Risk Factors for Development of Depression and Psychosis

Glucocorticoid Receptors and Pituitary Implications for Treatment with Antidepressant and Glucocorticoids

Carmine M. Pariante

Sections of Perinatal Psychiatry & Stress, Psychiatry and Immunology, Division of Psychological Medicine and Psychiatry Institute of Psychiatry, King's College London, London, United Kingdom

Increased levels of glucocorticoid hormones—the main product of the hypothalamic-pituitary-adrenal (HPA) axis—have been considered to be "depressogenic," but this notion has largely derived from studies in patients with endocrine conditions, such as Cushing's syndrome or exogenous treatment with synthetic glucocorticoids. In these conditions, it is likely that the full impact of the high glucocorticoid levels is felt on the brain, through over-stimulation of the glucocorticoid receptors (GRs); indeed, normalizing these high levels leads to an improvement of mood in these patients. However, a completely different mechanism may be operating in major depression, where the increased levels of glucocorticoid hormones are conceptualized as driven by an impairment in GR function (glucocorticoid resistance), and therefore as a "compensatory" mechanism. Moreover, clinical and experimental studies have shown that antidepressants increase GR function, thus leading to resolution of glucocorticoid resistance. Interestingly, a number of studies have also demonstrated that manipulating GR function with both agonists and antagonists has an antidepressant effect, and indeed that other drugs targeting the HPA axis and cortisol secretion—even drugs with opposite effects on the HPA axis—have antidepressant effects. These studies do not support the notion that "high levels of glucocorticoids" always have a depressogenic effect, nor that decreasing the effects of these hormones always has an antidepressant effects.

Key words: **antidepressants; depression; corticosteroid receptor; glucocorticoid receptor; hypothalamic-pituitary-adrenal axis; mifepristone; metyrapone; mineralocorticoid receptor; multidrug resistance P-glycoprotein; psychosis**

The HPA Axis in Psychiatric Disorders

The hypothalamic-pituitary-adrenal (HPA) axis is the main hormonal system involved in psychiatric disorders, but the mechanisms underlying its abnormalities in these patients are still unclear. HPA axis activity is governed by the secretion of adrenocorticotrophic hormone (ACTH)-releasing factor (CRF) and vasopressin from the hypothalamus, which in turn activate the secretion of ACTH from the pituitary, which finally stimulates the secretion of the glucocorticoids (cortisol in humans and corticosterone in rodents) from the adrenal cortex. Glucocorticoids then interact with their receptors in multiple target tissues, including the HPA axis, where they are responsible for feedback inhibition of the secretion of ACTH from

Address for correspondence: Carmine M. Pariante, MD, MRCPsych, PhD, Sections of Perinatal Psychiatry & Stress, Psychiatry and Immunology, Institute of Psychiatry, Kings College London, Centre for the Cellular Basis of Behaviour, Room 2-055, The James Black Centre, 125 Coldharbour Lane, London SE5 9NU, UK. Voice: +44(0) 20 7848 0807; fax: +44 (0) 20 7848 0051. carmine.pariante@kcl.ac.uk

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the pituitary and CRF from the hypothalamus (see below).[1]

Hyperactivity of the HPA axis in major depression is one of the most consistent findings in psychiatry (reviewed in Ref. 2). A significant percentage of depressed patients have been shown to hypersecrete cortisol, as manifested by increased 24-h urinary free cortisol and elevated plasma and cerebrospinal fluid concentrations of cortisol; nonsuppression of cortisol, beta-endorphin, and ACTH following dexamethasone administration, in the dexamethasone suppression test and in the dexamethasone/CRF test; and increased volume of the pituitary gland and of the adrenal glands. For example, we have shown that inpatients with chronic, treatment resistant major depression have cortisol outputs throughout the day that are double those of age- and sex-matched controls.[3]

Interestingly, this increased activation of the HPA axis is not specific to the acute phase of depression or indeed to depression itself. In fact, subjects "at risk" of developing depression because of personality traits,[4] and healthy first-degree relatives of patients with major depression, have also been described to show HPA axis hyperactivity.[5] Moreover, patients who are in the acute phase of a psychotic disorder, at their first-episode, with florid symptoms, newly hospitalized or unmedicated, also have an elevated HPA axis activity as shown by raised cortisol and ACTH levels, and nonsuppression of cortisol secretion by dexamethasone in the dexamethasone suppression test and in the dexamethasone/CRF test (reviewed in Ref. 6). Moreover, we have shown an increased pituitary volume in patients with recent onset schizophreniform or affective psychoses.[7,8] Finally, and similar to depression, we and others have shown HPA axis hyperactivity in subjects "at risk" of developing psychosis,[9,10] as well as in healthy first-degree relatives of patients with a psychotic disorder.[11] Taken together, these lines of evidence indicate that increased activity of the HPA axis characterize not only individuals during the acute phases of psychiatric disorders (especially depression and psychosis) but also those at risk to develop these disorders in the future. The mechanisms underlying this abnormality, however, have yet to be clarified.

Glucocorticoid Resistance in Psychiatric Disorders

We will claim in this chapter that the increased activity of the HPA axis in both depression and psychosis is related, at least in part, to altered feedback inhibition by endogenous glucocorticoids, also known as "glucocorticoid resistance." Through binding to their receptors in HPA axis tissues, endogenous glucocorticoids serve as potent negative regulators of HPA axis activity, including the synthesis and release of CRF in the paraventricular nucleus.[12] Data supporting the notion that glucocorticoid-mediated feedback inhibition is impaired in major depression comes from the studies demonstrating nonsuppression of cortisol secretion following administration of the synthetic glucocorticoid dexamethasone.[13] As an example representing myriad of similar studies, we have recently shown that healthy controls have 85% suppression of cortisol output throughout the day following a small (0.5 mg) dose of dexamethasone, while in contrast depressed patients only show approximately 45% of suppression.[3] Moreover, the increased pituitary volume described by in patients with depression and psychosis also indicates a lack of efficient negative feedback by circulating glucocorticoid hormones on the pituitary cells producing ACTH, leading to an increase in the size and number of these cells.[6] Indeed, increased size and number of ACTH-producing cells and increased volume of the pituitary are present also in subjects with a lack of negative inhibitory feedback by circulating glucocorticoid hormones because of Addison's disease.[14] Moreover, previous studies in psychiatric populations have also shown a positive correlation between pituitary volume and postdexamethasone cortisol levels, indicating

that the pituitary is larger in those patients who show less suppression of cortisol secretion by dexamethasone and thus have more glucocorticoid resistance.[15,16] Finally, although this review will not focus on the psychoneuroimmunology of depression, the presence of both HPA axis hyperactivity and increased inflammation in patients with psychiatric disorders also support the notion of "glucocorticoid resistance"—specifically, of the presence of resistance, in the immune cells, to the physiological anti-inflammatory action of endogenous glucocorticoids.[17] Indeed, we have recently described increased cortisol levels together with increased levels of the inflammatory marker interleukin-6 (IL-6) in patients with chronic, treatment-resistant depressed patients[18]—the same clinical features, but not the same patients, as in the study by Juruena *et al*.[3] To understand the molecular mechanisms underlying glucocorticoid resistance, it is important to illustrate the status of the glucocorticoid receptor (GR) in patients with depression and other psychiatric disorders.

As mentioned before, glucocorticoids mediate their actions, including feedback regulation of the HPA axis, through two distinct intracellular corticosteroid receptor subtypes referred to as the type I or mineralocorticoid receptor (MR), and the type II or GR. The MR has a high affinity for endogenous corticosteroids and is believed to play a role in the regulation of circadian fluctuations in these hormones (especially the regulation of ACTH secretion during the diurnal trough in cortisol secretion). In contrast to the MR, the GR has a high affinity for dexamethasone and a lower affinity for endogenous glucocorticoids. The GR is therefore believed to be more important in the regulation of the response to stress when endogenous levels of glucocorticoids are high.[12] Because patients with psychiatric disorders exhibit impaired HPA negative feedback in the context of elevated circulating levels of cortisol, a number of studies have considered the possibility that the number or function of GR, or both, are reduced in these patients, as the mechanism directly underlying glucocorticoid resistance. There are few studies that have specifically looked at MR in depression, and these will also be reviewed.

Over the past 30 years, a number of studies have assessed GR function in patients with major depression. In general, these studies have measured GR function either directly, in peripheral cells (blood cells and skin fibroblasts) isolated and cultivated *in vitro*, or indirectly, in peripheral cells *in vivo* using metabolic or vascular markers. Studies using both approaches have found a lack of response of the GR in depressed patients, especially in those who are nonsuppressors to the dexamethasone suppression test (reviewed in Refs. 1, 19). In other words, these studies directly confirm the notion that GR function is impaired in depression. Recently, we confirmed these findings in a whole-blood experimental system in patients with chronic, treatment resistant depressed patients.[18] In these patients, GR function, measured as dexamethasone-induced suppression of lipopolysaccharide (LPS)-stimulated IL-6 levels, is similar in patients and in controls; patients, however, have much higher (endogenous) cortisol levels in the whole-blood culture, thus indicating that GR function is indeed reduced as the total amount of GR stimulation (endogenous + exogenous) is higher in depressed patients. Whether these GR abnormalities normalize with recovery is still unclear.[20]

Interestingly, there is virtually no data on GR function in cells from patients with psychosis. One study examined GR function in a group of patients with psychiatric disorders, and found that patients with schizophrenia (as those with depression) had the lowest number of GR.[21] A recent study in prodromal subjects (before the onset of schizophrenia) found that there was no differences in GR expression between those who later develop psychosis and those who do not, although the sample size was very small (4 and 13, respectively).[22] Indirectly, however, GR resistance is psychosis is also supported by studies showing, similar

to depression, increased inflammation in the context of hypercortisolemia.[23] Therefore, while very little *in vitro* evidence is available, HPA axis and immune data (including those discussed above) confirm the notion of GR resistance in psychosis. It is also of note that these GR functional studies are consistent with neurophathological findings in postmortem human brain. In postmortem research, studies have found reduced levels of the GR (and of the MR) in brains of patients with major depression and with schizophrenia.[24–27] Finally, it is also important to highlight that an impairment in GR function does not necessarily indicate a specific GR abnormality, as several protein that interact with the GR (and regulate its function) have been shown to be abnormal in psychiatric disorders.[28,29]

As mentioned above, only a few studies have examined MR function in psychiatric disorders. Studies using dexamethasone only probe GR function, as this synthetic steroid has a much higher affinity for GR than for MR.[30] Young *et al.* have been the first to use the MR antagonist, spironolactone, to test HPA axis response in depressed patients and controls. Healthy subjects respond to spironolactone with an increase in HPA axis activity due to blocking of MR-mediate feedback inhibition.[31] In their study,[30] they found that depressed patients respond even more than controls to spironolactone, indicating not only that MR-mediated negative feedback is intact in depression but also that it may be hyperactive, perhaps in an attempt to compensate for the lack of effective GR action. Recently, we developed a suppressive test using another synthetic glucocorticoid, prednisolone, which has a high affinity for both the GR and the MR and therefore should probe both receptors.[32] Our results confirm the notion that MR-mediated negative feedback in depression is intact or increased in depressed patients.[3] The study was conducted in the same subjects described above, who were administered also the dexamethasone suppression test, and showed that the same depressed patients who are resistant to dexamethasone can suppress to prednisolone normally. An intact or hyperactive MR could explain these findings. Interestingly, a very recent postmortem study has found for the first time that patients with major depression have indeed increased expression of the MR in the hypothalamus,[33] thus for the first time directly supporting this model.

Taken together, these data support our proposed model in which the main neuroendocrinological abnormality in depression is a *reduction* of the GR-mediated effects of glucocorticoids hormones on the brain (glucocorticoid resistance) because of decreased GR function or expression in the brain. As claimed by us and others, in this model the elevated levels of circulating cortisol in depression are therefore a compensatory mechanism aiming to overcome the glucocorticoid resistance, and not a toxic mechanism leading to depression.[34,35] Moreover, according to this model, part of the therapeutic action of psychotropic medications —especially of antidepressants—is to increase glucocorticoid signal in the brain by increasing GR expression and function. The next section of this review will provide evidence supporting this last claim.

The GR as a Target for Antidepressant Action

There are now a series of animals and *in vitro* studies demonstrating a direct effect of antidepressants on the GR (and the MR), leading to increased receptor expression and function, and thus to increased negative feedback on the HPA axis (reviewed in Refs. 1, 19, 36–38). In animals, a number of studies have shown that long-term antidepressant treatment upregulates GR and MR in the brains of rodents, and decreases their basal and stress-induced glucocorticoid secretion. Moreover, direct *in vitro* treatment with antidepressants regulates GR function in neuronal cells, fibroblasts, and peripheral blood mononuclear cells, although the effects are dependent on the experimental

conditions.[18,39–43] Indeed, these *in vitro* experimental systems are particularly significant to our understanding of the mechanisms underlying the effects of antidepressants on the GR. In particular, these studies indicate that inhibition of noradrenaline or serotonin reuptake is not involved in the antidepressant-induced changes in GR function. Specifically, our work over a number of years has identified at least two mechanisms by which antidepressants regulate GR function. First, treatment with antidepressants is able to inhibit steroid transporters localized on the membranes of cells, such as the multidrug resistance P-glycoprotein, which expels glucocorticoids from cells; thus, the resulting effect from this action is an antidepressant-induced increase in intracellular concentrations of glucocorticoids, and thus, indirectly, an increase in GR function. Second, and at the same time, antidepressants activate GR translocation from the cytoplasm into the nucleus and thus decrease GR expression consequent of the increased nuclear compartmentalization; thus, the resulting effect from this action is an antidepressant-induced decreased in GR expression and thus, directly, a decrease in GR function. Therefore, if cells are treated in experimental conditions that do elicit the effects on the transporter, such as when cells are incubated with antidepressants and a glucocorticoid that is expelled by the transporter, like dexamethasone or cortisol, an enhanced GR function is evident[1,39,40,44]: this is because the increase in the intracellular levels of the glucocorticoid overcomes the GR downregulation. However, if cells are treated in experimental conditions that do not elicit the effects on the transporter, the GR downregulation leads to a reduced GR function: for example, when cells are incubated with antidepressants and corticosterone,[43] which is not a substrate of P-glycoprotein; or in the presence of the transporter inhibitor, verapamil[43]; or when cells are treated with antidepressants alone.[45]

Interestingly, this model is supported by our most recent papers on mice and humans. In mice, treatment with the antidepressant desipramine induces GR downregulation in P-glycoprotein knockout mice, and therefore, in a condition that is similar to the *in vitro* experiments that do *not* elicit the effect on the transporter—while inducing GR upregulation in control mice—and therefore in a condition that similar to the *in vitro* experiments that *do* elicit effect on the transporter.[46] In humans, we have recently demonstrated that incubation of whole blood cells with the antidepressant clomipramine reduced GR function, measured as described above.[18] We interpret these data as indicating that the antidepressant induces GR translocation and thus reduces GR expression in the peripheral blood mononuclear cell (in the whole blood) in the absence of any compensatory action of steroid transporters, which have been described at very low levels in human peripheral blood mononuclear cells. More interestingly, depressed patients—the chronic, treatment-resistant sample mentioned above—do not show this effect; that is, the GR in the peripheral blood mononuclear cells of these "treatment-resistant patients" is also is "resistant *in vitro*" to the effects of antidepressants.[18]

Similarly to the lack of studies on GR function in patients with schizophrenia, there are very little data on the effects of antipsychotics on GR function. *In vitro* data show that clozapine, cloropromazine, and sulpiride all affect GR function, but not in the same directions.[47,48] Moreover, quetiapine and olanzapine (but not haloperidol) directly decrease HPA axis activity in healthy volunteers.[49,50] Overall, therefore, there are similarities between antidepressants and at least some antipsychotics in the effects on the GR and the HPA axis.

How Can We Manipulate the GR?

In humans, clinical studies have also shown that manipulation of GR function by both GR agonists and antagonists has antidepressant effects. On one side, treatment with GR and MR agonists, like dexamethasone, prednisolone

and cortisol, has shown antidepressant action[51–53] and ameliorating effects on declarative memory[54] in depressed patients. While some studies described only an acute, transient improvement in depressive symptoms, subsequent studies have shown that a short-term treatment with a GR agonist has persistent antidepressant effects.[51–53] On the other hand, GR antagonists, like mifepristone (RU486), have therapeutic effects in the treatment of psychotic depression[55,56] and bipolar disorder.[57] These findings could appear to contradict each other. Indeed, GR antagonists were first proposed as antidepressant agents within the theoretical model that the hypercortisolemia exerts a "toxic" action on the brain that needs to be reduced in order to obtain a therapeutic response. However, the therapeutic effects of GR antagonists could also be explained within the "glucocorticoid resistance" model. In fact, these drugs completely block the negative feedback and thus cause a further elevation of cortisol levels, persistent for days or weeks. It is therefore possible that the therapeutic effects are induced by these overly elevated cortisol levels, which in turn increase the cortisol signal in the brain. Indeed, during treatment with a GR antagonist, the MR remains available to cortisol as it is not blocked by these drugs; or, the GR can be displaced temporarily by the peak levels of cortisol. Interestingly, studies using mifrepristone have shown not only that this drug increases the HPA axis but also that it normalizes the circadian rhythm (albeit at a higher level) of cortisol secretion. Therefore, it is possible that GR antagonists do not exert the therapeutic action by blocking a "depression-inducing" effect of the hypercortisolemia, but rather by resetting the HPA axis function.[56]

Interestingly, cortisol synthesis inhibitors, such as metyrapone, have also been used as antidepressant agents. Similar to the GR antagonists, these compounds have been originally proposed as therapeutic agents because of their ability of reducing the putative "toxic" effects of hypercortisolemia on the brain.[58] However, once again, the effectiveness of these drugs in ameliorating depressive symptoms does not unequivocally support the "toxic hypercortisolemia" model, nor is it in contrast to the "glucocorticoid resistance" model. In fact, these compounds show antidepressant effects even in the absence of any changes in cortisol levels—that is, even when the hypothesized mechanism of action is lacking.[58] Indeed, for these compounds, the main therapeutic pharmacological action could be mediated by the increased production of neurosteroids with potential antidepressant effects, such as 11-deoxycortisol and dehydroepiandrosterone (DHEA).[58]

What Does "Hypercortisolemia" Really Mean?

Having reviewed the evidence supporting the notion of glucocorticoid resistance in depression, it is important to highlight that there is not only one single "hypercortisolemia" state. In the context of depression—and in this context only—it is scientifically legitimate to claim that the hypercortisolemia represents a compensatory mechanism and thus does not exert "depression-inducing" effects on the brain. However, there is no doubt that other forms of hypercortisolemia, in other clinical context, may be "depression-inducing." For example, in the context of Cushing's disease, due to adrenal or pituitary tumors, the hypercortisolemia has clear mood-changing effects, with depression been the most frequent psychiatric complication. In this context, the changes in mood are reversed by normalization of glucocorticoid levels, and therefore the "depression-inducing" effects of the high levels of cortisol are evident. Similarly, pharmacological administration of synthetic glucocorticoids also has a clear "mood-affecting" component although, interestingly, dysphoria, irritability and elation are more frequent than depression in these circumstances. Again, stopping or decreasing exogenous glucocorticoid administration in these states improves mood, thus supporting a causative role of the high level of

glucocorticoids in these mood changes. What is also apparent, however, is that both of these conditions can be conceptualized as quite different from depression: during Cushing's disease or exogenous glucocorticoid administration, the high levels of endogenous or exogenous glucocorticoids (often much higher that those reached in depression) alter brain function via an apparently normal GR; in contrast, in depression it is an impaired GR that leads to the increased cortisol levels. While this may seem to be only a semantic distinction, it is in fact a very important one, because according to this model—the model proposed in this paper—decreasing cortisol action will only work as an effective antidepressant strategy during Cushing's disease or exogenous glucocorticoid administration, but not in major depression. Therefore, a correct understanding and conceptualization of hypercortisolemia (or, better, *hypercortisolemias*) in the context of different psychiatric and medical conditions is essential to develop new, effective therapeutic tools for these patients.

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Conflicts of Interest

The author declares no conflicts of interest.

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