Interactions between the Hypothalamic–Pituitary–Adrenal Axis and the Female Reproductive System: Clinical Implications

George P. Chrousos, MD; David J. Torpy, MB, BS; and Philip W. Gold, MD

The hypothalamic-pituitary-adrenal axis exerts profound, multilevel inhibitory effects on the female reproductive system. Corticotropin-releasing hormone (CRH) and CRH-induced proopiomelanocortin peptides inhibit hypothalamic gonadotropin-releasing hormone secretion, whereas glucocorticoids suppress pituitary luteinizing hormone and ovarian estrogen and progesterone secretion and render target tissues resistant to estradiol. The hypothalamic–pituitary–adrenal axis is thus responsible for the hypogonadism of the Cushing syndrome. Conversely, estrogen directly stimulates the CRH gene promoter and the central noradrenergic system, which may explain adult women's slight hypercortisolism; preponderance of affective, anxiety, and eating disorders; and mood cycles and vulnerability to autoimmune and inflammatory disease, both of which follow estradiol fluctuations. Several components of the hypothalamic–pituitary–adrenal axis and their receptors are present in reproductive tissues as autacoid regulators. These include ovarian and endometrial CRH, which may participate in the inflammatory processes of the ovary (ovulation and luteolysis) and endometrium (blastocyst implantation and menstruation), and placental CRH, which may participate in the physiology of pregnancy and the timing of labor and delivery. The hypercortisolism of the latter half of pregnancy can be explained by high levels of placental CRH in plasma. This hypercortisolism causes a transient postpartum adrenal suppression that, together with estrogen withdrawal, may partly explain the depression and autoimmune phenomena of the postpartum period.

Dr. George P. Chrousos (Developmental Endocrinology Branch, National Institute of Child Health and Human Development [NICHD], National Institutes of Health [NIH], Bethesda, Maryland): Ancient physicians knew of the adverse effects of stress on the reproductive system (1, 2). In the 5th century BCE, Hippocrates of Cos explained the impotence and infertility of the Scythians, nomadic tribes living in what is now southern Ukraine, as a result of their rough lives. About the men, he wrote, "From the cold and tiredness they forget their sexual drive and their desire to come into union with the other sex"; about the women, he stated, "... nor is their menstrual discharge such as it should be, but scanty and at too long intervals." About 500 years later, Soranos of Ephesus published the following differential diagnosis of amenorrhea in his pioneering treatise on gynecology and perinatology:

Of those who do not menstruate, some have no ailment and it is physiological for them not to menstruate, either because of their age, as in those too young or too old, or because they are pregnant, or barren singers and athletes. Others, however, do not menstruate because of a disease of the uterus or of the rest of the body, for example when subjected to under-nourishment, great emaciation and wasting or to the accumulation of fatty flesh, or cachexia, or fevers and long ailment.

The hypothalamic–pituitary–adrenal axis, together with the arousal and autonomic nervous systems, constitutes the stress system (Figure 1). This system is activated during stress and produces the clinical phenomenology of what Hans Selye described as the stress syndrome (3). Indeed, during stress, several changes take place in the central nervous system and periphery of mammals, changes that help preserve the individual and the species. These include the mobilizing of adaptive behaviors and peripheral functions and the inhibiting of biologically costly behaviors and vegetative functions, such as reproduction, feeding, and growth.

The principal molecular regulators of the hypothalamic–pituitary–adrenal axis are corticotropin-releasing hormone (CRH), a 41-amino acid peptide, and the nonapeptide arginine-vasopressin, both of which are secreted by parvicellular neurons of the paraventricular nucleus of the hypothalamus into...
the hypothalamic-pituitary-adrenal axis and locus ceruleus-norepinephrine system (left) primarily through (1) suppression of hypothalamic gonadotropin-releasing hormone secretion by corticotropin-releasing hormone (CRH) and CRH-induced β-endorphin; (2) inhibition of hypothalamic gonadotropin-releasing hormone (GnRH), pituitary luteinizing hormone (LH), and ovarian estradiol (E2) secretion by cortisol; and (3) cortisol-induced target tissue resistance to estradiol. The locus ceruleus-norepinephrine system (right) provides positive input to the reproductive system, which is frequently overcome by the stress-activated hypothalamic-pituitary-adrenal axis. However, sexual stimulation and GnRH neuron activation may render the gonadal axis resistant to suppression by the hypothalamic-pituitary-adrenal axis. Through estradiol, the reproductive system provides positive input to both components of the stress system by stimulating CRH secretion and inhibiting reuptake and catabolism of catecholamines. α-MSH = melanocyte-stimulating hormone; ACTH = adrenocorticotropic hormone; AVP = arginine-vasopressin; FSH = follicle-stimulating hormone; NE (α) = norepinephrine stimulation via α-norenergic receptors; POMC = proopiomelanocortin. Solid line = stimulation; dotted line = inhibition.

The female reproductive system is regulated by the hypothalamic-pituitary-ovarian axis (Figure 1). Neurons that secrete gonadotropin-releasing hormone in the preoptic and arcuate nucleus areas of the hypothalamus secrete into the hypophyseal portal system and stimulate the production of follicle-stimulating and luteinizing hormones, which then activate the ovary to secrete estradiol and progesterone (4). In addition to acting on their other target tissues (other components of the central nervous system, uterus, genitalia, and skin), both of the gonadal steroids and another ovarian hormone, inhibin, exert negative feedback effects on the secretion of follicle-stimulating and luteinizing hormones.

An excellent example of the effect of stress on the female reproductive system is so-called stress-induced or functional hypothalamic amenorrhea (5, 6). Indeed, the prevalence of sustained secondary amenorrhea in normal young women is about 2%. This rate increases markedly in proportion to chronic stress, all the way up to 100% in prisoners before execution. Thus, if severe enough, stress can completely inhibit the female reproductive system.

During her reproductive years, a normal woman is exposed to a monthly fluctuation of circulating estradiol and progesterone that may affect her behavior, mood, and immune and other functions. Indeed, epidemiologic data underscore the effect of gonadal function on nonreproductive processes (7, 8). Thus, suicide attempts and allergic bronchial asthma attacks correlate with the phase of the menstrual cycle, with fourfold increases in prevalence seen when the plasma estradiol level is at its lowest (that is, in the late luteal and menstruation phases) (9, 10). Other studies have suggested that the period of peak estradiol secretion in the state immediately before ovulation is associated with elevations in mood, a phenomenon that might contribute to fecundity.

### Hypothalamic-Pituitary-Adrenal Axis and the Female Reproductive System

Dr. David Torpy (Developmental Endocrinology Branch, NICHD, NIH): The hypothalamic-pituitary-adrenal axis, when activated by stress, has an inhibitory effect on the reproductive system; teleologically, this makes sense (Figure 1; Table 1). Indeed, the hypothalamic CRH neurons innervate and inhibit directly or indirectly, through proopiomelanocortin neurons, the hypothalamic control center of the gonadal axis (11). In addition, glucocorticoids secreted from the adrenal cortex act at the levels of the hypothalamic, pituitary, gonadal, and end-target tissues to suppress the gonadal axis. On the other hand, estradiol exerts a negative, although indirect, effect on the activity of the gonadotropin-releasing

| Stress System | Hypothalamic-pituitary-adrenal axis | Locus ceruleus-norepinephrine system | Reproductive system |
|---------------|-----------------------------------|-------------------------------------|--------------------|
| CRH inhibits gonadotropin-releasing hormone secretion | CRH inhibits β-endorphin | β-endorphin inhibits gonadotropin-releasing hormone secretion | Estradiol stimulates CRH synthesis |
| Cortisol inhibits gonadotropin-releasing hormone secretion | Cortisol inhibits β-endorphin | Cortisol inhibits luteinizing hormone secretion | Estradiol stimulates cortisol-binding globulin secretion |
| Cortisol inhibits estradiol and progesterone biosynthesis | Cortisol inhibits estradiol actions | Estradiol inhibits estradiol actions | Estradiol potentiates noradrenergic actions |

*CRH = corticotropin-releasing hormone.
Glucocorticoids also inhibit estradiol-stimulated uterine growth (16). In one placebo-controlled experiment done in rats, dexamethasone and estradiol were administered for 5 days. Estradiol alone produced the expected increase in uterine weight; this increase was significantly attenuated by daily coadministration of dexamethasone, the effect of which may be partly explained by the reduced intracellular estrogen receptor concentrations measured in this experiment. Most likely, however, glucocorticoid receptor–mediated inhibition of the c-fos/c-jun transcription factor by protein–protein interaction is primarily responsible for this inhibition (17); this factor is used in the signal transduction pathways of many growth factors and is directly or indirectly stimulated by estrogen (18).

Estrogen, which is derived principally from the ovaries, stimulates the hypothalamic–pituitary–adrenal axis (Figure 1). This had been suspected on the basis of sex differences in hypothalamic–pituitary–adrenal axis responses to stimuli in both animals and humans (19). Compared with controls, pregnant women and women receiving high-dose estrogen therapy had elevated levels of free cortisol in both morning and evening plasma samples (20). In addition, hypothalamic–pituitary–adrenal axis responsiveness is greater in women than in men. When ACTH and cortisol responses to ovine CRH were compared in 24 men and 19 women (21), the ACTH peak response was significantly greater in women and the cortisol response was characteristically prolonged in response to higher peak ACTH levels.

Estrogen can induce hyperresponsiveness of the hypothalamic–pituitary–adrenal axis to stimuli in normal men; thus, this effect seems to be due to estrogen rather than to other factors specific to female physiology (22). Recently, estradiol patches were given to normal men who were then subjected to a psychosocial stressor—unprepared public speaking—for 15 minutes. Cortisol and ACTH responses were greater in the estradiol recipients than in the placebo recipients. Similarly, the plasma noradrenaline response in these men was augmented by estrogen, possibly because of the stimulation of CRH neurons (which innervate and stimulate central noradrenergic neurons) or because of direct effects on the production or metabolism of norepinephrine (23, 24). Estrogen stimulation of the hypothalamic–pituitary–adrenal axis may be exerted through interaction of the ligand-activated estrogen receptor with specific DNA sequences, the estrogen-responsive elements, in the promoter of the human CRH gene (25, 26).

Estrogen may exert some of its physiologic negative feedback effect on the reproductive axis through a subpopulation of CRH and proopiomelanocortin neurons in the hypothalamus that secrete gonadotropin-releasing hormone. Generally, this adipose tissue-derived hormone inhibits the hypothalamic–pituitary–adrenal axis and stimulates the reproductive axis. Leptin inhibits the hypothalamic–pituitary–adrenal axis at both the hypothalamic and adrenocortical levels. By contrast, leptin provides positive input to the female reproductive axis through inhibition of the hypothalamic–pituitary–adrenal axis and arcuate proopiomelanocortin neuronal system and through activation of the locus ceruleus-norepinephrine system. The inhibitory effect of proopiomelanocortin neurons on the expression of neuropeptide Y via α-melanocyte-stimulating hormone (α-MSH) and melanocortin receptor type 4 should be noted.

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Figure 3. Hormonal changes and periods of increased vulnerability to mood disturbances and autoimmune disorders during a woman's life span. The increasing activity of the reproductive axis during puberty and the decreasing activity of the same axis during the first stages of menopause are associated with changes in the activity of the stress system, represented here by changes in hypothalamic corticotropin-releasing hormone (CRH) secretion. The monthly concurrent fluctuation of ovarian estradiol and hypothalamic CRH secretion is also shown (see figure 4 for details).

The newly discovered adipocyte-derived peptide hormone leptin interacts directly and indirectly with both the adrenal and gonadal axes, and its levels are higher in women than in men (31, 32) (Figure 2). By promoting satiety and sympathetic system output, leptin is thought to provide the peripheral signal to a central mechanism regulating the size of body fat stores (33). Leptin suppresses the hypothalamic-pituitary-adrenal axis by inhibiting hypothalamic CRH and adrenocortical cortisol secretion (34, 35) while it stimulates gonadal function by potentiating the activity of the gonadotropin-releasing hormone neuron (36). Thus, increasing leptin may be involved in the control of the onset of puberty, a phenomenon long known to be temporally related to the acquisition of a certain fat mass (36-38). Low leptin levels may be involved in the adaptive activation of the hypothalamic-pituitary-adrenal axis and the inhibition of gonadal function that takes place in starvation and anorexia nervosa (39-41). Some of the effects of leptin on the central nervous system are mediated by inhibition of the potent orexogen neuropeptide Y, which normally stimulates the CRH neuron and inhibits the locus ceruleus-norepinephrine system (42-44).

Central and Peripheral Roles of Corticotropin-Releasing Hormone

Dr. George P. Chrousos: The marked changes that take place in a woman's reproductive system during her life are bound to affect the functioning of the stress system. The first of these changes takes place at puberty, when gonadarche is slowly established with increasing ovarian follicle growth and circulating estradiol levels first and then the estab-
lishment of ovulatory menstrual cycles within the next 2 to 3 years (Figure 3). During this time, the stress system receives increasing intermittent positive input from estradiol. Puberty is a period of increasing vulnerability to disorders or states characterized by disturbances or changes in hypothalamic CRH secretion (3, 45), such as melancholic and atypical depression, eating disorders, chronic active alcoholism or other addictions, and chronic active athleticism, as well as seasonal affective disorder, the chronic fatigue and fibromyalgia syndromes, and several autoimmune disorders (Table 2).

Once established, the monthly fluctuations of estradiol that accompany menstrual cycles are expected to influence the secretion of central nervous system CRH and catecholamines until menopause (Figure 4). Decreased secretion of CRH in the late luteal and menstruation phases would be expected and might help explain the presence of luteal dysphoric mood disorder (the premenstrual tension syndrome) and the increased incidence of suicides and enhanced vulnerability to autoimmune and allergic inflammatory phenomena seen during these periods (7, 8, 46, 47) (Table 2). Finally, during the perimenopausal period and early menopause, there is a progressive, intermittent decrease in estradiol levels that would be expected to be associated with decreased activity of the CRH and locus ceruleus-norepinephrine systems and might help explain the characteristic “hot flashes” and so-called climacteric depression (Table 2).

“Reproductive” CRH has been identified in various reproductive tissues and can, accordingly, be ovarian, testicular, endometrial, or placental. It is a form of “tissue” corticotropin-releasing factor (CRH found in peripheral tissues) and is analogous to the “immune” CRH found in immune organs and inflammatory sites (48). The functions of immune CRH may shed light on those of reproductive CRH and are briefly discussed below.

Inflammatory sites examined by immunohistochemistry and extraction-chromatography contain large amounts of immune CRH, which is identical to hypothalamic CRH (48). Endothelial cells, macrophages, and tissue fibroblasts all have CRH in their cytoplasm. Immune neutralization and CRH antagonists experiments have demonstrated marked inhibition of inflammation indices, such as the volume of the inflammatory exudate and its leukocyte concentration (48-51). Immune CRH is present at high levels in many sites of experimental inflammation in the rat and mouse and in all natural inflammatory sites examined thus far in humans. The latter include the inflamed joints of patients with rheumatoid arthritis and osteoarthritis and the thyroid glands of patients with Hashimoto thyroiditis (52, 53). The exact mechanisms by which immune CRH exerts its proinflammatory actions are not known, but one mechanism is the degranulation of mast cells (54). Indeed, CRH causes vasodilation, increases vascular permeability, and allows extravasation of plasma through the capillary vessel walls (48).

In inflammatory sites, CRH is not only generated by immune cells but is also secreted from the terminals of sympathetic postganglionic nerves and primary afferent nerves, whose cell bodies in the sympathetic and dorsal root ganglia contain large amounts of CRH (48). Secretion of immune CRH is suppressed by glucocorticoids and somatostatin. Female rats have greater inflammatory responses and produce more immune CRH in inflammatory sites than male rats do, and the presence of estrogen seems to cause the difference. Despite high local production of immune CRH in inflammatory sites, concurrent plasma concentrations are extremely low, probably as a result of rapid clearance mechanisms.

Corticotropin-releasing hormone and its receptors are also present in rat and human ovaries (Table 3). Ovarian CRH is primarily found in the theca and stroma and also in the cytoplasm of the ovum itself (55, 56). Corticotropin-releasing hormone receptors, which are type 1 (similar to those of the anterior pituitary), are also found primarily in the stroma and theca and in the cumulus oophorus, whereas the follicular fluid contains CRH as well.

### Table 2. Potential Pathogenic Effects of Central and Peripheral Corticotropin-Releasing Hormone in Women*

| Changes                        | States                                      |
|--------------------------------|---------------------------------------------|
| Central CRH                    | Psychiatric hyperconisolism                  |
| Increased secretion            | Melancholic depression                       |
|                                | Eating disorders                             |
|                                | Atypical depression                          |
|                                | Seasonal affective disorder                  |
| Decreased secretion            | Chronic fatigue and fibromyalgia syndromes  |
|                                | Rheumatoid arthritis                         |
|                                | Postpartum blues, depression, and autoimmunity |
|                                | Premenstrual tension syndrome                |
|                                | Climacteric depression                       |

| Peripheral CRH                 | Infammatory disorders                        |
|                                | Premature labor                              |
|                                | Delayed labor                                |
| Increased secretion of immune CRH | Ovarian dysfunction                        |
| Increased secretion of placental CRH | Agranulation                                 |
| Decreased secretion of placental CRH | Defective corpus luteum function             |
| Increased secretion of ovarian CRH | Early menopause                             |
| Decreased secretion of endometrial CRH | Infertility                                 |
|                                | Early spontaneous abortion                   |

*CRH = corticotropin-releasing hormone.
Figure 4. Hormonal changes and period of increased vulnerability to mood disorders and autoimmune phenomena during the menstrual cycle. The decreased activity of the reproductive axis in the late luteal and early follicular phases is associated with concurrent changes in the activity of the stress system, represented here by changes in hypothalamic corticotropin-releasing hormone (CRH) secretion.

The findings suggest that CRH may participate in the communication between the ovum and the cumulus oophorus and may influence ovarian steroid biosynthesis. Incubation of granulosa-lutein cells with CRH suppresses estradiol and progesterone secretion in a dose-dependent, interleukin-1-mediated manner (57, 58). In this sense, ovarian CRH has antireproductive actions that might be related to the earlier menopausal failure of ovaries in women exposed to high psychosocial stress (59). We believe that a major physiologic function of ovarian CRH is its participation in the "aseptic" inflammatory phenomena of the ovary, including ovulation and luteolysis.

The human endometrium also contains CRH (Table 3). In fact, the endometrial glands are full of CRH during both the proliferative and the secretory phases of the cycle (60). In the luteal phase, CRH is probably secreted into the lumen of the uterus, where it may participate in the inflammatory phenomena of blastocyst implantation and (later in the cycle) of menstruation. Compared with interimplantation sites, implantation sites in rat endometrium show local extravasation of plasma and contain increased amounts of CRH messenger RNA and CRH (61). We found CRH expression in human decidualized endometrial stroma and, other researchers demonstrated that CRH itself decidualized endometrial stroma cells synergistically with progesterone (60, 62). It is interesting that the effect of estradiol on CRH transcription in immortalized human uterine epithelial cells seems to be inhibitory rather than stimulatory; this may explain, to some extent, the contraceptive properties of the "day after" pill, which contains high doses of estrogen (63).

The latter half of human pregnancy is associated with hypercortisolism (Figure 5). Indeed, the levels of free plasma cortisol and 24-hour urinary free cortisol excretion in pregnancy overlap with levels in patients with mild Cushing syndrome (64). In the same vein, dexamethasone cannot properly suppress cortisol in late pregnancy, just as it cannot in the Cushing syndrome. Placental CRH causes this hypercortisolism of human pregnancy (Table 3). By 28 to 30 weeks’ gestation, CRH levels in plasma are similar to those in the portal system, whereas the levels of CRH-binding protein are similar to those in nonpregnant women and normal men (65, 66). At 34 to 35 weeks’ gestation, CRH-binding protein concentrations decrease by two thirds, whereas total and free CRH levels are markedly increased in plasma during labor and return to undetectable amounts within hours after delivery.

In the early 1980s, several groups demonstrated that placental CRH was produced by the syncytiotrophoblast, chorion, amnion, and decidua and that it was the product of the same gene that produces hypothalamic CRH (65, 67). Incubation of human placental tissue with CRH caused secretion of β-endorphin and α-melanocyte-stimulating hormone in a dose-dependent manner (68). In addition, CRH caused stimulation of prostaglandin-E2 and prostaglandin-F2α, both of which have a role in labor and delivery; in contrast, CRH receptors were shown in the myometrium, where CRH had a constrictive effect in synergy with oxytocin (69–71). In addition, CRH was found to stimulate nitric oxide production by the endothelium of placental vessels.
and to cause the dilation of these vessels, thus facilitating fetoplacental circulation (72).

To determine whether placental CRH was secreted in a pulsatile or circadian fashion in the third trimester of pregnancy and whether there were any correlations over time between placental CRH and the hypothalamic-pituitary-adrenal axis hormones, we studied normal pregnant women in the 34th week of pregnancy (Figure 6). We found CRH, ACTH, and cortisol pulsations but, in contrast to ACTH and cortisol (which were secreted in a circadian fashion), plasma CRH did not have a circadian rhythm (73). In the time cross-correlation analyses, CRH levels correlated positively with those of ACTH and cortisol, which means that either CRH causes secretion of ACTH and cortisol or cortisol stimulates placental CRH secretion, or both. Indeed, glucocorticoids stimulate placental CRH secretion in cultured human placental cells (74). Thus, in the last trimester of pregnancy, the placenta secretes CRH, which seems to be under the positive influence of cortisol. Circulating placental CRH then causes ACTH secretion, in synergy with portal parvicellular arginine-vasopressin, which thus seems to be responsible for generating the pulsations and circadian rhythm of ACTH and cortisol (75). The persistent elevation of plasma ACTH and α-melanocyte-stimulating hormone levels then may cause some hypertrophy of the adrenal cortices in normal pregnant women.

Thus, placental CRH seems to be responsible for the maternal hypercortisolism of pregnancy; for

| Table 3. Reproductive Corticotropin-Releasing Hormone and Its Potential Physiologic Functions* |
|-----------------------------------------------|
| **Site of Production** | **Function** |
|-------------------------|--------------|
| Ovarian CRH (theca, stroma, ovum) | Suppression of ovarian steroidogenesis |
|                         | Inflammatory phenomena |
|                         | Ovulation |
|                         | Luteolysis |
| Endometrial CRH (endometrial glands, decidua) | Inflammatory phenomena |
|                         | Decidualization |
|                         | Implantation |
|                         | Menstruation |
| Placental CRH (cytotrophoblast, syncytiotrophoblast, amnion, chorion) | Maternal hypercortisolism |
|                         | Fetoplacental circulation |
|                         | Fetal adrenal function |
|                         | Timing of labor |
|                         | Labor and delivery |

* CRH = corticotropin-releasing hormone.
maintaining proper blood supply to the fetus (probably by activating the nitric oxide synthase of these vessels); and, later, before labor begins, for causing increased myometrial contractility. Plasma levels of CRH are markedly elevated in preeclamptic or eclamptic mothers, in mothers with intrauterine infections, and in healthy pregnant women during normal labor. Longitudinal studies of many hundreds of pregnant women demonstrated that in the latter half of pregnancy, one could predict the onset of labor by plasma levels of CRH (76). Thus, women who delivered prematurely had higher levels of CRH, equivalent to those of women close to term; the opposite biochemical profile was seen in women with postmature labor. On the basis of these data, CRH was proposed to be the biological clock that times labor and delivery.

Anoxia, the inflammatory cytokines, several prostaglandins, and glucocorticoids themselves cause placental CRH secretion in vitro and in vivo. This means that sustained anoxia caused by preeclampsia or eclampsia, increases of circulating cytokine levels caused by infection or inflammation, and increases of glucocorticoid concentration caused by physical or emotional stress may all initiate premature labor through increases in CRH secretion (Figure 7). Potent CRH receptor antagonists that might be helpful in delaying premature labor and delivery are being developed, and preliminary results are promising (51).

The clinical implications of placental CRH extend beyond pregnancy, labor, and delivery (76, 77) (Figures 5 and 6). The postpartum period is characterized by an increased incidence of psychiatric and autoimmune manifestations. Indeed, the “post-

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**Figure 6.** Top. The hypothalamic-pituitary-adrenal axis in the nonpregnant (left), pregnant (middle), and postpartum (right) states. Bottom. Heuristic, simplified representation of the secretion of the hypothalamic-pituitary-adrenal axis hormones in the morning and afternoon, corresponding to the states shown in the upper panels. During pregnancy, placental corticotropin-releasing hormone (CRH)-induced hypercortisolism suppresses the hypothalamic CRH neuron. In the immediate postpartum period, the loss of placental CRH and of estradiol input to the hypothalamic CRH neuron results in a period of low hypothalamic CRH secretion and, hence, increased vulnerability to mood disturbances, such as postpartum blues, depression, or psychosis, or to autoimmune disorders, such as postpartum thyroiditis. In the nonpregnant state, the pulsatility and circadian rhythm of the hypothalamic-pituitary-adrenal axis are maintained by pulsations of hypothalamic CRH and arginine-vasopressin (AVP). In the pregnant state, peripheral placental CRH usurps the role of hypothalamic CRH and causes hypercortisolism while pulsatility and circadian rhythm are maintained by arginine-vasopressin. In the postpartum state, hypothalamic (portal) CRH is initially suppressed and gradually returns to normal. During this period, pulsatility and circadian rhythm are possibly maintained by portal arginine-vasopressin as input from portal CRH gradually increases over time; the predominance of arginine-vasopressin might explain the decreased cortisol suppressibility by dexamethasone previously seen in the early postpartum period. ACTH = adrenocorticotropic hormone; E2 = estradiol; P4 = progesterone. Solid line = stimulation; dotted line = inhibition. Adapted from reference 73.
partum blues,” a mild form of transient depression, occurs in 60% to 70% of women; full-blown postpartum depression affects about 10%; and very severe postpartum psychosis affects about 1 in 1000. In addition, autoimmune diseases, such as “postpartum thyroiditis” and rheumatoid arthritis, frequently develop or are acutely exacerbated during the first few months postpartum.

Although several depressive conditions, such as melancholic depression and anorexia nervosa, are typically associated with high hypothalamic CRH secretion, other states, such as atypical or seasonal depression, the chronic fatigue and fibromyalgia syndromes, and the Cushing syndrome before and during the first year after cure, are all associated with decreased production of hypothalamic CRH (3, 77-79). We hypothesized that the postpartum period might be associated with low hypothalamic CRH secretion, which would predispose patients to atypical depression and autoimmune phenomena. We prospectively studied 17 pregnant women who were healthy and had no personal or family history of depression (77). Psychometric testing was done serially beginning with the 20th week of pregnancy and continuing up to a year postpartum. We did ovine CRH stimulation tests at 3, 6, and 12 weeks postpartum. Nine women had normal affect throughout, but 7 developed postpartum blues and 1 developed full-fledged postpartum depression. Plasma levels of ACTH before and after ovine CRH showed little response at 3 weeks, a better but still suppressed response at 6 weeks, and an almost normal response at 12 weeks. Cortisol levels remained in the upper normal range throughout, mostly because plasma cortisol-binding globulin levels were about twice the normal level at 3 weeks, and it took about 3 months or longer for them to decrease to within the normal range. When we separated the women at 3, 6, and 12 weeks into those with the blues or depression and those without a mood dis-
ponents of the stress response, CRH seems to have direct reproductive regulatory roles at the hypothalamus, influencing gonadotropin-releasing hormone secretion, and at the periphery, promoting inflammatory phenomena, such as ovulation and implantation. Placental CRH drives the pituitary-adrenal axis to produce high cortisol secretion during the latter part of pregnancy. Withdrawal of placental CRH after delivery provokes a secondary hypothalamic CRH deficiency with varying consequences for mood disorders and autoimmune phenomena. Corticotropin-releasing hormone may be the placental clock determining the onset of parturition. Thus, disturbances in placental CRH production may account for premature or delayed parturition in some cases. In addition to its profound feminizing effects, estrogen stimulates CRH gene expression and noradrenergic function. Alterations in estrogenic tone during the menstrual cycle, the postpartum period, and the climacteric may be involved in the mood disturbances and alterations in immune function seen at these times.

The World Health Organization has determined that unipolar depression confers greater overall morbidity on women than any other cause does. It is conservatively estimated that 9% to 12% of adult women are affected by unipolar depression, with a ratio of affected females to affected males of at least 2:1. The classic form of depression, melancholia, is a state of pathologic hyperarousal characterized by profound anxiety about the adequacy of self, dread for the future prospects of such a deficient self, insomnia, anorexia, loss of libido, and other manifestations compatible with a hyperfunctional stress system (3, 82). We and others have demonstrated hypersecretion of central nervous system CRH in melancholia, which results not only in the hypercortisolism and increased sympathetic activity of this condition but also in many of its other clinical and biochemical manifestations, including hypogonadism, inhibition of the growth hormone and thyroid axes, and mild immunosuppression (3, 48, 83). The constellation of these biochemical changes leads to several serious public health consequences, including osteoporosis and increased risk for bone fracture (84) and shortened life expectancy, mostly from cardiovascular disease (85). Patients with melancholia have a twofold increased risk for dying from ischemic heart disease and a mortality rate of approximately 50% after acute, serious physical illness (this rate is 10% in nondepressed patients) (86, 87). This may be due to the adverse effects of chronic hypercortisolism on visceral fat, lipid metabolism, insulin sensitivity, blood coagulation, and arterial pressure (for example, changes constituting the metabolic syndrome X and participating in the development of atherosclerosis) (88). Long-term administration of antidepressant agents leads to suppression of CRH secretion and, it is hoped, to alleviation of its long-term behavioral, biochemical, and somatic sequelae (89, 90).

Although melancholic depression is easier to recognize, another prevalent form of major depression— atypical depression—is also more common in women than in men (3, 82). Atypical depression seems to be the antithesis of melancholia. Patients feel lethargic, fatigued, and unmotivated and demonstrate hyperphagia and hypersomnia. Dysphoria in patients with atypical depression more closely reflects feeling less alive than usual rather than intense anxiety about self. Several lines of evidence suggest that the lethargy, fatigue, hypersomnia, and hyperphagia of atypical depression are associated with hyposecretion of CRH (3). This hyposecretion may contribute to a significant increase in the incidence of allergic and autoimmune phenomena in this form of depression and in its two homolog transient states, the postpartum blues or depression and the posture state of patients with the Cushing syndrome (48, 77, 79).

Glossary

Arcuate nucleus: Hypothalamic nucleus that contains neurons secreting peptides of importance to reproduction and the stress response, including gonadotropin-releasing hormone; neuropeptide Y; and proopiomelanocortin-derived peptides, such as β-endorphin and α-melanocytestimulating hormone.

c-fos/c-jun transcription factor: A heterodimeric factor that stimulates the promoters of many genes related to cellular growth and replication.

Locus coeruleus–norepinephrine system: Noradrenergic nuclei of the brain stem that regulate arousal and sympathetic system activity.

Orexigen: Any substance with appetite-stimulating properties, such as neuropeptide Y.

Paraventricular nucleus: Hypothalamic nucleus containing neurons secreting CRH and arginine–vasopressin, which regulate pituitary corticotropin secretion.

Parvicellular neurons: Small-cell body neurons of the hypothalamus that secrete CRH or arginine–vasopressin in the hypophyseal portal system. Contrast with magnocellular neurons that secrete arginine–vasopressin into the systemic circulation.

Proopiomelanocortin: Precursor molecule for corticotropin, β-endorphin, and α-melanocyte-stimulating hormone expressed primarily in the arcuate nucleus of the hypothalamus and the anterior pituitary gland.

Stress: State of threatened homeostasis.
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