CHAPTER SIX

THE HYPOTHALAMIC-PITUITARY-ADRENOCORTICAL SYSTEM

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Introduction

The hypothalamic-pituitary-adrenal (HPA) axis has undoubtedly received more psychobiologic scrutiny than any other endocrine axis. Historically, one rationale for the intensive study of adrenocortical function in patients with primary psychiatric disorders was the observation that patients with primary endocrine disorders such as Addison’s disease (Fava, Sonino, and Murphy, 1987; Lobo et al., 1988) or Cushing’s syndrome (Loosen, Chambliss, DeBold, Shelton, Orth et al., 1992; Kling et al., 1993) exhibited a higher than expected psychiatric morbidity. This led to the so-called neuroendocrine window strategy based on a large literature which indicates that the secretion of the target endocrine organs, for example, the adrenal or thyroid, is largely controlled by their respective pituitary trophic hormones. The pituitary tropic hormones, in turn, are controlled primarily by the secretion of their respective hypothalamic release and/or release-inhibiting hormones. There is now considerable evidence that the secretion of these hypothalamic hypophysiotropic hormones is controlled by serotonin, acetylcholine, and
norepinephrine, neurotransmitters previously posited to play a preeminent role in the pathophysiology of affective and/or anxiety disorders. This neuroendocrine window strategy remains an impetus for continuing investigation of the major endocrine axes in psychiatric disorders. However, the hypothesis that information about higher central nervous system (CNS) neuronal activity, such as the activity of serotonergic neurons in a particular disease state, may be inferred solely by measuring the activity of a specific endocrine axis is far from proven and is fraught with problems. It is unclear if alterations in peripheral adrenal hormone secretion or altered secretion of pituitary and hypothalamic hormones primarily contribute to the pathogenesis of depression. What the neuroendocrine window strategy has provided, however, is clear evidence for alterations in the activity of the HPA axis in depression and an appreciation of the complexity of the regulation of its activity in women and in men. This chapter briefly reviews the major findings concerning altered HPA-axis activity in unipolar depression, the relationship between HPA-axis and ovarian physiology, HPA-axis morphology in depression, and implications for future research.

Pathophysiology of the HPA axis in major depression and other affective disorders

The most intensive scrutiny of the HPA axis have been conducted in patients with major depression. Corticotropin-releasing factor (CRF), composed of 41 amino acids, is released from the hypothalamus and is the major physiologic mediator of the secretion of adrenocorticotropic hormone (ACTH) and β-endorphin from the anterior pituitary (Vale et al., 1981). Neurons containing CRF project from the hypothalamic paraventricular nucleus to the median eminence (Swanson et al., 1983). Activation of this circuit occurs in response to stress, resulting in an increase in synthesis and release of ACTH, β-endorphin, and other pro-opiomelanocortin (POMC) products. As discussed later, numerous reports document HPA-axis hyperactivity in drug-free patients with major depression, including CNS (i.e., CRF), pituitary (i.e., ACTH), and adrenal (i.e., glucocorticoid) involvement. CRF neurons, both hypothalamic and extrahypothalamic, coordinate the endocrine, behavioral, autonomic, and immune responses to stress.

Evidence for the involvement of CRF in the pathophysiology of depression includes elevated CRF concentrations in cerebrospinal fluid (CSF), which has been documented in multiple studies of drug-free patients with major depression (Nemeroff et al., 1984; Arato et al., 1986; Banki et al., 1987; France et al., 1988; Banki et al., 1992; Risch et al., 1992) as well as in suicide victims (Arato et al., 1989), with the exception of Roy and colleagues, 1987, who found no such rela-
tionship. In that study, however, dexamethasone test (DST) nonsuppressors had higher CSF CRF concentrations than DST suppressors. Elevations of CRF concentrations in CSF are believed to be due to central CRF hypersecretion (Post et al., 1982). Reductions in CSF CRF concentrations have been observed following administration of desipramine, a tricyclic antidepressant, in healthy, nondepressed volunteers (Veith et al., 1992) and following treatment of depressed patients with ECT (Nemeroff et al., 1991) or with fluoxetine, a selective serotonin reuptake inhibitor (DeBellis et al., 1993). Thus, CSF CRF concentrations are elevated in major depression, normalize after treatment with antidepressants or ECT in depressed patients, and are reduced by desipramine in normal controls.

There are several methods for assessing the HPA-axis activity, which are outlined later. One particularly sensitive method to assess the activity of the HPA axis is the CRF stimulation test. CRF is administered intravenously (usually in a dose of 1 µg/kg or a fixed 100-µg bolus), and the subsequent ACTH (or β-lipotropin [LPH]/β-endorphin) and cortisol response is measured over a 2- to 3-hour period (Hermus et al., 1984; Watson et al., 1986). In drug-free depressed patients, the ACTH and β-endorphin response to exogenously administered ovine CRF (oCRF) is attenuated compared with that of normal comparison subjects (Gold et al., 1984; Holsboer et al., 1984; Gold et al., 1986; Amsterdam et al., 1988; Katoh et al., 1989; Young et al., 1990). The blunted ACTH response to CRF occurs in depressed DST nonsuppressors but not in DST suppressors (Krishnan et al., 1993). The diminished ACTH response to CRF is likely, at least in part, due to chronic hypersecretion of CRF from the median eminence resulting in downregulation of adenohypophyseal CRF receptor number and decreased pituitary responsivity to CRF, as has previously been demonstrated in laboratory animals (Wynn et al., 1983; Wynn et al., 1984; Aguilera et al., 1986; Holmes, Catt, and Aguilera, 1987; Wynn et al., 1988). Further evidence for hyperactivity of hypothalamic CRF neurons in depression has been provided by Raadsheer et al. (1994, 1995) who reported that postmortem tissue of depressed patients exhibits a fourfold increase in the numbers of CRF-containing paraventricular hypothalamic neurons as well as a marked increase in CRF mRNA expression, as assessed by in situ hybridization. Moreover, decreased CRF receptor numbers in the frontal cortex have been reported in postmortem tissue of suicide victims (Nemeroff et al., 1988), likely due to CRF receptor downregulation secondary to CRF hypersecretion.

The majority of the work in HPA-axis activity in depression has used measures of cortisol hypersecretion, for example, elevated plasma corticosteroid concentrations (Gibbons and McHugh, 1962; Carpenter and Bunney, 1971), and increased levels of cortisol metabolites (Sachar et al., 1970). Elevated 24-hour urinary free cortisol concentrations and nonsuppression of plasma
hydroxycorticosteroid levels after the administration of dexamethasone (using the DST) have also been utilized. In the standard DST paradigm, patients ingest 1 mg of dexamethasone, a synthetic glucocorticoid, by mouth at 11 p.m. Blood samples, which were originally utilized to confirm screening measures of hypercortisolemia, are obtained at 4 p.m. and 11 p.m. the following day to measure plasma cortisol concentrations. One half to two thirds of depressed patients exhibit dexamethasone nonsuppression (plasma cortisol concentrations \( \geq 5 \) ng/ml) whereas healthy, nonobese patients will almost always suppress plasma cortisol concentrations to <5 ng/ml (Schulkin, 1988).

Since the initial study by Carroll (1968), the DST has generated remarkable controversy (Arana and Mossman, 1988) regarding its diagnostic utility (Carroll, 1982). The rate of cortisol nonsuppression after dexamethasone administration generally has been found to be correlated with the severity of depression; for example, almost all patients with psychotic depression exhibit DST nonsuppression (Evans and Nemeroff, 1983b; Schatzberg et al., 1984; Arana, Baldessarini, and Orteen, 1985; Krishnan et al., 1985). Hyperactivity of the HPA axis also occurs in patients with bipolar disorder (Kiriike et al., 1988; Stokes and Sikes, 1987), particularly in mixed states (Evans and Nemeroff, 1983a; Krishnan, Maltbie, and Davidson, 1983; Swann et al., 1992), and in rapid-cycling patients (Godwin, Greenberg, and Shulka, 1984; Kennedy et al., 1989). Furthermore, DST nonsuppressors also have higher CSF CRF concentrations than DST suppressors (Roy et al., 1987; Pitts et al., 1995) (Table 6.1).

HPA-axis activity, including the DST, usually normalizes after recovery from

Table 6.1. Alterations in the activity of the hypothalamic-pituitary-adrenal axis in major depression

- Increased corticotropin-releasing factor (CRF) concentrations in cerebrospinal fluid
- Blunted adrenocorticotropic hormone (ACTH) and \( \beta \)-endorphin responses after intravenous CRF administration
- Increased density of CRF receptors in frontal cortex of suicide victims
- Pituitary gland enlargement
- Adrenal gland enlargement in major depression and in suicide victims
- Increased cortisol production, hypercortisolemia, and cerebrospinal fluid cortisol concentrations
- Increased plasma glucocorticoid, ACTH, and \( \beta \)-endorphin nonsuppression after dexamethasone administration
- Increased urinary free cortisol concentrations
- Increased 5-hydroxytryptophan-induced cortisol secretion
- Increased ACTH-induced cortisol secretion
- Increased ACTH and cortisol responses to CRF despite dexamethasone pretreatment
depression (Carroll, 1968; Nemeroff, and Evans, 1984), and such normalization may be the harbinger of early relapse or poor prognosis (Arana et al., 1985) as do persistently elevated CSF CRF concentrations (Banki et al., 1992). Increased incidence of DST nonsuppression in depressed patients may, in part, be due to the more rapid metabolism of dexamethasone that occurs in depressed patients (Ritchie et al., 1990). Therefore, the well-documented HPA-axis hyperactivity in depressed patients may be explained by hypersecretion of CRF and secondary pituitary and adrenal gland hypertrophy, although impaired negative feedback of glucocorticoids at various CNS sites and the pituitary also likely contributes. DST nonsuppression, like hypercortisolemia (Sachar et al., 1970), hypersecretion of CRF (Nemeroff et al., 1991; DeBellis et al., 1993), blunting of the ACTH response to CRF (Amsterdam et al., 1988), and adrenal gland hypertrophy (Rubin et al., 1995), all appear, in fact, to be state dependent.

Treatment with glucocorticoid agonists and antagonists

Cushing’s syndrome, due to prolonged exposure to excessive cortisol or other related glucocorticoids, is accompanied by psychiatric symptoms of anxiety and/or depression that generally remit with diminution of abnormal glucocorticoid concentrations. Thus, agents that reduce adrenal steroid availability have recently undergone investigation in the treatment of unipolar depression. Metapyrone, an inhibitor of the 11-hydroxylation reaction of steroid synthesis, not only reduces cortisol and corticosterone production but alleviates depression in patients whose symptoms were unresponsive to antidepressant treatment (Murphy et al., 1991). Ketoconazole, an imidazole antifungal drug, also inhibits cortisol synthesis and is a potent glucocorticoid receptor antagonist as well. Hypercortisolemic depressed patients administered ketoconazole experience significant alleviation of their depression in association with lowered serum cortisol concentrations (Wolkowitz et al., 1993). Conversely, depressed patients treated with dexamethasone also experience improvement of their depression (Arana et al., 1994), an effect likely due to a reduction in CRF synthesis and release. Clearly, further studies with glucocorticoid agonists and antagonists are warranted.

Investigations of the hypothalamic-pituitary-gonadal axis in depression

Despite the higher incidence of depression in women than men and the purportedly increased occurrence of depression during and after menopause, the
hypothalamic-pituitary-gonadal (HPG) axis has received relatively little scrutiny in patients with mood disorders. As with the HPA axis, the HPG axis is organized in a “hierarchical” fashion. Driven by a “pulse generator” in the arcuate nucleus of the hypothalamus, gonadotropin-releasing hormone (GnRH) secretion occurs in a pulsatile fashion (Knobil, 1990). GnRH causes secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from gonadotrophs in the anterior pituitary (Midgely and Jaffee, 1971). The ebb and flow of LH concentration in the peripheral circulation is used as an indication of pulses of GnRH secretion (Clarke and Cummins, 1982). In the follicular phase of the menstrual cycle, LH pulses of nearly constant amplitude occur with regular frequency (every 1–2 hours) (Reame et al., 1984). In the luteal phase, LH pulse amplitude (reflecting GnRH secretion) is more variable, with pulse frequency declining to one pulse every 2–6 hours (Jaffe et al., 1990). Through negative feedback, gonadal steroids inhibit the secretion of GnRH from the hypothalamus as well as the secretion of LH and FSH from the pituitary. GnRH secretion is also inhibited by CRF (Jaffe et al., 1990) and β-endorphin (Ferin and Vande-Wiele, 1987).

Sachar and colleagues (1972) measured the plasma concentrations of LH and FSH in depressed postmenopausal women. No significant change in the concentrations of either hormone were observed in 8 postmenopausal women before or after recovery from depression. Moreover, the plasma concentrations of LH or FSH did not differ between these depressed women and a comparison group of nondepressed postmenopausal women (n = 24). However, a group of postmenopausal women suffering recurrent endogeneous depressions (n = 9) exhibited lower LH plasma concentrations than postmenopausal women without depression or postmenopausal women diagnosed before or after a single depressive episode (n = 10).

Rather than measure baseline plasma levels of the pituitary gonadotrophins in depressed patients, other investigators have studied the gonadotropin response to the administered GnRH. Winokur and colleagues (1982) found normal LH and FSH responses to a high dose (250 µg) of GnRH in male and female depressed (pre- and postmenopausal) patients. The sample size was not large enough to analyze baseline LH levels or the response to GnRH stimulation separately for men and pre- and postmenopausal women. Using a lower dose of GnRH (150 µg), Brambilla and colleagues (1990) reported a decreased LH response to GnRH in 15 premenopausal and 32 postmenopausal depressed women. Lower baseline LH concentrations (4 samples obtained over 60 minutes) were observed in the postmenopausal depressed women than in their matched controls. In a depressed cohort including both sexes, Unden et al.
(1988) observed no change in baseline or TRH/GnRH-stimulated (combined 200 μg thyroxin-releasing hormone [TRH] and 100 μg GnRH intravenously) LH or FSH concentrations (analyses of men and pre- and postmenopausal women were not separately performed). Considerable additional research of the HPG axis in depression with greater numbers of subjects of different ages is clearly warranted, including CSF GnRH measures, gonadotropin-induced gonadal steroid secretion, and other measures.

Influence of gonadal steroids upon the HPA axis and age-related changes

Of paramount importance are the increasing data concerning the influence of estrogens (estradiol, estrone, and estradiol) and progesterone upon regulation of the HPA axis. As discussed in Chapters One and Two, estrogen is crucial for the development of female secondary reproductive characteristics, and progesterone is vital in the preparation of the endometrium for maintenance of pregnancy. This section briefly reviews the influence of ovarian gonadal steroids upon the HPA axis, aging of the HPA axis in women, and HPA dysregulation in depressed women.

The biologic activity of any drug or hormone, including cortisol and gonadal steroids, depends upon its circulating concentrations, particularly the fraction that is not bound to carrier proteins and is therefore "free" to interact with its receptor. In addition to their effects upon maintenance of vaginal, uterine, and breast tissue, estrogens have multiple systemic effects, including stimulating the production of proteins by the liver. Indeed, as estrogen concentrations slowly rise during the follicular phase of the menstrual cycle, so do the levels of a hepatic-synthesized carrier protein, corticosteroid-binding globulin (CBG), an α₁ globulin. During the usual 9 months of a human pregnancy, plasma levels of CBG rise, likely stimulated by increased concentrations of circulating estrogens. CBG binds cortisol and thus spuriously raises total cortisol levels in maternal circulation while minimally changing the fraction of unbound cortisol. Estrogens may provide a buffer from stress-induced HPA activity by their stimulation of CBG production, thereby diminishing any acute elevations in unbound cortisol. It is also important to note that the CRF is manufactured in very large quantities by the placenta; a CRF-binding protein prevents very much of an increase in "free" CRF plasma concentrations.

Like estrogens, circulating progesterone is mostly (>90%) bound to the carrier proteins albumin and CBG. In fact, progesterone binds to CBG with an
affinity equal to that of glucocorticoids. Progesterone is generally present in much lower concentrations in plasma than is cortisol. However, during the menstrual luteal phase, the concentration of progesterone is greatest (20–25 ng/ml), similar to that of basal diurnal levels of cortisol. At the morning height of cortisol secretion, however, CBG is saturated with cortisol. At such times, progesterone’s competition for CBG may subsequently increase concentrations of free cortisol. During pregnancy, characterized by high progesterone levels, it is well known that concentrations of both cortisol and CBG are elevated (Carr et al., 1981; Nolten and Rueckert, 1981; Demey-Ponsart et al., 1982). Postpartum progesterone levels fall precipitously, which has been posited to play a role in the development of postpartum depression.

Preclinical studies have determined that, in addition to competing with cortisol for CBG, progesterone binds to and enhances the dissociation of corticosteroids from Type II glucocorticoid receptors (Rousseau, Baxter, and Tomkins, 1972; Suthers, Presley, and Funder, 1976; Svec, 1988), the low-affinity and high-capacity receptors for endogenous glucocorticoids. Furthermore, progesterone demonstrates a significant affinity for the human Type I glucocorticoid (mineralocorticoid-prefering) receptor (Arriza et al., 1987), the high-affinity and low-capacity receptor for endogeneous glucocorticoids. Indeed, progesterone administration has been shown to contribute to the restoration of Type II glucocorticoid receptor reactivity throughout the hippocampus of the female, but not male rat (Ahima et al., 1992). The hippocampus, an integral part of the limbic system, contains a high concentration of both Type I and II corticosteroid receptors, and is well documented to exert an inhibitory influence upon HPA-axis activity (Jacobson and Sapolsky, 1991). Progesterone’s competition with corticosterone for glucocorticoid receptors might explain the greater numbers of glucocorticoid receptors within the hippocampus of female rats in comparison to male rats (Turner and Weaver, 1985). Taken together, these observations suggest that estrogen and progesterone exert important actions on certain elements of the HPA axis in women, possibly functioning as a buffer against elevated circulating glucocorticoids, as occur during episodes of major depression.

Evidence for age-related changes in the HPA axis has been reported in animal (Sapolsky, Krey, and McEwen, 1983, 1986; Heroux, Grigoriaides, and DeSouza, 1991; Tizabi, Aguilera, and Gilad, 1992) and in human (Halbreich et al., 1984; Pavlov et al., 1986; Heuser et al., 1991) studies. However, most aspects of adrenocortical regulation appear intact in aged humans. Although age is most frequently positively correlated with hyperactivity of the HPA axis in patients with depression or Alzheimer’s disease (Jacobson and Sapolsky, 1991), aging in women is not accompanied by increased baseline plasma corti-
sol concentrations. With menopause, however, comes the loss of the modulatory effects of estrogen and progesterone upon the HPA axis. Depressed postmenopausal women might not experience modulation of depression-induced increases in cortisol secretion as would premenopausal women with higher levels of CBG. The hypothesized beneficial effects of the glucocorticoid antagonist progesterone would also theoretically be diminished in postmenopausal women. In general, depressed women do not exhibit higher rates of β-LPH/β-endorphin or cortisol nonsuppression after dexamethasone administration than do depressed men (Young et al., 1993). However, dexamethasone nonsuppression is indeed more common in postmenopausal women when compared to premenopausal women (Young, 1995).

To determine the antagonistic effects of progesterone upon HPA-axis activity, Young (1995) studied eight premenopausal women and eight age-matched men who were without psychiatric disorders. The effect of an infusion of cortisol (5 μg/kg/minute for 1 hour) or β-LPH/β-endorphin secretion was examined. The β-LPH/β-endorphin responses of the women with increased progesterone concentrations (>5.00 ng/ml) were compared to those of the women with low progesterone concentrations (<1.00 ng/ml). Although estradiol concentrations were similar in both groups of women, the women with low plasma progesterone levels (in the follicular phase) exhibited suppressed β-LPH/β-endorphin plasma concentrations identical to the male controls following cortisol infusion. However, the women with high progesterone plasma levels (in the luteal phase) exhibited a rebound increase of β-LPH/β-endorphin concentrations in the second hour after cortisol infusion in comparison to the men. Thus, the increased concentration of progesterone in the luteal phase appears to antagonize the inhibitory effects of cortisol upon the HPA axis in women.

In addition, Young (1995) examined the effects of gender and depression upon morning cortisol plasma concentrations. Morning cortisol concentrations were measured in depressed premenopausal women (n = 8), depressed men (n = 8), and their age- and gender-matched controls (the mean age of patients and controls was identical, 32.5 years). Only the depressed premenopausal women exhibited elevated plasma concentrations of cortisol. The adrenocortical hyperactivity observed in the premenopausal depressed women might be at least partly due to their higher levels of CBG, resulting in lower free cortisol concentrations. Such diminished concentrations of free cortisol probably results in the increased β-endorphin secretion in depressed women following administration of metapyrone, an inhibitor of cortisol synthesis (Young, 1995).

Furthermore, to examine whether the absence of ovarian steroids might affect HPA-axis hyperactivity, Young (1995) measured baseline levels of cortisol in
premenopausal (n = 38) and postmenopausal (n = 14) depressed women prior to a DST. Adenohypophyseal (e.g., β-LPH/β-endorphin) and adrenocortical (e.g., cortisol) secretion were subsequently measured. Only the premenopausal women who exhibited nonsuppression of β-LPH/β-endorphin exhibited elevated cortisol concentrations at baseline in comparison to those premenopausal women who were cortisol suppressors. Basal cortisol concentrations were similar in the postmenopausal women who were β-LPH/β-endorphin nonsuppressors and suppressors, respectively. Increased basal cortisol concentrations appear necessary for DST nonsuppression in premenopausal depressed women. The premenopausal β-LPH/β-endorphin nonsuppressors did not exhibit significantly increased baseline cortisol levels in comparison to the postmenopausal β-LPH/β-endorphin nonsuppressors (10.5 vs. 9.8 ng/ml). However, as CBG is saturated at concentrations of cortisol greater than 10 ng/ml, the cortisol levels in the premenopausal β-LPH/β-endorphin nonsuppressors may be much greater than was assayed. Considering the loss of the protective effects of increased levels of CBG and the antigliucocorticoid effects of progesterone, depressed postmenopausal women most likely exhibit higher rates of dexamethasone nonsuppression due to the resulting lower baseline concentrations of cortisol than premenopausal women who are dexamethasone nonsuppressors.

**Pituitary and adrenal imaging studies in affective disorders**

Although the data regarding sex differences are still accumulating, structural changes in the various components of the HPA axis (e.g., the pituitary and adrenal gland) have been reported in depressed patients. Other morphologic and functional brain imaging alterations in patients with affective disorders are discussed by Drs. Casper and Marsh in Chapter Four.

Depressed patients exhibit pituitary gland enlargement on magnetic resonance imaging (MRI) (Krishnan et al., 1991). To assess if this and other alterations in HPA axis morphology are associated with abnormal function, investigators have utilized computerized tomography (CT) and MRI studies of the CNS in conjunction with neuroendocrine stimulation tests, neuropsychological testing, monitoring patients’ clinical course, response to treatment, and so on. Indeed, the pituitary gland enlargement exhibited by depressed patients significantly correlates with plasma cortisol concentrations after dexamethasone administration (Axelson et al., 1992). MRI studies determining normative size and shape of the pituitary reveal transient enlargement of the pituitary in periods of intense neuroendocrine activity: pregnancy, the immediate puerperium
(Elster et al., 1991), and adolescence (Elster et al., 1990). Normal maturation of the pituitary gland in adolescence involves a period of physiologic hypertrophy in both sexes, though it is more prominent in females. Other than adolescence and pregnancy, there have been no other documented differences in pituitary size between the sexes (Doraiswamy et al., 1992; Tien et al., 1992). In contrast, reduction of pituitary gland size is associated with increasing age (Lurie et al., 1990; Krishnan et al., 1991) and anorexia nervosa (Doraiswamy et al., 1990). The stability or state dependency of depression-associated pituitary enlargement is unknown.

As mentioned earlier, another HPA-axis structure, the adrenal gland, has been found to exhibit structural alterations in depressed patients. Enlargement of the adrenal gland has been reported postmortem in suicide victims (Zis and Zis, 1987; Szigethy et al., 1994) and in depressed patients using CT and MRI (Amsterdam et al., 1987; Nemeroff et al., 1992; Rubin et al., 1995), a finding probably due to chronic ACTH hypersecretion.

Adrenocortical hypertrophy most likely explains the normal plasma cortisol response to CRF in depressed patients, a sharp contrast to the blunted ACTH and β-endorphin response to the peptide (Gold et al., 1984, 1986; Holsboer et al., 1984; Amsterdam et al., 1987; Kathol et al., 1989; Young et al., 1990; Krishnan et al., 1993). For each pulse of ACTH, depressed patients with an enlarged adrenal cortex would be expected to secrete greater quantities of glucocorticoids than control subjects. Adrenocortical hypertrophy likely underlies the markedly enhanced cortisol response to high doses of ACTH in depression (Kalin et al., 1982; Amsterdam et al., 1985; Linkowski et al., 1985; Jaekle et al., 1987; Krishnan et al., 1991). Indeed, the significant positive correlation between adrenocortical thickness and increased adrenal gland weight of suicide victims suggests that the increased adrenal mass is due to cortical hyperplasia (Szigethy et al., 1994). Multiple studies have observed that adrenal hypertrophy in depressed patients is significantly associated with body weight and not age or gender (Zis and Zis, 1987; Szigethy et al., 1994). Furthermore, adrenal gland enlargement occurring during an episode of major depression appears to be state dependent in that the adrenal glands revert to the size range of nondepressed control subjects after successful antidepressant treatment (Rubin et al., 1995).

Prospective longitudinal studies should help determine whether patients afflicted with a major mood disorder exhibit structural and functional brain alterations before, during, or as a result of affective episodes, and whether these findings exhibit gender-specific “normalization” with clinical improvement. Further research will also determine the diagnostic specificity of morphologic and functional abnormalities associated with the major affective disorders.
Requiring further scrutiny are those brain structures with corticosteroid receptors or major neuroanatomic connections with the HPA axis (e.g., the amygdala and hippocampus) and relevant cortical areas such as the cingulate and medial prefrontal cortex. Vulnerability to affective dysfunction may derive from disruption of neuronal or hormonal connections between the hippocampus and the HPA axis (Jacobson and Sapolsky, 1991) or from interruption of pathways connecting the limbic system and prefrontal cortex (Alexander, Delong, and Strick, 1986; Krishnan et al., 1991).

Conclusions

In summary, HPA-axis hyperactivity in depressed patients can be explained by hypersecretion of CRF and secondary pituitary and adrenal gland hypertrophy, though impaired negative feedback at various CNS sites and the pituitary also likely contributes. HPA-axis activity, as measured by a variety of parameters, including DST nonsuppression (Carroll, 1968; Nemeroff and Evans, 1984), hypercortisolemia (Sachar et al., 1972), hypersecretion of CRF (Nemeroff et al., 1991; DeBellis et al., 1993), blunting of the ACTH response to CRF (Amsterdam et al., 1988), and adrenal gland hypertrophy (Rubin et al., 1995), all appear to be state dependent, usually normalizing after recovery from depression (Carroll, 1968; Nemeroff and Evans, 1984). Indeed, persistence of DST nonsuppression after treatment may predict early relapse or poor prognosis (Arana et al., 1985), as do persistently elevated CSF CRF concentrations. Thus, it is not surprising that agents which alter steroid availability (metapyrone, ketoconazole, dexamethasone) may alleviate depressive symptoms, though it is difficult to reconcile the effectiveness of both glucocorticoid agonists and antagonists (Murphy et al., 1991; Wolkowitz et al., 1993; Arana et al., 1994). Indeed, premenopausal depressed women have increased quantities of an endogenous glucocorticoid antagonist (progesterone) and CBG, a protein capable of binding free cortisol and whose synthesis is stimulated by estrogen. The decreased amounts of ovarian gonadal steroids in depressed postmenopausal women likely contribute to their increased rates of dexamethasone nonsuppression in comparison to depressed premenopausal women. Undoubtedly, future investigations of affective disorders in women will scrutinize the HPG axis and attend to the interplay of the HPA axis with gonadal steroids. Those brain structures with high concentrations of corticosteroid and/or gonadal steroid receptors should be scrutinized via morphologic and functional imaging in order to further characterize the neuroendocrine pathophysiology of unipolar depression.
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