

Mifepristone (RU-486) treatment for depression and psychosis: a review of the therapeutic implications

Peter Gallagher

Allan H Young

Stanley Research Centre, School of Neurology, Neurobiology and Psychiatry; University of Newcastle upon Tyne, UK

Abstract: The mechanisms underlying the pathophysiology of severe psychiatric illnesses are complex, involving multiple neuronal and neurochemical pathways. A growing body of evidence indicates that alterations in hypothalamic–pituitary–adrenal (HPA) axis function may be a trait marker in both mood disorders and psychosis, and may exert significant causal and exacerbating effects on symptoms and neurocognition. At present, however, no available treatments preferentially target HPA axis abnormalities, although many drugs do increase feedback-regulation of the HPA axis at the level of the glucocorticoid receptor (GR). This action may in part underpin their therapeutic efficacy. Therapeutic interventions directly targeted at GR function may therefore have clinical benefit. The present review examines the current literature for the clinical utility of GR antagonists (specifically mifepristone) in mood disorders and psychosis. At present, most studies are at the “proof-of-concept” stage, although the results of preliminary, randomized, controlled trials are encouraging. The optimum strategy for the clinical application of GR antagonists is yet to be established, their potential role as first-line or adjunctive treatments being unclear. The therapeutic utility of such drugs will become known within the next few years following the results of larger clinical trials currently underway.

Keywords: mifepristone, RU486, glucocorticoid receptor, cortisol, mood disorders, psychosis, treatment

Introduction

Overview

Dysfunction of the hypothalamic–pituitary–adrenal (HPA) axis has long been implicated in the pathogenesis and etiology of severe psychiatric illness. Studies have found evidence of reduced glucocorticoid receptor (GR) mRNA expression in post-mortem brain tissue samples from patients with mood disorders and psychosis (Knable et al 2001; Webster et al 2002; Lopez et al 2003). Many antidepressant drugs increase GR binding and/or number in brain tissue, suggesting that GR regulation may be one aspect of the therapeutic mechanism of action of antidepressants (and mood stabilizers), and the ability of a drug to regulate GR number may be a good predictor of therapeutic efficacy in patients with hypercortisolemia (McQuade and Young 2000). No drugs primarily or preferentially target the GR for use in psychiatry, although several are at present being examined for this purpose. The present review examines the current literature and proof-of-concept evidence for the clinical utility of GR antagonists (specifically mifepristone) in mood disorders and psychosis.

Correspondence: Peter Gallagher
School of Neurology, Neurobiology and Psychiatry, University of Newcastle upon Tyne, Leazes Wing (Psychiatry), Royal Victoria Infirmary, Queen Victoria Road, Newcastle upon Tyne, NE1 4LP, UK
Tel + 44 191 282 4065
Fax + 44 191 222 6162
Email peter.gallagher@ncl.ac.uk

Search strategy

In order to include other antiglucocorticoid agents that specifically target the GR, the terms (“mifepristone” or “RU 486” or “RU 38486” or “ORG 34850” or “ORG 34116” or “ORG 34517”) were used in the initial search and combined with the terms (“mood disorders” or “psychosis” or “depression” or “bipolar disorder” or “schizophrenia”). The following databases were searched electronically: EMBASE (1980 to present), Medline (1966 to present), CINAHL (1982 to present), PsycINFO (1887 to present), and ISI Web of Science (1981 to present). Citation lists of relevant studies and reviews were checked for other relevant trials.

Background

The hypothalamic–pituitary–adrenal (HPA) axis

One of the major hormonal systems activated during stress is the HPA axis. Neurons in the paraventricular nucleus (PVN) of the hypothalamus secrete corticotrophin-releasing hormone (CRH) which is transported via the hypothalamo-pituitary portal circulation to the anterior pituitary where adrenocorticotrophic hormone (ACTH) is secreted through stimulation of pituitary corticotrophs. ACTH then enters the peripheral circulation and stimulates the adrenal cortex to secrete glucocorticoids: corticosterone in rats, and cortisol in humans.

Cortisol is essential for life. It is involved in the maintenance of glucose production from protein, facilitates fat metabolism, supports responsiveness of the vascular tree, modulates central nervous system function, and profoundly affects the immune system (Berne and Levy 1998). Importantly, it is a major regulator of the physiological stress response, through a negative feedback mechanism via corticosteroid receptors. Two distinct corticosteroid receptor subtypes have been identified: the mineralocorticoid receptor (MR; Type I) and the glucocorticoid receptor (GR; Type II). Both receptor types have been implicated in mediating glucocorticoid feedback (Reul and de Kloet 1985), but there are several differences in the distribution, occupancy, and binding properties of the two receptors that affect their physiological role.

The MR is highly expressed in the limbic system whereas the GR is ubiquitous, being present in both subcortical and cortical structures, with a preferential distribution in the prefrontal cortex (Patel et al 2000). Glucocorticoids bind to the MR with 6–10 times higher affinity than to GR (de Kloet et al 1999). Consequently, at basal levels near complete

occupation (~90%) of MRs occurs. GRs, however, are little occupied at this point (~10%), and only during times of high cortisol secretion, such as the circadian peak or during stress, do MRs become saturated and GR occupancy increases (to ~67%–74%) (Reul and de Kloet 1985). GR function is therefore critical in the regulation of the HPA axis at times of glucocorticoid excess and it is now recognized that disruption of this self-regulating system may be a major factor in the pathophysiology of mood disorders and psychosis.

The HPA axis in mood disorders and psychosis

The first observations of an elevation in basal cortisol levels in patients with depression were made almost half a century ago by Board and colleagues, and these observations have been repeatedly replicated (Board et al 1956; Gibbons 1964). It should be noted that the extent of HPA axis dysfunction differs by severity and subtype of depression. For example, a recent study found no evidence of hypercortisolism in women with major depression from a community-based setting (Strickland et al 2002), while pronounced HPA axis dysfunction has been described in depressed subjects with psychotic features (Posener et al 2000). The presence of psychosis may be related to hypercortisolism independently of mood symptoms (Christie et al 1986). Hypercortisolism has also been recognized in symptomatic schizophrenic patients (Ritsner et al 2004; Ryan et al 2004).

Improvements in the methodology utilized has overcome some of the complexities surrounding the profiling of HPA axis dysfunction, revealing alterations in the diurnal pattern of cortisol secretion in depression (Deuschle et al 1997; Posener et al 2000), while employing less precise techniques such as total 24-hour cortisol output can fail to detect dysfunction (Brouwer et al 2005). Similarly, the measurement of the molar ratio of cortisol to other adrenal steroids can reveal differences – in the absence of hypercortisolism per se – in moderately depressed, non-psychotic outpatients (Young et al 2002). The most sensitive tests of HPA axis function, however, are “activating” tests, whereby neuroendocrine responses are measured following pharmacological challenge. These are preferred not only because of their increased sensitivity, but because they elucidate functional changes in the HPA axis at the receptor level.

The GR agonist dexamethasone has been used widely to examine HPA axis negative feedback integrity (Rush et al 1996). An abnormal (nonsuppressed) cortisol response

to dexamethasone administration has been described in schizophrenia (Castro et al 1983; Muck-Seler et al 1999) (but also see Ismail et al 1998) and mood disorders (Rush et al 1996), and may be exacerbated by psychotic features (Duval et al 2000). The combined dexamethasone–corticotrophin-releasing hormone (dex–CRH) test is also abnormal in bipolar patients during relapse and recovery (Schmider et al 1995; Rybakowski and Twardowska 1999; Watson et al 2004). Furthermore, GR abnormalities have been observed in post-mortem studies which show evidence of reduced GR mRNA expression in post-mortem brain tissue samples from patients with bipolar disorder and schizophrenia (Knable et al 2001; Webster et al 2002; Lopez et al 2003).

Consequences of HPA axis dysregulation and implications for treatment

Pronounced neurocognitive dysfunction is frequently described in mood disorder (Porter et al 2003; Thompson et al 2005); this may be worse in patients with psychotic features (Fleming et al 2004). In schizophrenia, the symptomatic clinical profile of the illness is complex and diverse, but neurocognitive impairment is consistently reported and some authors have argued that such impairments may be the cardinal feature of the illness (Elvevag and Goldberg 2000).

Elevated levels of corticosteroids are known to impair learning and memory. This has been demonstrated by acute (Lupien and McEwen 1997; Modell et al 1997) and subchronic (Young et al 1999) administration of exogenous corticosteroids in healthy volunteers and in conditions associated with a chronic elevation of endogenous cortisol levels, for example Cushing's disease (Starkman et al 2001; Forget et al 2002), which is also associated with a high incidence of depression that notably resolves with correction of the hypercortisolemia (Dorn et al 1997). Patients receiving systemic corticosteroid therapy also often exhibit cognitive impairment and, in some instances, symptoms of (hypo)mania, depression, and psychosis (Brown and Chandler 2001). HPA axis dysregulation therefore has been suggested to be one of the principal causes of both low mood and neurocognitive impairment, possibly through interactions with other neurotransmitter system (McAllister-Williams et al 1998; Porter et al 2004).

The known consequences of hypercortisolemia on neurocognitive function and mood, and the central role of

corticosteroid receptors in HPA axis regulation, therefore indicate a possible use for antiglucocorticoid drugs and make the GR specifically a potentially viable target for therapeutic intervention.

Mifepristone (RU-486) Discovery and development

Mifepristone (or RU-486) is a synthetic steroid with both antiprogesterone and antiglucocorticoid properties. The compound is a 19-nor steroid with substitutions at positions C11 and C17 (17 beta-hydroxy-11 beta-[4-dimethylamino phenyl] 17 alpha-[1-propynyl]estra-4,9-dien-3-one) which antagonizes cortisol action competitively at the receptor level (Nieman et al 1985). It was discovered in the early 1980s by the French pharmaceutical company Roussel–Uclaf (Herrmann et al 1982; Jung-Testas and Baulieu 1983). At present it is licenced in the UK for the medical termination of pregnancy (trade name: Mifegyne[®]; marketing authorization holder: Exelgyn Laboratories, Paris, France). Mifepristone was the first antiprogesterone to be developed and it has been evaluated extensively for its use as an abortifacient. The original target for the research group, however, was the discovery and development of compounds with antiglucocorticoid properties (Hazra and Pore 2001), and it is these properties that are of greatest interest for their application in the treatment of severe mood disorders and psychosis.

Pharmacokinetics and pharmacodynamic activity

The pharmacokinetics of mifepristone are dose-dependent in humans (Ashok et al 2002). Due to saturation of the serum-binding capacity, high-dose mifepristone results in nonlinear kinetics, whereas lower doses show a linear pattern (Leminen et al 2003). For example, following administration of doses of 50–800 mg, after the absorption and distribution phase of approximately 4–6 hours, the serum concentration of mifepristone remains in the micromolar range for the next 24–48 hours. Within the dose range of 2–25 mg, serum concentrations of mifepristone, as well as the areas under the concentration–time curves (AUC), increase according to dose (Sitruk-Ware and Spitz 2003).

Following a single oral dose of 600 mg mifepristone, the binding equivalent is present in measurable concentrations 7 days after administration, only decreasing below assay detection limits >7–14 days (Foldesi et al 1996). In this study, the concentration of the mifepristone binding

equivalent reached a peak within approximately 2 hours (doses 200–600 mg), indicating rapid absorption. Peak levels were significantly greater following the 600 mg dose ($C_{\max} = 12.3 \mu\text{mol/L}$ vs 200 mg: $6.30 \mu\text{mol/L}$), while the bioavailability as assessed by the AUC was significantly greater following 600 mg dose than both 200 and 400 mg. These were not, however, directly proportional to the dose increase (Foldesi et al 1996).

In contrast to mifepristone plasma concentrations, plasma concentrations of its metabolites do increase in a dose-dependent manner when larger doses are administered, so that serum metabolite concentrations are close to, or even in excess of, those of the parent compound (Lahteenmaki et al 1987). These metabolites have some antiprogesterone and antiglucocorticoid properties, and therefore may mediate some of the actions of mifepristone (Spitz and Bardin 1993).

Side effects of chronic mifepristone administration

Laue and colleagues reported that in healthy male normal volunteers who received mifepristone (10 mg/kg/day), 8 of 11 subjects developed generalized exanthem after 9 days. One subject developed symptoms and signs consistent with the diagnosis of adrenal insufficiency (Laue et al 1990). For immune function, it was reported that total white blood cell counts, absolute lymphocyte, neutrophil, and eosinophil counts, erythrocyte sedimentation rate, and quantitative immunoglobulins did not change. Similarly, T-, B-, and natural killer cell subsets did not change during treatment. Furthermore, functional evaluation of lymphocyte cytotoxicity and proliferation revealed no changes.

A study using lower doses (200 mg/day for 2 to >31 months) in 14 patients with unresectable meningiomas reported milder side effects. Most commonly, fatigue was noted in 11 of the 14 patients (Grunberg et al 1991). However, in a study of mifepristone (200 mg/day for up to 8 weeks) in chronic depression, 1 of 4 patients discontinued treatment prematurely because of the appearance of a rash (Murphy et al 1993). In patients with psychotic depression receiving mifepristone (50–1200 mg/day for 7 days), 2 of 10 patients in the 600-mg group and 1 of 9 in the 1200-mg group reported uterine cramping, while 1 of 11 patients in the 50-mg group and 1 of 9 patients in the 1200-mg group (but none in the 600-mg group) reported a rash. In both cases, this had abated 1–2 months after study completion (Belanoff et al 2002).

Antiglucocorticoid effects of mifepristone

A large amount of human clinical data on the anti-glucocorticoid actions of mifepristone have come from studies in Cushing's disease (Sartor and Cutler 1996). Nieman and colleagues administered mifepristone orally at increasing doses of 5, 10, 15, and 20 mg/kg/day for a 9-week period to a patient with Cushing's syndrome due to ectopic ACTH secretion. Following treatment, the somatic features associated with Cushing's syndrome ameliorated and blood pressure normalized. Importantly, suicidal ideation and depression also resolved, and all biochemical glucocorticoid-sensitive parameters normalized (Nieman et al 1985).

Mifepristone has also been shown to rapidly reverse acute psychosis in Cushing's syndrome (van der Lely et al 1991). More recently, high-dose (up to 25 mg/kg/day), long-term mifepristone administration was shown to normalize all biochemical glucocorticoid-sensitive measurements, as well as significantly reverse psychotic depression in a patient with Cushing's syndrome caused by an ACTH-secreting pituitary macroadenoma (Chu et al 2001). Although the adrenal axis also normalized, the 18-month-long mifepristone treatment course led to the development of severe hypokalemia (attributed to excessive cortisol activation of MRs), which responded to spironolactone administration.

Use of mifepristone in mood disorders and psychosis (Table 1)

Early work highlighted the potential for antiglucocorticoid strategies in depression. Initially the focus of studies utilizing mifepristone was on the effect on endocrine parameters (Kling et al 1989; Krishnan et al 1992). In the first open trial of mifepristone treatment of major depression, Murphy and colleagues administered mifepristone (200 mg each morning) for as long as it was tolerated, for up to 8 weeks to 4 patients with "drug-resistant" depression. Data were presented as a case-series and showed improvements of between 16% and 66% on the Hamilton Depression Rating Scale (HDRS) (Murphy et al 1993). The trial terminated, however, due to problems obtaining the trial medication (the supplier cancelled the contract).

Recent studies have renewed interest in the potential therapeutic efficacy of GR antagonists in the treatment of mood disorders and psychosis.

Table 1 Studies of glucocorticoid receptor antagonists in mood disorders and psychosis (see text for further details)

Study	Drug	Dose	Study design	N	Patient group	Concomitant medications	Effects on symptoms	Effects on neurocognitive function
(Kling et al 1989)	Mifepristone	10 mg/kg single dose	^a Experimental	8	MDD	Drug-free (2 weeks)	n/a	n/a
(Krishnan et al 1992)	Mifepristone	400 mg single dose	^a Experimental	7	MDD	Drug-free (1 week)	n/a	n/a
(Murphy et al 1993)	Mifepristone	200 mg/day, up to 8 weeks	Open-label	4	MDD	Drug-free; benzodiazepines and acetaminophen permitted	HDRS scores decreased between 16% and 66% for all patients.	n/a
(Høyberg et al 2002)	ORG34517	150–300 mg/day, 450–600 mg/day, up to 4 weeks	Double-blind, randomized, paroxetine controlled	142	MDD	Drug-free; benzodiazepines permitted	All groups improved. Larger improvement from baseline in low-dose ORG group at day 10. Patients reaching full remission significantly higher in low- than both the high-dose and paroxetine-treated groups (39.1% vs 20.5% and 31.0% respectively).	n/a
(Belanoff et al 2001)	Mifepristone	600 mg/day, 4 days	Double-blind, placebo controlled, crossover	5	Psychotic MDD	Antipsychotic free (3 days); benzodiazepines and acetaminophen permitted	HDRS scores declined during mifepristone treatment in all patients. BPRS scores declined in 4 of 5 patients.	n/a
(Belanoff et al 2002)	Mifepristone	50, 600, 1200 mg/day, 7 days	Open-label	30	Psychotic MDD	Stable for 1 week prior	HDRS response by dose in 2/11 (18.2%) 5/10, (50%), 3/9 (33%) patients respectively. BPRS response in 4/11 (36.4%), 7/10 (70%), 6/9 (66.7%) respectively.	n/a
(Simpson et al 2005)	Mifepristone	200 mg tid, 6 days	Open-label	20	Psychotic MDD	Drug-free (1 week) except for lorazepam	CGI and HDRS improved after week 1, and between week 1 to 4. BPRS improved after week 4	n/a
(Young et al 2004)	Mifepristone	600 mg/day, 7 days	Double-blind, placebo controlled RCT	20	Bipolar disorder (depressed)	Stable for 6 weeks prior	HDRS (5.1 points), MADRS (6 points), BPRS (4 points) improved from baseline at day 14 with active drug.	SWM improved 19.8% over placebo at day 21. Spatial recognition, verbal fluency improved from baseline following active drug.
(Gallagher et al 2005)	Mifepristone	600 mg/day, 7 days	Double-blind, placebo controlled RCT	20	Schizophrenia (chronic, symptomatic)	Stable for 6 weeks prior	No effect on BPRS or Calgary. Improvements in HDRS and MADRS in both arms of the study (nonspecific effect).	No effect

^a These studies examined HPA axis responses only.

Abbreviations: BPRS, Brief Psychiatric Rating Scale; Calgary, Calgary Depression Scale; CGI, Clinical Global Impression; HDRS, Hamilton Depression Rating Scale; HPA, hypothalamic–pituitary–adrenal; MADRS, Montgomery–Åsberg Depression Rating Scale; MDD, Major Depressive Disorder; n/a, not assessed; RCT, randomized clinical trial; SWM, Spatial Working Memory (CANTAB); tid, three times daily.

Psychotic depression

In a double-blind, placebo-controlled crossover case-series in 5 patients with psychotic depression, Belanoff and colleagues found a rapid improvement in depression ratings and psychotic symptoms following 4 days' treatment with mifepristone (Belanoff et al 2001). Subsequently they have replicated these findings in an open-label study in 30 psychotic depressed patients (Belanoff et al 2002). Patients received mifepristone, either 50 mg/day ($n=11$), 600 mg/day ($n=10$), or 1200 mg/day ($n=9$) for 7 days. Criteria for response were defined as a 50% reduction on the Hamilton Rating Scale for Depression-21 (HAMD-21), a 30% reduction on the Brief Psychiatric Rating Scale (BPRS), and a 50% reduction on the BPRS positive symptom subscale. Using these criteria, respectively, it was found that 18.2%, 36.4%, and 27.3% of patients responded to 50 mg/day; 50%, 70%, and 60% responded to 600 mg/day, and 33%, 66.7%, and 66.7% responded to 1200 mg/day. The results of this study also suggested that high-dose treatment (≥ 600 mg) for short periods (≤ 7 days) was the optimal method of administration.

A second trial has been carried out recently with a longer follow-up period (Simpson et al 2005). Twenty MDD patients (with psychotic features) were treated with mifepristone 200 mg 3 times daily, open-label for 6 days. All patients had been psychotropic medication-free (except lorazepam for sleep) for at least 1 week prior to baseline ratings. Significant improvements in HDRS and Clinical Global Impression (CGI) scores were observed in the group (from baseline) after 1 week and between weeks 1 and 4. This effect remained stable to follow-up at 8 weeks. BPRS scores also improved after week 4. A number of patients did not complete the trial, however, because of good clinical response (discharged and lost to follow-up) or nonresponse (alternative clinical intervention required).

Preliminary communications have also been made on the results of larger trials ($n > 200$) of mifepristone in psychotic depression (Belanoff and DeBattista 2004; DeBattista and Belanoff 2004). These studies suggest that the effect on psychotic symptoms, particularly, may be rapid and persistent. The publication of these results is awaited and will provide clearer data on the efficacy of GR antagonists in this condition.

Bipolar disorder

We have recently completed the first proof-of-concept study on the use of GR antagonists in the treatment of bipolar

depression, in a double-blind, placebo-controlled crossover design (Young et al 2004). We hypothesized that mifepristone (administered adjunctively to existing medication) would improve neurocognitive function and attenuate depressive symptoms in this disorder. Twenty patients, ages 18 to 65, with a diagnosis of bipolar depression (confirmed using the Structured Clinical Interview for DSM-IV; SCID [First et al 1995]) and residual depressive symptoms were recruited. Patients' medication had been unchanged for 6 weeks prior to participation and remained so throughout the study period.

On the basis of previous research, it was predicted that the principal cognitive domains that would be most sensitive to changes in HPA axis function were working memory and verbal declarative memory. Neurocognitive tests were therefore administered to explore these domains. Following treatment with mifepristone, selective improvement in neurocognitive functioning was observed. Spatial working memory performance was significantly improved compared with placebo (19.8% improvement over placebo). Measures of verbal fluency and spatial recognition memory also significantly improved from baseline levels after mifepristone. No significant change occurred after placebo.

Beneficial effects on mood were found; HDRS scores were significantly reduced compared with baseline (mean reduction of 5.1 points) as were Montgomery-Åsberg Depression Rating Scale scores (mean reduction of 6.05 points). No significant change occurred after placebo. Furthermore, baseline cortisol output correlated positively with the percentage improvement in spatial working memory error rate following mifepristone administration.

Schizophrenia

Utilizing the same experimental design as described above (Young et al 2004), we have recently completed the first trial to examine the efficacy of adjunctive mifepristone administration in schizophrenia (Gallagher et al 2005). In contrast to the findings on bipolar disorder, mifepristone had no significant effect on symptoms or neurocognitive functioning despite a pronounced effect on the HPA axis. There are several possible explanations for this discrepancy. As described above, mifepristone has been shown to have some positive effects on depressive symptoms in bipolar disorder as well as on psychosis in psychotic major depression. Also, the effects of mifepristone were more pronounced on neurocognitive function in bipolar patients. This may suggest that affective symptoms or affective

psychosis may be modulated primarily by the HPA axis and that neurocognitive dysfunction in mood disorders is steroid-dependent and a consequence of HPA axis dysregulation, whereas in schizophrenia these may be attributable to different underlying neurobiological abnormalities.

Alternatively, it may be that the schizophrenic patients recruited in this study did not have an abnormal HPA axis at baseline. There is some evidence that the chronicity of psychotic illness directly affects the neurobiology of the HPA axis. Pariante and colleagues (2004) found that first-episode psychosis was associated with a larger pituitary volume, which was suggested to be a consequence of activation of the HPA axis. In “established” schizophrenia (such as in the population in our study), smaller pituitary volume was observed (Pariante et al 2004b). Therefore, the schizophrenic patients may not respond to a GR antagonist in the same manner as patients with affective illnesses.

Other GR antagonists

ORG 34517 was designed as a specific antiglucocorticoid to selectively target the GR. A preliminary report comparing low- and high-dose ORG 34517 administration and paroxetine found that all treatment groups showed improvements in HDRS scores over the 4-week treatment period (Høyberg et al 2002). Low-dose ORG 34517 appeared to increase the speed of response, however, HDRS scores being significantly lower (from baseline) than both other treatment arms by day 10 of the trial. This effect was greater in subjects with a higher degree of HPA axis dysfunction. The proportion of subjects in full remission by the end of the trial was also significantly greater than the proportion of both the high-dose and paroxetine-treated groups (39.1% vs 20.5% and 31.0% respectively).

Mechanisms of action

Corticosteroid receptor imbalance

The mechanism through which mifepristone may be exerting effects on symptoms and neurocognitive function is unclear. It has been suggested that by blocking the GR a “resetting” of the HPA axis may occur (Belanoff et al 2002). Interestingly, animal work has shown that in comparison with other selective GR antagonists, mifepristone was the only compound to increase GR binding in the frontal cortex, although an increase in MR binding was also observed (Bachmann et al 2003). In the neocortex, however, mifepristone selectively decreased MR binding.

GR integrity has consistently been shown to be lowered in patients with severe psychiatric disorders both functionally, using the DST (Rush et al 1996), and structurally, with reduced GR mRNA expression in post-mortem brain tissue samples (Webster et al 2002). There is some evidence, however, that MR function may be normal or even enhanced in mood disorders (Young et al 2003). Although speculative, some of the therapeutic actions of mifepristone may operate through the ability of the drug to modulate corticosteroid receptor balance (ie, exposing brain MR to the elevated cortisol levels caused by GR blockade). This may be particularly so for neurocognitive functioning, which depends on the relative ratio of corticosteroid receptor occupancy (Lupien and McEwen 1997).

Transport of cortisol into the brain

Recent work has shown that many antidepressant drugs have actions on blood-brain barrier steroid transporters (such as multidrug resistance p-glycoprotein). Plasma cortisol cannot freely enter the brain by passive diffusion because its access is limited by such membrane steroid transporters which actively expel cortisol from the brain. It has been suggested that some antidepressants may inhibit membrane steroid transporters at the blood-brain barrier and in neurones, so that more cortisol is able to enter the brain (Pariante 2004; Pariante et al 2004a), thereby restoring glucocorticoid-mediated negative feedback of the HPA axis (Pariante et al 2004a). Hypercortisolemia is therefore argued to be a possible compensatory adaptive response to a central *hypocortisolemic* state (Pariante 2003). Considering mifepristone: the antagonist action of mifepristone on GR causes a robust (2- to 3-fold) elevation in cortisol levels and this may facilitate HPA axis negative feedback. Certainly, this may be the case when mifepristone is administered adjunctively with other antidepressant medications (see above). This mechanism may underlie some of the clinical benefits of the drug.

Speed of response

One notable characteristic of antiglucocorticoid strategies in studies to date is that they appear to initiate a rapid, short-term clinical response. The study of the ORG 34517 by Høyberg and colleagues in medication-free patients with major depression showed that differences between treatment arms emerged after day 7 of the trial, with significant benefits being observed at day 10–14. This was especially pronounced in patients with clearly defined HPA axis

abnormalities. After this time, response rates were approximately equivalent (Høyberg et al 2002). Rapid responses have also been observed following mifepristone administration in psychotic depression (Belanoff et al 2001; Belanoff et al 2002; Simpson et al 2005).

Alternative antiglucocorticoid strategies such as cortisol synthesis inhibition similarly alter the course of clinical response. Jahn and colleagues administered metyrapone or placebo to 63 (psychotropic) medication-free patients with major depression. A higher proportion of patients receiving metyrapone showed a positive treatment response, but importantly the response began within a week of initiation of treatment, suggesting an earlier onset of action (Jahn et al 2004).

The ability of such drugs to rapidly improve treatment response suggests that they may be used either to increase efficacy of treatment regimens in medicated patients or initiate a response that can be maintained with conventional treatments. The optimum strategy for the clinical application of GR antagonists has yet to be established, with their potential role as either first-line or adjunctive treatments being unclear.

Effects on neurocognitive function

Although few studies to date have examined the neurocognitive effects, mifepristone may be efficacious in this respect in mood disorder.

In a recent study in rats, mifepristone was the only GR antagonist examined to increase both MR and GR binding in the frontal cortex (Bachmann et al 2003). This may underpin the selective pattern of improvement in neurocognitive function seen in our study (Young et al 2004), which was restricted to tests that have been shown to be sensitive to frontal lobe dysfunction. Oitzl and colleagues have shown that mifepristone (RU-38486) injected locally into the dorsal hippocampus dose-dependently improved the performance of male Wistar rats in the water maze 24 hours after treatment (Oitzl et al 1998a). Importantly, opposing effects on spatial memory have been shown to occur after either phasic or continuous blockade of brain GR by intracerebroventricular administration of mifepristone. Phasic blockade was found to dose-dependently impair spatial memory (Morris water maze), examined after a daily pretraining administration, whereas continuous GR blockade resulted in a long-lasting facilitation of spatial performance (Oitzl et al 1998b). In humans, aspects of spatial memory are affected in various

degrees in patients with hippocampal lesions (Kessels et al 2001), some tasks such as (spatial) working memory being more dependent on the integrity of the frontal lobes (Owen et al 1995; Owen et al 1996; Kessels et al 2000; Kessels et al 2001). Consequently, the effects of mifepristone on corticosteroid receptor expression may explain the observed pattern of neurocognitive improvement observed in studies to date.

Neuroprotection

The potential neuroprotective actions of mifepristone have been demonstrated preclinically. Mifepristone was found to protect rat primary hippocampal neurons, clonal mouse hippocampal cells, and organotypic hippocampal slice cultures against oxidative stress-induced neuronal cell death induced by amyloid beta protein, hydrogen peroxide, and glutamate (Behl et al 1997). Interestingly, this effect was independent of the presence and activation of glucocorticoid or progesterone receptors. Other studies have also subsequently demonstrated neuroprotective effects of mifepristone (Ghoumari et al 2003), although the precise mechanism through which these actions are exerted is unclear. Nevertheless, these actions may be of therapeutic benefit.

Conclusions and future directions

The use of mifepristone and other GR antagonists in the treatment of mood disorders and psychosis is very much at the proof-of-concept stage. Results are encouraging and several larger-scale clinical trials are underway to better establish the clinical utility of this class of drug. Drugs targeting other facets of the HPA axis, such as CRH-1-receptor antagonists and vasopressin-1b-receptor antagonists, are also being examined (Zobel et al 2000; Holmes et al 2003; Kunzel et al 2003), as well as the application of GR antagonists in the treatment of mood symptoms and cognitive impairment in neurological disorders such as Alzheimer's disease (Pomara et al 2002). Several important questions remain to be answered, including how long the treatment effects persist and the optimal method of administration, ie, continuous or repeated, short-term administrations. These data will provide valuable information on the overall efficacy and safety of this class of treatment (see Mackin et al 2005) and may ultimately lead to the development of specific antiglucocorticoid compounds for use in severe psychiatric illness.

References

- Ashok PW, Wagaarachchi PT, Templeton A. 2002. The antiprogestogen mifepristone: a review. *Current Medicinal Chemistry - Immunology, Endocrine & Metabolic Agents*, 2:71–90.
- Bachmann CG, Linthorst AC, Holsboer F, et al. 2003. Effect of chronic administration of selective glucocorticoid receptor antagonists on the rat hypothalamic-pituitary-adrenocortical axis. *Neuropsychopharmacology*, 28:1056–67.
- Behl C, Trapp T, Skutella T, et al. 1997. Protection against oxidative stress-induced neuronal cell death – a novel role for RU486. *Eur J Neurosci*, 9:912–20.
- Belanoff JK, DeBattista C. 2004. Mifepristone in psychotic major depression. *Biol Psychiatry*, 55(Suppl):191S.
- Belanoff JK, Flores BH, Kalezhan M, et al. 2001. Rapid reversal of psychotic depression using mifepristone. *J Clin Psychopharmacol*, 21:516–21.
- Belanoff JK, Rothschild AJ, Cassidy F, et al. 2002. An open label trial of C-1073 (mifepristone) for psychotic major depression. *Biol Psychiatry*, 52:386–92.
- Berne RM, Levy MN 1998. *Physiology*. 4th ed. St Louis: Mosby Inc.
- Board F, Persky H, Hamburg DA. 1956. Psychological stress and endocrine functions; blood levels of adrenocortical and thyroid hormones in acutely disturbed patients. *Psychosom Med*, 18:324–33.
- Brouwer JP, Appelhof BC, Hoogendijk WJG, et al. 2005. Thyroid and adrenal axis in major depression: a controlled study in outpatients. *Eur J Endocrinol*, 152:185–91.
- Brown ES, Chandler PA. 2001. Mood and cognitive changes during systemic corticosteroid therapy. *Prim Care Companion J Clin Psychiatry*, 3:17–21.
- Castro P, Lemaire M, Toscano-Aguilar M, et al. 1983. Abnormal DST results in patients with chronic schizophrenia. *Am J Psychiatry*, 140:1261.
- Christie JE, Whalley LJ, Dick H, et al. 1986. Raised plasma cortisol concentrations a feature of drug-free psychotics and not specific for depression. *Br J Psychiatry*, 148:58–65.
- Chu JW, Matthias DF, Belanoff J, et al. 2001. Successful long-term treatment of refractory Cushing's disease with high-dose mifepristone (RU 486). *J Clin Endocrinol Metab*, 86:3568–73.
- de Kloet ER, Oitzl MS, Joels M. 1999. Stress and cognition: are corticosteroids good or bad guys? *Trends Neurosci*, 22:422–6.
- DeBattista C, Belanoff J. 2004. A double-blind, placebo controlled trial of C-1073 (mifepristone) in the treatment of psychotic major depression. *Neuropsychopharmacology*, 29(Suppl):S98.
- Deuschle M, Schweiger U, Weber B, et al. 1997. Diurnal activity and pulsatility of the hypothalamus-pituitary-adrenal system in male depressed patients and healthy controls. *J Clin Endocrinol Metab*, 82:234–8.
- Dorn LD, Burgess ES, Friedman TC, et al. 1997. The longitudinal course of psychopathology in Cushing's syndrome after correction of hypercortisolism. *J Clin Endocrinol Metab*, 82:912–9.
- Duval F, Mokrani MC, Crocq MA, et al. 2000. Dopaminergic function and the cortisol response to dexamethasone in psychotic depression. *Prog Neuropsychopharmacol Biol Psychiatry*, 24:207–25.
- Elvevag B, Goldberg TE. 2000. Cognitive impairment in schizophrenia is the core of the disorder. *Crit Rev Neurobiol*, 14:1–21.
- First MB, Spitzer RL, Williams JBW, et al. 1995. Structured clinical interview for DSM-IV (SCID-I), research version. New York: Biometrics Research Department, New York State Psychiatric Institute.
- Fleming SK, Blasey C, Schatzberg AF. 2004. Neuropsychological correlates of psychotic features in major depressive disorders: a review and meta-analysis. *J Psychiatr Res*, 38:27–35.
- Foldesi I, Falkay G, Kovacs L. 1996. Determination of RU486 (mifepristone) in blood by radioreceptorassay; a pharmacokinetic study. *Contraception*, 54:27–32.
- Forget H, Lacroix A, Cohen H. 2002. Persistent cognitive impairment following surgical treatment of Cushing's syndrome. *Psychoneuroendocrinology*, 27:367–83.
- Gallagher P, Watson S, Smith MS, et al. 2005. Effects of adjunctive mifepristone (RU-486) administration on neurocognitive function and symptoms in schizophrenia. *Biol Psychiatry*, 57:155–61.
- Ghoumari AM, Dusart I, El-Etr M, et al. 2003. Mifepristone (RU486) protects Purkinje cells from cell death in organotypic slice cultures of postnatal rat and mouse cerebellum. *Proc Natl Acad Sci U S A*, 100:7953–8.
- Gibbons JL. 1964. Cortisol secretion rate in depressive illness. *Arch Gen Psychiatry*, 10:572–5.
- Grunberg SM, Weiss MH, Spitz IM, et al. 1991. Treatment of unresectable meningiomas with the antiprogestone agent mifepristone. *J Neurosurg*, 74:861–6.
- Hazra BG, Pore VS. 2001. Mifepristone (RU-486), the recently developed antiprogestone drug and its analogues. *J Indian Inst Sci*, 81:287–98.
- Herrmann W, Wyss R, Riondel A, et al. 1982. The effects of an antiprogestone steroid in women: interruption of the menstrual cycle and of early pregnancy. *C R Seances Acad Sci III*, 294:933–8.
- Holmes A, Heilig M, Rupniak NMJ, et al. 2003. Neuropeptide systems as novel therapeutic targets for depression and anxiety disorders. *Trends Pharmacol Sci*, 24:580–8.
- Høyberg ØJ, Wik G, Mehtonen OP, et al. 2002. ORG 34517, a selective glucocorticoid receptor antagonist with potent antidepressant activity: First clinical results. *Int J Neuropsychopharmacol*, 5:S148.
- Ismail K, Murray RM, Wheeler MJ, et al. 1998. The dexamethasone suppression test in schizophrenia. *Psychol Med*, 28:311–17.
- Jahn H, Schick M, Kiefer F, et al. 2004. Metyrapone as additive treatment in major depression: a double-blind and placebo-controlled trial. *Arch Gen Psychiatry*, 61:1235–44.
- Jung-Testas I, Baulieu EE. 1983. Inhibition of glucocorticosteroid action in cultured L-929 mouse fibroblasts by RU 486, a new anti-glucocorticosteroid of high affinity for the glucocorticosteroid receptor. *Exp Cell Res*, 147:177–82.
- Kessels RP, de Haan EH, Kappelle LJ, et al. 2001. Varieties of human spatial memory: a meta-analysis on the effects of hippocampal lesions. *Brain Res Brain Res Rev*, 35:295–303.
- Kessels RP, Postma A, Wijnalda EM, et al. 2000. Frontal-lobe involvement in spatial memory: evidence from PET, fMRI, and lesion studies. *Neuropsychol Rev*, 10:101–13.
- Kling MA, Whitfield HJJ, Brandt HA, et al. 1989. Effects of glucocorticoid antagonism with RU 486 on pituitary-adrenal function in patients with major depression: time-dependent enhancement of plasma ACTH secretion. *Psychopharmacol Bull*, 25:466–72.
- Knable MB, Torrey EF, Webster MJ, et al. 2001. Multivariate analysis of prefrontal cortical data from the Stanley Foundation Neuropathology Consortium. *Brain Res Bull*, 55:651–9.
- Krishnan KR, Reed D, Wilson WH, et al. 1992. RU486 in depression. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, 16:913–20.
- Kunzel HE, Zobel AW, Nickel T, et al. 2003. Treatment of depression with the CRH-1-receptor antagonist R121919: endocrine changes and side effects. *J Psychiatr Res*, 37:525–33.
- Lahteenmaki P, Heikinheimo O, Croxatto H, et al. 1987. Pharmacokinetics and metabolism of RU 486. *J Steroid Biochem*, 27:859–63.
- Laue L, Lotze MT, Chrousos GP, et al. 1990. Effect of chronic treatment with the glucocorticoid antagonist RU 486 in man: toxicity, immunological, and hormonal aspects. *J Clin Endocrinol Metab*, 71:1474–80.
- Leminen R, Ranta S, von Hertzen H, et al. 2003. Pharmacokinetics of 10 mg of mifepristone. *Contraception*, 68:427–9.

- Lopez JF, Little KY, Lopez-Figueroa AL, et al. 2003. Glucocorticoid and mineralocorticoid receptor mRNA levels in the hippocampus and prefrontal cortex of subjects with mood disorders and schizophrenia. *Biol Psychiatry*, 53:489.
- Lupien SJ, McEwen BS. 1997. The acute effects of corticosteroids on cognition: integration of animal and human model studies. *Brain Res Brain Res Rev*, 24:1–27.
- Mackin P, Gallagher P, Froom K, et al. 2005. Antigluco-corticoid treatments in mood disorders: efficacy and safety. (Protocol). *The Cochrane Database Syst Rev*, 1 [online]. Art nr CD005168. DOI: 10.1002/14651858.CD005168. URL: <http://www.thecochranelibrary.com>.
- McAllister-Williams RH, Ferrier IN, Young AH. 1998. Mood and neuropsychological function in depression: the role of corticosteroids and serotonin. *Psychol Med*, 28:573–84.
- McQuade R, Young AH. 2000. Future therapeutic targets in mood disorders: the glucocorticoid receptor. *Br J Psychiatry*, 177:390–5.
- Modell S, Yassouridis A, Huber J, et al. 1997. Corticosteroid receptor function is decreased in depressed patients. *Neuroendocrinology*, 65:216–22.
- Muck-Seler D, Pivac N, Jakovljevic M, et al. 1999. Platelet serotonin, plasma cortisol, and dexamethasone suppression test in schizophrenic patients. *Biol Psychiatry*, 45: 1433–9.
- Murphy BEP, Filipini D, Ghadirian AM. 1993. Possible uses of glucocorticoid receptor antagonists in the treatment of major depression: Preliminary results using RU-486. *J Psychiatry Neurosci*, 18:209–13.
- Nieman LK, Chrousos GP, Kellner C, et al. 1985. Successful treatment of Cushing's syndrome with the glucocorticoid antagonist RU 486. *J Clin Endocrinol Metab*, 61:536–40.
- Oitzl MS, Fluttert M, de Kloet ER. 1998a. Acute blockade of hippocampal glucocorticoid receptors facilitates spatial learning in rats. *Brain Res*, 797:159–62.
- Oitzl MS, Fluttert M, Sutanto W, et al. 1998b. Continuous blockade of brain glucocorticoid receptors facilitates spatial learning and memory in rats. *Eur J Neurosci*, 10:3759–66.
- Owen AM, Morris RG, Sahakian BJ, et al. 1996. Double dissociations of memory and executive functions in working memory tasks following frontal lobe excisions, temporal lobe excisions or amygdalo-hippocampectomy in man. *Brain*, 119:1597–615.
- Owen AM, Sahakian BJ, Semple J, et al. 1995. Visuo-spatial short-term recognition memory and learning after temporal lobe excisions, frontal lobe excisions or amygdalo-hippocampectomy in man. *Neuropsychologia*, 33:1–24.
- Pariante CM. 2003. Depression, Stress and the Adrenal axis. *J Neuroendocrinol*, 15:811–12.
- Pariante CM. 2004. Glucocorticoid receptor function in vitro in patients with major depression. *Stress*, 7:209–19.
- Pariante CM, Thomas SA, Lovestone S, et al. 2004a. Do antidepressants regulate how cortisol affects the brain? *Psychoneuroendocrinology*, 29:423–47.
- Pariante CM, Vassilopoulou K, Velakoulis D, et al. 2004b. Pituitary volume in psychosis. *Br J Psychiatry*, 185:5–10.
- Patel PD, Lopez JF, Lyons DM, et al. 2000. Glucocorticoid and mineralocorticoid receptor mRNA expression in squirrel monkey brain. *J Psychiatr Res*, 34:383–92.
- Pomara N, Doraiswamy PM, Tun H, et al. 2002. Mifepristone (RU 486) for Alzheimer's disease. *Neurology*, 58:1436–7.
- Porter RJ, Gallagher P, Thompson JM, et al. 2003. Neurocognitive impairment in drug-free patients with major depressive disorder. *Br J Psychiatry*, 182:214–20.
- Porter RJ, Gallagher P, Watson S, et al. 2004. Corticosteroid-serotonin interactions in depression: a review of the human evidence. *Psychopharmacology (Berl)*, 173:1–17.
- Posener JA, DeBattista C, Williams GH, et al. 2000. 24-hour monitoring of cortisol and corticotropin secretion in psychotic and nonpsychotic major depression. *Arch Gen Psychiatry*, 57: 755–60.
- Reul JM, de Kloet ER. 1985. Two receptor systems for corticosterone in rat brain: microdistribution and differential occupation. *Endocrinology*, 117:2505–11.
- Ritsner M, Maayan R, Gibel A, et al. 2004. Elevation of the cortisol/dehydroepiandrosterone ratio in schizophrenia patients. *Eur Neuropsychopharmacol*, 14:267–73.
- Rush AJ, Giles DE, Schlessler MA, et al. 1996. The dexamethasone suppression test in patients with mood disorders. *J Clin Psychiatry*, 57:470–84.
- Ryan MC, Sharifi N, Condren R, et al. 2004. Evidence of basal pituitary-adrenal overactivity in first episode, drug naive patients with schizophrenia. *Psychoneuroendocrinology*, 29:1065–70.
- Rybakowski JK, Twardowska K. 1999. The dexamethasone/corticotropin-releasing hormone test in depression in bipolar and unipolar affective illness. *J Psychiatr Res*, 33:363–70.
- Sartor O, Cutler GB, Jr. 1996. Mifepristone: treatment of Cushing's syndrome. *Clin Obstet Gynecol*, 39:506–10.
- Schmider J, Lammers CH, Gotthardt U, et al. 1995. Combined dexamethasone/corticotropin-releasing hormone test in acute and remitted manic patients, in acute depression, and in normal controls: I. *Biol Psychiatry*, 38:797–802.
- Simpson GM, El Sheshai A, Loza N, et al. 2005. An 8-week open-label trial of a 6-day course of mifepristone for the treatment of psychotic depression. *J Clin Psychiatry*, 66:598–602.
- Sitruk-Ware R, Spitz IM. 2003. Pharmacological properties of mifepristone: toxicology and safety in animal and human studies. *Contraception*, 68:409–20.
- Spitz IM, Bardin CW. 1993. Clinical pharmacology of RU 486—an antiprogesterin and antigluco-corticoid. *Contraception*, 48:403–44.
- Starkman MN, Giordani B, Berent S, et al. 2001. Elevated cortisol levels in Cushing's disease are associated with cognitive decrements. *Psychosom Med*, 63:985–93.
- Strickland PL, Deakin JF, Percival C, et al. 2002. Bio-social origins of depression in the community. Interactions between social adversity, cortisol and serotonin neurotransmission. *Br J Psychiatry*, 180: 168–73.
- Thompson JM, Gallagher P, Hughes JH, et al. 2005. Neurocognitive impairment in euthymic bipolar disorder. *Br J Psychiatry*, 186:32–40.
- van der Lely AJ, Foeken K, van der Mast RC, et al. 1991. Rapid reversal of acute psychosis in the Cushing syndrome with the cortisol-receptor antagonist mifepristone (RU 486). *Ann Intern Med*, 114:143–4.
- Watson S, Gallagher P, Ritchie JC, et al. 2004. Hypothalamic-pituitary-adrenal axis function in patients with bipolar disorder. *Br J Psychiatry*, 184:496–502.
- Webster MJ, Knable MB, O'Grady J, et al. 2002. Regional specificity of brain glucocorticoid receptor mRNA alterations in subjects with schizophrenia and mood disorders. *Mol Psychiatry*, 7:985–94.
- Young AH, Gallagher P, Porter RJ. 2002. Elevation of the cortisol-dehydroepiandrosterone ratio in drug-free depressed patients. *Am J Psychiatry*, 159:1237–9.
- Young AH, Gallagher P, Watson S, et al. 2004. Improvements in neurocognitive function and mood following adjunctive treatment with mifepristone (RU-486) in bipolar disorder. *Neuropsychopharmacology*, 29:1538–45.
- Young AH, Sahakian BJ, Robbins TW, et al. 1999. The effects of chronic administration of hydrocortisone on cognitive function in normal male volunteers. *Psychopharmacology (Berl)*, 145:260–6.
- Young EA, Lopez JF, Murphy-Weinberg V, et al. 2003. Mineralocorticoid receptor function in major depression. *Arch Gen Psychiatry*, 60:24–8.
- Zobel AW, Nickel T, Kunzel HE, et al. 2000. Effects of the high-affinity corticotropin-releasing hormone receptor 1 antagonist R121919 in major depression: the first 20 patients treated. *J Psychiatr Res*, 34: 171–81.