REVIEW ARTICLE

Glucocorticoid receptor dysfunction: consequences for the pathophysiology and treatment of mood disorders

AJU ABRAHAM, STUART WATSON, ALLAN H YOUNG

ABSTRACT

Background: Hypothalamic-pituitary-adrenal (HPA) axis dysfunction in mood disorders is one of the most robust findings in biological psychiatry. However, considerable debate surrounds the nature of the core abnormality, its cause, consequences and treatment implications.

Aims: To review the evidence for the role of HPA axis dysfunction in the pathophysiology of mood disorders with particular reference to corticosteroid receptor pathology.

Methods: A selective review of the published literature in this field, focusing on human studies.

Results: The nature of basal HPA axis dysregulation described in both manic and depressed bipolars appears to be similar to those described in MDD. But studies using the dexamethasone/ corticotropin releasing hormone (dex/CRH) test and dexamethasone suppression test (DST) have shown that HPA axis dysfunction is more prevalent in bipolar than in unipolar disorder. There is robust evidence for corticotropin releasing hormone (CRH) hyperdrive and glucocorticoid receptor (GR) dysfunction in mood disorders, with increasing evidence for disorders within the AVP system.

Conclusion: HPA axis dysfunction is prevalent in patients with mood disorder, particularly those with psychotic disorders and bipolar affective disorder. This may be secondary to genetic factors, early life adversities or both. Dysfunction of GR may be the underlying abnormality and preliminary findings suggest that it is a potential target for novel therapies.

Declaration of interest: None

Key words: Mood disorders, pathophysiology, Glncocorticoid Receptor

Mood disorders are common, often severe, life long; associated with significant handicap and disability and are associated with a high risk of death by both suicide (6-15%-(Goodwin, *et al*, 1990; Inskip, *et al*, 1998) and physical disorders. It is still uncertain whether modern treatments have substantially changed either the length of episodes or the number of relapses.

Contemporary studies have found a lifetime prevalence of major depressive disorder of 4-19%. Traditionally episodes of unipolar depression were pictured as acute illnesses, self-limiting and lasting approximately 6-9 months from the time of onset to full recovery. A number of studies , however, show potential for great variation from this. Recovery may take much longer, or not occur at all. Moreover the risk of relapse and recurrence must be considered (Angst, 2000). At 5 years, 12% of unipolar depressed patients have still not recovered (Keller, *et al*, 1992) and by 10 years 7% have not recovered (Solomon, *et al*, 1997).

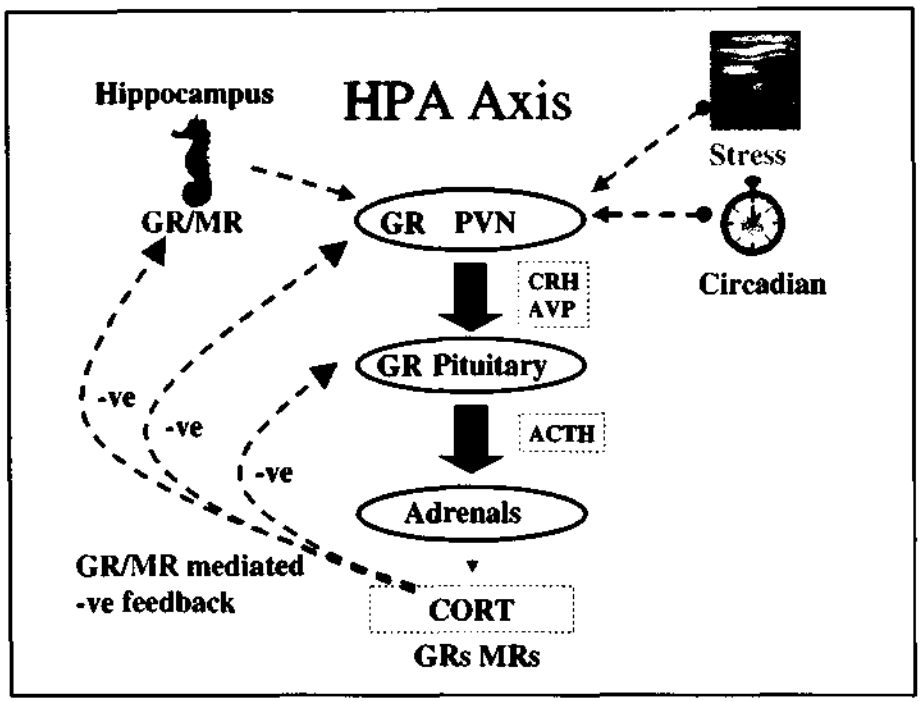
For Bipolar I Disorder, the majority of epidemiological studies indicate lifetime prevalence rates of approximately 0.5-1% (Kessler, *et al*, 1994; Weissman, *et al*, 1996). Classically, bipolar disorder manifests as repeated periods of illness with complete recovery (Kraepelin, 1899). However, many patients have a poor outcome, a third suffer chronic symptoms and up to a quarter may develop rapid cycling disorder, where four or more episodes occur within a year. This poor clinical outcome is associated with significant disability in terms of social, marital and occupational dysfunction (Zarate, *et al*, 2000). Co-morbid illnesses include anxiety disorders, substance abuse and personality disorders (Kay, *et al*, 1999; McElroy, *et al*, 2001). A much wider, less well characterised bipolar spectrum also exists. This includes not only bipolar II disorder, characterised by episodes of depression and hypomania but also less well recognised sub-syndromes combining hypomania and minor depression or manic/ hypomanic symptoms alone.

Hypothalamic-pituitary-adrenal (HPA) axis

The hypothalamic-pituitary-adrenal (HPA) axis is a multifaceted regulatory system which integrates neuronal and endocrine function and consists of the hypothalamus, pituitary, adrenal cortex, and the associated regulatory inputs, releasing factors and hormones (see Fig. 1). The neurosecretory cells in the paraventricular nucleus (PVN) of the hypothalamus secrete corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP) into the microportal circulatory system of the pituitary stalk. They induce the release of adrenocorticotropic hormone (ACTH) from the anterior lobe of the pituitary into the systemic circulation. ACTH in turn promotes the release of the glucocorticoid - cortisol from the zona fasciculata and zona reticularis of the adrenal cortex, and mineralocorticoid - aldosterone from the zona glomerulosa of the adrenal cortex.

The HPA axis has an extrinsic and intrinsic regulatory mechanism. The extrinsic regulatory inputs are received by the secretory cells in the PVN of the hypothalamus, from many brain regions, including amygdala, hippocampus and nuclei of the midbrain. In addition to these

HPA Axis, Stress & Circadian Rhythm

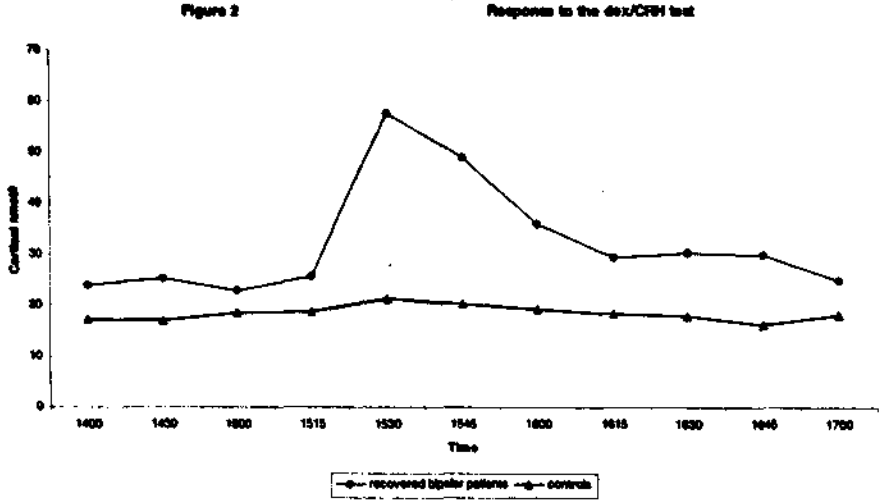


there are excitatory and inhibitory afferents, including those containing 5-hydroxytryptamine (5-HT), noradrenaline, acetylcholine, and both excitatory and inhibitory amino acids, (Jones, *et al*, 1987). The intrinsic autoregulatory mechanism plays a crucial role in the regulation of the HPA axis. The glucocorticoid receptors (GR) play a key role in this feed back mechanism. The endogenous cortisol, by binding to the GR in the HPA axis tissues and the hippocampus, acts as a potent negative regulator of HPA activity (Sapolsky, *et al*, 1986). This autoregulatory role of endogenous cortisol via the GR is crucial to the maintenance of the intrinsic homeostasis of the HPA axis (Jacobson, *et al*, 1991; Sapolsky, *et al*, 1986).

The set point of pituitary feedback is determined by the hypothalamus acting through the hypothalamic releasing hormones CRH and vasopressin. (Antoni, 1986; Vale, *et al*, 1983). Glucocorticoids act on both the pituitary corticotropes and the hypothalamic neurones that secrete CRH and vasopressin. A still higher level of feedback control is exerted by glucocorticoid responsive neurones in the hippocampus that project to the hypothalamus and affect the activity of CRH hypophyseotropic neurones and in turn determine the set point of pituitary responsiveness to glucocorticoids (Sapolsky, *et al*, 1986).

CORT (cortisol in man, corticosterone in rats), in some respects the final product of the HPA axis, has both central and peripheral effects. It is lipid soluble and enter the brain through the blood-brain barrier (de Kloet, *et al*, 1993). CORT maintains basal activity of the HPA system. It also exerts rapid non genomic effects. CORT promotes co-ordination of circadian events, such as the sleep/wake cycle and food intake and is involved in processes underlying selective attention, integration of sensory information and response selection. It facilitates an animals ability to cope with, adapt to, and recover from stress and promotes learning and memory processes (De Kloet, *et al*, 1998). CORT acts on both type 1 - mineralocorticoid receptors (MR) and type 2 - glucocorticoid receptors (GR) (De Kloet, *et al*, 1998). MR have a relatively restricted distribution, being particularly expressed in the hippocampus. GR are more widely distributed, have a 10-fold lower affinity for CORT and therefore their activation, in contrast to MR, varies widely across the diurnal range of CORT concentrations. MR are saturated by basal levels of glucocorticoids, whereas GR are not saturated under basal conditions, but approach saturation during peak phases of circadian rhythm and during stress. De Kloet and colleagues (De Kloet, *et al*, 1987; De Kloet, *et al*, 1998) have hypothesised that tonic influences of CORT are exerted via hippocampal MRs, while the additional occupancy of GRs with higher levels of CORT mediates feedback actions aimed to restore balances in homeostasis.

Figure 2 Response to the dex/CRH test



Role of HPA axis in the Pathophysiology of mood disorders

HPA axis dysfunction in mood disorders is suggested by the findings that 20-24% of patients with unipolar depression are hypercortisolaemic (Young, *et al*, 2001). 27-43% of mood disorder patients have an abnormal DST response (Rush, *et al*, 1996) and 80% of unipolar depressed patients have an abnormal response to the dex/CRH

test (Heuser, *et al*, 1994). These findings raise a number of questions discussed below.

1) What is the cause of HPA axis dysfunction?

EARLY LIFE ADVERSITY

Rodent studies show that early life adversity such as maternal separation is associated with persistent changes in the HPA axis, including alteration of hypothalamic CRH mRNA, median eminence CRH content and stress induced release in adult rats (Ladd, *et al*, 1996; Plotsky, *et al*, 1993)

Studies in grown monkeys who were exposed as infants to adverse early rearing conditions showed that in comparison to monkeys reared by mothers foraging under predictable conditions, infant monkeys exposed to early stress of being raised by mothers foraging under unpredictable conditions exhibited persistently elevated cerebrospinal fluid (CSF) concentrations of CRF. (Coplan, *et al*, 1996) These studies suggested that the increased risk of developing mood and anxiety disorders in adulthood that is consequent on childhood abuse and neglect and parental loss may be mediated by persistent alterations in CRH systems (Baker, *et al*, 1999; Coplan, *et al*, 1996; Ladd, *et al*, 1996; Plotsky, *et al*, 1993).

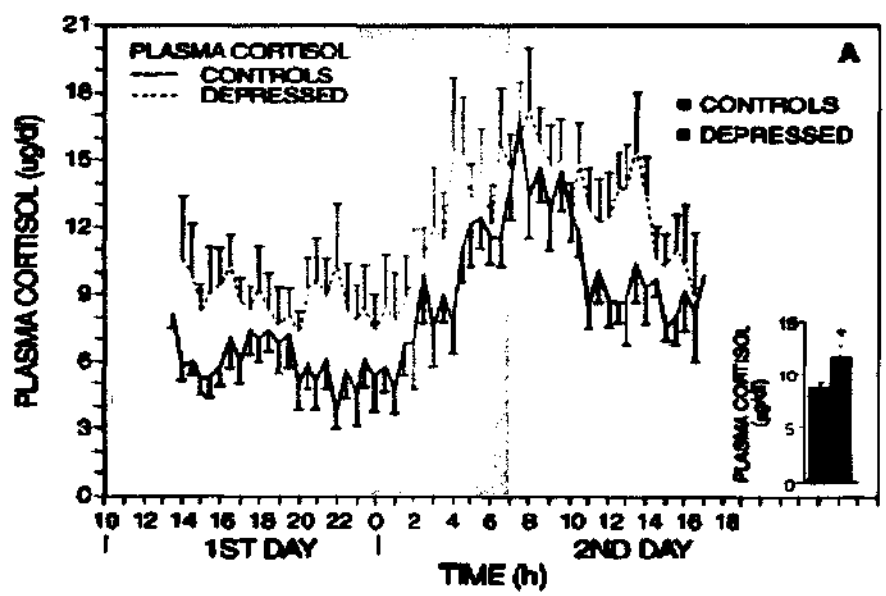
Non-depressed women with a history of childhood physical or sexual abuse have been shown to have an enhanced ACTH response to both the Trier social stress test (Heim, *et al*, 2000) and to CRH challenge (Heim, *et al*, 2001). The same group has shown that abused women without major depressive disorder exhibited greater than usual ACTH responses to CRH administration, whereas abused women with major depressive disorder and depressed women without early life stress demonstrated blunted ACTH responses. In the ACTH stimulation test, abused women without major depressive disorder exhibited lower baseline and stimulated plasma cortisol concentrations. Abused women with co-morbid depression more often suffered from posttraumatic stress disorder and reported more recent life stress than abused women without major depressive disorder. These findings suggest sensitisation of the anterior pituitary and counter-regulative adaptation of the adrenal cortex in abused women without major depressive disorder. On subsequent stress exposure, women with a history of childhood abuse may hypersecrete CRF, resulting in down-regulation of adenohypophyseal CRH receptors and symptoms of depression and anxiety (Heim, *et al*, 2001).

GENETICS

The Swedish twin registry study has shown that mood disorders are highly heritable. The authors estimated a heritability of 64 to 83%. The same genetic and environmental factors appeared to influence liability to affective illness in men and women to the same degree, although women had a lower threshold of manifestation. The heritability of bipolar disorder has more recently been estimated at between 85 and 89% (McGuffin, *et al*, 2003) and may share common genetic risk factors with schizophrenia (Cardno, *et al*, 2002). The complex inheritance of bipolar disorder and the failure of multiple genome wide scans to detect major gene effects suggests that bipolar susceptibility loci probably have small to moderate effects. The Munich vulnerability study suggests that the familial association may be mediated via the HPA axis (Lauer, *et al*, 1998), however the heritability of bipolar disorder has not yet been convincingly shown to be mediated by genes acting on the HPA axis.

2) Are some patients with mood disorder more likely than others to have an abnormal HPA axis?

The HPA axis has been less well studied in bipolar disorder than in MDD. However, the nature of HPA axis dysregulation described in both manic and depressed bipolars appears to be similar to those described in MDD. Abnormal neuroendocrine function in mood disorders has been most convincingly demonstrated using the dexamethasone/ corticotropin releasing hormone (dex/ CRH) test (Heuser, *et al*, 1994). Studies using this technique and the dexamethasone suppression test (DST) have shown that HPA axis dysfunction is more prevalent in bipolar than in unipolar disorder (Rush, *et al*, 1996; Rybakowski, *et al*, 1999). DST abnormalities in mixed mania (71%) and bipolar depression (25-60%) are more common than in major depressive disorder (37%-41%) (Rush, *et al*, 1996); (Nelson, 1987). During mania, there is large variation in the results of different studies, with the rate of non-suppression being the same as in normal controls (Carroll, *et al*, 1976; Greden, *et al*, 1982) or equivalent to that seen in bipolar depression (Arana, *et al*, 1983; Goodwin, 1984; Graham, *et al*, 1982). One explanation for this discrepancy in mania may be variation in the clinical state of patients sampled, e.g. the presence or absence of psychotic or depressive symptoms or the severity of the mania.



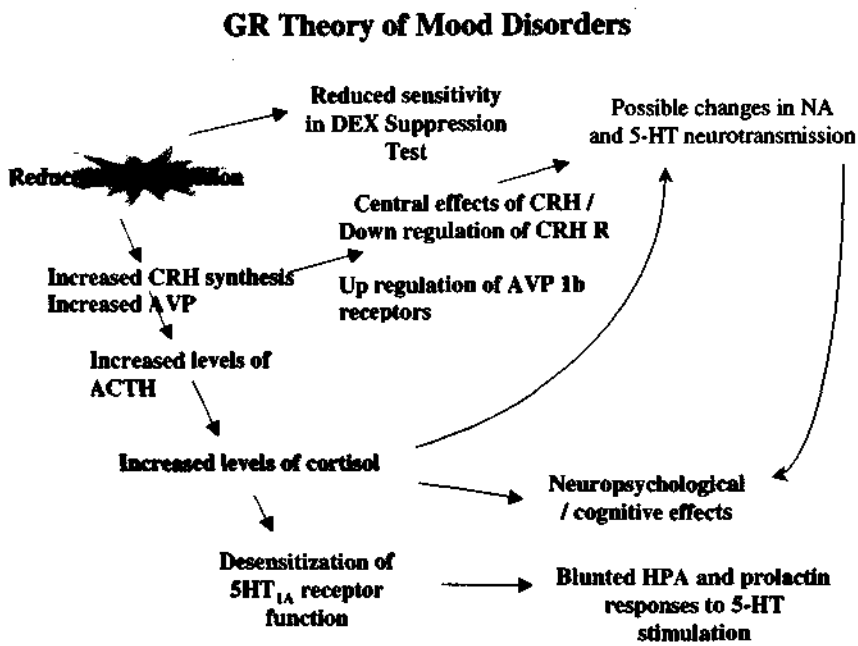
3) What facets of HPA axis are abnormal?

BASAL CORTISOL

State dependent hypercortisolaemia associated with depression were first demonstrated by (Gibbons, 1964) and has since been repeatedly replicated although more recent studies suggest more moderate abnormalities than the original description (Dubrovsky, 1993); (Kirschbaum, *et al*, 1994; Rybakowski, *et al*, 1999; Schmider, *et al*, 1995; Swann, *et al*, 1992; Whalley, *et al*, 1989); (Vieta, *et al*, 1997; Watson, *et al*, 2001; Young, *et al*, 2001). A flattening of the diurnal cortisol rhythm with an elevation in the afternoon trough appears to be a more robust finding fig. 3 (Cervantes, *et al*, 2001; Sachar, 1975). This abnormal rhythm can be expected to alter the activation of MR and GR.

CRH HYPOTHESIS

Professor Nemeroff's group has hypothesised CRH overdrive (increased synthesis and release of CRH) to be central to the aetiopathophysiology of affective disorders (Nemeroff, 1988): Extra-hypothalamic CRH sites may play an important role in the mediation of behavioural response to stress and in the pathophysiology of anxiety and depression (Arborelius, *et al*, 1999). CRH immunoreactivity is present in the raphe nuclei and locus coeruleus (LC) which form the origin of the major serotonergic and noradrenergic projections to the forebrain (Valentino, *et al*, 1993). The amygdala, thought to mediate fear and anxiety (Davis, 1992) is also innervated by CRH nerve terminals. Moreover, central administration of CRH to laboratory animals produces stress like effects including an increase in locomotor activity, an increased responsiveness to acoustic stimuli and reduced exploratory behaviour. It also produces depression like effects, including diminished food intake, decreased sexual activity and disturbed sleep (Dunn, *et al*, 1990). The number of CRH secreting neurones is increased in limbic areas of the brain (Raadsheer, *et al*, 1994) and the CRH concentration of CSF is increased (Nemeroff, *et al*, 1984).



Gold and colleagues (Gold, *et al*, 1984) have shown that both depressed unipolar and bipolar patients have a blunted ACTH response to intravenously infused CRH, but a normal cortisol response. The blunted ACTH response may be mediated by subsensitivity of pituitary receptors to CRH, secondary to downregulation via CRH hyperdrive or to homeostatic effects of elevated cortisol levels. The anatomical correlate of this functional change is the reduced size of the pituitary gland that has been recorded in bipolar patients (Sassi, *et al*, 2001). The normal cortisol response despite the reduced ACTH secretion is in keeping with the demonstration that depressed patients have an increased cortisol response to ACTH (Amsterdam, *et al*, 1988; Amsterdam, *et al*, 1983; Jaeckle, *et al*, 1987). Interestingly in Gold's study, in contrast to depressed patients, euthymic and manic patients had a normal ACTH response to CRH challenge (Gold, *et al*, 1984). Vieta and colleagues similarly demonstrated that bipolar patients who had been well for 6 months did not have a blunted ACTH response to CRH. Those patients with a more blunted response were more likely to have a depressive relapse within 12 months and those with an exagerated response were at increased risk of subsequent mania (Vieta, *et al*, 1997; Vieta, *et al*, 1999). It is the CRH_1 rather than the CRH_2 receptor that appears to convey anxiety and possibly, depression related signalling (Liebsch, *et al*, 1999). CRH_1 receptor deficient mice display less anxiety related behaviour (Timpl, *et al*, 1998).

ARGININE VASOPRESSIN

Like CRH, AVP is a hypothalamic hormone. It acts synergistically with CRH to facilitate ACTH and hence cortisol release. Physiologically, it appears to allow an acute stress response in conditions of chronic stress. Post-mortem studies of unipolar and bipolar patients who died by suicide show that AVP is increased in the PVN and that there is an increase in the number of CRH neurones co-expressing AVP (Purba, *et al*, 1996; Raadsheer, *et al*, 1994). AVP release is suppressed by GR activation (Erkut, *et al*, 1998). This suggests that the increase in plasma and CSF AVP levels which have been shown in some but not all studies in depression (Scott, *et al*, 1998), suggesting that AVP changes in patients may be secondary to GR dysfunction. This hypothesis is supported by our unpublished data showing that AVP levels are greater in bipolar patients than controls after pre-treatment with the glucocorticoid, dexamethasone.

THE GLUCOCORTICOID RECEPTOR (GR) HYPOTHESIS

It has been hypothesised that dysfunction of GR is the core underlying pathophysiological abnormality in mood disorders. See fig. 4 (McQuade, *et al*, 2000; Pariante, *et al*, 2001). Two post-mortem studies have shown low levels of GR mRNA in the frontal cortex and hippocampus in mood disorder patients (Lopez, *et al*, 2003; Webster, *et al*, 2002) Glucocorticoid mediated negative feedback can be examined using the dexamethasone suppression test (DST) and the dex/CRH test. An abnormal response on the DST and the dex/CRH test ie. non-supression of cortisol secretion, suggests dysregulation of GR mediated feedback. GR knockout mice have impaired feedback regulation within the HPA axis, with elevated levels of plasma ACTH and corticosterone (Cole, *et al*, 1995; Cole, *et al*, 2001). A number of studies have examined GR number in peripheral blood mononuclear cells in affective disorder patients with largely inconsistent results (Pariante, *et al*, 2001). The CRH neurones in many brain areas are inhibited by GR activation. Therefore, it is suggested that the CRH overdrive, which has previously been hypothesised to be central to the aetiopathophysiology of affective disorders, could be a result of the underlying GR dysfunction. Reduced function of GR may be expected to exert greater effect on cortisol level during the afternoon trough when the influence of other factors such as CRH and AVP is relatively less. It has not been satisfactorily shown experimentally, but one can speculate that reduced GR function may give rise to the characteristic flattened diurnal cortisol rhythm of mood disorder patients

DEHYDROEPIANDROSTERONE (DHEA)

DHEA is an androgen secreted by the adrenal gland and to a lesser extend by the ovaries and testes. It can also be converted in to other steroid hormones such as oestrogen and testesterone and exists in both a free, and sulphated (DHEA-S) form. Animal studies show that DHEA counteracts the deleterious effects of corticosteroids on long-term potentiation, a neurophysiological correlate of learning and memory (Kaminska, *et al*, 2000). DHEA levels regulate glucocorticoid action in the brain. The ratio of cortisol to DHEA therefore reflects the degree of 'functional' hypercortisolaemia and has recently been shown to be enhanced in a drug free population of patients with major depressive disorder (Young, *et al*, 2002a).

4) Is HPA axis dysfunction a cause or consequence of affective disorder?

Two separate groups have demonstrated that bipolar patients when manic or depressed show abnormalities on the dex/CRH test (Rybakowski, *et al*, 1999; Schmider, *et al*, 1995). They both re-examined the patients on symptomatic recovery and showed that the cortisol response, whilst partially normalising still remained significantly different from the response of healthy controls (Rybakowski, *et al*, 1999; Schmider, *et al*, 1995). Similarly, bipolar patients with a stringent prospective diagnosis of euthymia have been shown to have an abnormally enhanced cortisol response using the same test . This suggests that this measure of HPA axis dysfunction may be a trait abnormality and as such may potentially represent a vulnerability factor for bipolar disorder. In a longitudinal follow up study, (Goodwin, 1984) found that individual's DST responses were consistent over time, regardless of their clinical state, providing further support for the hypothesis that the HPA axis dysfunction is a trait abnormality of bipolar disorder. This has been further addressed by the Munich vulnerability study (Lauer, *et al*, 1998), in which 32% of healthy volunteers with a family history of mood disorder had an abnormal response to the dex/CRH test. Unfortunately, the high drop out in this study will make it difficult to determine if these relatives have an increased risk of developing bipolar disorder (Modell, *et al*, 1998). However, researchers in the UK have demonstrated that morning salivary cortisol concentrations are a risk factor for subsequent development of unipolar major depressive disorder (Harris, *et al*, 2000).

CONSEQUENCES OF HPA AXIS DYSFUNCTION

In recent years it has become clear that, in addition to effects on metabolic and inflammatory processes, corticosteroids also play an extensive modulatory role in neurotransmission. Studies in experimental animals have indicated that expression and function of neurotransmitter receptors and enzymes, long-term potentiation and even cell survival are all influenced by corticosteroids. Glucocorticoid therapy has been shown to be associated with a range of psychopathology including depression, euphoria, mood lability, cognitive impairment and psychosis (Baker, *et al*, 1999). It is unsurprising, therefore, that behavioural indices of neurotransmitter function, such as mood and cognition, are also influenced by corticosteroid manipulations.

MONOAMINE SYSTEMS

Disorders of the serotonin system have been thought to be of aetiological and therapeutic importance in depression since the 1960's. A number of strands of evidence converge to suggest a pathophysiological role for reduced transmission through post synaptic 5-HT_{1A} receptors in depression. Chronic elevation of corticosteroids reduces post synaptic 5-HT_{1A} receptor number, an effect which may promote depression (McAllister-Williams, *et al*, 1998). In contrast, acutely elevated plasma cortisol levels, induced by acute stress or administration of hydrocortisone reduces somatodendritic rather than post-synaptic 5-HT_{1A} receptor function, thereby facilitating 5-HT_{1A} neurotransmission in an antidepressant like way (Laaris, *et al*, 1999; Young, *et al*, 1994a; Young, *et al*, 1994b) and has been shown to exert a mood elevating effect (DeBattista, *et al*, 2000). Our group has shown that flattening the rhythm without increasing the 24 hour output results in reduced $5HT_{1A}$ neurotransmission (Leitch, *et al*, 2003).

Pre-clinical studies have also shown that corticosteroids increase dopamine neurotransmission. This mechanism has been hypothesised to be pathophysiological im-

portance in mania, psychotic depression and substance misuse (Schatzberg, *et al*, 1985)

ENDOCRINE DISORDERS

Cushing's disease in which ACTH and hence cortisol are increased is associated with depression in 70% of patients. Memory disturbances, in particular, biasing toward negative contents, overlapping sleep abnormalities (marked reduction of stages 3 and 4), increased fatigue and loss of energy, attentional deficits and irritability, are just part of the common symptoms presented by patients with both Cushing's disorder and depression. All of these behavioural manifestations are known to be affected by adrenal steroid hormones (Dubrovsky, 1993). Whilst antidepressants offer some benefit, controlling cortisol levels appears to be the most effective treatment.

Addison's disease, in which cortisol synthesis is defective, is also associated with high rates of psychiatric disorder, which improve on successful steroid replacement. A number of chronic medical diseases such as multiple sclerosis are also associated with both elevated cortisol levels and high rates of psychopathology.

NEUROGENESIS

Mood disorders are associated with a loss of brain cells, particularly glia and schizophrenia is associated with neuronal atrophy. Throughout adult life new neurones continue to be made in brain areas including the hippocampus and olfactory bulb. Corticosteroids have an important role in mediating neurogenesis and survival of new cells. Although difficult to study in humans, it has been hypothesised that reduced neurogenesis is causative in depression and that the therapeutic effect of antidepressants is mediated by an enhancement of new cell production and survival, perhaps via effects on the HPA axis. Evidence for this includes the demonstration that stress reduces neurogenesis and causes learned helplessness in rodents, effects that are prevented by chronic treatment with an antidepressant (Gould, *et al*, 2000).

NEUROCOGNITIVE IMPAIRMENT

Corticosteroids are essential for cognitive performance. MR appear to promote reactivity in novel situations whereas GR are involved in consolidation of learned information. It may therefore seem paradoxical that disorders (including Cushing's disease and severe mood disorders) and experimental conditions in which endogenous or exogenous corticosteroids are elevated either acutely or chronically are associated with a significant degree of cognitive impairment. It appears that the effects of corticosteroids on cognition can become maladaptive when the activity of the two types of receptor becomes either persistently imbalanced or out of context with the situation (De Kloet, *et al*, 1998).

Sapolsky has suggested a causal link between chronic hypercortisolaemia, hippocampal atrophy and neurocognitive impairment (Sapolsky, *et al*, 1986). Evidence for this is growing and includes studies in experimental animals which has shown that chronic administration of corticosteroids results in deficits in learning and memory (Lupien, *et al*, 1997; White-Gbadebo, *et al*, 1993) and atrophy of neurones in the hippocampal formation. Chronic administration of corticosteroids in healthy humans is also associated with cognitive impairment (Young, *et al*, 1999). Furthermore, the cognitive tests which are most affected are dependent on intact function of frontal-hippocampal activity. Studies comparing mood disorder patients with normal controls suggest that the cognitive deficits in patients are irreversible and suggest long term hypercortisolaemia-induced damage to crucial neuronal circuits (Ferrier, *et al*, 1999). The findings that cortisol levels after pretreatment with dexamethasone correlate with neurocognitive impairment and tests of executive function in recovered bipolar patients suggest that the causal link may be driven by GR dysfunction rather than simple hypercortisolaemia (Watson, *et al*, 2002). An early re-establishment of normal HPA activity in mood disorders before permanent deficits in cognitive function occur may therefore be an important therapeutic goal.

What are the treatment implications?

CURRENTLY AVAILABLE TREATMENTS

Currently available psychotropic drugs may act via the HPA axis. Thus, (Heuser, *et al*, 1996) and colleagues have shown that successful treatment of unipolar depression with amitryptiline is associated with a reduction in the cortisol response to the dex/CRH test. This may be mediated by normalisation of dysfunctional corticosteroid receptors (McQuade, *et al*, 2000). It is of interest that whilst some drugs such as lithium which appear to act on GR, stabilise mood in bipolar disorder, others such as the tricyclics increase cycle frequency rate and can induce mania (McQuade, *et al*, 2000; Wehr, *et al*, 1987).

IMPLICATIONS FOR NOVEL TREATMENTS ANTIGLUCOCORTICOID TREATMENT

Antiglucocorticoid treatment, which is aimed at lowering cortisol levels, has been investigated using ketoconazole, aminoglutethimide or metyrapone in several studies in MDD and one in bipolar disorder. The majority of the trials have been open studies but there have also been two randomised-controlled trials. Side-effects are common but the data suggests that in the patients who are able to tolerate the treatment there is an association with improvement in mood, particularly in those patients with previously demonstrated hypercortisolaemia (Brown, *et al*, 2001). The equivocal results may be explained by the mechanism of action of antiglucocorticoids, which exert effects on the steroid biosynthesis pathway. They therefore reduce the synthesis of cortisol but also exert profound effects on the synthesis of other adrenal steroids. Cortisol synthesis inhibitors are unlikely to become routine drugs in the treatment of bipolar disorder, largely because of side effects and drug interactions. However, their efficacy in some patients supports the use of other pharmacological interventions that target specific sites in the HPA axis.

RHYTHM

The biochemical, cognitive or mood effects of the flattened cortisol rhythm seen in bipolar disorder patients has not yet been examined in man, however it is possible to speculate that modulation of the cortisol rhythm of mood disorder patients may have effects on mood and cognition and may represent a novel therapeutic approach.

CRH-1 RECEPTOR ANTAGONIST

The CRH_1 receptor antagonist R121919 has been used in an open treatment trial of 24 patients with major depression and appears to be safe and well tolerated and is associated with a reduction in anxiety and depression (Zobel, *et al*, 2000).

GR ANTAGONISTS

The GR antagonist mifepristone has been shown to reduce depressive symptoms in open trials of patients with psychotic and non-psychotic depression (Belanoff, *et al*, 2001), to reduce depressive and psychotic symptoms in Cushing's syndrome (Nieman, *et al*, 1985; van der Lely, *et al*, 1991) and improve cognitive performance in Alzheimer's disease (Pomara, *et al*, 2002). It may exert acute therapeutic effect by blocking GR receptors thereby creating a "functional hypocortisolaemia". Additionally, it is hypothesised that prolonged blockade may increase corticosteroid receptor function or number and reset the homeostatic set point thereby restoring the characteristic diurnal rhythm and potentially offering long-term benefit. Its use in bipolar disorder is being examined in a placebo controlled cross-over trial by our group and preliminary results presented at the society of biological psychiatry annual meeting in Philadelphia suggest an association with an improvement in executive function (Young, *et al*, 2002b).

Org 34517 has been shown in vitro, in animals and humans to be a selective glucocorticoid receptor antagonist. A multicentre, randomised, double-blind, paroxetine controlled study of Org34517 in patients with major depressive has shown that it is well tolerated during the 4 weeks treatment period in the dose range of 150-600 mg (Hoyberg, *et al*, 2002). Although it was not shown to be significantly more effective than 20-40 mg paroxetine in subjects with moderate to severe MDD, when focusing on patients with detectable HPA disturbances, a clear indication was found for stronger efficacy of the low dose (150-300mg) Org regimen as compared with paroxetine. This effect was more pronounced in DST-nonsuppressors and during the first two weeks of treatment. High dose Org34517 increased cortisol, DHEA-s and testosterone levels, which is evidence for a detectable degree of GR-blockade. Subjects who seemed to benefit from treatment with low dose Org34517 did not show a detectable increase in cortisol and other HPA driven hormones levels during the first weeks of treatment.

AVP_{1b} RECEPTOR ANTAGONISTS

The AVP_{1b} receptor antagonists, SSR149415 and $d(CH_2)Tyr(Et)VAVP$ (Griebel, *et al*, 2002; Liebsch, *et al*, 1996) have been shown to have anxiolytic properties in animal studies and represent an exciting potential pharmacological strategy for the treatment of mood disorders.

DEHYDROEPIANDROSTERONE (DHEA)

Improvements in cognition have been observed after administration of DHEA to middle-aged and elderly depressed patients (Wolkowitz, *et al*, 1997) and the antidepressant actions of DHEA have recently been demonstrated in a small randomised controlled trial in depression (Wolkowitz, *et al*, 1999). Case reports of mania induced by massive DHEA doses (Dean, 2000; Kline, *et al*, 1999; Markowitz, *et al*, 1999) suggest the need for caution, however DHEA administration represents an exciting potential novel therapeutic approach in bipolar disorder.

CONCLUSIONS

HPA axis dysfunction is prevalent in patients with mood disorder, particularly the psychotic disorders and bipolar affective disorder. It has implications in the pathophysiology and cognitive impairment in mood disorders. It is more overt when patients are unwell, but still present in euthymia and present in a third of apparently healthy patients with genetic loading. The HPA axis dysfunction may be secondary to genetic factors or early life adversities. Elevated cortisol levels are not consistently shown but tests which incorporate examination of glucocorticoid receptor function reveal higher rates of abnormality. It appears that dysfunction of GR may be the underlying abnormality in mood disorders, and preliminary findings suggest that it is a potential target for novel therapies.

REFERENCES

Amsterdam, J., Maislin, G., Winokur, A., *et al* (1988) The oCRH stimulation test before and after clinical recovery from depression. *Journal of Affective Disorders*, 14, 213-222.

Amsterdam, J. D., Winokur, A., Abelman, E., *et al* (1983) Cosyntropin (ACTH alpha 1-24) stimulation test in depressed patients and healthy subjects. *American Journal of Psychiatry*, 140, 907-909.

Angst, J. (2000) Course and prognosis of mood disorders. In *New Oxford textbook of psychiatry* (eds M. G. Gelder, J. J. Lopez-Ibor Jr & N. C. Andreasen), pp. 719-725. Oxford: Oxford University Press.

Antoni, F. A. (1986) Hypothalamic control of adrenocorticotropin secretion: advances since the discovery of 41-residue corticotropin-releasing factor. *Endocr Rev*, 7, 351-378.

Arana, G. W., Barreira, P. J., Cohen, B. M., *et al* (1983) The dexamethasone suppression test in psychotic disorders. *American Journal of Psychiatry*, 140, 1521-1523.

Arborelius, L., Owens, M. J., Plotsky, P. M., *et al* (1999) The role of corticotropin-releasing factor in depression and anxiety disorders. *Journal of Endocrinology*, 160, 1-12.

Baker, D. G., West, S. A., Nicholson, W. E., *et al* (1999) Serial CSF corticotropin-releasing hormone levels and adrenocortical activity in combat veterans with posttraumatic stress dis-

order. *American Journal of Psychiatry*, 156, 585-588.

Belanoff, J. K., Flores, B. H., Kalezhan, M., et al (2001) Rapid reversal of psychotic depression using mifepristone. *Journal of Clinical Psychopharmacology*, 21, 516-521.

Brown, E. S., Bobadilla, L. & Rush, A. J. (2001) Ketoconazole in bipolar patients with depressive symptoms: a case series and literature review. *Bipolar Disorder*, 3, 23-29.

Cardno, A. G., Rijsdijk, F. V., Sham, P. C., et al (2002) A twin study of genetic relationships between psychotic symptoms. *American Journal of Psychiatry*, 159, 539-545.

Carroll, B. J., Curtis, G. C. & Mendels, J. (1976) Neuroendocrine regulation in depression. II. Discrimination of depressed from nondepressed patients. *Archives of General Psychiatry*, 33, 1051-1058.

Cervantes, P., Gelber, S., Kin, F. N., et al (2001) Circadian secretion of cortisol in bipolar disorder. *J Psychiatry Neurosci*, 26, 411-416.

Cole, T. J., Blendy, J. A., Monaghan, A. P., et al (1995) Targeted disruption of the glucocorticoid receptor gene blocks adrenergic chromaffin cell development and severely retards lung maturation. *Genes Dev*, 9, 1608-1621.

Cole, T. J., Myles, K., Purton, J. F., et al (2001) GRKO mice express an aberrant dexamethasone-binding glucocorticoid receptor, but are profoundly glucocorticoid resistant. *Molecular & Cellular Endocrinology*, 173, 193-202.

Coplan, J. D., Andrews, M. W., Rosenblum, L. A., et al (1996) Persistent elevations of cerebrospinal fluid concentrations of corticotropin-releasing factor in adult nonhuman primates exposed to early-life stressors: implications for the pathophysiology of mood and anxiety disorders. *Proceedings of the National Academy of Sciences USA*, 93, 1619-1623.

Davis, M. (1992) The role of the amygdala in fear and anxiety. *Annual Review of Neuroscience*, 15, 353-375.

De Kloet, E. R., Oitzl, M. S. & Joels, M. (1993) Functional implications of brain corticosteroid receptor diversity. *Cellular & Molecular Neurobiology*, 13, 433-455.

De Kloet, E. R. & Reul, J. M. (1987) Feedback action and tonic influence of corticosteroids on brain function: a concept arising from the heterogeneity of brain receptor systems. *Psychoneuroendocrinology*, 12, 83-105.

De Kloet, E. R., Vreugdenhil, E., Oitzl, M. S., et al (1998) Brain corticosteroid receptor balance in health and disease. *Endocrine Reviews*, 19, 269-301.

Dean, C. E. (2000) Prasterone (DHEA) and mania. *Ann Pharmacother*, 34, 1419-1422.

DeBattista, C., Posener, J., Kalehzan, B., et al (2000) Acute Antidepressant Effects of Intravenous Hydrocortisone and CRH in depressed patients: A double-blind, placebo-controlled study. *American Journal of Psychiatry*, 157, 1334-1337.

Dubrovsky, B. (1993) Effects of adrenal cortex hormones on limbic structures: some experimental and clinical correlations related to depression. *J Psychiatry Neurosci*, 18, 4-16.

Dunn, A. J. & Berridge, C. W. (1990) Physiological and behavioral responses to corticotropin-releasing factor administration: is CRF a mediator of anxiety or stress responses? *Brain Research - Reviews*, 15, 71-100.

Erkut, Z. A., Pool, C. & Swaab, D. F. (1998) Glucocorticoids suppress corticotropin-releasing hormone and vasopressin expression in human hypothalamic neurons. *Journal of Clinical Endocrinology and Metabolism*, 83, 2066-2073.

Ferrier, I. N., Stanton, B. R., Kelly, T. P., et al (1999) Neuropsychological function in euthymic patients with bipolar disorder. *British Journal of Psychiatry*, 175, 246-251.

Gibbons, J. (1964) Cortisol secretion rate in depressive illness. *Archives of General Psychiatry*, 10, 572-575.

Gold, P. W., Chrousos, G., Kellner, C., et al (1984) Psychiatric implications of basic and clinical studies with corticotropin-releasing factor. *American Journal of Psychiatry*, 141, 619-627.

Goodwin, F. & Jamison, K. (1990) *Manic Depressive Illness*. New York: Oxford University Press.

Goodwin, F. K. (1984) The biology of depression: conceptual issues. *Advances in Biochemical Psychopharmacology*, 39, 11-26.

Gould, E., Tanapat, P., Rydel, T., et al (2000) Regulation of hippocampal neurogenesis in adulthood. *Biological Psychiatry*, 48, 715-720.

Graham, P. M., Booth, J., Boranga, G., et al (1982) The dexamethasone suppression test in mania. *Journal of Affective Disorders*, 4, 201-211.

Greden, J. F., DeVigne, J. P., Albala, A. A., et al (1982) Serial dexamethasone suppression tests among rapidly cycling bipolar patients. *Biological Psychiatry*, 17, 455-462.

Griebel, G., Simiand, J., Serradeil-Le Gal, C., 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. *Proceedings of the National Academy of Sciences USA*, 16, 16.

Harris, T. O., Borsanyi, S., Messari, S., et al (2000) Morning cortisol as a risk factor for subsequent major depressive disorder in adult women. *British Journal of Psychiatry*, 177, 505-510.

Heim, C., Newport, D. J., Bonsall, R., et al (2001) Altered pituitary-adrenal axis responses to provocative challenge tests in adult survivors of childhood abuse. *American Journal of Psychiatry*, 158, 575-581.

Heim, C., Newport, D. J., Miller, A. H., et al (2000) Long-term neuroendocrine effects of childhood maltreatment. *JAMA*, 284, 2321.

Heuser, I. J., Schweiger, U., Gotthardt, U., et al (1996) Pituitary-adrenal-system regulation and psychopathology during amitriptyline treatment in elderly depressed patients and normal comparison subjects. *American Journal of Psychiatry*, 153, 93-99.

Heuser, I. J., Yassouridis, A. & Holsboer, F. (1994) The combined dexamethasone/CRH test: a refined laboratory test for psychiatric disorders. *Journal of Psychiatric Research*, 28, 341-356.

Hoyberg, O. J., Wik, G., Mehtonen, O. P., et al (2002) Org 34517, a selective glucocorticoid receptor antagonist with potent antidepressant activity: first clinical results. *The International Journal of Neuropsychopharmacology*, 5, S148.

Inskip, H., Harris, E. & Barraclough, B. (1998) Lifetime risk of suicide for affective disorder, alcoholism and schizophrenia. *British Journal of Psychiatry*, 172, 35-37.

Jacobson, L. & Sapolsky, R. (1991) The role of the hippocampus in feedback regulation of the hypothalamic-pituitary-adrenocortical axis. *Endocrine Reviews*, 12, 118-134.

Jaeckle, R. S., Kathol, R. G., Lopez, J. F., et al (1987) Enhanced adrenal sensitivity to exogenous cosyntropin (ACTH alpha 1-24) stimulation in major depression. Relationship to dexamethasone suppression test results. *Archives of General Psychiatry*, 44, 233-240.

Jones, M. T., Gillham, B., Campbell, E. A., et al (1987) Pharmacology of neural pathways affecting CRH secretion. *Ann N Y Acad Sci*, 512, 162-175.

Kaminska, M., Harris, J., Gijsbers, K., et al (2000) Dehydroepiandrosterone sulfate (DHEAS) counteracts decremental effects of corticosterone on dentate gyrus LTP. Implications for depression. *Brain Research Bulletin*, 52, 229-234.

Kay, J. H., Altshuler, L. L., Ventura, J., et al (1999) Prevalence of axis II comorbidity in bipolar patients with and without alcohol use disorders. *Ann Clin Psychiatry*, 11, 187-195.

Keller, M. B., Lavori, P. W., Mueller, T. I., et al (1992) Time to recovery, chronicity, and levels

of psychopathology in major depression. A 5-year prospective follow-up of 431 subjects. *Archives of General Psychiatry*, 49, 809-816.

Kessler, R. C., McGonagle, K. A., Zhao, S., et al (1994) Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Results from the National Comorbidity Survey. *Archives of General Psychiatry*, 51, 8-19.

Kirschbaum, C. & Hellhammer, D. H. (1994) Salivary cortisol in psychoneuroendocrine research: recent developments and applications. *Psychoneuroendocrinology*, 19, 313-333.

Kline, M. D. & Jaggers, E. D. (1999) Mania onset while using dehydroepiandrosterone. *American Journal of Psychiatry*, 156, 971.

Kraepelin, E. (1899) *Psychiatrie ein lehrbuch fur studierende und arzte* (6th edn). Leipzig, Germany: Barth.

Laaris, N., Le Poul, E., Laporte, A., et al (1999) Differential effects of stress on presynaptic and postsynaptic 5-hydroxytryptamine-1A receptors in the rat brain: an in vitro electrophysiological study. *Neuroscience*, 91, 947-958.

Ladd, C. O., Owens, M. J. & Nemeroff, C. B. (1996) Persistent changes in corticotropin-releasing factor neuronal systems induced by maternal deprivation. *Endocrinology*, 137, 1212-1218.

Lauer, C., Schreiber, W., Modell, S., et al (1998) The Munich vulnerability study on affective disorders: overview of the cross-sectional observations at index investigation. *Journal of Psychiatric Research*, 32, 393-401.

Leitch, M. M., Ingram, C. D., Young, A. H., et al (2003) Flattening the corticosterone rhythm attenuates $5HT_{1A}$ autoreceptor function in the rat: relevance for depression. Neuropsychopharmacology. In Press.

Liebsch, G., Landgraf, R., Engelmann, M., et al (1999) Differential behavioural effects of chronic infusion of CRH 1 and CRH 2 receptor antisense oligonucleotides into the rat brain. *Journal of Psychiatric Research*, 33, 153-163.

Liebsch, G., Wotjak, C. T., Landgraf, R., et al (1996) Septal vasopressin modulates anxiety-related behaviour in rats. *Neurosci Lett*, 217, 101-104.

Lopez, J. F., Little, K.Y., Lopez-Figueroa, A.L., et al (2003) Glucocorticoid and mineralocorticoid receptor mRNA levels in the hippocampus and prefrontal cortex of subjects with mood disorders and schizophrenia. *Biological Psychiatry*, 53, abstract 489.

Lupien, S. J. & McEwen, B. S. (1997) The acute effects of corticosteroids on cognition: integration of animal and human model studies. *Brain Research - Brain Research Reviews*, 24, 1-27.

Markowitz, J. S., Carson, W. H. & Jackson, C. W. (1999) Possible dihydroepiandrosterone-induced mania. *Biological Psychiatry*, 45, 241-242.

McAllister-Williams, R. H., Ferrier, I. N. & Young, A. H. (1998) Mood and neuropsychological function in depression: the role of corticosteroids and serotonin. *Psychological Medicine*, 28, 573-584.

McElroy, S., Altshuler, L., Suppes, T., et al (2001) Axis I Psychiatric co-morbidity and its relationship to historical illness variables in 288 patients with bipolar disorder. *American Journal of Psychiatry*, 158, 420-426.

McGuffin, P., Rijsdijk, F., Andrew, M., et al (2003) The heritability of bipolar affective disorder and the genetic relationship to unipolar depression. *Archives of General Psychiatry*, 60, 497-502.

McQuade, R. & Young, A. H. (2000) Future therapeutic targets in mood disorders: the glucocorticoid receptor. *British Journal of Psychiatry*, 177, 390-395.

Modell, S., Lauer, C., Schreiber, W., et al (1998) Hormonal response pattern in the combined DEX-CRH test is stable over time in subjects at high familial risk for affective disorders. *Neuropsychopharmacology*, 18, 253-262.

Nelson, J. (1987) The use of antipsychotic drugs in the treatment of depression. In *Treating Resistant Depression* (eds J. Zohar & R. Belmaker), pp. 131-146. New York: PMA Corp.

Nemeroff, C., Widerlov, E., Bissette, G., et al (1984) Elevated concentrations of CSF corticotropin-releasing factor-like. *Science*, 226, 1342-1344.

Nemeroff, C. B. (1988) The role of corticotropin-releasing factor in the pathogenesis of major depression. *Pharmacopsychiatry*, 21, 76-82.

Nieman, L. K., Chrousos, G. P., Kellner, C., et al (1985) Successful treatment of Cushing's syndrome with the glucocorticoid antagonist RU 486. *Journal of Clinical Endocrinology & Metabolism*, 61, 536-540.

Pariante, C. M. & Miller, A. H. (2001) Glucocorticoid receptors in major depression: relevance to pathophysiology and treatment. *Biological Psychiatry*, 49, 391-404.

Plotsky, P. M. & Meaney, M. J. (1993) Early, postnatal experience alters hypothalamic corticotropin-releasing factor (CRF) mRNA, median eminence CRF content and stress-induced release in adult rats. *Brain Res Mol Brain Res*, 18, 195-200.

Pomara, N., Doraiswamy, M., Tun, H., et al (2002) Mifepristone (RU 486) for Alzheimer's disease-preliminary findings. *Biological Psychiatry*, 51, no. 219.

Purba, J. S., Hoogendijk, W. J., Hofman, M. A., et al (1996) Increased number of vasopressin- and oxytocin-expressing neurons in the paraventricular nucleus of the hypothalamus in depression. *Archives of General Psychiatry*, 53, 137-143.

Raadsheer, F. C., Hoogendijk, W. J., Stam, F. C., et al (1994) Increased numbers of corticotropin-releasing hormone expressing neurons in the hypothalamic paraventricular nucleus of depressed patients. *Neuroendocrinology*, 60, 436-444.

Rush, A. J., Giles, D. E., Schlesser, M. A., et al (1996) The dexamethasone suppression test in patients with mood disorders. *Journal of Clinical Psychiatry*, 57, 470-484.

Rybakowski, J. K. & Twardowska, K. (1999) The dexamethasone/corticotropin-releasing hormone test in depression in bipolar and unipolar affective illness. *Journal of Psychiatric Research*, 33, 363-370.

Sachar, E. J. (1975) Twenty-four-hour cortisol secretory patterns in depressed and manic patients. *Progress in Brain Research*, 42, 81-91.

Sapolsky, R. M., Krey, L. C. & McEwen, B. S. (1986) The neuroendocrinology of stress and aging: the glucocorticoid cascade hypothesis. *Endocrine Reviews*, 7, 284-301.

Sassi, R. B., Nicoletti, M., Brambilla, P., et al (2001) Decreased pituitary volume in patients with bipolar disorder. *Biological Psychiatry*, 50, 271-280.

Schatzberg, A. F., Rothschild, A. J., Langlais, P. J., et al (1985) A corticosteroid/dopamine hypothesis for psychotic depression and related states. *Journal of Psychiatric Research*, 19, 57-64.

Schmider, J., Lammers, C., 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. *Biological Psychiatry*, 38, 797-802.

Scott, L. V. & Dinan, T. G. (1998) Vasopressin and the regulation of hypothalamic-pituitary-adrenal axis function: implications for the pathophysiology of depression. *Life Sciences*, 62, 1985-1998.

Solomon, D. A., Keller, M. B., Leon, A. C., et al (1997) Recovery from major depression. A 10-year prospective follow-up across multiple episodes. *Archives of General Psychiatry*, 54, 1001-1006.

Swann, A. C., Stokes, P. E., Casper, R., et al (1992) Hypothalamic-pituitary-adrenocortical

function in mixed and pure mania. *Acta Psychiatrica Scandinavica*, 85, 270-274.

Timpl, P., Spanagel, R., Sillaber, I., et al (1998) Impaired stress response and reduced anxiety in mice lacking a functional corticotropin-releasing hormone receptor 1110ee comments]. *Nat Genet*, 19, 162-166.

Vale, W., Rivier, C., Brown, M. R., et al (1983) Chemical and biological characterization of corticotropin releasing factor. *Recent Prog Horm Res*, 39, 245-270.

Valentino, R. J., Foote, S. L. & Page, M. E. (1993) The locus coeruleus as a site for integrating corticotropin-releasing factor and noradrenergic mediation of stress responses. *Ann N Y Acad Sci*, 697, 173-188.

van der Lely, A. J., Foeken, K., van der Mast, R. C., et al (1991) Rapid reversal of acute psychosis in the Cushing syndrome with the cortisol-receptor antagonist mifepristone (RU 486). *Ann Intern Med*, 114, 143-144.

Vieta, E., Gasto, C., Martinez de Osaba, M. J., et al (1997) Prediction of depressive relapse in remitted bipolar patients using corticotrophin-releasing hormone challenge test. *Acta Psychiatr Scand*, 95, 205-211.

Vieta, E., Martinez-De-Osaba, M. J., Colom, F., et al (1999) Enhanced corticotropin response to corticotropin-releasing hormone as a predictor of mania in euthymic bipolar patients. *Psychological Medicine*, 29, 971-978.

Watson, S., Del-Estal, D., Smith, M., et al (2001) The hypothalamic-pituitary-adrenal axis in euthymic bipolar patients. *Journal of Psychopharmacology*, s15, B7.

Watson, S., Thompson, J. M., Ferrier, I. N., et al (2002) Association between neurocognitive and HPA axis function in euthymic bipolar patients. *Bipolar Disorder*, 4, 78.

Webster, M. J., Knable, M. B., O'Grady, J., et al (2002) Regional specificity of brain glucocorticoid receptor mRNA alterations in subjects with schizophrenia and mood disorders. *Mol Psychiatry*, 7, 985-994, 924.

Wehr, T. A. & Goodwin, F. K. (1987) Do antidepressants cause mania? *Psychopharmacol Bull*, 23, 61-65.

Weissman, M. M., Bland, R. C., Canino, G. J., et al (1996) Cross-national epidemiology of major depression and bipolar disorder. *JAMA*, 276, 293-299.

Whalley, L. J., Christie, J. E., Blackwood, D. H., et al (1989) Disturbed endocrine function in the psychoses. I: Disordered homeostasis or disease process? *British Journal of Psychiatry*, 155, 455-461.

White-Gbadebo, D. & Hamm, R. J. (1993) Chronic corticosterone treatment potentiates deficits following traumatic brain injury in rats: implications for aging. *J Neurotrauma*, 10, 297-306.

Wolkowitz, O. M., Reus, V. I., Keebler, A., et al (1999) Double-blind treatment of major depression with dehydroepiandrosterone. *American Journal of Psychiatry*, 156, 646-649.

Wolkowitz, O. M., Reus, V. I., Roberts, E., et al (1997) Dehydroepiandrosterone (DHEA) treatment of depression. *Biological Psychiatry*, 41, 311-318.

Young, A. H., Gallagher, P. & Porter, R. J. (2002a) Elevation of the cortisol-dehydroepiandrosterone ratio in drug-free depressed patients. *American Journal of Psychiatry*, 159, 1237-1239.

Young, A. H., Goodwin, G. M., Dick, H., et al (1994a) Effects of glucocorticoids on 5-HT1A presynaptic function in the mouse. *Psychopharmacology*, 114, 360-364.

Young, A. H., Sahakian, B. J., Robbins, T. W., et al (1999) The effects of chronic administration of hydrocortisone on cognitive function in normal male volunteers. *Psychopharmacology*, 145, 260-266.

Young, A. H., Sharpley, A. L., Campling, G. M., et al (1994b) Effects of hydrocortisone on brain 5-HT function and sleep. *Journal of Affective Disorders*, 32, 139-146.

Young, A. H., Watson, S., Gallagher, P., et al (2002b) The effects of glucocorticoid antagonists in unipolar and bipolar disorders. *Biological Psychiatry*, 51, 83S.

Young, E. A., Carlson, N. E. & Brown, M. B. (2001) Twenty-four-hour ACTH and cortisol pulsatility in depressed women. *Neuropsychopharmacology*, 25, 267-276.

Zarate, C. A., Jr., Tohen, M., Land, M., et al (2000) Functional impairment and cognition in bipolar disorder. *Psychiatr Q*, 71, 309-329.

Zobel, A. W., Nickel, T., Kunzel, H. E., et al (2000) Effects of the high-affinity corticotropin-releasing hormone receptor 1 antagonist R121919 in major depression: the first 20 patients treated. *Journal of Psychiatric Research*, 34, 171-181.

AJU ABRAHAM, MBBS, MRCPsych, Specialist Registrar in Psychiatry; *STUART WATSON, MBBS, MRCPsych, Specialist Registrar in Psychiatry; ALLAN H YOUNG, MBChB, MPhil, PhD, MRCPsych, Professor of Psychiatry; Stuart.watson@ncl.ac.uk, School of Neurology, Neurobiology and Psychiatry, Leazes Wing, Royal Victoria Infirmary, Queen Victoria Road, Newcastle upon Tyne, NE1 4LP United Kingdom, Tel: 0044 191 2824473, Fax: 0044 191 2275108

***Correspondence**