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Hypothalamic-pituitary-adrenal Axis and Bipolar Disorder

C. Daban, PhD[a], E. Vieta, MD, PhD[a],
P. Mackin, MB, BS, PhD, MRCPsych[b,*],
A.H. Young, MB, ChB, MPhil, PhD, FRCPsych[b,c]

[a]*Bipolar Disorders Program, Hospital Clinic, University of Barcelona, Barcelona, Spain*
[b]*University of Newcastle Upon Tyne, Newcastle Upon Tyne, NE1 7RU United Kingdom*
[c]*University of Barcelona, Gran Via Corts Catalanes, 585 08007 Barcelona, Spain*

The role of dysfunctional endocrine systems in the pathogenesis of mood disorders has been the focus of research for many decades. The complexity of endocrine systems and their interaction with neural networks frustrated early attempts to establish links between endocrinology and neuropsychiatry [1]. In the past 40 years, considerable advances have been made in the field of neuroendocrinology, highlighting the etiopathogenic significance of endocrine systems in mood disorders. More recently, the hypothalamic-pituitary-adrenal (HPA) axis has been the focus of research investigating the pathogenesis of bipolar disorder. Novel therapeutic approaches targeting the HPA axis have also evolved. This article focuses specifically on the role of the HPA axis in bipolar disorder.

Glucocorticoids

Glucocorticoids are hormones that are end products of the HPA axis and are central to the stress response. During the acute stress response, glucocorticoids induce short-term adaptive changes such as mobilizing energy reserves. They are also involved in long-term adaptive changes such as shaping and regulating a number of physiologic processes including immune responsiveness and activation of the sympathetic nervous system Overproduction of glucocorticoids is generally linked to significant disruption of

* Corresponding author. University of Newcastle Upon Tyne, Newcastle Upon Tyne, NE1 7RU United Kingdom.
E-mail address: Paul.Mackin@newcastle.ac.uk (P. Mackin).

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cellular functioning, which in turn leads to widespread physiologic dysfunction.

The hypothalamic-pituitary-adrenal axis

The HPA axis, as it name indicates, is a feedback loop including the hypothalamus, pituitary, and adrenal glands, regulatory neural inputs, and a variety of releasing factors and hormones (Fig. 1).

During physical or psychological stress, the HPA axis is activated. The hypothalamus secretes two hormones, corticotropin-releasing hormone (CRH) and arginine vasopressin. CRH acts on the pituitary to stimulate adrenocorticotropic hormone (ACTH) release. ACTH reaches the adrenal cortex through the systemic circulation and interacts with receptors on adrenocortical cells stimulating the production and release of cortisol.

Cortisol is a glucocorticoid stress hormone that has a panoply of central and peripheral effects mediated by two intracellular specialized glucocorticoid receptor subtypes: the high-affinity type I receptor or mineralocorticoid receptor (MR), and the low-affinity type II receptor or glucocorticoid receptor (GR). The relative contribution of the two receptors (GR and MR) in the regulation of HPA activity is not yet clear. MRs have a high affinity

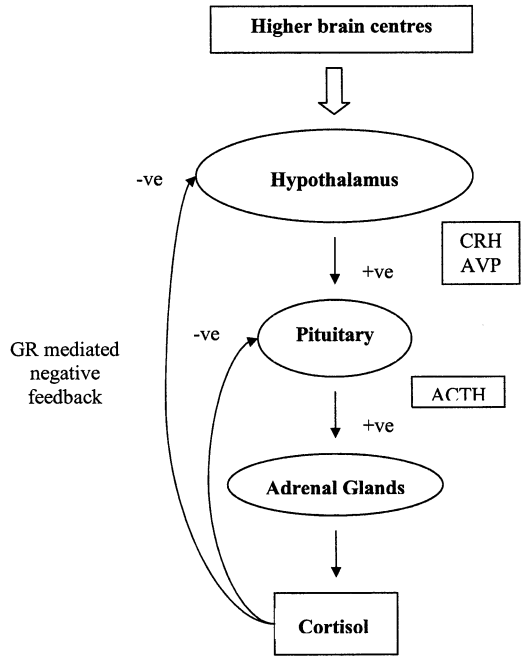

Fig. 1. The HPA axis. ACTH, adrenocorticotropic hormone; AVP, arginine vasopressin; CRH, corticotropin-releasing hormone; GR, glucocorticoid receptor; −ve, negative feedback; +ve, positive feedback.