ABSTRACT

The neuroendocrine system, which plays an integral role in regulation of mood, is dysfunctional in patients with affective disorders. This paper reviews data from anatomic, functional, and clinical studies elucidating neuroendocrine function in patients with bipolar disorder. In an anatomic study using magnetic resonance imaging, patients with bipolar disorder had significantly smaller pituitary volumes compared with healthy controls or patients with unipolar depression. In functional studies, bipolar disorder is characterized by abnormalities of hypothalamic-pituitary-adrenal function as reflected primarily in a blunted response to the dexamethasone suppression test; blunted release of thyrotropin-stimulating hormone in response to administration of exogenous thyrotropin-releasing hormone; and blunted prolactin and growth hormone responses. Some or all of these abnormalities may be attributed at least partly to central serotonergic dysfunction. In clinical studies, a high incidence of menstrual irregularities reflecting dysregulation of the hypothalamic-pituitary-gonadal axis was observed in patients with bipolar disorder. The degree to which these functional, anatomic, and clinical neuroendocrine abnormalities cause or result from mood pathology—or both—is difficult to determine on the basis of available data. It is likely that the primary clinical manifestation of neuroendocrine dysfunction in bipolar disorder is the illness itself. That is, abnormalities in the neuroendocrine system with or without other central or peripheral nervous system pathologies may constitute the pathophysiologic basis of bipolar disorder. Much work remains before the clinical significance of the neuroendocrine abnormalities in bipolar disorder is understood. To improve the quality of care for patients, additional research is needed to define the clinical implications of specific aspects of neuroendocrine dysfunction in bipolar disorder. Research should assess the degree to which specific hormonal responses that are blunted in bipolar disorder contribute to mood symptoms and the impact on mood symptoms of medications that normalize specific aspects of neuroendocrine function. (Adv Stud Med. 2003;3(8A):S726-S732)

Among its myriad functions, the neuroendocrine system plays an important role in mood regulation. The neuroendocrine system is dysfunctional in patients with affective disorders, unipolar major depression, and bipolar disorder, although the degree to which neuroendocrine abnormalities cause or result from mood pathology—or both—is difficult to determine on the basis of available data. The relationship between neuroendocrine dysfunction and affective disorders is best established for unipolar...
major depression but is becoming increasingly well defined for bipolar disorder. Evidence shows that the neuroendocrine correlates of bipolar disorder, although sometimes similar to those of unipolar major depression, are often unique. This paper reviews the major neuroendocrine pathways that regulate mood and discusses data from clinical, imaging, and functional studies elucidating neuroendocrine function in bipolar disorder.

**Main Neuroendocrine Pathways**

The neuroendocrine system comprises cells that release hormones into the circulation in response to a neural stimulus. Most neuroendocrine responses involve hormonal release by the hypothalamus, which secretes hormones in response to neural stimulation from brain areas including the amygdala, hippocampus, and reticular formation, and the anterior pituitary gland, which releases hormones into the bloodstream in response to hypothalamic hormones. The major neuroendocrine pathways involving the hypothalamus and anterior pituitary are presented in Figure 1. The hormones released from the hypothalamus and anterior pituitary regulate mood, motivational states, and arousal; the integrity of hypothalamic-pituitary end-organ neuroendocrine pathways is necessary for adaptive responses to stressors originating from both inside and outside of the body.

The hypothalamus and anterior pituitary each release hormones that act on target organs to influence their function. A common scenario involves hypothal-
amic release of a hormone that modulates the anterior pituitary's release of a hormone, which, in turn affects the function of a target organ, such as the ovary, thyroid, or adrenal cortex (Figure 1):

(1) The hypothalamus releases a hormone into the system of portal vessels located between the hypothalamus and the pituitary. The synthesis and release of hypothalamic hormones is regulated by central neurotransmitters, including serotonin, norepinephrine, and opiates, released from brain areas such as the nucleus raphe, amygdala, and hippocampus.

(2) The hypothalamic hormone stimulates (or inhibits) secretion from the anterior pituitary of a hormone that reaches the bloodstream via the venous circulation. Anterior pituitary hormones, which act upon the gonads, include follicle-stimulating hormone and luteinizing hormone and cause gonads to secrete hormones such as estrogen, progesterone, and testosterone, which mediate the reproductive cycle and sexual function; growth hormone, which acts upon the liver and many other organs and tissues to regulate protein synthesis as well as carbohydrate and lipid metabolism; and adrenocorticotropin hormone, which stimulates the adrenal cortex to secrete cortisol, a hormone integrally involved in adaptations of the body to stress (Figure 2). As shown in Figure 1, thyrotropin-stimulating hormone is typically released from the anterior pituitary in response to hypothalamic thyrotropin-releasing hormone. Thyrotropin-stimulating hormone, in turn, stimulates the thyroid to secrete thyroxine and triiodothyronine.

(3) The pituitary hormone stimulates (or inhibits) one of several endocrine glands (eg, the adrenal gland, the thyroid gland, the gonads) found throughout the body to cause the endocrine gland to secrete (or to cease secretion of) hormones, neurotransmitters, or other proteins. Hormones released by organs downstream of the anterior pituitary interact at diverse systems to mediate a variety of functions. For example, adipose tissue has recently been determined to be a target organ for glucocorticoids, such as cortisol, which has been shown in in vitro studies with human tissue to reduce the basal rate of lipolysis (ie, the chemical decomposition of fat).4,5

In addition to the feed-forward mechanisms described above, negative and positive feedback mechanisms modulate the function of neuroendocrine pathways. For example, negative feedback produced by high blood levels of cortisol can decrease release of the hormones that are responsible for stimulating cortisol secretion (Figure 2). Cortisol released by the adrenal cortex in response to stimulation by anterior pituitary-derived adrenocorticotropin hormone can act directly on the hypothalamus to reduce secretion of corticotropin-releasing hormone—which

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Data from Chaouloff.2
in turn causes reductions in secretion by the anterior pituitary of adrenocorticotropic hormone and a consequent fall in cortisol.¹

Functional and structural studies reveal that the neuroendocrine pathways diagrammed in Figure 1 are dysfunctional in patients with bipolar disorder. Neuroendocrine dysfunction likely contributes to the pathophysiology of bipolar disorder, although the nature of the causal relationship between bipolar disorder and neuroendocrine abnormalities has not been definitively established.

**FUNCTIONAL STUDIES SHOWING NEUROENDOCRINE DYSFUNCTION IN BIPOLAR DISORDER**

**HYPOTHALAMIC-PITUITARY-ADRENAL ABNORMALITIES**

Abnormalities of hypothalamic-pituitary-adrenal function have frequently been reported in patients with bipolar disorder. Patients with bipolar disorder generally have a blunted response to the dexamethasone suppression test.⁶⁻⁸ Administration of the cortisol analogue dexamethasone fails to provoke the decrease in peripheral cortisol levels normally arising as a result of negative feedback to the hypothalamus and anterior pituitary (Figure 2). Hypothalamic-pituitary-adrenal axis abnormalities as reflected in dexamethasone non-suppression are also reliable biologic indicators of unipolar depression.⁹⁻¹¹ However, dexamethasone non-suppression appears to be more marked and to occur more frequently among patients with bipolar disorder—even those in remission—compared with patients who have unipolar depression.⁶⁻⁸

**HYPOTHALAMIC-PITUITARY-THYROID ABNORMALITIES**

Patients with bipolar disorder also have a blunted release of thyrotropin-stimulating hormone in response to administration of exogenous thyrotropin-releasing hormone.⁵⁻¹² Like dexamethasone non-suppression, the blunted response to the thyrotropin-releasing hormone stimulation test is also observed in patients with unipolar major depression but is more common in bipolar disorder.⁶ In one sample, 44% of patients with bipolar disorder compared with 25% of patients with endogenous depression exhibited a blunted response to the thyrotropin-releasing hormone stimulation test.⁶

**HYPOTHALAMIC-PITUITARY-GONADAL ABNORMALITIES**

Few functional studies of hypothalamic-pituitary-gonadal abnormalities in bipolar disorder have been conducted. Abnormalities in hypothalamic-pituitary-gonadal hormones including elevated basal luteinizing hormone; reduced basal follicle-stimulating hormone; and elevated serum testosterone and androstenedione were observed in a sample of 12 women with manic-depressive or psychotic symptoms whose symptoms fluctuated in association with the menstrual cycle.¹³ These findings are consistent with results of research, described below, showing a high incidence of menstrual abnormalities in patients with bipolar disorder.

**OTHER NEUROENDOCRINE ABNORMALITIES**

Blunted prolactin and growth hormone responses have also been observed in patients with bipolar disorder.¹⁴⁻¹⁶ However, not all studies assessing for these abnormalities have found them.

**ROLE OF SEROTONIN**

A dysfunction in the central serotonergic system, among other neurotransmitters, may contribute to neuroendocrine abnormalities observed in bipolar disorder. Serotonin, a neurotransmitter that is released by several of the brain areas that innervate the hypothalamus, influences release of many of the hypothalamic and pituitary hormones shown to be dysregulated in bipolar disorder. For example, serotonergic projections from the nucleus raphe in the brain stem to the hypothalamus modulate the release of prolactin, growth hormone, cortisol, and adrenocorticotropic hormone.¹⁹⁻²² In studies of the effects of administration of serotonin-releasing or serotonin-stimulating agents, such as fenfluramine (a serotonin releaser) and buspirone (a serotonin receptor agonist), on neurohormonal responses, patients with bipolar disorder exhibit abnormal responses compared with those with unipolar major depression or individuals without a mood disorder.²³ Aside from projections from the raphe nucleus, reciprocal interactions between the amygdala and hippocampus and the hypothalamic-pituitary axis are hypothesized to play an important role in neuroendocrine function.²⁴

**DECREASED PITUITARY VOLUME IN PATIENTS WITH BIPOLAR DISORDER**

The anatomical correlates of the functional neuroendocrine abnormalities in patients with bipolar disorder were recently studied with neuroimaging techniques. Pituitary gland volume was measured by
magnetic resonance imaging in 23 patients with bipolar disorder, 13 patients with unipolar major depression, and 34 healthy control subjects. The results demonstrate that patients with bipolar disorder had significantly smaller pituitary volumes compared with healthy controls or patients with unipolar depression, whereas the pituitary volume of patients with unipolar depression did not differ from that of healthy controls. The mean pituitary volumes in patients with bipolar disorder, patients with unipolar major depression, and controls were 0.55 mL, 0.68 mL, and 0.70 mL, respectively. The authors suggested that the reduced pituitary volume may reflect a dysfunctional hypothalamic-pituitary-adrenal axis in bipolar disorder.

**Clinical Manifestations of Neuroendocrine Dysfunction in Bipolar Disorder**

It is likely that the primary clinical manifestation of neuroendocrine dysfunction in bipolar disorder is the illness itself. That is, abnormalities in the neuroendocrine system with or without other central or peripheral nervous system pathologies may constitute the pathophysiologic basis of bipolar disorder. However, most research conducted to date permits only the establishment of an association of neuroendocrine abnormalities with bipolar disorder; whether the association is explained by a causal role of the neuroendocrine abnormalities has yet to be elucidated.

Neuroendocrine dysfunction in bipolar disorder is also clinically manifest in studies of reproductive function in women with bipolar illness. A high incidence of menstrual irregularities, reflecting dysregulation of the hypothalamic-pituitary-gonadal axis, was observed in a study of 22 female outpatients (18 to 45 years of age) with a Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV), diagnosis of bipolar disorder. Regardless of which medication was used to control mood symptoms, women reported high rates of menstrual disturbances. Ten of 10 women taking lithium, 6 of 10 women taking valproate, and 2 of 2 women taking both drugs experienced menstrual dysfunction, most commonly manifested as dysmenorrhea (60%), oligomenorrhea (20%), miscarriages (20%), and infertility (10%) in the lithium group and oligomenorrhea (30%), menorrhagia (30%), and amenorrhea (10%) in the valproate group. These abnormalities preceded the development of bipolar illness and psychotropic medication use in all but 2 cases.

This finding suggests neither bipolar illness nor medication use caused the abnormalities, and is consistent with the possibility that neuroendocrine dysfunction plays a causal role in the development of bipolar illness.

Long menstrual cycles (29–35 days per full cycle) were also found in a study of 17 women with bipolar disorder who recorded mood, menstrual data, and psychiatric medications daily for 3 months. Long menstrual cycles were observed in 59% of patients and occurred regardless of whether women were taking oral contraceptives. Most women (65%) reported significant mood changes across the menstrual cycle.

Other research illustrates a potential causal role of hypothalamic-pituitary-gonadal dysfunction in bipolar illness by showing that women with bipolar disorder are more likely to experience mood episodes during times of reproductive neurohormonal fluctuation. In a study of 50 women with bipolar disorder meeting DSM-IV criteria, 20 of the 30 women with children reported a postpartum mood episode within 1 month of delivery. Furthermore, among 22 perimenopausal or postmenopausal women in the study,
12 reported that menopause exacerbated mood symptoms or increased the frequency of mood episodes. Menopause-coincident worsening of affective symptoms was more likely to occur in women taking hormone replacement therapy compared with women who were not taking hormone replacement therapy.

Other studies show an association between unipolar major depression and polycystic ovary syndrome (PCOS). In one case report, treatment-resistant major depression in a 30-year-old woman with untreated PCOS resolved coincident with initiation of treatment of PCOS with metformin and spironolactone. In a study of 32 women with PCOS, 16 were determined to have depression, and depression was associated with PCOS features, including insulin resistance and higher body mass index. Although no definitive conclusions can be drawn about these circumstantial findings, they are consistent with the possibility that neuroendocrine changes can contribute to and/or exacerbate bipolar illness as well as unipolar depression.

**Influences on Neuroendocrine Function in Bipolar Disorder**

Multiple factors, including genetic influences, use of psychotropic medications, and obesity, appear to contribute to neuroendocrine dysfunction in bipolar disorder. Patients with bipolar disorder, for example, are often overweight. In the 22 18- to 45-year-old female outpatients with a DSM-IV diagnosis of bipolar disorder described above, the majority of the women were obese. Medications, such as valproate, may contribute to neuroendocrine abnormalities in patients with bipolar disorder. Possibly, weight gain associated with use of valproate mediates this effect; however, the evidence regarding the possible impact of weight on neuroendocrine dysfunction in bipolar disorder is inconclusive. In a recent open-label, cross-sectional study, valproate-treated women (who tended to be overweight) compared with lithium-treated women had a higher incidence of menstrual abnormalities as well as biochemical evidence of both hyperandrogenism and adverse metabolic parameters. In another study, clozapine-induced weight gain was not associated with menstrual disturbances among 13 female premenopausal schizophrenic, bipolar, or schizoaffective outpatients who took clozapine with no conventional antipsychotics for at least 6 months.

**Conclusion**

That neuroendocrine dysfunction occurs in bipolar disorder is well established, and recent data reveal that the pituitary gland—the master gland of the neuroendocrine system—is small in patients with bipolar disorder compared with either patients with unipolar major depression or healthy controls. Notwithstanding the progress in documenting neuroendocrine abnormalities in bipolar disorder, much work remains before the clinical significance of the abnormalities is understood. To improve the quality of care for patients, additional research is needed to define the clinical implications of specific aspects of neuroendocrine dysfunction in bipolar disorder. Studies should assess the degree to which specific hormonal responses that are blunted in bipolar disorder contribute to mood symptoms and the impact on mood symptoms of medications that normalize specific aspects of neuroendocrine function.

**REFERENCES**