BDNF reduce neuronal function, while most antidepressant treatments, including electroconvulsive therapy, appear to increase BDNF activity. Interestingly, glucocorticoids decrease BDNF mRNA in the dentate gyrus of the hippocampus, while antidepressant pre-treatment antagonises the effect [37,38]. The second hypothesis, central to the current review, is that antidepressants may exert their clinical benefit through direct modulation of the GR. A great number of studies, using a variety of structurally different antidepressants, have reported antidepressant-induced GR upregulation in the brain and an enhancement of HPA axis feedback inhibition in normal animals and in animal models of HPA axis dysregulation [39]. These data are consistent with clinical reports of normalisation of HPA axis function with successful

Table 1. Antiglucocorticoid treatment of major depression.

Author	Method	Subjects (n)	Intervention	Ref.
Murphy *et al.* Ghadirian *et al.*	Open-label	20	Aminoglutethimide, ketoconazole, metyrapone	[45,46,61] [50]
Murphy	Open-label	4	RU-486	[67]
Wolkowitz *et al.*	Open-label	10	Ketoconazole	[47]
Amsterdam *et al.*	Open-label	6	Ketoconazole	[48]
Anand *et al.*	Double-blind for 4 wks; single-blind for 14 wks	1	Ketoconazole	[49]
O'Dwyer *et al.* & Raven *et al.*	Single-blind, crossover	8	Metyrapone	[51,53]
Sovner & Fogelman	Open-label	2	Ketoconazole	[54]
Thakore & Dinan	Open-label	8	Ketoconazole	[52]
Iizuka *et al.*	Open-label	6	Metyrapone	[55]
Wolkowitz *et al.*	Double-blind	20	Ketoconazole	[64]
Malison *et al.*	Double-blind	16	Ketoconazole	[65]
Brown *et al.*	Open-label	6	Ketoconazole	[66]
Bech	Open-label	1	Ketoconazole	[56]

Adapted from [1].

drug treatment and with observations that continued HPA dysfunction represents a strong indicator of risk of therapeutic relapse. *In vitro* cell culture studies have documented that antidepressants can increase GR mRNA and amplify GR-mediated transcription in the presence of corticosteroid incubation [40,41]. Similarly, in a transgenic mouse model involving inactivation of the GR, treatment with the antidepressant amitriptyline reduced levels of ACTH and corticosterone, increased GR mRNA concentrations and GR binding capacity and reversed behavioural changes in a time course that correlated with that usually seen in the development of clinical response [42,43]. At this point, the data does not indicate whether HPA axis normalisation and clinical recovery are dependent on an initial effect inducing GR upregulation and consequent improvement in feedback inhibition or, alternatively, on an initial facilitation of GR function followed by facilitated feedback inhibition and subsequent GR upregulation [25]. Secondary effects of lower cortisol activity would include decreased expression of genes under glucocorticoid regulatory control, such as those related to biogenic amine neurotransmission, a finding that would parallel known effects of antidepressant drug response over time [44].

5.1 Antiglucocorticoid treatment of major depression

It is surprising, given the results noted in the treatment of patients with Cushing's syndrome and the findings of widespread HPA dysregulation in depression, that relatively few clinical trials have assessed whether direct pharmacological lowering of cortisol levels in depression would be therapeutic [45-56]. Animal studies have suggested that corticosteroid synthesis inhibitors have beneficial effects on brain reward mechanisms and ameliorate stress-induced pathological behaviours and effects, [57-59] but, until recently, published reports of antiglucocorticoid treatment of depression have been open label and based on exceedingly small numbers of subjects [1,60,61]. Most investigations have utilised ketoconazole but positive findings have been noted with all antiglucocorticoids studied, including aminoglutethimide, metyrapone and RU-486 (Table 1).

One reason for the relative dearth of clinical trials may be that the ideal antiglucocorticoid agent does not yet exist. All currently available compounds are either non-specific in their action or have significant side effects. Metyrapone inhibits hydroxylation at position C_{11} of the steroid molecule, leading to decreased cortisol and increased 11-deoxycortisol levels. Compensatory increases in ACTH drive often overcome cortisol synthesis inhibition and necessitate dose adjustment. Side effects include nausea, headache, sedation and rash and increases in mineralocorticoid and androgenic precursors may result in hirsutism, acne and hypertension. Some of the secondary neurosteroid increases, however, may exert their own genomic and non-genomic behavioural effects and underlie aspects of behavioural improvement seen in certain classes of antidepressants [32,33]. In two studies utilising metyrapone, one a single-blind crossover trial, approximately three-quarters of patients showed a reduction in depression ratings and an increase in 11-deoxycortisol metabolites that was significantly correlated with antidepressant effect.

Aminoglutethimide blocks cholesterol side chain cleavage and hydroxylation at C_{11} and C_{18}, resulting in a diminution of oestrogen, as well as cortisol, synthesis. A transient pruritic rash is common and significant side effects are frequent, including fever, headache, somnolence and dizziness. Hyperthyroidism, bone marrow suppression, cholestasis and aldosterone deficiency can also occur. Usage of aminoglutethamide in a few patients in published case reports resulted in 'prompt and complete remission.'

Ketoconazole, at doses of 400 mg/day or greater, inhibits cholesterol side chain cleavage, the enzymes 17, 20 lyase and

11β-hydroxylase and, to a somewhat lesser degree, 17- and 18-hydroxylase. Ketoconazole can also block the GR, although it is unclear if this is a substantial effect at clinical dosage levels. Like metyrapone, ketoconazole administration results in increases in pregnenolone and progesterone production but unlike metyrapone or aminoglutethimide, there is no compensatory increase in ACTH level. Side effects include GI distress, menstrual irregularities, headache, impaired sexual function, alterations in serum transaminases and, rarely, hepatotoxicity and hypoadrenalism. Transient increases in liver enzymes occur in 5 - 10% of subjects but true hepatic injury occurs in less than 1% of patients. Ketoconazole is also known to inhibit the hepatic cytochrome P450 isoenzyme, IIIA 3/4, which is responsible for the metabolism of a variety of medications, including some that can result in fatal toxicity when co-administration occurs.

In a series of open-label studies (and one double-blind report of one patient), ketoconazole treatment resulted in significant decrease in depression ratings in approximately 60 -70% of subjects studied. In the first double-blind investigation, Wolkowitz and colleagues [64] studied twenty medication-free depressed patients, administering ketoconazole (400 - 800 mg/day) or placebo for 4 weeks. Active drug treatment was associated with significant improvement in mood but only in hypercortisolaemic depressed patients. Ketoconazole resulted in a marked increase in pregnenolone and pregnenolone sulfate levels and was generally well-tolerated. More recently, Malison *et al.* [65] gave ketoconazole (600 - 1200 mg/day) or placebo to 16 patients with treatment-refractory depression and reported a 25% response rate with active drug, *versus* no response in the placebo group, although as a group patients who received ketoconazole showed no significant changes in depression ratings or in overall clinical global assessment. Unfortunately, this study did not assess indices of HPA function. In another recent open-label case series, all patients who received at least 400 mg/day of ketoconazole experienced substantial reduction in depressive symptoms [66].

An alternative approach to lowering glucocorticoid activity is direct antagonism of the Type II GR. Unfortunately, the agent that has been utilised, RU-486 (mifepristone), primarily blocks progesterone receptors and occupies GR only at dosage levels that may cause significant side effects. Exfolliative dermatitis has occurred in some patients and only short-term usage has been reported. In the only efficacy study published, Murphy and colleagues [67] reported that 200 mg/day of mifepristone decreased depression scores in three out of four refractory depressed patients, although adverse effects and unavailability of the drug led to premature termination of the trial itself. It has been suggested on the basis of animal work, that only a brief administration of a specific receptor antagonist may be necessary and that GR number may be increased rapidly and normal HPA function sustained even after drug treatment has ended [26]. In a trial recently concluded, RU-486 (600 mg/week) resulted in a marked antidepressant response without significant adverse side effects (A Schatzberg, personal communication) in a group of patients with psychotic depression. The development of more selective GR antagonists that induce rapid upregulation is eagerly awaited [68]. One specific GR agonist, ORG 34517, is currently in stage II trials for treatment of depression.

In addition to treatment interventions directed at glucocorticoid function itself, investigators have began to explore the behavioural effects of CRH antagonists [69]. Although a number of selective compounds have been developed, it is still unclear how various CRH receptors relate to component parts of HPA system function and the overall clinical stress response network. In the first open label trial of a CRH-1 receptor antagonist (R121919), depressed patients had significant decreases in both depressive and anxiety-related symptoms, measured both objectively and subjectively [70]. One concern that has emerged is whether longer term treatment might result in significant CRH receptor upregulation and enhanced CRH secretion that would result in an adverse withdrawal reaction once the drug was discontinued.

6. Expert opinion

The rationale for antiglucocorticoid therapies in patients with major depression and other stress-related conditions is compelling, but pharmacological evidence of efficacy is at this point still equivocal. Evidence for a central defect in HPA regulation is undeniable but most of the data pertinent to GR receptor regulation is based almost exclusively on tissue culture and animal models. Thus far, direct demonstration of changes in GR regulation in antidepressant-treated patients is lacking. Similarly, interpretation of studies of antiglucocorticoid treatment is problematic, given the uncontrolled nature of most studies, the small sample sizes and heterogeneous groups studied, the varying compounds utilised and their relatively non-specific neuroendocrine effects. It is clear also that no ideal means of normalising HPA dysregulation currently exists. Given current awareness that the mechanism of available antidepressant agents may be dependent on regularisation of GR function, it may be possible to hasten antidepressant response and to provide increased efficacy in treatment resistant cases through conjoint usage of a traditional agent and an antiglucocorticoid drug; this concept remains to be empirically tested. Naturally-occurring compounds that serve to modulate glucocorticoid effects *in vivo*, such as dehydroepiandrosterone, may also exert antidepressant benefit, either as a sole treatment or combined with a proven antidepressant drug [71].

Additional studies will be required to determine the appropriate role of antiglucocorticoid intervention in depression. Confirmation of initial suggestive evidence utilising the agents described would be expected to hasten the development of safer and more selective compounds and expand our understanding of the pathophysiology of depressive illness.

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