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Psychoneuroendocrinology

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1.5 Psychoneuroendocrinology The term psychoneuroendocrinology encompasses the structural and functional relationships between hormonal systems and the central nervous system (CNS) and behaviors that modulate and are derived from both. Classically, hormones have been defined as the products of endocrine glands transported by the blood to exert their action at sites distant from their release. Advances in neuroscience have shown, however, that in the CNS the brain not only serves as a target site for regulatory control of hormonal release but also has secretory functions of its own and serves as an end organ for some hormonal actions. These complex interrelationships make classic distinctions between the origin, structure, and function of neurons and those of endocrine cells dependent of physiological context. **HORMONE SECRETION** Hormone secretion is stimulated by the action of a neuronal secretory product of neuroendocrine transducer cells of the

hypothalamus. Examples of hormone regulators (Table 1.5-1) include corticotropin-releasing hormone (CRH), which stimulates adrenocorticotropin (adrenocorticotrophic hormone [ACTH]); thyrotropin-releasing hormone (TRH), which stimulates release of thyroid-stimulating hormone (TSH); gonadotropin-releasing hormone (GnRH), which stimulates release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH); and somatostatin (somatotropin

release-inhibiting factor [SRIF]) and growth-hormone-releasing hormone (GHRH), which influence growth hormone (GH) release. Chemical signals cause the release of these neurohormones from the median eminence of the hypothalamus into the portal hypophyseal bloodstream and subsequent transport to the pituitary to regulate the release of target hormones. Pituitary hormones in turn act directly on target cells (e.g., ACTH on the adrenal gland) or stimulate the release of other hormones from peripheral endocrine organs. In addition, these hormones have feedback actions that regulate secretion and exert neuromodulatory effects in the CNS. Table 1.5-1 Examples of Regulating Hormones Hormones are divided into two general classes: (1) proteins, polypeptides, and glycoproteins, and (2) steroids and steroid-like compounds (Table 1.5-2); these are secreted by an endocrine gland into the bloodstream and are transported to their sites of action. Table 1.5-2 Classifications of Hormones

DEVELOPMENTAL PSYCHONEUROENDOCRINOLOGY Hormones can have both organizational and activational effects. Exposure to gonadal hormones during critical stages of neural development directs changes in brain morphology and function (e.g., sex-specific behavior in adulthood). Similarly, thyroid hormones are essential for the normal development of the CNS, and thyroid deficiency during critical stages of postnatal life will severely impair growth and development of the brain, resulting in behavioral disturbances that may be permanent if replacement therapy is not instituted. **ENDOCRINE ASSESSMENT** Neuroendocrine function can be studied by assessing baseline measures and by measuring the response of the axis to some neurochemical or hormonal challenge. The first method has two approaches. One approach is to measure a single time point—for example, morning levels of growth hormone; this approach is subject to significant error because of the pulsatile nature of the release of most hormones. The second approach is to collect blood samples at multiple points or to collect 24-hour urine samples; these measurements are less susceptible to major errors. The best approach, however, is to perform a neuroendocrine challenge test, in which the person is given a drug or a hormone that perturbs the endocrine axis in some standard way. Persons with no disease show much less variation in their responses to such challenge studies than in their baseline measurements.

HYPOTHALAMIC-PITUITARY-ADRENAL AXIS Since the earliest conceptions of the stress response, by Hans Selye and others, investigation of hypothalamic-pituitary-adrenal (HPA) function has occupied a central position in psychoendocrine research. CRH, ACTH, and cortisol levels all rise in response to a variety of physical and psychic stresses and serve as prime factors in maintaining homeostasis and developing adaptive responses to novel or challenging stimuli. The hormonal response depends both on the characteristics of the stressor itself and on how the individual assesses and is able to cope with it. Aside from generalized effects on arousal, distinct effects on sensory processing, stimulus habituation and sensitization, pain, sleep, and memory storage and retrieval have been documented. In primates, social status can influence adrenocortical profiles and, in turn, be affected by exogenously induced changes in hormone concentration. Pathological alterations in HPA function have been associated primarily with mood disorders, posttraumatic

stress disorder (PTSD), and dementia of the Alzheimer's type, although recent animal evidence points toward a role of this system in substance use disorders as well. Disturbances of mood are found in more than 50 percent of patients with Cushing's syndrome (characterized by elevated cortisol concentrations), with psychosis or suicidal thought apparent in more than 10 percent of patients studied. Cognitive impairments similar to those seen in major depressive disorder (principally in visual memory and higher cortical functions) are common and relate to the severity of the hypercortisolemia and possible reduction in hippocampal size. In general, reduced cortisol levels normalize mood and mental status. Conversely, in Addison's disease (characterized by adrenal insufficiency), apathy, social withdrawal, impaired sleep, and decreased concentration frequently accompany prominent fatigue. Replacement of glucocorticoid (but not of electrolyte) resolves behavioral symptomatology. Similarly, HPA abnormalities are reversed in persons who are treated successfully with antidepressant medications. Failure to normalize HPA abnormalities is a poor prognostic sign. Alterations in HPA function associated with depression include elevated cortisol concentrations, failure to suppress cortisol in response to dexamethasone, increased adrenal size and sensitivity to ACTH, a blunted ACTH response to CRH, and, possibly, elevated CRH concentrations in the brain.

HYPOTHALAMIC-PITUITARY-GONADAL AXIS

The gonadal hormones (progesterone, androstenedione, testosterone, estradiol, and others) are steroids that are secreted principally by the ovary and testes, but significant amounts of androgens arise from the adrenal cortex as well. The prostate gland and adipose tissue, also involved in the synthesis and storage of dihydrotestosterone, contribute to individual variance in sexual function and behavior. The timing and presence of gonadal hormones play a critical role in the development of sexual dimorphisms in the brain. Developmentally, these hormones direct the organization of many sexually dimorphic CNS structures and functions, such as the size

of the hypothalamic nuclei and corpus callosum, neuronal density in the temporal cortex, the organization of language ability, and responsivity in Broca's motor speech area. Women with congenital adrenal hyperplasia—a deficiency of the enzyme 21-hydroxylase, which leads to high exposure to adrenal androgens in prenatal and postnatal life, in some studies—have been found to be more aggressive and assertive and less interested in traditional female roles than control female subjects. Sexual dimorphisms may also reflect acute and reversible actions of relative steroid concentrations (e.g., higher estrogen levels transiently increase CNS sensitivity to serotonin). Testosterone is the primary androgenic steroid, with both androgenic (i.e., facilitating linear body growth) and somatic growth functions. Testosterone is associated with increased violence and aggression in animals and in correlation studies in humans, but anecdotal reports of increased aggression with testosterone treatment have not been substantiated in investigations in humans. In hypogonadal men, testosterone improves mood and decreases irritability. Varying effects of anabolic-androgenic steroids on mood have been noted anecdotally. A prospective, placebo-controlled study of anabolic-androgenic steroid administration in normal subjects reported positive mood symptoms, including euphoria, increased energy, and sexual arousal, in addition to increases in the negative mood symptoms of irritability, mood swings, violent feelings, anger, and hostility. Testosterone is important for sexual desire in both men and women. In males, muscle mass and strength, sexual activity, desire, thoughts, and intensity of sexual feelings depend on normal testosterone levels, but these functions are not clearly augmented by supplemental testosterone in those with normal androgen levels. Adding small amounts of testosterone to normal hormonal replacement in postmenopausal women has proved, however, to be as beneficial as its use in hypogonadal men. Dehydroepiandrosterone (DHEA) and

DHEA sulfate (DHEA-S) are adrenal androgens secreted in response to ACTH and represent the most abundant circulating steroids. DHEA is also a neurosteroid that is synthesized in situ in the brain. DHEA has many physiological effects, including reduction in neuronal damage from glucocorticoid excess and oxidative stress. Behavioral interest has centered on its possible involvement in memory, mood, and a number of psychiatric disorders. Adrenarche is the prepubertal onset of adrenal production of DHEA-S and may play a role in human maturation through increasing the activity of the amygdala and hippocampus and promoting synaptogenesis in the cerebral cortex. DHEA has been shown to act as an excitatory neurosteroid and to enhance memory retention in mice, but studies of DHEA administration to humans have not consistently shown any improvement in cognition. Several trials of DHEA administration point to an improvement in well-being, mood, energy, libido, and

functional status in depressed individuals. Administration of DHEA to women with adrenal insufficiency (e.g., Addison's disease) has repeatedly been demonstrated to enhance mood, energy, and sexual function; effects in men remain to be assessed. Mood, fatigue, and libido improved in human immunodeficiency virus (HIV)-positive patients treated with DHEA in one study, and DHEA and DHEA-S have been found to be inversely correlated with severity in attention-deficit/hyperactivity disorder (ADHD). Women diagnosed with fibromyalgia have significantly decreased DHEA-S levels, but supplementation does not improve outcome. Several cases of possible DHEA-induced mania have been reported, and DHEA has been reported to be inversely related to extrapyramidal symptoms (EPS) in patients with schizophrenia who are treated with antipsychotics. DHEA administration in these cases improves EPS. Double-blind treatment studies have shown antidepressant effects of DHEA in patients with major depression, midlife-onset dysthymia, and schizophrenia, although beneficial effects on memory have not been reliably demonstrated. A small, double-blind trial of DHEA treatment of Alzheimer's disease failed to reveal significant benefit, although a near-significant improvement in cognitive function was seen after 3 months of treatment. Animal studies suggest that DHEA may be involved in eating behavior, aggressiveness, and anxiety as well, with its effects resulting from its transformation into estrogen, testosterone, or androsterone from its antiglucocorticoid activity, or from direct effects on GABA_A, N-methyl-D-aspartate (NMDA), and σ receptors. Because of the putative antiglucocorticoid effects, the ratio of cortisol to DHEA levels may be particularly important in understanding adaptive responses to stress. Both cortisol and DHEA appear to be involved in fear conditioning, with the cortisol/DHEA ratio hypothesized to be an index of the degree to which an individual is buffered against the negative effects of stress. This ratio has been found to be related to some measures of psychopathology and response to treatment, predicting the persistence of the first episode major depression and being related to degree of depression, anxiety, and hostility in patients with schizophrenia and response to antipsychotic treatment. Patients with PTSD have higher DHEA levels and lower cortisol/DHEA ratios related to symptom severity, suggesting a role in PTSD recovery. Fear-potentiated startle is larger in individuals with high as compared to low cortisol/DHEA-S ratios and is positively associated with cortisol and negatively with DHEA-S. Greater DHEA response to ACTH is related to lower PTSD ratings, and the cortisol/DHEA ratio to negative mood symptoms. A genetic variation in an ACTH receptor promoter has been found to influence DHEA secretion in response to dexamethasone and may underlie some individual differences in stress response. Estrogen and Progesterone Estrogens can influence neural activity in the hypothalamus and limbic system directly through modulation of neuronal excitability, and they have complex multiphasic effects on nigrostriatal dopamine receptor sensitivity. Accordingly,

evidence indicates that the antipsychotic effect of psychiatric drugs can change over the menstrual cycle and that the risk of tardive dyskinesia depends partly on estrogen concentrations. Several studies have suggested that gonadal steroids modulate spatial cognition and verbal memory and are involved in impeding age-related neuronal degeneration. Increasing evidence also suggests that estrogen administration decreases the risk and severity of dementia of the

Alzheimer's type in postmenopausal women. Estrogen has mood-enhancing properties and can also increase sensitivity to serotonin, possibly by inhibiting monoamine oxidase. In animal studies, long-term estrogen treatment results in a decrease in serotonin 5-HT₁ receptors and an increase in 5-HT₂ receptors. In oophorectomized women, significant reductions in tritiated imipramine binding sites (which indirectly measures presynaptic serotonin uptake) were restored with estrogen treatment. The association of these hormones with serotonin is hypothetically relevant to mood change in premenstrual and postpartum mood disturbances. In premenstrual dysphoric disorder, a constellation of symptoms resembling major depressive disorder occurs in most menstrual cycles, appearing in the luteal phase and disappearing within a few days of the onset of menses. No definitive abnormalities in estrogen or progesterone levels have been demonstrated in women with premenstrual dysphoric disorder, but decreased serotonin uptake with premenstrual reductions in steroid levels has been correlated with the severity of some symptoms. Most psychological symptoms associated with the menopause are actually reported during perimenopause rather than after complete cessation of menses. Although studies suggest no increased incidence of major depressive disorder, reported symptoms include worry, fatigue, crying spells, mood swings, diminished ability to cope, and diminished libido or intensity of orgasm. Hormone replacement therapy (HRT) is effective in preventing osteoporosis and reinstating energy, a sense of well-being, and libido; however, its use is extremely controversial. Studies have shown that combined estrogen- progestin drugs (e.g., Premarin) cause small increases in breast cancer, heart attack, stroke, and blood clots among menopausal women. Studies of the effects of estrogen alone in women who have had hysterectomies (because estrogen alone increases the risk for uterine cancer) are ongoing.

HYPOTHALAMIC-PITUITARY-THYROID AXIS Thyroid hormones are involved in the regulation of nearly every organ system, particularly those integral to the metabolism of food and the regulation of temperature, and are responsible for optimal development and function of all body tissues. In addition to its prime endocrine function, TRH has direct effects on neuronal excitability, behavior, and neurotransmitter regulation. Thyroid disorders can induce virtually any psychiatric symptom or syndrome, although no consistent associations of specific syndromes and thyroid conditions are found. Hyperthyroidism is commonly associated with fatigue, irritability, insomnia, anxiety, restlessness, weight loss, and emotional lability; marked impairment in concentration and memory may also be evident. Such states can progress into delirium or mania or they can be episodic. On occasion, a true psychosis develops, with paranoia as a particularly common presenting feature. In some cases, psychomotor retardation, apathy, and withdrawal are the presenting features rather than agitation and anxiety. Symptoms of mania have also been reported following rapid normalization of thyroid status in hypothyroid individuals and may covary with thyroid level in individuals with episodic endocrine dysfunction. In general, behavioral abnormalities resolve with normalization of thyroid function and respond symptomatically to traditional

psychopharmacological regimens. The psychiatric symptoms of chronic hypothyroidism are generally well recognized (Fig. 1.5-1). Classically, fatigue, decreased libido, memory impairment,

and irritability are noted, but a true secondary psychotic disorder or dementia-like state can also develop. Suicidal ideation is common, and the lethality of actual attempts is profound. In milder, subclinical states of hypothyroidism, the absence of gross signs accompanying endocrine dysfunction can result in its being overlooked as a possible cause of a mental disorder. FIGURE 1.5-1 Hands of a patient with hypothyroidism (myxedema), illustrating the swelling of the soft parts, the broadening of the fingers, and their consequent stumpy or pudgy appearance. (Reprint from Douthwaite AH, ed. French's Index of Differential Diagnosis. 7th ed. Baltimore: Williams & Wilkins; 1954, with permission.)

GROWTH HORMONE Growth hormone deficiencies interfere with growth and delay the onset of puberty. Low GH levels can result from a stressful experience. Administration of GH to individuals with GH deficiency benefits cognitive function in addition to its more obvious somatic effects, but evidence indicates poor psychosocial adaptation in adulthood for children who were treated for GH deficiency. A significant percentage of patients with major depressive disorder and dysthymic disorder may have a GH deficiency. Some prepubertal and adult patients with diagnoses of major depressive disorder exhibit hyposecretion of GHRH during an insulin tolerance test, a deficit that has been interpreted as reflecting alterations in both cholinergic and serotonergic mechanisms. A number of GH abnormalities have been noted in patients with anorexia nervosa. Secondary factors, such as weight loss, however, in both major depressive disorder and eating disorders, may be responsible for alterations in endocrine release. Nonetheless, at

least one study has reported that GHRH stimulates food consumption in patients with anorexia nervosa and lowers food consumption in patients with bulimia. Administration of GH to elderly men increases lean body mass and improves vigor. GH is released in pulses throughout the day, but the pulses are closer together during the first hours of sleep than at other times.

PROLACTIN Since its identification in 1970, the anterior pituitary hormone prolactin has been examined as a potential index of dopamine activity, dopamine receptor sensitivity, and antipsychotic drug concentration in studies of CNS function in psychiatric patients and as a correlate of stress responsivity. The secretion of prolactin is under direct inhibitory regulation by dopamine neurons located in the tuberoinfundibular section of the hypothalamus and is, therefore, increased by classical antipsychotic medications. Prolactin also inhibits its own secretion by means of a short-loop feedback circuit to the hypothalamus. In addition, a great number of prolactin-releasing or prolactin-modifying factors have been identified, including estrogen, serotonin (particularly through the 5HT₂ and 5-HT₃ receptors), norepinephrine, opioids, TRH, T₄, histamine, glutamate, cortisol, CRH, and oxytocin, with interaction effects possible. For example, estrogen may promote the serotonin-stimulated release of prolactin. Prolactin is primarily involved in reproductive functions. During maturation, prolactin secretion participates in gonadal development, whereas, in adults, prolactin contributes to the regulation of the behavioral aspects of reproduction and infant care, including estrogen-dependent sexual receptivity and breast-feeding. In female rats, prolactin secretion is strongly stimulated with exposure to pups. In women, basal prolactin levels are elevated in the postpartum period before weaning, and prolactin release is stimulated by suckling. Hyperprolactinemia is associated with low testosterone in men and reduced libido in men and women. In rodents, prolactin level is increased along with corticosterone in response to such stressful stimuli as immobilization, hypoglycemia, surgery, and cold exposure and may be specifically associated with the use of passive coping in the face of a stressor. Prolactin promotes various stress-related behaviors in rats, depending on the condition, such as increasing object-directed exploration while decreasing other exploration. Patients with hyperprolactinemia often

complain of depression, decreased libido, stress intolerance, anxiety, and increased irritability. These behavioral symptoms usually resolve in parallel with decrements in serum prolactin when surgical or pharmacological treatments are used. In psychotic patients, prolactin concentrations and prolactin-related sexual disturbances have been positively correlated with the severity of tardive dyskinesia. Prolactin levels are also positively correlated with negative symptoms in schizophrenia. MELATONIN

Melatonin, a pineal hormone, is derived from the serotonin molecule and it controls photoperiodically mediated endocrine events (particularly those of the hypothalamic-pituitary-gonadal axis). It also modulates immune function, mood, and reproductive performance and is a potent antioxidant and free-radical scavenger. Melatonin has a depressive effect on CNS excitability, is an analgesic, and has seizure-inhibiting effects in animal studies. Melatonin can be a useful therapeutic agent in the treatment of circadian phase disorders such as jet lag. Intake of melatonin increases the speed of falling asleep, as well as its duration and quality. OXYTOCIN Oxytocin, also a posterior pituitary hormone, is involved in osmoregulation, the milk ejection reflex, food intake, and female maternal and sexual behaviors. Oxytocin is theorized to be released during orgasm, more so in women than in men, and is presumed to promote bonding between the sexes. It has been used in autistic children experimentally in an attempt to increase socialization. INSULIN Increasing evidence indicates that insulin may be integrally involved in learning and memory. Insulin receptors occur in high density in the hippocampus and are thought to help neurons metabolize glucose. Patients with Alzheimer's disease have lower insulin concentrations in the cerebrospinal fluid (CSF) than controls, and both insulin and glucose dramatically improve verbal memory. Depression is frequent in patients with diabetes, as are indexes of impaired hormonal response to stress. It is not known whether these findings represent direct effects of the disease or are secondary, nonspecific effects. Some antipsychotics are known to dysregulate insulin metabolism. ENDOCRINE VARIABLES IN PSYCHIATRIC DISORDERS Although it is clear that alterations in endocrine regulation are involved in the pathophysiology and treatment responses of many psychiatric disorders, incorporating these findings into clinical diagnostic assessment and decision-making remains problematic. Large-scale longitudinal or cost-effectiveness studies are rare, despite indications that baseline alterations in glucocorticoid regulation and thyroid status (two of the best studied abnormalities) may actually be useful in subtyping psychiatric disorders and in prediction of outcome. Alterations in HPA/stress regulation underlie a number of psychiatric diagnoses and may serve as complementary independent variables in assigning treatment response and course of illness to the classical behavioral categories that have thus far defined psychiatric practice. Studying genetic polymorphisms in factors regulating hormonal response may help us better understand the influence of hormonal variability on the illness and also possible underlying differences in the nature of the illness reflected in these genetic subtypes.

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