Neuroendocrinology

David A. Gutman and Charles B. Nemeroff

For publication in: Textbook of Biological Psychiatry
Introduction

The occurrence of psychiatric symptoms such as thought disturbances and depressed mood in patients with primary endocrine disorders is common; in addition a significant percentage of patients with psychiatric disorders demonstrate a consistent pattern of endocrine dysfunction. Our understanding of the neurobiology of depression and other psychiatric disorders has been aided tremendously by a systematic analysis of the neuroendocrine axes and the actions of neurohormones in the pituitary gland and throughout the central nervous system (CNS). The occurrence of prominent psychiatric symptoms in patients with primary endocrine disorders including Cushing’s disease and primary hypothyroidism provided a rationale for exploring the connection between hormones and both affective and cognitive function. In fact, disorders of neuroendocrine dysregulation in subpopulations of psychiatric patients are among the most consistent neurobiological findings in all of biological psychiatry.

Bleuler was among the earliest investigators to systematically investigate the association between hormones, mood and behavior. He first demonstrated that patients with primary endocrine disorders have higher than expected psychiatric morbidity, which often resolved after correcting the primary hormonal abnormality. Work over the past 25 years has clearly demonstrated that the CNS tightly regulates endocrine gland secretion, and further, that neurons are directly influenced by hormones.

The concept that neurons are capable of synthesizing and releasing hormones initially sparked a controversy in endocrinology and neuroscience when first introduced in the 1950s; namely, is it possible that certain neurons subserve endocrine functions? Two major findings fueled this debate. First, neurohistologists working with mammalian, as well as lower vertebrate and invertebrate species made several key observations. Led by a husband and wife team, the Scharrers, early researchers documented, by both light and electron microscopy, the presence of neurons that had all the characteristics of previously studied endocrine cells. These neurons
stained positive with the Gomori stain, which was believed to be specific to endocrine tissues, and further they contained granules or vesicles containing known endocrine substances. The second key area of research centered around the brain’s control of the secretion of pituitary trophic hormones. These trophic hormones were long known to control the secretion of peripheral target endocrine hormones, e.g. thyroid hormone, gonadal steroids, adrenal steroids, etc. These interactions were particularly compelling because of the earlier identification of an extremely important neuroendocrine system, namely the magnocellular cells of the paraventricular nucleus (PVN) of the hypothalamus, which synthesize vasopressin and oxytocin. These two nonapeptides were shown to be transported from PVN cell bodies down the axon to nerve terminals located in the posterior pituitary (neurohypophysis), and released in response to appropriate physiologic stimuli. Vasopressin, also known as antidiuretic hormone, is a critical regulator of fluid balance, and oxytocin regulates the milk-letdown reflex during breast-feeding.

The ability of neurons to function as true endocrine tissues has now been clearly established. Neural tissue can both synthesize and release substances, known as (neuro)hormones, that are released directly into the circulatory system, and have effects at sites far removed from the brain. One important example noted above is the action of vasopressin on the kidney. Although early in the development of the emerging discipline of neuroendocrinology it seemed important to document the ability of neurons to function as neuroendocrine cells, particularly those in the CNS, classification of specific chemical messengers as either endocrine versus neuronal versus neuroendocrine soon lost its heuristic value. It is now recognized that the same substance can act as a neurotransmitter and a hormone depending on its location within the CNS and periphery. A good example of this is epinephrine (adrenaline), which functions as a classical hormone in the adrenal medulla but as a conventional neurotransmitter in the mammalian CNS. Similarly it has been demonstrated that corticotropin-releasing factor (CRF) functions as a true peptide hormone in its role as a hypothalamic hypophysiotropic factor in promoting the release of adrenocorticotropin (ACTH) from the anterior pituitary, yet also
functions as a ‘conventional’ neurotransmitter in cortical and limbic areas. Thus the field now seeks to elucidate the role of particular chemical messengers in particular brain regions or endocrine axes.

The traditional endocrine and hormonal functions for several peptides discussed above have been well established, but many of these substances may also possess paracrine roles as well, i.e. secretion of these substances from one cell acts upon proximal cells. These paracrine interactions remain largely unexplored. The importance of these paracrine effects has been well demonstrated in the gastrointestinal tract where several peptides that act as hormones or neurotransmitter substances at other sites, including the CNS, have influences on local cellular function. Examples include vasoactive intestinal peptide, cholecystokinin and somatostatin.

**Overview of components and control mechanisms**

The hypothalamic-pituitary-end-organ axes generally are organized in an hierarchical fashion [Figure 1]. A large percentage of the neuroendocrine abnormalities in patients with psychiatric disorders are related to disturbances of target hormone feedback. A generic description is briefly outlined here. More comprehensive reviews on this topic are available (Levine 2000). In general, the hypothalamus contains neurons that synthesize and release factors that either promote or inhibit the release of anterior pituitary hormones, so-called release or release-inhibiting factors. These peptide hormones, as summarized in Table 1, are synthesized by transcription of the DNA sequence for the peptide prohormone. After translation in the endoplasmic reticulum, these prohormones are processed during axonal transport and packaged into vesicles destined for the nerve terminals. These now biologically active peptides are then released following appropriate physiological stimuli from the median eminence, the most ventral portion of the hypothalamus, and secreted into the primary plexus of the hypothalamo-hypophyseal portal vessels [Figure 2]. These peptides are transported in high concentration to the sinusoids of the anterior pituitary (adenohypophysis) where they bind to specific membrane receptors on their targets, the pituitary trophic-hormone producing cells. Activation of these
receptors promotes or inhibits the release of pituitary trophic hormones into the systemic circulation. The increase or decrease in the plasma concentrations of these pituitary trophic hormones produces a corresponding increase or decrease in their respective end-organ hormone secretion. The hormones of the end-organ axes, such as gonadal and adrenal steroids, feedback on both pituitary and hypothalamic cells to prevent further release, often referred to as “long-loop” negative feedback. Short-loop negative feedback circuits have also been identified in which pituitary hormones directly feedback on hypothalamic neurons to prevent further release of hypothalamic releasing factors.

Disturbances in the feedback regulation of the hypothalamic-pituitary-end organ axes are of considerable interest in psychiatry. The common occurrence of psychiatric symptoms in many primary endocrine disorders, such as hypothyroidism and Cushing’s syndrome, served as an impetus for investigation into the regulation of neuroendocrine systems in psychiatric disease states such as depression, schizophrenia and bipolar disorder. Thus, a large part of psychoneuroendocrinology has focused on identifying changes in basal levels of pituitary and end-organ hormones in patients with psychiatric disorders. For many of the axes discussed below, tests have been developed to assess the functional status of these feedback systems. In these so-called stimulation tests, hypothalamic and/or pituitary derived factors or their synthetic analogs are exogenously administered, and the hormonal response to this “challenge” is assessed. For example, in the standard corticotropin-releasing-factor (CRF) stimulation test, a $1 \mu g/kg$ dose of CRF is administered intravenously, and the adrenocorticotropin (ACTH) and cortisol response is measured over a period of 2 or 3 hours. This test is a very sensitive measure of hypothalamic-pituitary-adrenal (HPA) axis activity, and changes in the magnitude and/or duration of the response relative to normal control values are characteristic of one or another type of dysregulation of the HPA axis.

**Limitations of stimulation tests:**

Such studies as outlined above provide valuable information, but a brief discussion of some
inherent limitations is warranted before a detailed review of the literature is presented. Normal circadian rhythms and the pulsatile release of many of the hypothalamic-pituitary-end-organ axes components are often not taken into account when these stimulation tests are designed. Further, differences in assay sensitivity, gender differences, inclusion criteria for patients used in studies, and severity of symptoms in the target patient population studied can potentially generate confounding or at least quite variable results. Nevertheless, a great deal about the neurobiology of psychiatric disorders has been discovered through such experiments.

Although less commonly used today, an often-utilized strategy in the 1970s and 1980s was based on the perception that the neuroendocrine axes served as a “window” into CNS function. Peripheral neuroendocrine markers were often used to indirectly assess CNS function because the brain was relatively inaccessible for study, with the exception of cerebrospinal fluid (CSF) and postmortem studies. With the emergence of the monoamine theories of mood disorders and schizophrenia, many investigators attempted to draw conclusions about the activity of noradrenergic, serotonergic, and dopaminergic circuits in patients with various psychiatric disorders by measuring the basal and stimulated secretion of pituitary and end-organ hormones in plasma. Although these approaches have severe limitations, they have been useful in elucidating the pathophysiology of mood and anxiety disorders, and to a lesser extent, schizophrenia.

In summary neuroendocrinology broadly encompasses the following:

♦ The neural regulation of the secretion of peripheral, target-organ hormones, pituitary trophic hormones, and hypothalamic-hypophysiotropic hormones.

♦ The effects of each of the hormones that comprise the various endocrine axes on the CNS. This includes, for example, the effects of synthetic glucocorticoids on memory processes.
Study of alterations in the activity of the various endocrine axes in major psychiatric disorders, and conversely the behavioral consequences of endocrinopathies.

**HPA AXIS**

Dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis has frequently been reported in patients with psychiatric disorders and is among the most robustly demonstrated neurobiological changes among psychiatric patients. The primary regulator of this axis is corticotropin-releasing factor (CRF), also known as corticotropin-releasing hormone (CRH), a 41 amino acid containing peptide synthesized in parvocellular neurons located primarily in the paraventricular nucleus (PVN) of the hypothalamus. CRF containing cells in the PVN receive input from a variety of brain nuclei including the amygdala, bed nucleus of the stria terminalis, and other brain stem nuclei (Hauger 2000). These CRF-containing neurons in turn project to nerve terminals in the median eminence (Swanson, et al. 1983), and CRF is released into the hypophyseal-portal system where it activates CRF receptors on corticotrophs in the anterior pituitary to promote the synthesis of pro-opiomelanocortin (POMC) and the release of its post-translational products, adrenocorticotropin hormone (ACTH), β-endorphin and others [Figure 4]. Arginine-vasopressin (AVP) also promotes the release of ACTH from the anterior pituitary, though CRF is necessary for AVP to exert this effect. Chronic stress can also upregulate AVP expression in the PVN, where under these conditions it may be coexpressed in CRF containing neurons (Hauger 2000). ACTH released from the anterior pituitary in turn stimulates the production and release of cortisol, the primary glucocorticoid in humans, from the adrenal cortex [Figure 4].

The concentration of circulating glucocorticoids is modulated via long-loop negative feedback. An increase in circulating glucocorticoids inhibits hypothalamic CRF gene expression and ACTH secretion from the pituitary. This in turn prevents further glucocorticoid release. The HPA axis also undergoes a circadian rhythmicity in humans where serum cortisol levels peaks before immediately before awakening and reaches is nadir in the evening.
The biologic effects of glucocorticoids are regulated by two cytosolic receptors: the glucocorticoid receptor (GR) or the mineralocorticoid receptor (MR), which both belong to a large superfamily of steroid hormone receptors. Because the mineralocorticoid receptor has a much higher affinity for glucocorticoids than does the glucocorticoid receptor, MR binding sites may be saturated with glucocorticoids under physiological conditions. In contrast, the occupancy of GR binding sites change in response to changes in circulating glucocorticoid levels. The main genomic affects of glucocorticoids are mediated by GR binding to glucocorticoid response elements (GREs) in the promoter regions of specific genes. GRs may also inhibit or enhance the actions of other transcription factors such as AP-1, NF-κB, and CREB, by direct protein-protein interactions (Nestler 2001).

**The biology of Corticotropin-Releasing Factor (CRF)**

Although Saffron and Schally identified a crude extract which promoted the release of ACTH from the pituitary in 1955 (Saffran 1955), it was not until 1981 that CRF was isolated and chemically characterized. Working with extracts derived from 500,000 sheep hypothalami, Vale and colleagues at the Salk institute isolated, synthesized, and elucidated the structure of CRF (Vale, et al. 1981). This discovery led to the availability of synthetic CRF, which allowed a comprehensive assessment of the HPA axis to proceed. It is now clear CRF coordinates the endocrine, immune, autonomic and behavioral responses of mammals to stress. The regulation of CRF transcription is under control of a number of promoter elements. A cyclic AMP response element (CRE) is located in the 5’ flanking region of the human CRF gene, consistent with evidence that protein kinase A (PKA) activity regulates CFR gene expression. A glucocorticoid response element (GRE) is also located in the 5’ flanking region of the CRF gene, which is apparently the substrate where glucocorticoids act to inhibit CRF gene transcription (Hauger 2000).

Two CRF receptor subtypes, CRF₁ and CRF₂, with distinct anatomical localization and receptor pharmacology have been identified (Chalmers et al., 1996; Lovenberg et al., 1995;
Grigoriadis et al., 1996; Chang et al., 1993; Chen et al., 1993) in rats and humans. Both receptors are G-protein coupled receptors and are positively coupled to adenylyl cyclase via Gs. In addition, a putative CRF3 receptor has recently been identified in catfish (Arai 2001). The CRF1 receptor is predominant expressed in the pituitary, cerebellum, and neocortex in the rat (Primus, et al. 1997). A growing body of evidence from animal studies has shown that the CRF1 receptors may specifically mediate some of the anxiogenic-like behaviors observed after administration of CRF (Heinrichs, et al. 1997). The CRF2 receptor family is composed of two primary splice variants, CRF2A and CRF2B. The CRF2A receptor is more prevalent in subcortical regions, such as the ventromedial hypothalamus, lateral septum, and dorsal raphe nucleus, whereas CRF2B is more abundantly expressed in the periphery. A structurally related member of the CRF peptide family, urocortin, has also been identified in the mammalian brain. The endogenous neuropeptide urocortin has equally high affinity for both the CRF1 and CRF2 receptor subtypes (Vaughan, et al. 1995), whereas CRF displays a higher affinity at CRF1 receptors than it does at CRF2 receptors. The newly discovered urocortin II shows high selectivity for CRF2A receptors, though its anatomic localization does not correlate precisely with the distribution of the CRF2A receptor (Reyes 2001). With the discovery of a new ligand and a putative third receptor in the CRF family, much of the pharmacology and functional interactions between these ligands and receptors remains to be discovered.

**The effects of changes in glucocorticoid availability**

A deficiency of endogenous glucocorticoids produces overt clinical symptoms including weakness, fatigue, hypoglycemia, hyponatremia, hyperkalemia, fever, diarrhea, nausea and shock. This condition, also known as Addison’s disease, is most often caused by autoimmune destruction of the adrenal cortex. However it is important to note that abrupt withdrawal from exogenous corticosteroids or ACTH can also induce an Addisonian crisis, because the exogenous administration of these compounds suppresses endogenous HPA axis activity. This is why
tapering of the dose of adrenal steroids is essential before discontinuation. Glucocorticoid
deficiency may also produce mild to severe depression, or less commonly, psychosis.

Excessive glucocorticoid secretion leads to a number of characteristic symptoms
including moon facies, plaethoric appearance, truncal obesity, purple abdominal striae,
hypertension, protein depletion and signs of glucose intolerance or overt diabetes mellitus.
Psychiatric symptoms, specifically depression and anxiety, are also associated with
glucocorticoid excess. Cognitive impairment, especially decrements in memory function and
attention are also common, and may be due to the direct effects of corticosteroids on the
hippocampal formation (Sadock 2000).

The most common form of non-iatrogenic hypercortisolism is due to an ACTH secreting
pituitary adenoma, also known as Cushing’s disease. Harvey Cushing for whom the disease is
named, first documented the occurrences of psychiatric symptoms, particularly depression, in
1913 in his first description of the illness (1932). Other causes of hypercortisolism are often
referred to as Cushing’s syndrome. Since Dr. Cushing’s initial description, the occurrence of
depression in Cushing’s syndrome has been well documented (Spillane, 1951; Zeiger et al.,
1993).

**HPA axis abnormalities in depression**

The occurrence of depression and other psychiatric symptoms in both Cushing’s and
Addison’s disease served as an impetus for researchers to scrutinize HPA axis abnormalities in
depression and other psychiatric disorders. Most investigators would agree that one of the most
venerable findings in all of psychiatry is the hyperactivity of the HPA axis observed in a
significant subset of patients with major depression [Table 2]. Based on the work of research
groups led by Board, Bunney and Hamburg, as well as by Carroll, Sachar, Stokes and Besser,
literally thousands of studies have been conducted in this area.
The earliest studies in this field demonstrated elevated plasma cortisol concentrations in depressed patients (Carpenter and Bunney, 1971; Gibbons, 1962). Other markers of hypercortisolism that have been reliably demonstrated in depressed patients include elevated 24-hour urinary-free cortisol concentrations and increased levels of cortisol metabolites in urine (Sachar, et al. 1970). One commonly used test to measure HPA axis function is the dexamethasone suppression test (DST). In this test, 1 mg of dexamethasone is given at 11 P.M., blood is then drawn at 8 A.M. the following morning and cortisol levels measured. Dexamethasone is a synthetic steroid similar to cortisol, and suppresses ACTH secretion, and subsequently cortisol release, in healthy volunteers. Nonsuppression of plasma glucocorticoid levels following the administration of dexamethasone is common in depression. The rate of cortisol nonsuppression after dexamethasone administration generally correlates with the severity of depression (Evans and Nemeroff 1987); in fact nearly all patients with major depression with psychotic features exhibit DST non-suppression (Arana, et al. 1985, Evans and Nemeroff 1983). Since Carroll’s initial report (Carroll, et al. 1968, Carroll, et al. 1968) and subsequent claims for diagnostic utility (Carroll 1982), the dexamethasone suppression test has generated considerable controversy (Arana and Mossman 1988) as to its diagnostic utility. Diagnostic issues notwithstanding, the overwhelming conclusion from the myriad of studies demonstrates that a sizeable percentage of depressed patients exhibit HPA axis hyperactivity. Further, the magnitude of the HPA axis hyperactivity also appears to correlate with the severity of the depression.

Another method used to assess HPA axis activity is the CRF stimulation test, which became available shortly after the synthesis of CRF. In this paradigm, CRF is administered intravenously (usually a 1 μg/kg dose), and the ensuing ACTH and cortisol response is measured at 30 minute intervals over a 2-3 hour period (Hermus, et al. 1984). Numerous studies have now demonstrated a blunted ACTH and β-endorphin response to exogenously administered ovine
CRF (oCRF) or human CRF (hCRF) in depressed patients when compared to non-depressed subjects, though the cortisol response in depressed patients and non-depressed control subjects did not consistently differ (Amsterdam et al., 1988; Gold et al., 1984; Holsboer et al., 1984a; Kathol et al., 1989; Young et al., 1990). The attenuated ACTH response to CRF is presumably due to either chronic hypersecretion of CRF from nerve terminals in the median eminence, which results in down-regulation of CRF receptors in the anterior pituitary, and/or to the chronic hypercortisolemia. This receptor down-regulation results in a reduced responsivity of the anterior pituitary to CRF, as has been demonstrated in laboratory animals (Aguilera, et al. 1986, Holmes, et al. 1987, Wynn, et al. 1983, Wynn, et al. 1984, Wynn, et al. 1988). Following recovery from depression, the documented disturbances in the HPA axis generally remit.

A combined dexamethasone/CRF test has also been developed. In this test, 1.5 mg of dexamethasone is administered orally at night (23:00 h), and subjects receive an i.v. bolus of 100 μg of human CRF at 15:00 h the following day. Patients with HPA axis dysfunction, which is frequently encountered in depression, display a paradoxically increased release of ACTH and cortisol relative to controls. These abnormalities disappear following remission of depression, and normalization of HPA axis function seems to precede full clinical remission (Holsboer 2000, Heuser, et al. 1994). The combined DEX/CRF test appears to have much higher sensitivity for detecting subtle alterations in HPA axis function; and approximately 80% of patients with major depression exhibit an abnormal response to the DEX/CRF test. In contrast, only approximately 44% of patients with major depression demonstrate an abnormal response when the dexamethasone suppression test is administered alone (Holsboer 2000, Heuser, et al. 1994). Furthermore, otherwise healthy individuals with first degree relatives with an affective illness, which greatly increases their own risk for psychiatric disorders, demonstrated cortisol and ACTH responses to the DEX/CRF test which were higher than a control group, but less than patients currently suffering from major depression. This suggests that a genetically transmittable defect
in corticosteroid receptor function may render these individuals more susceptible to developing affective disorders (Holsboer, et al. 1995).

Structural changes in the components of the HPA axis have also been documented in depressed patients. Perhaps in part due to the trophic effects of CRF, pituitary gland enlargement has been documented in depressed patients as measured by MRI (Krishnan, et al. 1991). Enlargement of the adrenal glands, presumably due to ACTH hypersecretion, has repeatedly been demonstrated in both depressed patients post mortem (Nemeroff, et al. 1992, Amsterdam, et al. 1987) and in suicide victims (Dorovini-Zis and Zis 1987). It is reasonable to hypothesize that the normal plasma cortisol response to CRF seen in depressed patients is due to adrenocortical hypertrophy, in light of the blunted ACTH and \( \beta \)-endorphin responses to CRF seen in these same patients (Gold, et al. 1984, Kathol, et al. 1989, Amsterdam, et al. 1987, Gold, et al. 1986, Holsboer, et al. 1984). Presumably, although the ACTH response to CRF is decreased in depressed patients, the enlarged adrenal cortex may secrete relatively greater quantities of cortisol when compared to control subjects in response to a given amount of ACTH. There are reports of increased cortisol responses to pharmacological doses of ACTH that support this hypothesis (Amsterdam, et al. 1983, Jaeckle, et al. 1987, Kalin, et al. 1982, Krishnan, et al. 1990, Linkowski, et al. 1985), though discordant findings have also been reported (Heim, et al. 2001).

The studies thus far discussed focused primarily on dysregulations of the HPA axis, but as mentioned earlier, CRF controls not only the neuroendocrine, but also the autonomic, immune, and behavioral responses to stress in mammals. Moreover, results from both clinical studies, and a rich body of literature conducted primarily in rodents and lower primates have indicated the importance of CRF at extrahypothalamic sites. In rodents, primates, and humans, CRF and its receptors have been heterogeneously localized in a variety of regions including the amygdala, thalamus, hippocampus, and prefrontal cortex, among others (Suda et al., 1984;
Sanchez et al., 1999; Van Pett, 2000; Charlton et al., 1987). These brain regions are important in regulating many aspects of the mammalian stress response, and in regulating affect. The presence of CRF receptors in both the dorsal raphe (DR) and locus coeruleus (LC), the major serotonergic and noradrenergic containing regions in the brain, respectively, also deserves comment. Because most available antidepressants including the tricyclics and selective serotonin reuptake inhibitors (SSRI) are believed to work via modulation of noradrenergic and/or serotonergic systems, the neuroanatomical proximity of CRF and monoaminergic systems suggests a possible site of interaction between CRF systems and antidepressants.

Involvement of extrahypothalamic CRF systems in the pathophysiology of depression is suggested by numerous studies showing elevated CRF concentration in the cerebrospinal fluid (CSF) of patients suffering from depression (Banki et al., 1987; Arato et al., 1989; France et al., 1988; Nemeroff, 1988; Risch et al., 1992), though discrepant results have been reported (Roy, et al. 1987). Elevated CSF CRF levels have also been detected in depressed people who committed suicide (Arato, et al. 1989). A reduction in concentrations of CRF in CSF has been reported in healthy volunteers treated with the tricyclic antidepressant desipramine (Veith, et al. 1993) providing further evidence of a possible interconnection between antidepressants, noradrenergic neurons and CRF systems. Similar effects have been reported with fluoxetine and ECT in depressed patients (Nemeroff, et al. 1991).

Depressed patients who are nonsuppressors on the dexamethasone suppression test (DST) also have significantly higher levels of CSF CRF than depressed patients with normal DST results. Presumably the elevated CSF concentrations of CRF are due to CNS CRF hypersecretion (Post, et al. 1982), which may be acting at sites throughout the brain and contribute to many of the behaviors characteristic of depression. A reduction in the density of CRF receptors in the frontal cortex has also been reported in the frontal cortex of suicide victims.
Presumably hypersecretion of CRF results in a downregulation of CRF receptors in the frontal cortex.

While the exact mechanism contributing to CRF hyperactivity remains obscure, studies from our group and others have documented long-term persistent increases in HPA axis activity and extrahypothalamic CRF neuronal activity after exposure to early untoward life events—for example, neglect and child abuse respectively in both laboratory animals (rat and non-human primates) and patients (Holsboer, et al. 1995, Nemeroff 1999, Holsboer, et al. 1987, Coplan, et al. 1996). Early life stress apparently permanently sensitizes the HPA axis and leads to a greater risk of developing depression later in life. In one schema, early sensitization of CRF systems results in heightened responses to stress later in life. To measure HPA responsivity to stress, the Trier Social Stress Test (TSST) was developed. This laboratory paradigm involves a simulated 10 minute public speech and a mental arithmetic task. The TSST has been validated as a potent activator of the HPA axis in humans (Kirschbaum, et al. 1993). Recently, our group has reported increased plasma adrenocorticotropic hormone (ACTH) and cortisol concentrations, presumably due to hypersecretion of CRF, after exposure to the TSST in women (both depressed and non-depressed) who were exposed to severe physical and emotional trauma as children (Heim, et al. 2000). These data provide evidence for functional hyperactivity of CRF systems that may be influenced by early adverse life events.

Space constraints do not permit an extensive review of the preclinical literature, however several additional points are worth interjecting. Numerous studies have documented that when CRF is directly injected into the CNS of laboratory animals it produces effects reminiscent of the cardinal symptoms of depression including decreased libido, reduced appetite and weight loss, sleep disturbances, and neophobia. Indeed, newly developed CRF₁ receptor antagonists represent a novel putative class of antidepressants. Such compounds show activity in nearly every preclinical screen for antidepressants and anxiolytics currently employed. Recently, a
small open label study examining the effectiveness of R121919, a CRF₁ receptor antagonist, in major depression was completed (Zobel, et al. 2000). Severity measures of both anxiety and depression were reduced in the depressed patients. Although this drug is no longer in clinical development, it is clear that CRF₁ antagonists may represent a new class of psychotherapeutic agents to treat anxiety and affective disorders.

**HPA Axis alterations in other psychiatric disorders**

Patients with other psychiatric disorders also exhibit HPA axis dysregulation, although the vast majority of the data is concerned with HPA axis alterations in depression. When depression is comorbid with a variety of other disorders such as multiple sclerosis, Alzheimer’s disease, multi-infarct dementia, Huntington’s disease, and others, both CRF hypersecretion and HPA axis hyperactivity are common. In contrast, HPA axis dysfunction has rarely been reported in schizophrenia. Consistent with the role of CRF in both depression-like and anxiety-like behaviors in preclinical animal studies, increased CSF CRF concentrations have been reported in post-traumatic stress disorder (PTSD) (Bremner, et al. 1997). A recent elegant study using indwelling cannula in the lumbar space, allowing repeated sampling of CSF several hours after the initial, and presumably stressful, lumbar puncture, demonstrated elevated CSF CRF levels in PTSD combat veterans (Baker, et al. 1999). In contrast, low serum cortisol and urinary free cortisol levels have been repeatedly, yet unexpectedly, been detected in PTSD. One possible mechanism that has been proposed by Yehuda and colleagues suggests heightened negative feedback within the HPA axis in chronic PTSD patients (Yehuda, et al. 1996). Finally, CRF neuronal degeneration is now well known to occur in the cerebral cortex of patients with Alzheimer’s disease with compensatory upregulation of CRF receptor numbers, and this effect precedes the better-studied cholinergic neuronal involvement (Bissette 1998).
OVERVIEW OF HPT AXIS COMPONENTS AND FUNCTION

The thyroid gland, composed of two central lobes connected by an isthmus, synthesizes the hormones thyroxine (T₄) and triiodothyronine (T₃). These iodine-containing compounds serve as global regulators of the body’s metabolic rate, and are also critical for brain development. The release and synthesis of these hormones is ultimately controlled by signals from the central nervous system.

The hypothalamic-pituitary-thyroid (HPT) axis is composed of three main parts, as its name suggests. The tripeptide (pGlu-His-Pro-NH₂) thyrotropin-releasing hormone (TRH) is synthesized predominantly in the paraventricular nucleus in the hypothalamus and stored in nerve terminals in the median eminence where it is released into the vessels of the hypothalamo-hypophyseal portal system [Figure 3]. TRH is then transported to the sinusoids in the anterior pituitary where it binds to thyrotropes and releases the peptide thyroid stimulating hormone (TSH) into the systemic circulation. TRH is heterogeneously distributed in the brain which strongly suggests a role for this peptide as a neurotransmitter, as well as a releasing hormone. Thus TRH itself can produce direct effects on the CNS independent of its actions on pituitary thyrotrophs. The HPT axis exhibits an ultradian rhythm where TSH secretion, and consequently T₃ and T₄ levels, rise in the afternoon and evening, peak sometime after midnight and decline throughout the day (Veldhuis 2000).

TSH is a 28 kDA glycoprotein composed of two noncovalently linked protein chains, TSH-α and TSH-β. The α subunit is identical to the α subunit contained in other pituitary hormones including follicle-stimulating hormone, luteinizing hormone and human chorionic gonadotropin. Upon release from the pituitary, TSH circulates through the blood and exerts its effects via binding to the TSH receptor in the thyroid, a G-protein coupled receptor that stimulates the activation of adenylate cyclase.

Upon stimulation by TSH, the thyroid gland releases the iodinated amino acids T₃ and T₄. Of the two hormones, T₃ is much more physiologically active. Although debate still exists in the
literature, T₄ is often considered a prohormone that becomes active after monodeiodination in peripheral tissues. Thyroid hormones influence gene expression via two major thyroid hormone receptors, TRα-1 and TRβ-1, which in turn bind to a specific DNA element, known as thyroid response elements (TREs) located in the promoter regions of a diverse number of genes. These receptors can function as homodimers, or bind with other nuclear factors such as thyroid hormone receptor auxiliary proteins, as heterodimers to modulate the transcription of target genes (Nestler 2001). T₃ directly regulates the HPT axis by inhibiting TSH release and gene expression in the pituitary, and TRH gene expression in the hypothalamus (DeVito 2000). This is characteristic of the end-product negative feedback seen in the hypothalamic-pituitary-end organ axes. In the circulation, these hormones are primarily bound to a carrier-protein, thyroglobulin, though it is the unbound form of these hormones that are metabolically active. Thyroid hormones have numerous effects on metabolism and increase heat production, oxygen consumption, lipid metabolism, intestinal absorption of carbohydrates, cardiac function, and the activity of the Na⁺-K⁺ ATPase. All of these functions are consistent with increasing metabolic rate.

DISORDERS OF THE HPT AXIS

Disorders of the HPT axis lead to numerous psychiatric manifestations ranging from mild depression to overt psychosis. Numerous conditions can lead to hypothyroid states, also known as myxedema, including CNS causes of decreased TSH or TRH secretion, severe iodine deficiency, thyroid surgery, drugs, or autoimmune disorders. The most common cause of hypothyroidism is Hashimoto’s thyroiditis, which is due to autoimmune destruction of thyroid tissue. Regardless of the etiology, hypothyroidism leads to a number of clinical manifestations including slowed mentation, forgetfulness, decreased hearing, cold intolerance, and ataxia. Decreased energy, weight gain, depression, cognitive impairment or overt psychosis (“myxedemia madness”) may also result. Due to the overlapping symptoms with clinical
depression, thyroid hormone deficiency must be ruled out when evaluating patients with depression.

Hypothyroidism is frequently subclassified into the following 4 groups:

♦ Grade 1 hypothyroidism is classic primary hypothyroidism (increased TSH), decreased peripheral thyroid hormone (T₃ and T₄) concentrations, and an increased TSH response to TRH

♦ Grade 2 hypothyroidism is characterized by normal, basal thyroid hormone concentrations, but an increase in basal TSH concentrations and an exaggerated TSH response to TRH.

♦ Grade 3 hypothyroidism can only be detected by a TRH-stimulation test; basal thyroid hormone and TSH concentrations are normal, but the TSH response to TRH is exaggerated

♦ Grade 4 hypothyroidism is defined as normal findings on the three thyroid axis function tests noted above, but the patients have the abnormal presence of anti-thyroid antibodies.

Without treatment, most patients will progress from grade 4 to grade 1 hypothyroidism.

The first treatments for hypothyroidism became available in the 1890s; prior to that many patients with this condition spent their final days in mental hospitals. One of the earliest descriptions of the effects of treatment with thyroid extracts was reported by Shaw and Stansfield in 1892. These physicians studied the effects of thyroid extracts in a patient suffering from severe thyroid deficiency secondary to trauma to her thyroid gland. Within 10 weeks time following treatment with a sheep thyroid extract, the mental signs associated with myxedema disappeared in this patient and she was discharged (Shaw 1892). Stansfield followed this patient’s progress for several months, and five months after the last injection of thyroid extract, symptoms of hypothyroidism began to recur. Following ingestion of additional thyroid extracts, the symptoms were once again ameliorated. These results clearly demonstrated the profound psychiatric effects of thyroid deficiency, and provided an early demonstration that treatment of primary endocrine abnormalities can resolve the psychiatric manifestations of the disease (DeVito 2000).
The first prospective study that scrutinized psychiatric comorbidity in patients with hypothyroidism was carried out by Whybrow and colleagues (1969). In this seminal study, 5 of the 7 patients manifested symptoms of depression at the time of the evaluation, while 6 of the 7 displayed cognitive impairment. Interestingly, of the 4 patients with depression who were followed, thyroid replacement alone ameliorated the symptoms of depression in all of the patients. In a later study, Jain et al (1972) studied 30 hypothyroid patients; in this study, 13 of 30 (43%) of the patients had a clinical depression, 10 (30%) had symptoms of anxiety, and 8 (27%) were confused. Furthermore, these symptoms were improved or resolved following treatment of the thyroid condition alone. These early studies clearly demonstrated that hypothyroid states have pronounced psychiatric manifestations, predominantly depression and dementia, which can be reversed following thyroid hormone replacement. Later studies have demonstrated varying degrees of cognitive disturbance in up to 48% of psychiatrically ill hypothyroid cases (Boswell 2001), and approximately 50% of unselected hypothyroid patients have symptoms characteristic of depression (Boswell 2001). Anxiety symptoms are also common, occurring in up to 30% of unselected patients. Mania and hypomanic states have been rarely reported in hypothyroid patients. Finally, although psychosis is the most common reported symptom in the case literature on hypothyroidism (52.9%), it only accounts for approximately 5% of the psychiatric morbidity in an unselected sample (Boswell 2001), presumably due to reporting bias.

**HPT Axis dysfunction in patients with primary psychiatric disorders**

Excluding patients with primary endocrine disorders, considerable data has revealed an elevated rate of HPT axis dysfunction, predominantly hypothyroidism, in patients with major depression [Table 3]. More than 25 years ago research groups led by Prange and Kastin demonstrated that approximately 25% of patients with major depression exhibit a blunted TSH response to TRH (Prange, et al. 1972, Kastin, et al. 1972). Presumably this is due to hypersecretion of TRH from the median eminence which leads to TRH receptor downregulation in the anterior pituitary resulting in reduced sensitivity of the pituitary to exogenous TRH. This
hypothesis seems plausible in light of evidence showing elevated TRH concentrations in the cerebrospinal fluid (CSF) of drug-free depressed patients (Banki, et al. 1988). Depressed patients have also been shown to have an increased occurrence of symptomless autoimmune thyroiditis (SAT), defined by the abnormal presence of antithyroglobulin and/or antimicrosomal thyroid antibodies consistent with Grade 4 hypothyroidism (Nemeroff, et al. 1985).

Recently, Duval et al (1996) performed a standard TSH stimulation test at both 8 A.M. and 11 P.M. in a depressed patient population and normal controls. The difference between the ΔTSH from 11 P.M. and the ΔTSH at the 8 A.M. time point was defined as ΔΔTSH. These researchers demonstrated that depressed patients had a much lower ΔΔTSH than did controls. Normal HPT axis function returned following remission from depression, but patients who did not respond to antidepressant medications continued to show blunted ΔΔTSH. This suggests that treatment with antidepressants per se is not responsible for the improvement in HPT axis function. Further, patients with the lowest pretreatment evening thyrotropin secretion also had the lowest rate of antidepressant response. This new methodology may serve as a more sensitive method to detect changes in HPT axis function.

Interestingly, Post’s group measured both cerebral blood flow and cerebral glucose metabolism using positron emission tomography (PET) in both clinically depressed and bipolar patients. Both measures of cerebral activity were inversely correlated with serum TSH levels, and the authors suggested that HPT axis function contributes to primary and secondary mood disorders (Marangell, et al. 1997). Also the current literature has clearly demonstrated elevated TRH release in some depressed patients, but whether this is a causative factor in depression remains unknown. This same group proposed that elevated TRH levels might instead be a compensatory response to depression. In fact they reported that a lumbar intrathecal infusion of 500 μg of TRH into medication-free inpatients with depression produced a clinically robust, but short-lived, improvement in mood and suicidality (Marangell, et al. 1997). Although this work
is preliminary, it does suggest the development of a systemically administered TRH receptor agonist may represent a novel class of antidepressant agents.

**Bipolar disorder and HPT abnormalities**

HPT axis abnormalities have also been reported in bipolar disorders. Both elevated basal plasma concentrations of TSH and an exaggerated TSH response to TRH have been demonstrated (Haggerty, et al. 1987, Loosen and Prange 1982). There is also evidence that bipolar patients with the rapid cycling subtype have a higher prevalence rate of hypothyroidism (Grades I, II and III) than bipolar patients who do not (Bauer, et al. 1990, Cowdry, et al. 1983). A blunted or absent evening surge of plasma TSH, a blunted TSH response to TRH, (Sack, et al. 1988, Souetre, et al. 1988), and the presence of antithyroid microsomal and/or antithyroglobulin antibodies (Lazarus, et al. 1986, Myers, et al. 1985) have also been demonstrated in bipolar patients.

**Treatment of Hypothyroid states:**

As noted above, thyroid hormone extracts from sheep or cattle were the first treatments used that demonstrated efficacy in ameliorating the signs and symptoms of hypothyroidism. Several synthetic derivatives were introduced in the 1960’s which quickly replaced desiccated thyroid tissue for the treatment of patients with thyroid disease. Among these are levothyroxine (Levoxyl, Levothroid, Synthroid), synthetic forms of thyroxine (T₄) and liothyronine (Cytomel), and the synthetic levorotary isomer of triiodothyronine (T₃). Moreover, in part due to the seminal work carried out by Prange and collaborators in the United States in the 1960’s, the use of thyroid hormones in augmenting antidepressant response in depression was established.

**HYPERTHYROID STATES:**

Although a number of conditions including pituitary adenomas can lead to hyperthyroid states, the most common non-iatrogenic cause of thyroid hormone excess is Graves’ disease. In Graves’ disease, the body generates an autoantibody to the TSH receptor which directly stimulates thyroid follicular cells to secrete excessive amounts of T₃ and T₄. In this state, the
normal negative feedback T₃ and T₄ exert on TRH and TSH release is disrupted. The clinical manifestations of thyroid hormone excess are exaggerations of the normal physiologic effects of T₃ and T₄; they include diaphoresis, heat intolerance, fatigue, dyspnea, palpitations, weakness (especially in proximal muscles), weight loss despite an increased appetite, hyperdefecation, increased psychomotor activity, and visual complaints. Psychiatric manifestations are also common and include anxiety (13% of unselected cases), depression (28% of patients), and cognitive changes (approximately 7% of patients). Psychotic manifestations and mania are less common, occurring in only 2% of unselected cases. Overall psychiatric morbidity is much less common in hyperthyroid states relative to hypothyroid states (Boswell 2001).

**HPT Axis: Conclusions**

Overall, there is clear evidence linking psychiatric symptomatology and thyroid disorders that extends back over 100 years. The observations that hypothyroid patients exhibit symptoms reminiscent of major depression led to a search for thyroid axis abnormalities in patients with affective illness. The efficacy of thyroid augmentation in the treatment of depression (Dording 2000) and other affective disorders provides further evidence linking HPT axis function and psychiatric illness (Prange 1996). Though work over the past 40 years has demonstrated a number of HPT axis abnormalities in depressed and bipolar patients, the etiologic connection between these findings remains elusive.

**HPG Axis**

The overall organization of the HPG axis is similar to the other major neuroendocrine axes. A “pulse” generator in the arcuate nucleus of the hypothalamus controls gonadotropin-releasing hormone (GnRH) secretion, which occurs in a pulsatile fashion (Knobil 1990) in intervals of 60-100 minutes (Nestler 2001). GnRH, previously known as luteinizing hormone-releasing hormone (LHRH), is released into the portal circulation connecting the hypothalamus and anterior pituitary where it binds to gonadotrophs and promotes the release of luteinizing hormone (LH) and follicle-stimulation hormone (FSH) into the systemic circulation (Midgley
These hormones then bind to Leydig cells in the testes to promote testosterone synthesis and secretion from Leydig cells and the ovaries to promote estrogen secretion. In females, FSH also promotes the development of ovarian follicles and the synthesis and secretion of androgen-binding proteins and inhibin. Inhibin acts directly on the anterior pituitary to inhibit FSH secretion without affecting LH release. In both sexes, testosterone/estradiol generated by the testes/ovaries feedback on the pituitary and hypothalamus to inhibit further FSH, LH and GnRH release. Gonadal steroids, like glucocorticoids, modulate gene transcription. Gonadal steroids can bind to androgen or estrogen response elements located in the regulatory regions of specific genes and directly modulate the expression of those genes. Gonadal steroids may also interact with transcription factors such as AP-1 or CREB, in turn influencing the expression of the genes controlled by those transcription factors (Nestler 2001).

Despite the significantly higher rates of depression in women, data on HPG abnormalities in psychiatric disorders remains remarkably limited. Early studies showed no differences in plasma concentrations of LH and FSH in depressed postmenopausal women compared with nondepressed matched control subjects (Nathan 1995). However a later study showed decreased plasma LH concentrations in depressed postmenopausal women compared to matched controls (Brambilla, et al. 1990). In a more recent study, significantly lower estradiol levels were detected in women with depression, but the blood levels of other reproductive hormones fell within the normal range (Young, et al. 2000). Because estradiol affects a number of neurotransmitter systems including norepinephrine and serotonin, these results merit further study.

The response to exogenous administration of GnRH in depressed patients has also been investigated. Normal LH and FSH responses to a high dose of GnRH (i.e. 250 μg) have been reported in male depressed and female depressed (pre and post menopausal) patients (Winokur, et al. 1982), whereas a decreased LH response to a lower dose of GnRH (150 μg) has been reported in pre- and postmenopausal depressed patients (Brambilla, et al. 1990).
colleagues observed no change in basal or TRH/LHRH stimulated LH concentrations in a depressed cohort including both sexes, though depressed males with an abnormal dexamethasone suppression test response showed a significantly higher increase in FSH compared to the controls (Unden, et al. 1988).

The prevalence of mood disorders in women including premenstrual syndrome and postpartum depression also deserves mention. Premenstrual dysphoric disorder (PMDD) is a cyclic recurrence of symptoms, which are both somatic (edema, fatigue, breast tenderness, headaches) and psychological (depression, irritability, and affective liability). The symptoms start following ovulation and disappear within the first day or two of menses followed by a symptom-free interval between menses and the next ovulation. In some cases (5 – 10%) symptoms may be severe enough to interfere with normal functioning leading to the diagnosis of PMDD (Altshuler, et al. 1995). GnRH agonists that produce a “clinical ovariectomy” by downregulation of GnRH receptors in the pituitary and reduced gonadotropin secretions have been shown to be an effective treatment for premenstrual syndrome (PMS) suggesting that the HPG axis is involved in the manifestation of symptoms (Freeman, et al. 1997). However significant variations in HPG axis function have yet to be identified in women especially susceptible to PMS.

Postpartum mood disorders are also common, occurring in approximately 10% of women after childbirth. Both postpartum depression and the less frequent postpartum psychosis occur with highest prevalence in the first three months after childbirth (Wisner and Stowe 1997). The timing of these syndromes would suggest that neuroendocrine dysregulation may contribute to the expression of such disorders, but no major abnormalities in HPG axis function were detected in a prospective investigation of postpartum disorders (O'Hara, et al. 1990). Additional research on the HPG axis in depression and in other mood states is needed.
Hypothalamic-Prolactin Axis

Unlike other anterior pituitary hormones, prolactin release is regulated via tonic inhibition by prolactin-inhibitory factor (PIF), which was later determined to be dopamine. Dopamine neurons in the tuberoinfundibular system of the hypothalamus directly inhibit prolactin release. Prolactin can also inhibit its own release by a short-loop negative feedback to the hypothalamus. Prolactin primarily regulates the behavioral aspects of reproduction and infant care. Serum prolactin levels are normally low through life in males. Basal prolactin levels increase in females following parturition, and suckling stimulates prolactin release. Prolactin itself stimulates breast growth and milk synthesis. TRH, oxytocin, serotonin, estrogen and other neuroregulators have prolactin-releasing factor activity (Fink 2000).

Excess circulating prolactin can lead to a number of clinical symptoms. The most common causes of hyperprolactinemia are tumors, usually microadenomas of pituitary lactotrophs, or following treatment with conventional antipsychotic medications because of their potent blockade of dopamine receptors. Hyperprolactinemia often leads to reduced testosterone secretion in men, and a decreased libido in both men and women. Patients may also complain of depression, stress intolerance, anxiety and increased irritability that usually resolve following treatments that reduce serum prolactin levels. Despite these effects, alterations in the hypothalamic-prolactin axis have not been clearly demonstrated in psychiatric disorders (Nicholas, et al. 1998). Because prolactin release is inhibited by dopamine, the prolactin response to infusions of dopaminergic agonists has also been used to estimate CNS dopaminergic tone, though it likely only reflects hypothalamic dopamine neuronal function.

Although abnormalities in prolactin secretion have not been clearly demonstrated in depression per se, a large number of reports have used provocative tests of prolactin secretion in patients with psychiatric disorders (For a review see (Van de Kar 1989)). Briefly, these tests use agents that increase serotonergic transmission, for example L-tryptophan, 5-hydroxytryptophan (5-HTP), and fenfluramine, among others. In general the prolactin response to agents that
increase serotonergic activity is blunted in depression (Mann et al., 1995; Golden et al., 1992), as well as in patients with cluster-B personality disorders (Coccaro, et al. 1997). This data suggests that the blunted prolactin response is mediated by alteration in 5-HT$_{1A}$ receptor responsiveness and that serotonergic transmission in these patients is dysfunctional.

**OXYTOCIN AND VASOPRESSIN**

Oxytocin and arginine-vasopressin (AVP), also known as anti-diuretic hormone (ADH), are nona-peptides synthesized in the magnocellular neurons of the paraventricular nucleus of the hypothalamus, and released directly into the bloodstream from axon terminals in the posterior pituitary. This is in contrast to the hypothalamic releasing factors we have discussed thus far which are released in the portal system from the median eminence and distinct from the anterior pituitary hormones that are released following the activation of pituicytes by the releasing factors synthesized in the hypothalamus.

AVP has prominent roles in controlling fluid balance via its effects on the kidney, in regulating blood pressure by its vasoconstrictive effects on blood vessels, and can directly promote the sensation of thirst. AVP also promotes the release of ACTH from the anterior pituitary in the presence of CRF, and is released following stressful stimuli (Insel 1997). In humans, oxytocin is predominantly involved in controlling smooth muscle contraction during parturition (myometrium), and during both breast-feeding, by mediating milk letdown in lactating mothers. In rodents, oxytocin promotes a number of reproductive (grooming, arousal, lordosis, orgasm, nesting, birthing) and maternal behaviors.

Although there are marked species differences in the effects of oxytocin, central infusion of this peptide in females of a monogamous prairie vole species promotes life-long pair bonding in the absence of mating. Furthermore, pair bonding in this species, which normally accompanies mating, can be blocked by oxytocin antagonists thus implicating oxytocin’s key role in the expression of this lifelong behavior. Rodent studies have also demonstrated that AVP has a pair-bonding function in males, analogous to the pair-bond promoting behaviors induced
by oxytocin administration in females. AVP promotes monogamy and paternal behavior in male prairie voles. These studies have led some researchers to speculate that oxytocin and AVP may play a role in psychiatric disorders characterized by disrupted affiliative behaviors such as Asperger’s disease and autism (Insel 1997). Clearly, more work is needed in order to better understand the function of these two hormones in the human brain.

The Pituitary Growth Hormone Axis

Growth hormone (GH) is synthesized and secreted from somatotrophs located in the anterior pituitary. Its release is unique in that it is controlled by two peptide hypothalamic hypophysiotropic hormones, growth-hormone-releasing factor (GHRF) and somatostatin. Somatostatin, also known as growth hormone-release-inhibiting hormone (GHIH) or somatotropin release-inhibitory factor (SRIF), was first isolated from ovine hypothalamus in 1974. It is a tetradecapeptide, containing a disulfide bridge linking the two cysteine residues. Somatostatin is released predominantly from the periventricular and paraventricular nucleus of the hypothalamus and inhibits GH release. Somatostatin has a wide extrahypothalamic distribution in brain regions including the cerebral cortex, hippocampus, and amygdala.

GHRF, also known as growth hormone releasing hormone (GHRH), was characterized and sequenced in 1981 after considerable difficulty. The long-postulated GHRF was discovered several years after the elucidation of the structure of somatostatin, from extracts of an ectopic tumor associated with acromegaly. GHRF is a 44 amino acid peptide, and has the most limited CNS distribution of all the hypothalamic-releasing hormones that have been identified. GHRF containing neurons are concentrated in the infundibular and arcuate nuclei of the hypothalamus and stimulate the synthesis and release of GH. Dopamine, norepinephrine and serotonin innervate GHRF-containing neurons to modulate GH release. Both GHRF and SRIF are released from the median eminence into the hypothalamo-hypophyseal portal system where they act on somatotrophs in the anterior pituitary to regulate GH release. Negative feedback is provided by GH, which stimulates somatostatin release preventing further GH release. The
growth hormone axis is unique in that it does not have a single target endocrine gland but instead growth hormone acts directly on targets including bone, muscle and liver. GH also stimulates the release of somatomedin from the liver and insulin like growth factors.

Growth hormone is released in a pulsatile fashion, with highest release occurring around the time of sleep onset and extending into the first non-REM period of sleep (Finkelstein, et al. 1972). A variety of stressors including starvation, exertion, or emotional stress also promote growth hormone release (Nestler 2001). Growth hormone is necessary for the longitudinal bone growth which occurs during late childhood; accordingly GH levels are high in children, reach their peak during adolescence and decline throughout adulthood. In additions to its effects on the long bones, growth hormone has predominantly anabolic effects and leads to increased muscle mass and decreased body fat.

Growth hormone release to a variety of stimuli including L-Dopa, a DA precursor (Boyd, et al. 1970), apomorphine, a centrally active DA agonist (Fink 2000), and the serotonin precursors L-tryptophan (Muller, et al. 1974) and 5-hydroxytryptophan (Imura, et al. 1973) has been demonstrated. Several findings indicate dysregulation of growth hormone secretion in depression [Table 4]. Studies have demonstrated a blunted nocturnal GH surge in depression(Schilkrut, et al. 1975), whereas daylight GH secretion seems to be exaggerated in both unipolar and bipolar depressed patients (Mendlewicz, et al. 1985). A number of studies have also demonstrated a blunted GH response to the α-adrenergic agonist clonidine in depressed patients (Siever, et al. 1982, Charney, et al. 1982). Siever et al. (1982) demonstrated the blunted GH response to clonidine was not related to age or sex, and this study provided evidence that the diminished GH response to clonidine may be secondary to decreased α2-adrenergic receptor sensitivity in depression. Using a GHRF stimulation test, our group later demonstrated a slight exaggeration of GH response to GHRF in depressed patients compared to controls, although this group difference was mainly attributable to 3 of the 19 depressed patients who exhibited markedly high GH responses to GHRF (Krishnan, et al. 1988). Others, however, have reported a
blunted GH response to GHRH in depressed patients. Thus it is unclear whether the blunted GH response to clonidine seen in depression is due to a pituitary defect in GH secretion, further implicating a subsensitivity of α-adrenergic receptors in depression, or to a GHRH deficit. Recently a diminished GH response to clonidine was demonstrated in children and adolescents at high risk for major depressive disorder. When considered with evidence demonstrating GH dysregulation in childhood depression (Ryan, et al. 1994), it suggests the blunted GH response seen in high-risk adolescents may represent a trait marker for depression in children and adolescents (Birmaher, et al. 2000). Arguably, the blunted GH response to clonidine seen in depression may be the most reproducible and specific finding in the biology of affective disorders.

A GHRH stimulation test has also been developed and studied in depressed patients. Two groups have shown a blunted GH response to GHRH in depressed patients (Lesch, et al. 1987a, Lesch, et al. 1987b, Risch 1991). However Krishnan and colleagues (Krishnan, et al. 1988, Krishnan, et al. 1988) found minimal differences in serum GH response to GHRH in between depressed and control patients. A comprehensive review of GHRH stimulation tests in depression, anorexia nervosa, bulimia, panic disorder, schizophrenia, and Alzheimer’s disease was conducted and the authors concluded that the results of this test are not always consistent and in some cases contradictory (Skare, et al. 1994). Factors including the variability of GHRH-stimulated GH among controls, lack of standard outcome measures, and age and gender related effects may account for some of this variability. Further studies using GHRH will help develop a standard stimulation test to further clarify the response to GHRH in depression and other psychiatric disorders.

Several studies have demonstrated decreased SRIF levels in the CSF of patients suffering depression (Agren and Lundqvist 1984, Gerner and Yamada 1982), dementia, schizophrenia (Bissette, et al. 1986) and Alzheimer’s disease (Molchan, et al. 1993) (Bissette 1998). Somatostatin concentrations are also markedly elevated in the basal ganglia of patients with
Huntington’s disease (Nemeroff, et al. 1983), though the implications of this finding are unknown. Somatostatin also inhibits the release of both CRF and ACTH (Brown, et al. 1984, Heisler, et al. 1982, Richardson and Schonbrunn 1981) indicating a direct interaction between the growth-hormone and HPA axes. No published studies measuring GHRH concentration and GHRH-mRNA expression have been conducted in postmortem tissue of depressed patients and matched controls which, in light of the evidence presented here, is of interest. Similarly, CSF studies of GHRH are also lacking.

**Summary and Conclusion**

Basic clinical observations of psychiatric disorders associated with primary endocrine disorders such as Cushing’s syndrome and hypothyroidism has led to our broader understanding of the role of neuroendocrine disturbances in a variety of psychiatric disorders including depression and bipolar disorders. These studies have led to major advances in biological psychiatry by helping to understand the brain circuits involved in the pathophysiology of mood and anxiety disorders. Foremost among these is the CRF theory of depression, which is supported by studies from a variety of disciplines, and which has led to the development of a novel therapeutic approach, namely CRF receptor antagonists. Further this work has provided a mechanism to explain the increase in depression seen in patients exposed to trauma early in life (first postulated by Freud in the early part of the twentieth century). If CRF truly is the ‘black bile’ of depression, CRF antagonists may represent a novel class of antidepressants with a unique mechanism of action from other commonly used antidepressants. Indeed, a number of CRF-receptor antagonists are now in clinical development as novel anxiolytics and antidepressants.

In addition to the HPA axis and CRF alterations observed in depression, HPT axis abnormalities are also very common; the majority of depressed patients, in fact, exhibit alterations in one of these two axes. Furthermore, there is widely replicated blunting of growth-hormone response to clonidine and the blunted prolactin response to serotonergic stimuli in
depressed patients. Although these studies have not added much understanding to the prevailing monoamine theory of depression, the mechanistic studies that have followed have been remarkably fruitful. Is it obvious that the vast majority of studies have been focused on patients with mood disorders, particularly unipolar depression. Clearly other disorders including eating disorders, anxiety disorders, schizophrenia, and axis II diagnoses should also be evaluated with similar scrutiny.

The availability of selective ligands that can be utilized with positron-emission tomography will mark the next major leap in our understanding of the neuroendocrine axes in psychiatric disorders. The ability to determine peptide-receptor alterations in the brain and pituitary of patients with psychiatric disorders will contribute immensely to our understanding of the neurobiological underpinnings of such disorders.

Finally, a growing number of studies have demonstrated that depression is a systemic disease that increases vulnerability to other disorders. Depressed patients demonstrate increased incidence of coronary artery disease and stroke, osteoporosis, and perhaps cancer. These observations may at least be partly attributed to the endocrine alterations observed in depression.

Acknowledgements:

We would like to thank Tomo Narashima and Julia Knox for their artistic assistance, and acknowledge support from MH-42088 and the Conte Center for the Neuroscience of Mental Disorders (MH-58922).
Bibliography:


Shaw C (1892) Case of myxedema with restless melancholia treated by injections of thyroid juice: recovery. British Journal of Medicine 451.


Figure 1. Overview of the common organizational motif of the neuroendocrine axis. The neurosecretion of hypothalamic factors into hypophyseal portal vessels is regulated by a set point of activity from higher brain centers. Neurohormones released from the hypothalamus into hypophyseal portal vessels in turn stimulate cells in the pituitary. These adenohypophyseal hormones then regulate the hormone output from the end-organ. The end organ then exerts negative feedback effects at the pituitary and hypothalamus to prevent further neurohormone and pituitary hormone release via “long-loop” negative feedback. Short-loop negative feedback may also occur where pituitary hormones feed back directly on hypothalamic neurons to prevent further neurohormone release.
Figure 2. Diagram of the neurovascular anatomy of the hypothalamic-pituitary axis. PVN, paraventricular nucleus. SON, supraoptic nucleus. POA, preoptic area. ARC, arcuate nucleus. PT, pars tuberalis. PI, pars intermedia. PD, pars distalis. PN, pars nervosa, MB, Mamillary Body, OC, Optic chiasm.
Figure 3- Overview of the feedback system of the Hypothalamic-Pituitary-Thyroid (HPT) axis. Thyroid-releasing hormone (TRH) from the hypothalamus stimulates TSH from the pituitary, which stimulates thyroid hormone release. As circulating thyroid hormone levels increase, they inhibit further release of TSH and TRH. Other hypothalamic-pituitary-end organ axes exhibit similar feedback control mechanisms.
Figure 4- Overview of the feedback mechanisms of the hypothalamic-pituitary-adrenal axis. Following relevant stimuli, including stress, corticotropin-releasing factor (CRF) is released from the hypothalamus into hypophyseal portal vessels where it is transported in high concentrations to the pituitary gland. CRF then promotes the release of adrenocorticotropin (ACTH), which in turn promotes the release of cortisol from the adrenal glands. Cortisol acts as an inhibitory signal at both the hypothalamus and pituitary preventing further CRF and ACTH release, respectively. Mounting evidence suggests that chronic overactivity of the axis, and particularly overproduction of corticotropin-releasing factor (CRF), may contribute to the pathophysiology of depression. Reproduced from (Nemeroff, CB 1998) with permission.
<table>
<thead>
<tr>
<th>Neurohormone/Releasing Factor</th>
<th>Hormone Stimulated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticotropin-releasing factor (CRF)</td>
<td>Adrenocorticotropic hormone (ACTH)</td>
</tr>
<tr>
<td>Thyrotropin-releasing hormone (TRH)</td>
<td>Thyroid-stimulating hormone</td>
</tr>
<tr>
<td>Gonadotropin-releasing hormone (GnRH)</td>
<td>Follicle-stimulating hormone (FSH)</td>
</tr>
<tr>
<td>Somatostatin (SRIF)</td>
<td>Growth Hormone (GH)</td>
</tr>
<tr>
<td>Growth-hormone-releasing hormone (GHRH)</td>
<td>GH</td>
</tr>
<tr>
<td>Arginine vasopressin (AVP)</td>
<td>ACTH Prolactin</td>
</tr>
<tr>
<td>Oxytocin</td>
<td>Prolactin</td>
</tr>
</tbody>
</table>
### Table 2:

**HPA Axis changes demonstrated in depression**

<table>
<thead>
<tr>
<th>Change</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑   Corticotropin-releasing factor (CRF) in cerebrospinal fluid</td>
<td></td>
</tr>
<tr>
<td>↓   Adrenocorticotropic hormone response (ACTH) to CRF stimulation</td>
<td></td>
</tr>
<tr>
<td>↓   Density of CRF receptors in frontal cortex of suicide victims</td>
<td></td>
</tr>
<tr>
<td>Enlarged pituitary gland in depressed patients</td>
<td></td>
</tr>
<tr>
<td>↑   Plasma cortisol during depression</td>
<td></td>
</tr>
<tr>
<td>↑   Urinary free cortisol concentrations</td>
<td></td>
</tr>
<tr>
<td>Non-suppression of plasma cortisol and ACTH after dexamethasone administration</td>
<td></td>
</tr>
</tbody>
</table>

*a State-dependent*
Table 3:

<table>
<thead>
<tr>
<th>Hypothalamic-pituitary-thyroid (HPT) axis alterations in depression</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑ CSF TRH in depressed patients</td>
</tr>
<tr>
<td>↓ Nocturnal plasma TSH</td>
</tr>
<tr>
<td>Blunted TSH in response to TRH stimulation (state dependent)</td>
</tr>
<tr>
<td>Exaggerated TSH response to TRH stimulation</td>
</tr>
<tr>
<td>↓ ΔΔTSH (difference between 11 P.M. ΔTSH and 8 A.M. ΔTSH after TRH administration)</td>
</tr>
<tr>
<td>Presence of antithyroglobulin and/or antimicrosomal thyroid antibodies</td>
</tr>
</tbody>
</table>
Table 4:

<table>
<thead>
<tr>
<th>Growth hormone (GH) axis changes in depression</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑ Circulating daily GH levels (uni- and bipolar depression)</td>
</tr>
<tr>
<td>↓ Nocturnal GH in depression</td>
</tr>
<tr>
<td>↓ Response of GH to clonidine</td>
</tr>
</tbody>
</table>
INDEX WORDS:
Hypothalamic-Pituitary-Axis
HPA Axis
CRF Stimulation Test
Corticotropin-Releasing Factor
Corticotropin-Releasing Hormone
Cortisol
Hypercortisolemia
Adrenocorticotropic Hormone (ACTH)
Glucocorticoids
Cortisol and depression
CRF receptors
Cushing’s Syndrome
Dexamethasone Suppression Test (DEX Test)
DEX/CRF Test
Trier Social Stress Test (TSST)
HPT Axis (Hypothalamic-Pituitary-Thyroid Axis)
Thyroid
T3 and T4
TSH (Thyroid Stimulating Hormone)
TRH (Thyrotropin Releasing Hormone)
Hypothyroidism
Hyperthyroidism
Hypothyroidism and Depression
HPG Axis (Hypothalamic-Pituitary-Gonadal Axis)
Follicle Stimulating Hormone (FSH)
Luteinizing Hormone (LH)
Postpartum Depression
Hypothalamic-Prolactin Axis
Prolactin
Hyperprolactinemia
Oxytocin
Vasopressin
Growth Hormone (GH)
Growth-Hormone-Releasing Factor (GHRF)
Growth-Hormone-Inhibiting Hormone (GHIH)
GH response to clonidine
GHRH Stimulation Test