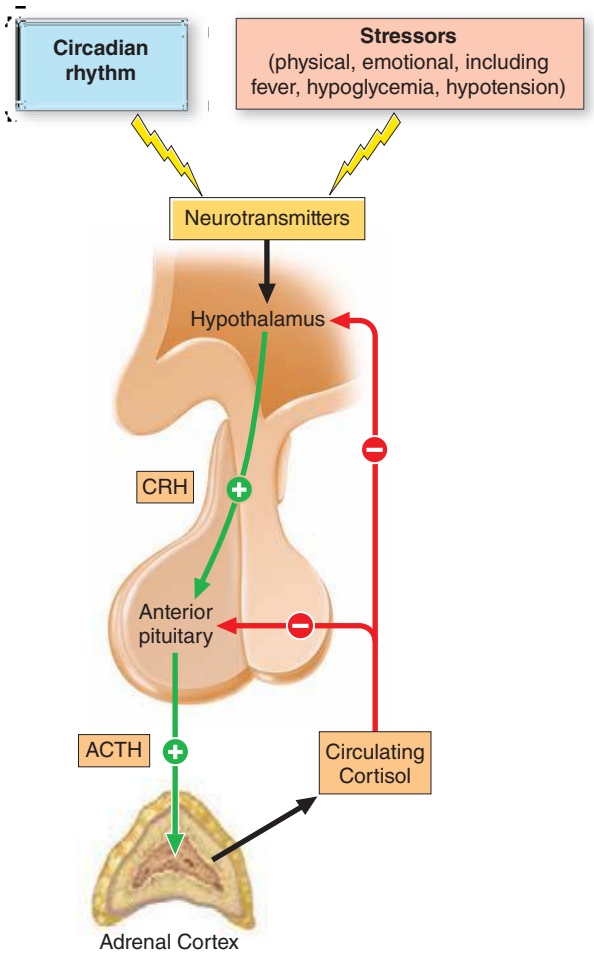

FIGURE 406-2 Regulation of the hypothalamic-pituitary-adrenal (HPA) axis. ACTH, adrenocorticotropic hormone; CRH, corticotropin-releasing hormone.

precursor DHEA. The orphan nuclear receptors SF1 (steroidogenic factor 1; encoded by the gene *NR5A1*) and DAX1 (dosage-sensitive sex reversal gene 1; encoded by the gene *NR0B1*), among others, play a crucial role during this period of development, as they regulate a multitude of adrenal genes involved in steroidogenesis.

REGULATORY CONTROL OF STEROIDOGENESIS

Production of glucocorticoids and adrenal androgens is under the control of the hypothalamic-pituitary-adrenal (HPA) axis, whereas mineralocorticoids are regulated by the renin-angiotensin-aldosterone (RAA) system.

Glucocorticoid synthesis is under inhibitory feedback control by the hypothalamus and the pituitary (Fig. 406-2). Hypothalamic release of corticotropin-releasing hormone (CRH) occurs in response to endogenous or exogenous stress. CRH stimulates the cleavage of the 241–amino acid polypeptide proopiomelanocortin (POMC) by pituitary-specific prohormone convertase 1 (PC1), yielding the 39–amino acid peptide ACTH. ACTH is released by the corticotrope cells of the anterior pituitary and acts as the pivotal regulator of adrenal cortisol synthesis, with additional short-term effects on mineralocorticoid and adrenal androgen synthesis. The release of CRH, and subsequently ACTH, occurs in a pulsatile fashion that follows a circadian rhythm under the control of the hypothalamus, specifically its suprachiasmatic nucleus (SCN), with additional regulation by a complex network of cell-specific clock genes. Reflecting the pattern of ACTH secretion, adrenal cortisol secretion exhibits a distinct circadian rhythm, starting to rise in the early morning hours prior to awakening, with peak levels in the morning and low levels in the evening (Fig. 406-3).

Diagnostic tests assessing the HPA axis make use of the fact that it is regulated by negative feedback. Glucocorticoid excess is diagnosed by employing a dexamethasone suppression test. Dexamethasone, a potent synthetic glucocorticoid, suppresses CRH/ACTH by binding hypothalamic-pituitary glucocorticoid receptors and, therefore, results in downregulation of endogenous cortisol synthesis. Various versions of the dexamethasone suppression test are described in detail in Chap. 403. If cortisol production is autonomous (e.g., adrenal nodule), ACTH is already suppressed and dexamethasone has little additional effect. If cortisol production is driven by an ACTH-producing pituitary adenoma, dexamethasone suppression is ineffective at low doses but usually induces suppression at high doses. If cortisol production is driven by an ectopic source of ACTH, the tumors are usually resistant to dexamethasone suppression. Thus, the dexamethasone suppression test is useful to establish the diagnosis of Cushing's syndrome and to assist with the differential diagnosis of cortisol excess.

Conversely, to assess glucocorticoid deficiency, ACTH stimulation of cortisol production is used. The ACTH peptide contains 39 amino acids but the first 24 are sufficient to elicit a physiologic response. The standard ACTH stimulation test involves administration of cosyntropin (ACTH 1-24), 0.25 mg IM or IV, and collection of blood samples at 0, 30, and 60 min for cortisol. A normal response is defined as a cortisol level >20 μg/dL (>550 nmol/L) 30–60 min after cosyntropin stimulation. A low-dose (1 μg cosyntropin IV) version of this test has been advocated; however, it has no superior diagnostic value and is more cumbersome to carry out. Alternatively, an insulin tolerance test (ITT) can be used to assess adrenal function. It involves injection of insulin to induce hypoglycemia, which represents a strong stress signal that triggers hypothalamic CRH release and activation of the entire HPA axis. The ITT involves administration of regular insulin 0.1 U/kg IV (dose should be lower if hypopituitarism is likely) and collection of blood samples at 0, 30, 60, and 120 min for glucose, cortisol, and growth hormone (GH), if also assessing the GH axis. Oral or IV glucose is administered after the patient has achieved symptomatic hypoglycemia (usually glucose <40 mg/dL). A normal response is defined as a cortisol >20 μg/dL and GH >5.1 μg/L. The ITT requires careful clinical

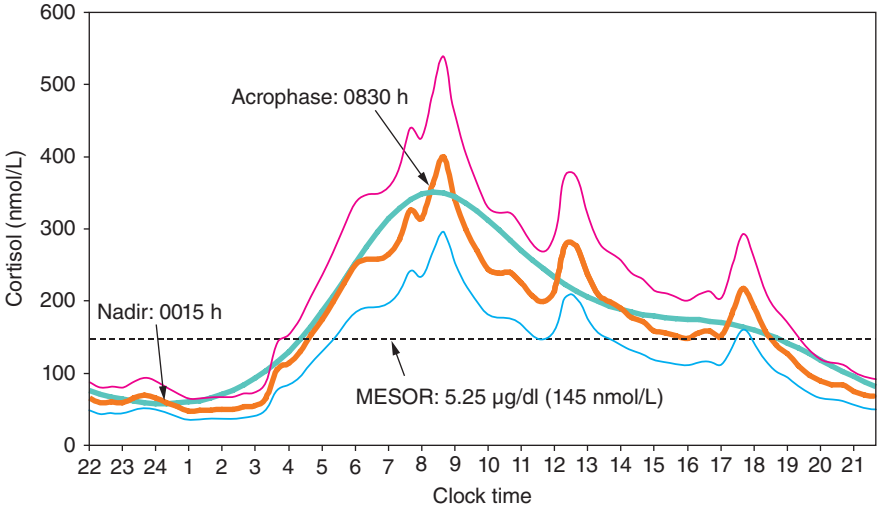

FIGURE 406-3 Physiologic cortisol circadian rhythm. Circulating cortisol concentrations (geometrical mean ± standard deviation values and fitted cosinor) drop under the rhythm-adjusted mean (MESOR) in the early evening hours, with nadir levels around midnight and a rise in the early morning hours; peak levels are observed ~8:30 AM (acrophase). *(Modified after M Debono et al: Modified-release hydrocortisone to provide circadian cortisol profiles. J Clin Endocrinol Metab 94:1548, 2009.)*