The HPA axis in major depression: classical theories and new developments

Carmine M. Pariante[1] and Stafford L. Lightman[2]

[1] Institute of Psychiatry, King's College London, Division of Psychological Medicine and Psychiatry, Centre for the Cellular Basis of Behaviour, Room 2-055, The James Black Centre, 125 Coldharbour Lane, London SE5 9NU, UK
[2] Henry Wellcome Laboratories for Integrative Neuroscience and Endocrinology, University of Bristol, Dorothy Hodgkin Building, Whitson Street, Bristol BS1 3NY, UK

Studies over the last 40 years have demonstrated that hyperactivity of the hypothalamic-pituitary-adrenal axis is one of the most consistent biological findings in major depression psychiatry, but the mechanisms underlying this abnormality are still unclear.

Introduction

Hypothalamic-pituitary-adrenal (HPA) axis activity is governed by the secretion of adrenocorticotrophic hormone-releasing factor (CRF) and vasopressin (AVP) from the hypothalamus, which in turn activate the secretion of adrenocorticotrophic hormone (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 both on CRF and AVP from the hypothalamus and directly on secretion of ACTH from pituitary corticotropes (see below). The activated HPA axis not only regulates body peripheral functions such metabolism and immunity but also has profound effects on the brain. For example, glucocorticoids regulate neuronal survival, neurogenesis, the sizes of complex anatomical structures such as the hippocampus, the acquisition of new memories and the emotional appraisal of events (reviewed in Ref. [1]). Considering its role at the interface between stress and brain functioning, it is perhaps not surprising that the HPA axis has been found abnormal in psychiatric disorders, and in particular in major depression. For example, a significant percentage of depressed patients have increased levels of cortisol in the saliva, plasma and urine, and increased size (as well as activity) of the pituitary and adrenal glands (reviewed in Ref. [2]).

This increased activity of the HPA axis is thought to be related, at least in part, to reduced feedback inhibition by endogenous glucocorticoids. Through binding to their cognate receptors in the HPA axis—the glucocorticoid receptor (GR) and the mineralocorticoid receptor (MR)—endogenous glucocorticoids serve as potent negative regulators of HPA axis activity, in particular the synthesis and release of CRF in the paraventricular nucleus and

proopiomelanocortin/ACTH in the pituitary. Data supporting the notion that glucocorticoid-mediated feedback inhibition is impaired in major depression come from a multitude of studies demonstrating that the HPA axis is not suppressed by pharmacological stimulation of the GR with an oral dose of the synthetic glucocorticoid dexamethasone; by contrast, even a small dose of dexamethasone induces a potent feedback inhibition of the HPA axis in healthy subjects, leading to reduced cortisol levels for up to 24 h. Reduced glucocorticoid receptor function in peripheral tissues, such as in peripheral blood mononuclear cells and skin cells, has also been described in depressed patients. Interestingly, successful antidepressant treatment is associated with resolution of the impairment in the negative feedback on the HPA axis by glucocorticoids (reviewed in Ref. [3]).

With this background in mind, covering the main findings from the last decades, this review will concentrate on the most recent advances and the newest and most promising translational developments in this research area. Specifically, we will present data supporting the hypothesis that HPA axis hyperactivity is not a simple consequence or an epiphenomenon of depression, but on the contrary that it is a risk factor predisposing to the development of depression, brought about by early life experiences programming molecular changes as well as by genetic liability.

HPA axis hyperactivity: chicken rather than egg?

One of the most striking developments in this field has been the discovery over the last few years that the increased activity of the HPA axis (and of CRF-containing circuits) might reflect a susceptibility that can be programmed through early life events. Indeed, laboratory animal studies have demonstrated that separating neonatal rodents and non-human primates from their mothers for long periods elicits HPA axis changes that persist into adulthood and that resemble those present in depressed adult individuals, including hyperactivity of the HPA axis and increased activity of CRF-containing circuits [4]. Clinical studies have also shown that women who are sexually or physically abused in childhood, as adults exhibit a markedly enhanced activation of the HPA axis. For example, even if not currently depressed, they exhibit

Corresponding author: Lightman, S.L. (stafford.lightman@bristol.ac.uk).

enhanced ACTH and heart rate responses when exposed to a standardised psychosocial stress (the Trier Social Stress Test; TSST); and if they are currently depressed, they exhibit the largest increase in ACTH secretion and heart rate, as well as a very large increase in cortisol secretion [5]. Moreover, a recent study using the dexamethasone-CRF test has also found persistent HPA axis hyperactivity in men with early life trauma [6]. Taken together, these findings suggest that the HPA axis hyperactivity previously described in depression might not be the consequence of depression *per se*, but rather the manifestation of persistent neurobiological abnormalities that predispose to depression. This could also explain why previous studies that have not taken into account early life stressors have been inconsistent in documenting the presence of HPA axis hyperactivity in depression.

Although most research has focused on the effects of early life events on programming changes in the HPA axis itself, concentrating on epigenetic modifications of genes encoding GR [7] and CRF [8], it is important to emphasise that there are many other closely related systems that might be susceptible to programming. A good example is the 5-hydroxytryptamine (5-HT) system, which can be clearly modified by maternal deprivation paradigms [9] and whose adult expression is context dependent [10], thus providing a good mechanism for development of a vulnerability trait.

It is also important to highlight recent findings that link early trauma to adult inflammation and provide a conceptual model to explain the presence of activated inflammatory biomarkers in adult depression. Increased peripheral plasma concentrations of interleukin (IL) 6, IL-1-b and tumor necrosis factor (TNF) α have been described in depressed patients, together with increased levels of C-reactive protein (CRP), an acute phase protein and peripheral marker of immune activation that is also a clinically relevant indicator of increased cardiovascular risk [11]. The increase in C-reactive protein is normalised by antidepressant treatment [12]. Within this context, recent studies have shown that a history of early life trauma, even in the absence of depression, is associated with clinically significant levels of inflammation in adulthood, as shown by elevated levels of CRP and increased production of IL-6 during the TSST [13,14]. Theoretically, HPA axis hyperactivity and inflammation in adult depressed individuals (and as responses to early childhood trauma) might be part of the same pathophysiological process: HPA axis hyperactivity is a marker of glucocorticoid resistance, that is, of ineffective action of glucocorticoid hormones on target tissues, which could lead to immune activation; and, equally, inflammation could stimulate HPA axis activity via both a direct action of cytokines on the brain and by inducing glucocorticoid resistance [11].

It is important to emphasise that the presence of biological mechanisms, described above, that potentially could explain the comorbidity between early life trauma and adult depression, does not imply that this putative causative link is inevitable or irreversible. Indeed, one of the most important notions that has arisen in mood disorders research in the last few years is that genetic polymorphisms in stress-related genes can modify that susceptibility to developing depression following life events. Within this context, this has been shown both for the genes encoding the 5-HT transporter [15] and CRF [16]. The notion that specific psychotherapies might be particularly effective in depressed patients with a history of early life trauma offers additional reassurances [17].

Glucocorticoid receptor: the weakest link?

As we have described above, the increased activity of the HPA axis is thought to be related, at least in part, to altered feedback inhibition by endogenous glucocorticoids, which is mediated by binding to the MR and the GR. This mechanism is explained in Figure 1. Basically, circulating glucocorticoids (cortisol in humans) bind to the GR outside the brain (such as in the pituitary) or inside the brain (hippocampus and hypothalamus). The activated GR, in turn, induces a feedback inhibition signal that leads to reduction of HPA axis activity. The figure also represents potential mechanisms regulating this feedback inhibition: (i) GR expression and function; (ii) availability of cortisol in the brain, as its entry is limited at the blood–brain barrier by transporters such as the multidrug-resistance P-glycoprotein; and (iii) environmental effects such as early life trauma, leading to changes in GR function by either direct epigenetic mechanisms or indirectly via inflammatory pathways (see below). These mechanisms can also be regulated by antidepressant treatment, leading to an increase in feedback inhibition and normalisation of HPA axis activity in depressed patients (reviewed in Ref. [3]).
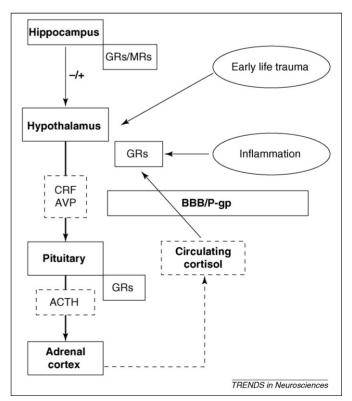

Figure 1. Schematic diagram of the hypothalamic-pituitary-adrenal (HPA) axis, including putative pathways leading to hyperactivity and possible molecular targets relevant for antidepressant response. Abbreviations: BBB, blood–brain barrier; P-gp, P-glycoprotein.

Recent evidence has indeed accumulated showing that abnormalities in the GR play a crucial role in the pathophysiology of HPA axis hyperactivity in depression. The MR has a high affinity for endogenous corticosteroids, whereas the GR has a high affinity for dexamethasone and a lower affinity for endogenous corticosteroids. The GR is therefore believed to be more important in the regulation of the response to stress when endogenous levels of glucocorticoids are high, such as in depression. Data supporting the notion that GR-mediated feedback inhibition is impaired in major depression originally came, as mentioned above, from studies showing both functional and expression changes in the GR in patients in major depression: nonsuppression of cortisol secretion following administration of dexamethasone; impaired GR function in peripheral blood mononuclear cells isolated and cultivated *in vitro*, or in peripheral cells examined *in vivo* using metabolic or vascular indices; and reduced GR expression in neuropathological studies of *post mortem* human brains. Moreover, consistent with the notion that impaired GR function is crucial for HPA axis hyperactivity in depression, antidepressant treatment has been shown to increase GR expression, GR function and GR-mediated HPA axis feedback inhibition in laboratory animals as well as in humans, thereby reducing resting and stimulated HPA axis activity. Finally, normalisation of GR function by antidepressant treatment has been found to be a significant predictor of long-term clinical outcome (reviewed in Ref. [3]).

In the last few years, this evidence has been further corroborated by animal and human studies. For example, experimental models of decreased GR expression have been shown to lead to the occurrence of depressive-like behavior [18]. From a molecular point of view, experimental models of GR resistance have identified that pro-inflammatory cytokines have the ability to reduce GR function via activation of the P38 mitogen-activated protein kinase [19], a finding that fits nicely with the notion, described above, that depression is characterised by increased inflammation in the context of HPA axis hyperactivity and glucocorticoid resistance. In relation to the role of the GR in antidepressant action, polymorphisms in both the GR and the GR-associated heat-shock protein FKBP5 have been shown to predict clinical response [20,21]. Moreover, molecular studies *in vitro* have clarified some of the mechanisms involved in the action of antidepressants on the GR. Specifically, incubation of cells with antidepressants has been shown to both decrease GR function (most likely via GR activation and subsequent downregulation or sequestration in the nucleus) and increase GR function (most likely via inhibition of membrane steroid transporters that expel glucocorticoids from cells) [22]. One of these transporters, the multidrug-resistance P-glycoprotein, has been shown to control the access of both antidepressants and cortisol to the brain, across the blood–brain barrier; and, interestingly, genetic polymorphisms in this transporter have recently been identified that predict clinical response to antidepressants [23].

HPA axis and depression: what now?

Several methods and approaches have recently been developed to assess novel aspects of HPA axis activity or to add a new level of sophistication to our understanding, and some of these have been tested in depression.

There has been increasing awareness of the importance of MR in regulation of HPA activity. MR is abundant in limbic areas of the brain and has a high affinity for cortisol and corticosterone. This would suggest that it is actively occupied at most times of the day. Two lines of research are making us rethink the role of MR. First, there is evidence for an important 'lower-affinity' MR that is also very important in feedback inhibition [24] and is involved in the so-called rapid glucocorticoid feedback, that is, the feedback inhibition induced by an intravenous bolus of glucocorticoids [25]. Second, there is increasing appreciation of the relevance of the combination of MR and GR in mediating the brain response to the normal secretion of glucocorticoids [26,27]. Under normal conditions, glucocorticoids are secreted in a pulsatile manner; this is reflected in a continuous activation of MR upon which is superimposed a phasic and short-acting activation of GR with each endogenous pulse [28]. It is the synergy of the MR and GR activation which is important in mediating glucocorticoid feedback inhibition.

The relevance of both MR and GR activation has also been investigated in humans. Because the two most important neuroendocrine tests used in psychiatry both use dexamethasone (alone or in combination with CRF), these tests only assess GR function, as dexamethasone only binds to the GR. By contrast, MR function can be assessed by using spironolactone, the precursor of the MR antagonist canreonate that is formed in body following administration of spironolactone. This agent is able to activate the HPA axis via blockade of MR-mediated negative feedback by endogenous glucocorticoids. Interestingly, the study that has investigated the effects of spironolactone in depressed patients has found that the response to spironolactone is increased in these patients compared to controls [29]. Based on these data, the authors conclude that MR activity is increased in depression. The second study uses a different tool, prednisolone. Prednisolone is a synthetic glucocorticoid but, different from dexamethasone, it is able to bind to the GR and the MR with similar affinities. In this study, the authors compared the response to dexamethasone and to prednisolone. Consistently with the data using spironolactone, they found that the response to prednisolone (GR/MR) is normal, whereas the response to dexamethasone (GR only) is impaired [30]. Therefore, these studies come to the same conclusion that MR function is spared in depression, perhaps to compensate for reduced GR function.

A different approach to further understand HPA axis hyperactivity in depression is the measurement of the salivary cortisol response to awakening. This tool measures the response of the HPA axis to stress (the physiological stress of awakening), while at the same time allowing a naturalistic measure of cortisol levels at individuals' homes and using noninvasive (saliva) sampling. In healthy individuals, a peak of cortisol level is measured around 30 min postawakening, followed by return to awakening levels at around 60 min. In depressed patients, even after recovery, the response to awakening is increased [31,32].

Two other developments should be mentioned, even if no data in depressed patients are available yet, because of the potential use in depressed patients in the very near future. First, inhalation of carbon dioxide (CO_2) has been developed as a new tool to activate stress pathways, including the HPA axis. Recent work in healthy subjects shows that inhalation of a single vital capacity breath of a mixture of CO_2 (35%) and oxygen (65%) induces an increase in blood pressure, plasma noradrenaline, salivary α-amylase (a marker of sympathetic activity) and salivary cortisol, over the following 30 min. Moreover, when the test is administered on two consecutive occasions a few weeks apart, most of the tested subjects reliably show the same reaction at both sessions, that is, either they show a post-CO_2 cortisol increase or show no change or a decrease in cortisol [33]. This test has the interesting ability of activating all components of the human stress response while at the same time limiting the variability and complexity of psychosocial stress tests. The second development in the assessment of the HPA axis that could have an impact on our understanding of depression comes from animal neuroendocrine research. Using repeated blood sampling in free-moving rats, studies have revealed a complex ultradian rhythm of endogenous levels of corticosterone, with discrete peaks occurring at approximately hourly intervals. The most interesting aspect of this new observation is that the HPA axis responsivity to stress is different during the different phases of this ultradian rhythm: during the phase leading to the peak, the HPA axis is responsive to stress, whereas after the peak the HPA axis is less responsive [34]. Repeated automatic sampling in healthy individuals and depressed patients might in the future lead to much more sophisticated insight into HPA axis pathophysiology.

A further area which will undoubtedly become important in the future for our understanding of glucocorticoids in depression is the question of cell-specific interactions between GR and DNA. GR interactions with DNA are associated with localised changes in chromatin structure, with GR rapidly shuttling on and off chromatin templates. Accessibility of the binding site for GR is either constitutive or hormone inducible, with cell-specific organisation of the chromatin environment [35]. We are only just beginning to have insight into these processes but they clearly play a vital role in determining tissue specificity in GR responsiveness and might well underlie changes in GR regulation in psychiatric disease.

With this background of our rapidly changing understanding of GR function, is there good evidence that the HPA axis will ever deliver as a target for discovering new antidepressants? The most important data have been provided by studies investigating antagonists of CRF1 receptors. These drugs possess antidepressant and anxiolytic properties both in experimental models and in clinical settings, but have not yet been licensed [36]. Vasopressin receptor 1b antagonists might have a role in the treatment of depression, but clinical data with this kind of drug are not available yet [37]. The GR antagonist mifepristone (RU486) exerts therapeutic effects in the treatment of cognitive dysfunction in bipolar disorder [26], but the data on core depressive symptoms in psychotic depression are less promising [38]. Other GR antagonists are available in preclinical study data, but again clinical data are lacking [34]. Indeed, considering the antidepressant effects obtained by short treatment with cortisol, dexamethasone and prednisolone, and the fact that GR antagonists themselves induce, if anything, an even higher activation of the HPA axis, it is yet unclear whether the therapeutic aspect of manipulating corticosteroid receptors resides in increasing an impaired GR or damping down a hyperstimulated GR [3]. However, taking into consideration the large amount of data showing direct effects of clinically effective antidepressants on HPA axis function, it is probably just a matter of time before the reverse direction will be successful—that is, discovering a new drug that changes HPA function and that is a clinically effective antidepressant.

References

1 Herbert, J. *et al.* (2006) Do corticosteroids damage the brain? *J. Neuroendocrinol.* 18, 393–411

2 Nemeroff, C.B. and Vale, W.W. (2005) The neurobiology of depression: inroads to treatment and new drug discovery. *J. Clin. Psychiatry* 66 (Suppl. 7), 5–13

3 Pariante, C.M. (2006) The glucocorticoid receptor: part of the solution or part of the problem? *J. Psychopharmacol.* 20, 79–84

4 Sanchez, M.M. *et al.* (2001) Early adverse experience as a developmental risk factor for later psychopathology: evidence from rodent and primate models. *Dev. Psychopathol.* 13, 419–449

5 Heim, C. and Nemeroff, C.B. (2002) Neurobiology of early life stress: clinical studies. *Semin. Clin. Neuropsychiatry* 7, 147–159

6 Heim, C. *et al.* (2008) The dexamethasone/corticotropin-releasing factor test in men with major depression: role of childhood trauma. *Biol. Psychiatry* 63, 398–405

7 Weaver, I.C. *et al.* (2006) Maternal care effects on the hippocampal transcriptome and anxiety-mediated behaviors in the offspring that are reversible in adulthood. *Proc. Natl. Acad. Sci. U. S. A.* 103, 3480–3485

8 Korosi, A. and Baram, T.Z. (2008) The central corticotropin releasing factor system during development and adulthood. *Eur. J. Pharmacol.* 583, 204–214

9 Gardner, K.L. *et al.* (2005) Early life experience alters behavior during social defeat: focus on serotonergic systems. *Neuroscience* 136, 181–191

10 Gardner, K.L. *et al.* (2006) Early life experience programs gene expression in serotonin neurons. Program no. 562.15. In *2006 Abstracts Viewer/Itinerary Planner* [CD ROM]. Washington, DC: Society for Neuroscience

11 Raison, C.L. *et al.* (2006) Cytokines sing the blues: inflammation and the pathogenesis of depression. *Trends Immunol.* 27, 24–31

12 O'Brien, S.M. *et al.* (2006) Antidepressant therapy and C-reactive protein levels. *Br. J. Psychiatry* 188, 449–452

13 Danese, A. *et al.* (2007) Childhood maltreatment predicts adult inflammation in a life-course study. *Proc. Natl. Acad. Sci. U. S. A.* 104, 1319–1324

14 Pace, T.W. *et al.* (2006) Increased stress-induced inflammatory responses in male patients with major depression and increased early life stress. *Am. J. Psychiatry* 163, 1630–1633

15 Caspi, A. *et al.* (2003) Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. *Science* 301, 386–389

16 Bradley, R.G. *et al.* (2008) Influence of child abuse on adult depression: moderation by the corticotropin-releasing hormone receptor gene. *Arch. Gen. Psychiatry* 65, 190–200

17 Nemeroff, C.B. *et al.* (2003) Differential responses to psychotherapy versus pharmacotherapy in patients with chronic forms of major depression and childhood trauma. *Proc. Natl. Acad. Sci. U. S. A.* 100, 14293–14296

18 Chourbaji, S. *et al.* (2008) Mice that under- or overexpress glucocorticoid receptors as models for depression or posttraumatic stress disorder. *Prog. Brain Res.* 167, 65–77

19 Miller, A.H. and Raison, C.L. (2006) Cytokines, p38 MAP kinase and the pathophysiology of depression. *Neuropsychopharmacology* 31, 2089–2090

20 Binder, E.B. *et al.* (2004) Polymorphisms in FKBP5 are associated with increased recurrence of depressive episodes and rapid response to antidepressant treatment. *Nat. Genet.* 36, 1319–1325

21 van Rossum, E.F. *et al.* (2006) Polymorphisms of the glucocorticoid receptor gene and major depression. *Biol. Psychiatry* 59, 681–688

22 Carvalho, L.A. *et al.* Clomipramine *in vitro* reduces glucocorticoid receptor function in healthy subjects but not depressed patients. *Neuropsychopharmacology* (in press)

23 Uhr, M. *et al.* (2008) Polymorphisms in the drug transporter gene ABCB1 predict antidepressant treatment response in depression. *Neuron* 57, 203–209

24 Karst, H. *et al.* (2005) Mineralocorticoid receptors are indispensable for nongenomic modulation of hippocampal glutamate transmission by corticosterone. *Proc. Natl. Acad. Sci. U. S. A.* 102, 19204–19207

25 Atkinson, H.C. *et al.* (2008) Corticosteroids mediate fast feedback of the rat hypothalamic-pituitary-adrenal axis via the mineralocorticoid receptor. *Am. J. Physiol. Endocrinol. Metab.* 294, E1011–E1022

26 Young, A.H. *et al.* (2004) Improvements in neurocognitive function and mood following adjunctive treatment with mifepristone (RU-486) in bipolar disorder. *Neuropsychopharmacology* 29, 1538–1545

27 Lightman, S.L. *et al.* (2008) The significance of glucocorticoid pulsatility. *Eur. J. Pharmacol.* 583, 255–262

28 Conway-Campbell, B.L. *et al.* (2007) Proteasome-dependent down-regulation of activated nuclear hippocampal glucocorticoid receptors determines dynamic responses to corticosterone. *Endocrinology* 148, 5470–5477

29 Young, E.A. *et al.* (2003) Mineralocorticoid receptor function in major depression. *Arch. Gen. Psychiatry* 60, 24–28

30 Juruena, M.F. *et al.* (2006) Different responses to dexamethasone and prednisolone in the same depressed patients. *Psychopharmacology (Berl)* 189, 225–235

31 Bhagwagar, Z. *et al.* (2003) Increase in concentration of waking salivary cortisol in recovered patients with depression. *Am. J. Psychiatry* 160, 1890–1891

32 Bhagwagar, Z. *et al.* (2005) Increased salivary cortisol after waking in depression. *Psychopharmacology (Berl.)* 182, 54–57

33 Wetherell, M.A. *et al.* (2006) The four-dimensional stress test: psychological, sympathetic-adrenal-medullary, parasympathetic and hypothalamic-pituitary-adrenal responses following inhalation of 35% CO_2. *Psychoneuroendocrinology* 31, 736–747

34 Spiga, F. *et al.* (2007) Effect of the glucocorticoid receptor antagonist Org 34850 on basal and stress-induced corticosterone secretion. *J. Neuroendocrinol.* 19, 891–900

35 John, S. *et al.* (2008) Interaction of the glucocorticoid receptor with the chromatin landscape. *Mol. Cell* 29, 611–624

36 Ising, M. and Holsboer, F. (2007) CRH-sub-1 receptor antagonists for the treatment of depression and anxiety. *Exp. Clin. Psychopharmacol.* 15, 519–528

37 Griebel, G. *et al.* (2002) Anxiolytic- and antidepressant-like effects of the non-peptide vasopressin V1b receptor antagonist, SSR149415, suggest an innovative approach for the treatment of stress-related disorders. *Proc. Natl. Acad. Sci. U. S. A.* 99, 6370–6375

38 Flores, B.H. *et al.* (2006) Clinical and biological effects of mifepristone treatment for psychotic depression. *Neuropsychopharmacology* 31, 628–636