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Cortisol in Mood Disorders

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Dysfunction of the hypothalamic–pituitary–adrenal (HPA) axis has been well-described in mood disorders. Hypercortisolaemia, which has been attributed to a breakdown in glucocorticoid-receptor-mediated negative feedback mechanisms within the HPA axis, may be central to the pathogenesis of both the depressive symptoms and the cognitive deficits, which characterise severe mood disorders. Strategies to normalise glucocorticoid receptor (GR) function, and thus restore HPA functional integrity, have been the focus of recent research. Preliminary preclinical and clinical studies report encouraging results which suggest that lowering circulating cortisol levels, by up-regulating GRs, may have therapeutic efficacy in terms of improvements in depressive symptoms and cognitive functioning.

Keywords: Antiglucocorticoids; Bipolar depression; Drugs; Mifepristone; Mood disorders; Neuroendocrinology

INTRODUCTION

Both Kraepelin and Freud suggested that endocrine factors are likely to be important in the causation and treatment of major psychiatric disorders (Kraepelin 1896, Freud 1905), and the role of dysfunctional endocrine systems in the pathogenesis of mood disorders has been the focus of research for some time. Poor understanding of the complexity of endocrine systems and their interaction with neural networks, combined with the primitive methodology then available, frustrated early attempts to establish links between endocrine dysfunction and mood disorders (Michael and Gibbons 1963). More recently, developments in the field of neuroendocrinology have highlighted the aetiopathogenic significance of endocrine systems in mood disorders. This article reviews some of these recent developments, with an emphasis on the role of cortisol and depression, and briefly reports some preliminary therapeutic findings.

THE HYPOTHALAMIC–PITUITARY–ADRENAL (HPA) AXIS

Cortisol, a glucocorticoid released from the adrenal cortex, is the end-product of the hypothalamic–pituitary–adrenal (HPA) axis. The HPA axis comprises the tissues of the hypothalamus, pituitary and adrenal cortices, regulatory neuronal inputs, and a variety of releasing factors and hormones (see Figure 1). Neurosecretory cells within the paraventricular nucleus of the hypothalamus secrete corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP) into the primary capillaries of the microportal circulatory system of the pituitary stalk. CRH and AVP cause the release of adrenocorticotropic hormone (ACTH) from the anterior lobe of the pituitary. Cortisol is released from the adrenal cortex in response to ACTH. Cortisol has a panoply of central and peripheral effects which are mediated via corticosteroid receptors, of two subtypes: glucocorticoid (GR) and mineralocorticoid (MR) receptors (de Kloet et al. 1998).

The activity of the HPA axis is highly regulated. Secretory cells within the paraventricular nucleus receive neuronal inputs from a number of brain regions including the amygdala, hippocampus and nuclei within the midbrain; a number of these brain regions have been implicated in mood disorders (Harrison 2002). The HPA axis also has an autoregulatory mechanism mediated by cortisol. Endogenous cortisol binds to GRs in the central and pituitary components of the HPA axis and acts as a potent negative regulator of HPA activity. These regulatory mechanisms are important in determining basal levels and circadian fluctuations in cortisol levels. Changes in GR number or function may be important in altering the homeostatic function of the HPA axis observed in healthy individuals (McQuade and Young 2000).

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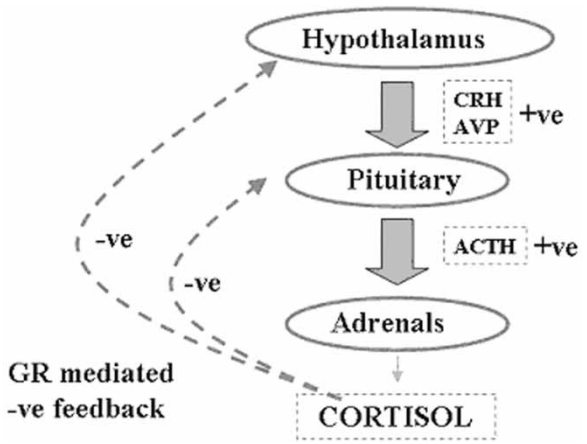

FIGURE 1 The hypothalamic–pituitary–adrenal (HPA) axis. CRH – corticotropin-releasing hormone; AVP – arginine vasopressin; ACTH – adrenocorticotropin hormone; GR – glucocorticoid receptor.

CORTISOL AND GR ABNORMALITIES IN DEPRESSION

The first observation of abnormalities of cortisol levels in patients with depression were made in late 1950s by Board et al. and these observations were repeatedly replicated (Board et al. 1956, Young et al. 2002). Subsequent studies have shown that HPA hyperactivity, as manifested by hypersecretion of CRH, increased cortisol levels in plasma, urine and cerebrospinal fluid, exaggerated cortisol responses to ACTH, and enlarged pituitary and adrenal glands, occur in individuals suffering from severe mood disorders. Hypersecretion of CRH causing hypercortisolaemia may be a result of impaired feedback mechanisms resulting from GR abnormalities, such as decreased receptor number or altered function. This view is supported by the demonstration of GR abnormalities in post-mortem studies of patients with severe mood disorders (Webster et al. 1999). The dexamethasone suppression test (DST) is a measure of the functional integrity of the GR-mediated negative feedback mechanism: the cortisol-suppressing activity of the synthetic glucocorticoid, dexamethasone, is an approximate indicator of GR status (McQuade and Young 2000). Reports of cortisol non-suppression in response to dexamethasone in both unipolar and bipolar disorders do indeed suggest a primary GR abnormality in these disorders (Zhou et al. 1987).

CONSEQUENCES OF HYPERCORTISOLAEMIA

It is now established that in conditions in which there are raised endogenous or exogenous corticosteroids (including Cushing's disease and severe mood disorders) there is also a significant degree of cognitive impairment (Wolkowitz et al. 1990). Studies in experimental animals have shown deficits in learning and memory following chronic administration of glucocorticoids (Lupien and McEwen 1997), as well as marked atrophy of neurons in the hippocampal formation. It has been postulated that a similar neurodegenerative effect of cortisol may underlie some of the cognitive deficits observed in humans suffering from severe mood disorders (Sapolsky et al. 1986).

Recent clinical data report that subacute treatment with hydrocortisone induces cognitive deficits in healthy humans, and these deficits appear to be mediated in part via the frontal lobe, suggesting that this brain area may also be sensitive to the effects of cortisol (Young et al. 1999). The deficits in healthy volunteer subjects are reversible, but this may not be the case with the cognitive deficits induced by hypercortisolaemia associated with mood disorders (Ferrier et al. 1999, Young et al. 1999). 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.

THERAPEUTIC TARGETS

There is increasing evidence to suggest that the consequences of HPA dysfunction described above are central to the pathogenesis of affective disorders and cognitive deficits. Modulation of the effects of hypercortisolaemia may provide potential treatments for mood disorders, and such strategies are the focus of considerable research interest. A systematic review of randomised control trials (RCT) of antiglucocorticoid therapies has begun and the publication of the final review is awaited with interest (Mackin et al. 2005).

Dehydroepiandrosterone

The adrenal steroid dehydroepiandrosterone (DHEA) has been used with some success in the treatment of depression (Wolkowitz et al. 1999). The physiological function of DHEA is unclear, but DHEA is known to possess antiglucocorticoid properties which may account for its therapeutic effects (Morfin 2002). Another explanation is that DHEA is partially metabolised to testosterone and oestrogen, both of which have effects on mood (Morfin 2002).

Steroid Synthesis Inhibitors

Inhibiting steroid synthesis is another strategy which has been employed to lower raised cortisol levels. The antifungal agent Ketaconazole is also a cortisol synthesis inhibitor (Wolkowitz and Reus 1999). Ketoconazole, administered daily, was shown to reduce both cortisol levels and depressive symptoms within 72 h in case of treatment-resistant depression (Ravaris et al. 1988). Subsequent studies have investigated the use of ketoconazole, as well as metyrapone and aminoglutethimide, as antidepressant therapies, but the results are inconsistent (Murphy 1997, Jahn et al. 2004).

Corticotropin-releasing Hormone (CRH) Antagonists

Over-secretion of CRH, resulting in hypercortisolaemia, may be normalised by blockade of CRH receptors (Nemeroff 1988). Preclinical studies have suggested that CRH antagonists will have clinical utility in conditions related to HPA hyperactivity, particularly anxiety disorders (Holsboer 2003). The results of ongoing clinical investigations are awaited with great interest.

Glucocorticoid Receptor Agonists

Activation of the GR-mediated negative-feedback mechanism that regulates cortisol levels is another strategy for reducing circulating cortisol levels. The synthetic glucocorticoid dexamethasone given at doses of 3–4 mg for 4 days has been shown to have antidepressant effects (Arana et al. 1995). At this dose, dexamethasone does not enter the central nervous system and consequently, central GRs are not activated (Pariante et al. 2004). Glucocorticoids at the level of the pituitary are activated leading to a lowering of endogenous circulating cortisol. The brief course of administration of dexamethasone in these studies avoids the side-effects associated with long-term treatment.

Glucocorticoid Receptor Antagonists

Glucocorticoid antagonists have also been advocated as agents with potential therapeutic properties for mood disorders. This is based on the ability of the GR antagonist to block any detrimental effect of hypercortisolaemia and on the ability of an antagonist to up-regulate its receptor. Administration of a GR antagonist results in an acute antiglucocorticoid effect, while presumably causing a compensatory up-regulation of GR number, leading to enhanced negative feedback on the HPA axis. Initial clinical studies using the GR antagonist RU-486 (mifepristone) have been encouraging, but some clinical efficacy may have been masked by the prolonged administration of the drug (Murphy et al. 1993). Animal studies suggest that GR numbers are increased rapidly (within hours) after the administration of RU-486, which may restore normal feedback, thus "resetting" the HPA axis. Such data suggest that a brief period of treatment with the antagonist may be adequate for restoring normal HPA axis function. Hypercortisolaemia may also cause or exacerbate neurocognitive impairment as well as depressive symptoms. We hypothesized that treatment with the corticosteroid receptor antagonist RU-486 would improve neurocognitive functioning and attenuate depressive symptoms in bipolar depression (Watson et al. 2004, Young et al. 2004). To test this hypothesis, 20 bipolar patients were treated with 600 mg/day of the corticosteroid receptor antagonist mifepristone (RU-486) or placebo for one week in a double-blind crossover design. Over the total 6-week study, neurocognitive and neuroendocrine function were evaluated at baseline, day 21 and day 42. Mood symptoms were evaluated weekly. Nineteen subjects completed the protocol; there were no drop-outs due to adverse events. Following treatment with mifepristone, selective improvement in neurocognitive functioning was observed. Spatial working memory performance was significantly improved compared to placebo (19.8% improvement over placebo). Measures of verbal fluency and spatial recognition memory were also improved after mifepristone. Beneficial effects on mood were found; Hamilton Depression Rating Scale scores were significantly reduced compared to baseline (mean reduction of 5.1 points) as were Montgomery-Åsberg depression rating scale scores (mean reduction of 6.05 points). No significant change occurred after placebo. These data require replication but provide preliminary evidence that GR antagonists may have useful cognitive-enhancing and possibly antidepressant properties in bipolar disorder.

It has also been suggested that hypercortisolaemia may cause or exacerbate both neurocognitive impairment and symptoms in schizophrenia. Again we hypothesized that treatment with a GR antagonist would improve neurocognitive functioning and clinical symptoms in this disorder (Gallagher et al. 2005). Twenty patients with schizophrenia were treated with 600 mg/day of the GR-antagonist mifepristone (RU-486) or placebo for one week in a double-blind, crossover design. Neurocognitive function was evaluated at baseline and 2 weeks after each treatment. Neuroendocrine profiling was performed at these times and also immediately after each treatment. Symptoms were evaluated weekly. Mifepristone administration resulted in a temporary 2–3-fold increase in plasma cortisol levels ($p < 0.0001$). No significant effects were observed on any measure of neurocognitive function, including the primary outcome measures of spatial working memory and declarative memory. Minor changes in symptoms occurred in both arms of the study and were indicative of a general improvement over time, irrespective of treatment. In contrast to our earlier report of positive effects in bipolar disorder, these data suggest that the GR-antagonist mifepristone has no effect on neurocognitive function or symptoms in this group of patients with schizophrenia. An important conclusion from this work is that future studies in schizophrenia should examine patients with demonstrable HPA axis dysfunction (Gallagher et al. 2005).

CONCLUSIONS

There is robust evidence demonstrating abnormalities of the HPA axis in mood disorders, particularly, bipolar disorder. Hypercortisolaemia may be central to the pathogenesis of depressive symptoms and cognitive deficits, which may result from the neurocytotoxic effects of raised cortisol levels. Manipulation of the HPA axis has been shown to have putative therapeutic effects in both preclinical and clinical studies, and recent data suggest

that direct antagonism of GRs may be a future therapeutic strategy in the treatment of mood disorders, particularly, treatment resistant bipolar depression. Large scale clinical trials examining this are now under process.

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