HPA axis function in mood disorders

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Our understanding of the neurobiology of mood disorders is advancing rapidly. Despite the initial enthusiasm for the monoamine theory of depression, it has been unable to explain the complex actions of antidepressant drugs or to provide a comprehensive explanation of the pathophysiology of the manifold biological, cognitive and psychological symptoms of mood disorders. In recent years, attention has turned to models of mood disorders that focus on adaptations to stress. Considerable experimental and clinical evidence supports a role for hypothalamic–pituitary–adrenal (HPA axis) dysfunction in the pathogenesis of major depression and bipolar disorders.

HPA axis anatomy and physiology

The HPA axis is a multifaceted regulatory system that integrates neuronal and endocrine function. It comprises the tissues of the hypothalamus, pituitary and adrenal cortex, and the associated regulatory inputs, releasing factors and hormones (Figure 1). In brief, the neurosecretory cells of the paraventricular nucleus (PVN) of the hypothalamus secrete corticotrophin-releasing hormone (CRH) and arginine vasopressin (AVP) into the microportal circulatory system of the pituitary stalk. These secretagogues induce the release of adrenocorticotrophic 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 adrenal cortex. Cortisol, in some respects the final product of the HPA axis, has a wide range of central and peripheral effects, which include: coordination of circadian events, such as the sleep/wake cycle and food intake; facilitation of our ability to cope with, adapt to and recover from stress; and promotion of learning and memory processes. The effects of cortisol are mediated by at least two types of intracellular, specialized steroid receptor family subtypes: the high-affinity, type I mineralocorticoid receptor (MR), and the low-affinity, type II glucocorticoid receptor (GR). Cortisol readily diffuses through the cellular membrane and binds

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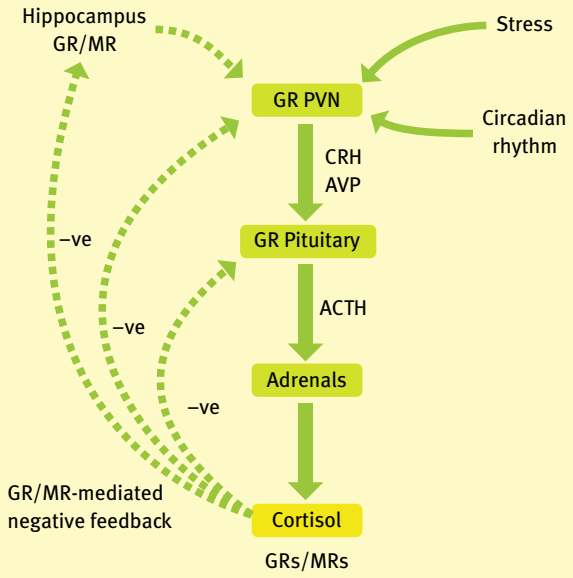
The hypothalamic–pituitary–adrenal (HPA) axis



GR, glucocorticoid receptor; MR, mineralocorticoid receptor; PVN, paraventricular nucleus; AVP, arginine vasopressin; CRH, corticotrophin-releasing hormone; ACTH, adrenocorticotrophic hormone.

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to these receptors, promoting their translocation to the nucleus. Once within the nucleus, the activated receptors interact with other transcription factors or bind to specific DNA, thus promoting the expression of various genes.

The activity of the HPA axis is highly regulated. Secretory cells in the paraventricular nucleus receive neuronal inputs from many regions including the amygdala, the hippocampus and the nuclei of the midbrain. The HPA axis also has an autoregulatory mechanism mediated by cortisol binding to GRs in the HPA axis and hippocampus. This auto-regulation is crucial to the maintenance of the intrinsic homeostasis of the HPA axis. Allostasis refers to the process of maintaining stability through change and it may be that mood disorders are associated with an allostatic change with an alteration of the homeostatic set point that is brought about by genetic vulnerability, early life adversity and/or chronic stress.

HPA axis abnormalities in mood disorders

The CRH hypothesis:[1] the relationship between major depressive disorder and hypercortisolaemia was first described more than 50 years ago. More recent studies show that average cortisol levels are higher in depression and that a quarter of depressed patients can be considered to be hypercortisolaemic. Numerous parameters of HPA axis function have been investigated in order to elucidate the pathophysiology of the HPA axis in depression. CRH overdrive may have a central role: CRH-expressing neurons are increased in the hypothalamus of mood-disorder patients; administration of CRH produces anxiety- and depression-like effects in laboratory animals; and cerebrospinal fluid (CSF) levels of CRH have been shown to be increased in depression. The blunted ACTH response to CRH in people with depression may be explained by homeostatic down-regulation as a result of chronically elevated CRH secretion.

The GR hypothesis: hypersecretion of CRH may be secondary to impaired feedback mechanisms resulting from reduced number or function of GRs, a view supported by the demonstration of GR abnormalities in post-mortem studies of patients with severe mood disorders and from the recent report that mice with an acquired forebrain-specific disruption of GR develop a number of abnormalities that mimic major depressive disorder, including hyperactivity of the HPA axis, impaired negative feedback regulation of the HPA axis and increased depression-like behaviour. Interestingly, a number of these abnormalities are normalized by chronic treatment with the tricyclic antidepressant imipramine.[2] Neuroendocrine tests such as the dexamethasone (dex) suppression test (DST) and its newer variant, the dex/CRH test reliably differentiate patients from controls. These tests measure the ability of the axis to suppress in the face of a synthetic steroid, a process reliant on the functional integrity of GR (see Figure 2).

AVP: elevated AVP concentrations and up-regulated AVP receptors may overcome the suppressant effect of dexamethasone and result in a non-suppressed response even with intact GRs. In animals exposed to chronic stress, the expression of AVP in CRH-secreting neurons of the PVN increases, AVP becomes the predominant regulator of ACTH secretion and the V1b receptor, which mediates the pituitary action of AVP, up-regulates, suggesting that vasopressinergic regulation of the HPA axis is critical for sustaining corticotroph responsiveness in the presence of high circulating glucocorticoid levels during chronic stress. There is increasing evidence that a similar process is seen in mood disorder.

Dehydroepiandrosterone (DHEA), like cortisol, is an adrenal steroid, which is cleaved from pregnenolone. It is part of the synthesis pathway for oestrogen and testosterone and exists in both a free and a sulphated (DHEA-S) form. DHEA is neuroprotective and modulates corticosteroid-induced cell death. An elevated cortisol/DHEA ratio is seen in adults and adolescents with depression, and appears to be an indicator of poor prognosis. Patients with Addison's disease (see below) fail to produce adrenal steroids, including cortisol and DHEA; adding DHEA to existing steroid replacement has been shown to improve self-esteem and to reduce fatigue.

Bipolar affective disorder[3]

The HPA axis has been less well studied in bipolar disorder than in major depressive disorder; however, both manic and depressed bipolar patients appear to have similar HPA axis dysregulation to that described in major depressive disorder. Interestingly, abnormalities are also seen in bipolar patients who are in remission, suggesting that HPA axis dysregulation is a trait abnormality in bipolar disorder.

Chronic fatigue syndrome

Chronic fatigue syndrome (CFS) is associated with low cortisol levels, a flattened cortisol rhythm and adrenal hypoplasia. In CFS, AVP appears to play a relatively greater regulatory role than CRH. Cortisol levels show a return towards normality with successful treatment using cognitive–behavioural therapy. Patients with post-traumatic stress disorder also have low baseline cortisol.