IGF-I PHYSIOLOGY Injected IGF-I (100 μg/kg) induces hypoglycemia, and lower doses improve insulin sensitivity in patients with severe insulin resistance and diabetes. In cachectic subjects, IGF-I infusion (12 μg/kg per hour) enhances nitrogen retention and lowers cholesterol levels. Longer-term subcutaneous IGF-I injections enhance protein synthesis and are anabolic. Although bone formation markers are induced, bone turnover also may be stimulated by IGF-I. IGF-I has only been approved for use in patients with GH-resistance syndromes.

IGF-I side effects are dose-dependent, and overdose may result in hypoglycemia, hypotension, fluid retention, temporomandibular jaw pain, and increased intracranial pressure, all of which are reversible. Avascular femoral head necrosis has been reported. Chronic excess IGF-I administration presumably would result in features of acromegaly.

ADRENOCORTICOTROPIC HORMONE

(See also Chap. 406)

Synthesis ACTH-secreting corticotrope cells constitute about 20% of the pituitary cell population. ACTH (39 amino acids) is derived from the POMC precursor protein (266 amino acids) that also generates several other peptides, including β-lipotropin, β-endorphin, met-enkephalin, α-melanocyte-stimulating hormone (α-MSH), and corticotropin-like intermediate lobe protein (CLIP). The POMC gene is potently suppressed by glucocorticoids and induced by corticotropin-releasing hormone (CRH), arginine vasopressin (AVP), and proinflammatory cytokines, including IL-6, as well as leukemia inhibitory factor.

CRH, a 41-amino-acid hypothalamic peptide synthesized in the paraventricular nucleus as well as in higher brain centers, is the predominant stimulator of ACTH synthesis and release. The CRH receptor is a GPCR that is expressed on the corticotrope and signals to induce POMC transcription.

Secretion ACTH secretion is pulsatile and exhibits a characteristic circadian rhythm, peaking at about 6 A.M. and reaching a nadir about midnight. Adrenal glucocorticoid secretion, which is driven by ACTH, follows a parallel diurnal pattern. ACTH circadian rhythmicity is determined by variations in secretory pulse amplitude rather than changes in pulse frequency. Superimposed on this endogenous rhythm, ACTH levels are increased by physical and psychological stress, exercise, acute illness, and insulin-induced hypoglycemia.

Glucocorticoid-mediated negative regulation of the hypothalamic-pituitary-adrenal (HPA) axis occurs as a consequence of both hypothalamic CRH suppression and direct attenuation of pituitary POMC gene expression and ACTH release. In contrast, loss of cortisol feedback inhibition, as occurs in primary adrenal failure, results in extremely high ACTH levels.

Acute inflammatory or septic insults activate the HPA axis through the integrated actions of proinflammatory cytokines, bacterial toxins, and neural signals. The overlapping cascade of ACTH-inducing cytokines (tumor necrosis factor [TNF]; IL-1, -2, and -6; and leukemia inhibitory factor) activates hypothalamic CRH and AVP secretion, pituitary POMC gene expression, and local pituitary paracrine cytokine networks. The resulting cortisol elevation restrains the inflammatory response and enables host protection. Concomitantly, cytokine-mediated central glucocorticoid receptor resistance impairs glucocorticoid suppression of the HPA. Thus, the neuroendocrine stress response reflects the net result of highly integrated hypothalamic, intrapituitary, and peripheral hormone and cytokine signals acting to regulate cortisol secretion.

Action The major function of the HPA axis is to maintain metabolic homeostasis and mediate the neuroendocrine stress response. ACTH induces adrenocortical steroidogenesis by sustaining adrenal cell proliferation and function. The receptor for ACTH, designated *melanocortin-2 receptor*, is a GPCR that induces steroidogenesis by stimulating a cascade of steroidogenic enzymes (Chap. 406).

GONADOTROPINS: FSH AND LH

Synthesis and Secretion Gonadotrope cells constitute about 10% of anterior pituitary cells and produce two gonadotropin hormones—LH and FSH. Like TSH and hCG, LH and FSH are glycoprotein hormones that comprise α and β subunits. The α subunit is common to these glycoprotein hormones; specificity of hormone function is conferred by the β subunits, which are expressed by separate genes.

Gonadotropin synthesis and release are dynamically regulated. This is particularly true in women, in whom rapidly fluctuating gonadal steroid levels vary throughout the menstrual cycle. Hypothalamic GnRH, a 10-amino-acid peptide, regulates the synthesis and secretion of both LH and FSH. Brain kisspeptin, a product of the *KISS1* gene regulates hypothalamic GnRH release. GnRH is secreted in discrete pulses every 60–120 min, and the pulses in turn elicit LH and FSH pulses (Fig. 401e-3). The pulsatile mode of GnRH input is essential to its action; pulses prime gonadotrope responsiveness, whereas continuous GnRH exposure induces desensitization. Based on this phenomenon, long-acting GnRH agonists are used to suppress gonadotropin levels in children with precocious puberty and in men with prostate cancer (Chap. 115) and are used in some ovulation-induction protocols to reduce levels of endogenous gonadotropins (Chap. 412). Estrogens act at both the hypothalamus and the pituitary to modulate gonadotropin secretion. Chronic estrogen exposure is inhibitory, whereas rising estrogen levels, as occur during the preovulatory surge, exert positive feedback to increase gonadotropin pulse frequency and amplitude. Progesterone slows GnRH pulse frequency but enhances gonadotropin responses to GnRH. Testosterone feedback in men also occurs at the hypothalamic and pituitary levels and is mediated in part by its conversion to estrogens.

Although GnRH is the main regulator of LH and FSH secretion, FSH synthesis is also under separate control by the gonadal peptides inhibin and activin, which are members of the transforming growth factor β (TGF-β) family. Inhibin selectively suppresses FSH, whereas activin stimulates FSH synthesis (Chap. 412).

Action The gonadotropin hormones interact with their respective GPCRs expressed in the ovary and testis, evoking germ cell development and maturation and steroid hormone biosynthesis. In women, FSH regulates ovarian follicle development and stimulates ovarian estrogen production. LH mediates ovulation and maintenance of the corpus luteum. In men, LH induces Leydig cell testosterone synthesis and secretion, and FSH stimulates seminiferous tubule development and regulates spermatogenesis.

THYROID-STIMULATING HORMONE

Synthesis and Secretion TSH-secreting thyrotrope cells constitute 5% of the anterior pituitary cell population. TSH shares a common α subunit with LH and FSH but contains a specific TSH β subunit. TRH is a hypothalamic tripeptide (pyroglutamyl histidylprolinamide) that acts through a pituitary GPCR to stimulate TSH synthesis and secretion; it also stimulates the lactotrope cell to secrete PRL. TSH secretion is stimulated by TRH, whereas thyroid hormones, dopamine, somatostatin, and glucocorticoids suppress TSH by overriding TRH induction.

Thyrotrope cell proliferation and TSH secretion are both induced when negative feedback inhibition by thyroid hormones is removed. Thus, thyroid damage (including surgical thyroidectomy), radiation-induced hypothyroidism, chronic thyroiditis, and prolonged goitrogen exposure are associated with increased TSH levels. Long-standing untreated hypothyroidism can lead to elevated TSH levels as well as thyrotrope hyperplasia and pituitary enlargement, which may be evident on magnetic resonance imaging.

Action TSH is secreted in pulses, although the excursions are modest in comparison to other pituitary hormones because of the low amplitude of the pulses and the relatively long half-life of TSH. Consequently, single determinations of TSH suffice to precisely assess its circulating levels. TSH binds to a GPCR on thyroid follicular cells to stimulate thyroid hormone synthesis and release (Chap. 405).