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ultrasound, and thyroid scan are also used for the diagnosis of endo crine disorders. However, these tests generally are employed only after a hormonal abnormality has been established by biochemical testing.

■ ■HORMONE MEASUREMENTS AND ENDOCRINE TESTING Immunoassays are the most important diagnostic tool in endocrinol ogy, as they allow sensitive, specific, and quantitative determination of steady-state and dynamic changes in hormone concentrations. Immu noassays use antibodies to detect specific hormones. For many peptide hormones, these measurements are now configured to use two differ ent antibodies to increase binding affinity and specificity. There are many variations of these assays; a common format involves using one antibody to capture the antigen (hormone) onto an immobilized sur face and a second antibody, coupled to a chemiluminescent (immuno chemiluminescent assay [ICMA]) or radioactive (immunoradiometric assay [IRMA]) signal, to detect the antigen. These assays are sensitive enough to detect plasma hormone concentrations in the picomolar to nanomolar range, and they can readily distinguish structurally related proteins, such as PTH from PTH-related peptide (PTHrP). A variety of other techniques are used to measure specific hormones, including mass spectroscopy, various forms of chromatography, and enzymatic methods; bioassays are now used rarely. Mass spectroscopy is increas ingly being used given its ability to quantitatively measure large num bers of peptides or steroids simultaneously. PART 12 Endocrinology and Metabolism Most hormone measurements are based on plasma or serum sam ples. However, urinary hormone determinations remain useful for the evaluation of some conditions. Urinary collections over 24 h provide an integrated assessment of the production of a hormone or metabolite, many of which vary during the day. It is important to ensure complete collections of 24-h urine samples; simultaneous measurement of creati nine provides an internal control for the adequacy of collection and can be used to normalize some hormone measurements. A 24-h urine-free cortisol measurement largely reflects the amount of unbound cortisol, thus providing a reasonable index of biologically available hormone. Other commonly used urine determinations include 17-hydroxycor ticosteroids, 17-ketosteroids, vanillylmandelic acid, metanephrine, catecholamines, 5-hydroxyindoleacetic acid, and calcium. The value of quantitative hormone measurements lies in their correct interpretation in a clinical context. The normal range for most hormones is relatively broad, often varying by a factor of two- to tenfold. The wide normal range reflects the effects of binding proteins as well as circadian rhythms and other physiologic variables. The normal ranges for many hormones are sex- and age-specific. Thus, using the correct normative database is an essential part of interpreting hormone tests. The pulsatile nature of

hormones and factors that can affect their secretion, such as sleep, meals, and medications, must also be considered. Cortisol values increase fivefold between midnight and dawn; reproductive hormone levels vary dramatically during the female menstrual cycle. For many endocrine systems, much information can be gained from basal hormone testing, particularly when different components of an endocrine axis are assessed simultaneously. For example, low testoster one and elevated LH levels suggest a primary gonadal disease, whereas a hypothalamic-pituitary disorder is likely if both LH and testosterone are low. Because TSH is a sensitive indicator of thyroid function, it is generally recommended as a first-line test for thyroid disorders. An elevated TSH level is almost always the result of primary hypothyroid ism, whereas a low TSH is most often caused by thyrotoxicosis. These predictions can be confirmed by determining the free thyroxine level. In the less common circumstance when free thyroxine and TSH are both low, it is important to consider secondary hypopituitarism caused by hypothalamic-pituitary disease. Elevated calcium and PTH levels suggest hyperparathyroidism, whereas PTH is suppressed in hypercal cemia caused by malignancy or granulomatous diseases. A suppressed ACTH in the setting of hypercortisolemia, or increased urine free cor tisol, is seen with hyperfunctioning adrenal adenomas. It is not uncommon, however, for baseline hormone levels associ ated with pathologic endocrine conditions to overlap with the normal range. In this circumstance, dynamic testing is useful to separate

the two groups further. There are a multitude of dynamic endocrine tests, but all are based on principles of feedback regulation, and most responses can be rationalized based on principles that govern the regulation of endocrine axes. Suppression tests are used in the setting of suspected endocrine hyperfunction. An example is the dexamethasone suppression test used to evaluate Cushing’s syndrome (Chaps. 392 and 398). Stimulation tests generally are used to assess endocrine hypo function. The ACTH stimulation test, for example, is used to assess the adrenal gland response in patients with suspected adrenal insuffi ciency. Other stimulation tests use hypothalamic-releasing factors such as corticotropin-releasing hormone (CRH) and growth hormone– releasing hormone (GHRH) to evaluate pituitary hormone reserve (Chap. 392). Insulin-induced hypoglycemia evokes pituitary ACTH and GH responses. Stimulation tests based on reduction or inhibition of endogenous hormones are now used infrequently. Examples include metyrapone inhibition of cortisol synthesis and clomiphene inhibition of estrogen feedback. ■ ■SCREENING AND ASSESSMENT OF COMMON ENDOCRINE DISORDERS Many endocrine disorders are prevalent in the adult population (Table 388-2) and can be diagnosed and managed by general inter nists, family practitioners, or other primary health care providers. The high prevalence and clinical impact of certain endocrine diseases justify vigilance for features of these disorders during routine physical examinations; laboratory screening is indicated in selected high-risk populations. ■ ■FURTHER READING Endocrine Society: The Endocrine Society Clinical Practice Guidelines. Available from https://www.endocrine.org/clinical-practice-guidelines. Loriaux DL: A Biographical History of Endocrinology. Hoboken, Wiley Blackwell, 2016. Robertson RP (ed): DeGroot’s Endocrinology: Adult and Pediatric, 8th ed. Philadelphia, Elsevier, 2023. J. Larry Jameson

Mechanisms of

Hormone Action The endocrine system, composed of various glands and the hormones they produce, regulates growth, metabolism, homeostasis, and repro duction. Because hormones circulate and act via receptors in target tissues, they serve to coordinate physiologic responses to external or internal cues. For example, the light-dark cycle, sensed through the visual system,

modulates hypothalamic corticotropin-releasing hor mone (CRH), which increases pituitary adrenocorticotropin hormone (ACTH) production, leading to increased adrenal cortisol production before the time of waking in the morning. Increased cortisol, in turn, circulates throughout the body, acting via the nuclear glucocorticoid receptor, to activate numerous genetic programs that influence metab olism, the cardiovascular system, behavior, and the immune system. This chapter provides an overview of the different types of hormones and how they function at the cellular level to control myriad physi ologic processes. CLASSES OF HORMONES Hormones can be divided into five major types: (1) amino acid deriva tives such as dopamine, catecholamine, and thyroid hormone; (2) small neuropeptides such as gonadotropin-releasing hormone (GnRH),

thyrotropin-releasing hormone (TRH), somatostatin, and vasopres sin; (3) large proteins such as insulin, luteinizing hormone (LH), and parathyroid hormone (PTH); (4) steroid hormones such as cortisol and estrogen that are synthesized from cholesterol-based precursors; and (5) vitamin derivatives such as retinoids (vitamin A) and vitamin D. A variety of peptide growth factors, such as insulin-like growth factor 1 (IGF1), share actions with hormones but often act more locally. As a rule, amino acid derivatives and peptide hormones interact with cellsurface membrane receptors. Steroids, thyroid hormones, vitamin D, and retinoids are lipid-soluble and bind to intracellular nuclear recep tors, although many also interact with membrane receptors or intracel lular signaling proteins as well. ■ ■HORMONE AND RECEPTOR FAMILIES Hormones and receptors can be grouped into families, reflecting struc tural similarities and evolutionary origins (Table 389-1). The evolution of these families generates diverse but highly selective pathways of hor mone action. Understanding these relationships is useful to extrapolate structural and mechanistic insights gleaned from one hormone or receptor to other family members. The glycoprotein hormone family, consisting of thyroid-stimulating hormone (TSH), follicle-stimulating hormone (FSH), LH, and human chorionic gonadotropin (hCG), illustrates many features of evolution arily related hormones. The glycoprotein hormones are heterodimers that share the α subunit in common; the β subunits are distinct and confer specific biologic actions. The overall three-dimensional archi tecture of the β subunits is similar, reflecting the locations of conserved disulfide bonds that constrain protein conformation. Evolutionary analysis suggests that the β-subunit genes arose from a common ancestral gene through gene duplication and divergence to evolve new biologic functions. As hormone families expand and diverge, their receptors have coevolved to create new biologic functions. Related G protein–coupled receptors (GPCRs), for example, have evolved for each of the glyco protein hormones. These receptors are also structurally similar, and each is coupled predominantly to the Gsα signaling pathway. Because of co-evolution with respective hormones to achieve specificity, there TABLE 389-1 Examples of Membrane Receptor Families and Signaling Pathways RECEPTORS EFFECTORS SIGNALING PATHWAYS G Protein–Coupled Seven-Transmembrane Receptor (GPCR) LH, FSH, TSH, β-adrenergic Stimulation of cyclic AMP production, protein kinase A Gsα, adenylate cyclase Glucagon, PTH, PTHrP, ACTH, MSH, GHRH, CRH Ca2+ channels Calmodulin, Ca2+-dependent kinases Somatostatin, α-adrenergic Giα Inhibition of cyclic AMP production Activation of K+, Ca2+ channels TRH, GnRH Gq, G11 Phospholipase C, diacylglycerol, IP3, protein kinase C, voltage-dependent Ca2+ channels Receptor Tyrosine Kinase Insulin, IGF-I Tyrosine kinases, IRS MAP kinases, PI 3-kinase; AKT Cytokine Receptor–Linked Kinase GH, PRL JAK, tyrosine kinases STAT, MAP kinase, PI 3-kinase, IRS-1 Serine Kinase Activin, TGF-β, MIS Serine kinase Smads Abbreviations: IP3, inositol triphosphate; IRS, insulin receptor substrates; MAP, mitogen-activated protein; MSH, melanocyte-stimulating hormone; PI, phosphatidylinositol; RSK, ribosomal S6 kinase; TGF-β, transforming growth factor β. For all other

abbreviations, see text. Note that most receptors interact with multiple effectors and activate networks of signaling pathways.

is minimal overlap of hormone binding. For example, TSH binds with high specificity to the TSH receptor but interacts minimally with the LH or FSH receptors. Nonetheless, there can be subtle physiologic con sequences of hormone cross-reactivity with other receptors. Very high levels of hCG during pregnancy weakly stimulate the TSH receptor and increase thyroid hormone levels, resulting in feedback inhibition and a compensatory decrease in TSH.

IGF1 and IGF2 have structural similarities that are most apparent when precursor forms of the proteins are compared. In contrast to the high degree of specificity seen with the glycoprotein hormones, there is moderate cross-talk among the members of the insulin/IGF family. High concentrations of an IGF2 precursor produced by certain tumors (e.g., sarcomas) can cause hypoglycemia, partly because of binding to insulin and IGF1 receptors. High concentrations of insulin also bind to the IGF1 receptor, accounting for some of the clinical manifestations seen in conditions with chronic hyperinsulinemia. Mechanisms of Hormone Action CHAPTER 389 Another important example of receptor cross-talk is seen with PTH and parathyroid hormone–related peptide (PTHrP) (Chap. 422). PTH is produced by the parathyroid glands, whereas PTHrP is expressed at high levels during development and by a variety of tumors (Chap. 98). These hormones have amino acid sequence similarity, particularly in their amino-terminal regions. Both hormones bind to the PTH1R receptor that is expressed in bone and kidney. Excessive production of either hormone results in hypercalcemia and hyperphosphatemia, making it difficult to distinguish hyperparathyroidism from hypercal cemia of malignancy solely on the basis of serum chemistries. However, sensitive and specific assays for PTH and PTHrP now allow these dis orders to be distinguished. Based on their specificities for DNA-binding sites, the nuclear receptor family can be subdivided into type 1 receptors (glucocorti coid receptor, mineralocorticoid receptor, androgen receptor, estrogen receptor, progesterone receptor) that bind steroids and type 2 receptors (thyroid hormone receptor, vitamin D receptor, retinoic acid receptor, peroxisome proliferator activated receptor) that bind thyroid hormone, vitamin D, retinoic acid, or lipid derivatives, respectively. Certain functional domains in nuclear receptors, such as the zinc finger DNAbinding domains, are highly conserved. However, selective amino acid differences within this domain confer DNA sequence specificity. The hormone-binding domains are more variable, providing great diversity in the array of small molecules that bind to different nuclear recep tors. With few exceptions, hormone binding is highly specific for a single type of nuclear receptor. One exception involves the glucocor ticoid and mineralocorticoid receptors. Because the mineralocorticoid receptor also binds glucocorticoids with high affinity, an enzyme (11β-hydroxysteroid dehydrogenase) in renal tubular cells inactivates glucocorticoids, allowing selective renal responses to mineralocorti coids such as aldosterone. However, when very high glucocorticoid concentrations occur, as in Cushing’s syndrome, the glucocorticoid degradation pathway becomes saturated, allowing excessive cortisol levels to bind mineralocorticoid receptors leading to sodium retention and potassium wasting. This phenomenon is particularly pronounced in ectopic ACTH syndromes (Chap. 398). Another example of relaxed nuclear receptor specificity involves the estrogen receptor, which can bind an array of compounds, some of which have little apparent struc tural similarity to the high-affinity ligand estradiol. This feature of the estrogen receptor makes it susceptible to activation by “environmental estrogens” such as resveratrol, octylphenol, and many other aromatic hydrocarbons. However, this lack of specificity provides an

opportu nity to synthesize clinically useful antagonists (e.g., tamoxifen) and selective estrogen response modulators (SERMs) such as raloxifene. These compounds generate distinct estrogen receptor conformations that alter receptor interactions with components of the transcription machinery (see below), thereby conferring their unique actions. ■ ■HORMONE SYNTHESIS AND PROCESSING The synthesis of peptide hormones and their receptors occurs through a classic pathway of gene expression: transcription → mRNA → protein → posttranslational protein processing → intracellular sorting, followed by membrane integration or secretion.

Many hormones are embedded within larger precursor polypep tides that are proteolytically processed to yield the biologically active hormone. Examples include proopiomelanocortin (POMC) → ACTH; proglucagon → glucagon; proinsulin → insulin; and pro-PTH → PTH, among others. In many cases, such as POMC and proglucagon, these precursors generate multiple biologically active peptides. For example, proglucagon generates glucagon, as well as glucagon-like peptide 1 (GLP1), among other peptides. It is provocative that hormone precur sors are typically inactive, presumably adding an additional level of control through peptide processing. Prohormone conversion occurs not only for peptide hormones but also for certain steroids (testosterone → dihydrotestosterone) and thyroid hormone (T4 → T3).

PART 12 Endocrinology and Metabolism Peptide precursor processing is intimately linked to intracellular sorting pathways that transport proteins to appropriate vesicles and enzymes, resulting in specific cleavage steps, followed by protein fold ing and translocation to secretory vesicles. Hormones destined for secretion are translocated across the endoplasmic reticulum guided by an amino-terminal signal sequence that subsequently is cleaved. Cell-surface receptors are inserted into the membrane via short seg ments of hydrophobic amino acids that remain embedded within the lipid bilayer. During translocation through the Golgi and endoplasmic reticulum, hormones and receptors are subject to a variety of post translational modifications, such as glycosylation and phosphorylation, which can alter protein conformation, modifying circulating half-life and biological activity. Synthesis of most steroid hormones is based on modifications of the precursor, cholesterol. Multiple regulated enzymatic steps are required for the synthesis of testosterone (Chap. 403), estradiol (Chap. 404), cortisol (Chap. 398), and vitamin D (Chap. 421). This large number of synthetic steps predisposes to multiple genetic and acquired disorders of steroidogenesis. Endocrine genes contain regulatory DNA elements similar to those found in many other genes, but their exquisite control by hormones reflects the presence of specific hormone response elements. For example, the TSH genes are repressed directly by thyroid hormones acting through the thyroid hormone receptor (TR), a member of the nuclear receptor family. Steroidogenic enzyme gene expression requires specific transcription factors, such as steroidogenic factor 1 (SF1), acting in conjunction with signals transmitted by trophic hor mones (e.g., ACTH or LH). Once activated, SF1 functions as a master regulator, inducing a large array of genes required for steroidogenic and metabolic pathways required for steroid synthesis. For some hormones, substantial regulation occurs at the level of translational efficiency. Insulin biosynthesis, although it requires ongoing gene transcription, is regulated primarily at the translational and secretory levels in response to the levels of glucose or amino acids. ■ ■HORMONE SECRETION, TRANSPORT, AND DEGRADATION The circulating level of a hormone is determined by its rate of secre tion and its half-life. After protein processing, peptide hormones (e.g., GnRH, insulin, growth hormone [GH]) are stored in secretory gran ules. As these granules mature, they are poised beneath the plasma membrane for imminent release into the circulation. In most instances, the stimulus for hormone

secretion is a releasing factor or neural signal that induces rapid changes in voltage-gated channel activity or intracel lular calcium concentrations, leading to secretory granule fusion with the plasma membrane and release of its contents into the extracellular environment and bloodstream. Steroid hormones, in contrast, diffuse into the circulation as they are synthesized. Thus, their secretory rates are closely aligned with rates of synthesis. For example, ACTH and LH induce steroidogenesis by stimulating the activity of the steroidogenic acute regulatory (StAR) protein, which transports cholesterol into the mitochondrion. These hormones also induce other rate-limiting enzy matic steps (e.g., cholesterol side-chain cleavage enzyme, CYP11A1) in specific steroidogenic pathways. Hormone transport and degradation dictate the rapidity with which a hormonal signal decays. Some hormone signals are evanescent (e.g., somatostatin), whereas others are longer-lived (e.g., TSH). Because

somatostatin exerts effects in virtually every tissue, a short half-life allows its concentrations and actions to be controlled locally. Structural modifications that impair somatostatin degradation have been useful for generating long-acting therapeutic analogues such as octreotide (Chap. 392). In contrast, the actions of TSH are highly specific for the thyroid gland. Its prolonged half-life generates relatively constant serum levels even though TSH is secreted in discrete pulses. An understanding of circulating hormone half-life is important for achieving physiologic hormone replacement, as the frequency of dosing and the time required to reach steady state are intimately linked to rates of hormone decay. T4, for example, has a circulating half-life of 7 days. Consequently, >1 month is required to reach a new steady state, and single daily doses are sufficient to achieve constant hormone levels. T3, in contrast, has a half-life of 1 day. Its administration is associated with more dynamic serum levels, and it must be administered two to three times per day. Similarly, synthetic glucocorticoids vary widely in their half-lives; those with longer half-lives (e.g., dexamethasone) are associ ated with greater suppression of the hypothalamic-pituitary-adrenal (HPA) axis. Most protein hormones (e.g., ACTH, GH, prolactin [PRL], PTH, LH) have relatively short half-lives (<20 min), leading to sharp peaks of secretion and decay. The only accurate way to profile the pulse frequency and amplitude of these hormones is to measure levels in frequently sampled blood (every 10 min or less) over long durations (8–24 h). Because this is not practical in a clinical setting, an alternative strategy is to pool three to four blood samples drawn at about 30-min intervals or interpret the results in the context of a relatively wide nor mal range. Rapid hormone decay is useful in certain clinical settings. For example, the short half-life of PTH allows the use of intraoperative PTH levels to confirm successful removal of a parathyroid adenoma. This is particularly valuable diagnostically when there is a possibility of multicentric disease or parathyroid hyperplasia, as occurs with mul tiple endocrine neoplasia (MEN) or renal insufficiency. Many hormones circulate in association with serum-binding pro teins. Examples include (1) T4 and T3 binding to thyroxine-binding globulin (TBG), albumin, and thyroxine-binding prealbumin (TBPA); (2) cortisol binding to cortisol-binding globulin (CBG); (3) androgen and estrogen binding to sex hormone–binding globulin (SHBG); (4) IGF1 and IGF2 binding to multiple IGF-binding proteins (IGFBPs); (5) GH interactions with GH-binding protein (GHBP), a circulating fragment of the GH receptor extracellular domain; and (6) activin binding to follistatin. These interactions provide a hormone reservoir, prevent otherwise rapid degradation of unbound hormones, restrict hormone access to certain sites (e.g., IGFBPs), and modulate the levels of unbound, or “free,” hormone concentrations. Although a variety of binding protein abnormalities have been identified, most have little clinical consequence aside from creating diagnostic problems. For example, TBG deficiency can reduce total thyroid hormone levels greatly, but the

free concentrations of T4 and T3 remain normal. Liver disease and certain medications can also influence binding protein lev els (e.g., estrogen increases TBG) or cause displacement of hormones from binding proteins (e.g., salsalate displaces T4 from TBG). In gen eral, only unbound hormone is available to interact with receptors and thus elicit a biologic response. Short-term perturbations in binding proteins change the free hormone concentration, which in turn induces compensatory adaptations through feedback loops. SHBG changes in women are an exception to this self-correcting mechanism. When SHBG decreases because of insulin resistance or androgen excess, the unbound testosterone concentration is increased, potentially contrib uting to hirsutism in women with polycystic ovary syndrome (PCOS) (Chap. 406). The increased unbound testosterone level does not result in an adequate compensatory feedback correction because estrogen, not testosterone, is the primary regulator of the reproductive axis. An additional exception to the unbound hormone hypothesis involves megalin, a member of the low-density lipoprotein (LDL) receptor family that serves as an endocytotic receptor for thyroglobu lin, carrier-bound vitamins A and D, and SHBG-bound androgens and estrogens. After internalization, the carrier proteins are degraded in lysosomes and release their bound ligands within the cells. Other membrane transporters have also been identified for thyroid hormones.

Hormone degradation can be an impor tant mechanism for regulating concentrations locally. As noted above, 11β-hydroxysteroid dehydrogenase inactivates glucocorticoids in renal tubular cells, preventing actions through the mineralocorticoid receptor. Thyroid hormone deiodinases convert T4 to T3 and can inactivate T3. During devel opment, degradation of retinoic acid by Cyp26b1 prevents primordial germ cells in the male from entering meiosis, as occurs in the female ovary. Activin/MIS/BMP TGF-β Serine kinase ■ ■HORMONE ACTION THROUGH RECEPTORS Receptors for hormones are divided into two major classes: membrane and nuclear. Mem brane receptors primarily bind peptide hor mones and catecholamines. Nuclear receptors bind small molecules that can diffuse across the cell membrane, such as steroids and vitamin D. Certain general principles apply to hormone-receptor interactions regardless of the class of receptor. Hormones bind to receptors with specificity and an affinity that generally coincides with the dynamic range of circulating hormone concentrations. Low con centrations of free hormone (usually 10−12 to 10−9 M) rapidly associate and dissociate from receptors in a bimolecular reaction such that the occupancy of the receptor at any given moment is a function of hor mone concentration and the receptor’s affinity for the hormone. Recep tor numbers vary greatly in different target tissues, providing one of the major determinants of tissue-specific responses to circulating hor mones. For example, ACTH receptors are located almost exclusively in the adrenal cortex, and LH receptors are found predominantly in the gonads. In contrast, insulin and TRs are widely distributed, reflecting the need for metabolic responses in all tissues. FIGURE 389-1 Membrane receptor signaling. MAPK, mitogen-activated protein kinase; PKA, C, protein kinase A, C; TGF, transforming growth factor. For other abbreviations, see text. ■ ■MEMBRANE RECEPTORS Membrane receptors for hormones can be divided into several major groups: (1) seven-transmembrane GPCRs, (2) tyrosine kinase receptors, (3) cytokine receptors, and (4) serine kinase receptors (Fig. 389-1). The seven-transmembrane GPCR family binds a huge array of hormones, including large proteins (e.g., LH, PTH), small pep tides (e.g., TRH, somatostatin), catecholamines (epinephrine, dopa mine), and even minerals (e.g., calcium). The extracellular domains of GPCRs vary widely in size and are the major binding site for large hormones. The transmembrane-spanning regions are composed of hydrophobic α-helical domains that traverse the lipid bilayer. Like some channels, these domains are thought to circularize and form a hydrophobic pocket into which certain small ligands fit.

Hormone binding induces conformational changes in these domains, transduc ing structural changes to the intracellular domain, which is a docking site for G proteins. The large family of G proteins, so named because they bind guanine nucleotides (guanosine triphosphate [GTP], guanosine diphosphate [GDP]), provides great diversity for coupling receptors to different signaling pathways. G proteins form a heterotrimeric complex that is composed of various α and βγ subunits (Fig. 389-2). The α subunit contains the guanine nucleotide–binding site and an intrinsic GTPase that hydrolyzes GTP → GDP. The βγ subunits are tightly associated and modulate the activity of the α subunit as well as mediating their own effector signaling pathways. G protein activity is regulated by a cycle that involves GTP hydrolysis and dynamic interactions between the α and βγ subunits. Hormone binding to the receptor induces GDP dissociation, allowing Gα to bind GTP and dissociate from the βγ com plex. Under these conditions, the Gα subunit is activated and mediates signal transduction through various enzymes, such as adenylate cyclase and phospholipase C. GTP hydrolysis to GDP allows reassociation with the βγ subunits and restores the inactive state. G proteins interact with

G protein–coupled Seven transmembrane Cytokine/GH/PRL Insulin/IGF-I Tyrosine kinase Membrane Mechanisms of Hormone Action CHAPTER 389 G protein PKA, PKC JAK/STAT Signaling pathways Ras/Raf MAPK Smads Nucleus Target gene other cellular proteins, including kinases, channels, G protein–coupled receptor kinases (GRKs), and arrestins, that mediate signaling as well as receptor desensitization and recycling. A variety of endocrinopathies result from mutations in GPCRs that alter their interactions with G proteins (Table 389-2). Loss-of-function mutations are generally recessive and inactivate the relevant hormone signaling pathway. Because many of these receptors are important for development as well as signaling, patient presentations resemble glandular failure syndromes (e.g., mutations in LH-R, FSH-R, TSH-R). Gain-of-function (GOF) mutations are more complex. Selected GOF mutations induce conformational changes in the GPCR that mimic the activated state normally induced by hormone binding. These GOF mutations result in a constitutively active state in which G protein coupling stimulates cell signaling pathways, most commonly via cyclic adenosine 5′-monophosphate (cAMP) and protein kinase A. When mutations occur in the germline, the conditions are heritable and pres ent in early life (e.g., LH-R, TSH-R). Sporadic, somatic mutations can also occur and result in clonal expansion of hyperfunctioning cells. Mutations in the TSH-R illustrate the range of possible clinical con sequences of GPCR mutations. Recessive inactivating mutations in the TSH-R cause congenital hypothyroidism with thyroid gland hypoplasia and resistance to TSH. Clinically, the hormone profile resembles pri mary hypothyroidism with low T4 and high TSH. On the other hand, germline activating mutations cause congenital hyperthyroidism. The disorder is autosomal dominant because an activating mutation of one TSH-R allele is sufficient to induce cellular hyperfunction and disease. Because the TSH-R is activated in every cell of the thyroid, there is hyperplastic growth and hyperfunction that resembles the pathology seen in Graves' disease. This unusual disorder presents in infancy and must be distinguished from the more common clinical circumstance in which maternal antibodies in women with active or previously treated Graves' disease cross the placenta and stimulate the thyroid gland of the fetus. If an activating TSH-R mutation occurs later in life, in the somatic tissue, there is clonal expansion of the thyrocyte harboring the mutation, ultimately leading to an autonomous hyperfunctioning thyroid nodule. Of note, a similar condition can be caused by somatic mutations in Gsα. In this case, the Gsα GTPase is inactivated and GTP cannot be converted to GDP. Consequently, the Gsα signaling pathway in this particular cell is constitutively active, mimicking chronic TSH stimulation and again leading to clonal expansion and an autonomous

hyperfunctioning thyroid nodule. About one-third of hyperfunction ing “hot” thyroid nodules harbor sporadic mutations in either the TSH-R or Gsα (TSH-R mutations are more common). Gsα mutations in tissues other than the thyroid can also cause endo crine disease. For example, Gsα mutations in pituitary somatotropes

G protein-coupled receptor Ligand bound Membrane β γ Gαs GTP GTP GDP PART 12 Endocrinology and Metabolism cAMP Cycling Cell growth and signaling FIGURE 389-2 G protein signaling. G protein–coupled receptors (GPCRs) signal via the family of G proteins, so named because they bind guanylyl nucleotides. In the example shown, a GPCR bound to a ligand induces GDP dissociation, allowing Gsα to bind GTP and dissociate from the βγ complex. GTP-bound Gsα increases cAMP production by adenylyl cyclase and activates the protein kinase A pathway. Not shown are separate signaling pathways activated by the βγ complex. When GTP is converted to GDP by an intrinsic GTPase, the βγ subunits reassociate with GDP-bound Gsα and the complex returns to an inactive state. As noted in the text, mutations in Gsα that eliminate GTPase activity result in constitutive activation of receptor signaling pathways because GTPbound Gsα cannot be converted to its GDP-bound inactive state. cAMP, cyclic adenosine 5′-monophosphate; GDP, guanosine diphosphate; Gsα, G protein α; GTP, guanosine triphosphate. mimic activation of the growth hormone–releasing hormone (GHRH) pathway and lead to GH-producing adenomas and acromegaly. Rarely, mutations in other components of the protein kinase A pathway in somatotropes can also cause GH-producing adenomas. Gsα mutations that occur early in development (typically mosaic) cause McCuneAlbright syndrome (Chap. 424), and the clinical features are mani fest because the activated G protein pathway mimics the actions of various hormones (PTH, melanocyte-stimulating hormone [MSH], TSH, GHRH) in different tissues. Germline inactivating Gsα muta tions cause a range of disorders that are transmitted and expressed in a complex manner because the locus is imprinted (Chap. 422). These conditions include Albright’s hereditary osteodystrophy (AHO), pseu dopseudohypoparathyroidism (PPHP), and pseudohypoparathyroid ism types 1b, 1c, and 2. The tyrosine kinase receptors transduce signals for insulin and a variety of growth factors, such as IGF1, epidermal growth factor (EGF), nerve growth factor, platelet-derived growth factor, and fibro blast growth factors. The cysteine-rich extracellular domains contain binding sites for the growth factors. After ligand binding, this class of receptors undergoes autophosphorylation, inducing interactions with intracellular adaptor proteins such as Shc and insulin receptor sub strates (IRS). In the case of the insulin receptor, multiple kinases are activated, including the Raf-Ras-MAPK and the Akt/protein kinase B pathways. The tyrosine kinase receptors play a prominent role in cell growth and differentiation as well as in intermediary metabolism. The GH and PRL receptors belong to the cytokine receptor family. Analogous to the tyrosine kinase receptors, ligand binding induces receptor interaction with intracellular kinases—the Janus kinases (JAKs), which phosphorylate members of the signal transduction and activators of transcription (STAT) family—as well as with other signal ing pathways (Ras, PI3-K, MAPK). The activated STAT proteins trans locate to the nucleus and stimulate expression of target genes. The serine kinase receptors mediate the actions of activins, trans forming growth factor β, müllerian-inhibiting substance (MIS; also known as anti-müllerian hormone [AMH]), and bone morphogenic proteins (BMPs). This family of receptors (consisting of type I and II subunits) signals through proteins termed smads (fusion of terms for Caenorhabditis elegans sma + mammalian mad). Like the STAT proteins, the smads serve a dual role of transducing the receptor signal and acting as transcription factors. The pleomorphic actions of these

growth factors dictate that they act primarily in a local (paracrine or autocrine) manner. Bind ing proteins such as follistatin (which binds activin and other members of this family) func tion to inactivate the growth factors and restrict their distribution. Ligand unbound Disease-causing mutations also occur in each of these classes of receptors. For example, insulin receptor mutations cause an extreme form of insulin resistance. GH receptor muta tions cause Laron-type dwarfism, character ized by low IGF1 and high GH. AMH receptor mutations cause persistent müllerian duct syn drome. These hormone resistance syndromes are autosomal recessive and relatively uncom mon. Unlike the GPCRs, activating mutations are unusual, although they do occur for the RET tyrosine kinase receptor, which causes the autosomal dominant disorder MEN type 2 (MEN2) (Chap. 400). Gαs β γ GDP ■ ■NUCLEAR RECEPTORS The family of nuclear receptors has nearly 100 members, many of which are still classified as orphan receptors because their ligands, if they exist, have not been identified (Fig. 389-3). Otherwise, most nuclear receptors are classi fied on the basis of their ligands. Although all nuclear receptors ultimately act to increase or decrease gene transcription, some (e.g., glucocorticoid receptor) reside primarily in the cytoplasm, whereas others (e.g., TR) are located in the nucleus. After ligand binding, the cytoplasmically localized recep tors translocate to the nucleus. There is growing evidence that certain ligands and their nuclear receptors (e.g., glucocorticoid, estrogen) can also act at the membrane or in the cytoplasm to modulate signal transduction pathways, providing a mechanism for cross-talk between membrane and nuclear receptors. The structures of nuclear receptors have been studied extensively, including by x-ray crystallography. The DNA-binding domain, consist ing of two zinc fingers, contacts specific DNA recognition sequences in target genes. Most nuclear receptors bind to DNA as dimers. Conse quently, each monomer recognizes an individual DNA motif, referred to as a “half-site.” The steroid receptors, including the glucocorticoid, estrogen, progesterone, and androgen receptors, bind to DNA as homodimers. Consistent with this twofold symmetry, their DNA rec ognition half-sites are palindromic. The thyroid, retinoid, peroxisome proliferator activated, and vitamin D receptors bind to DNA pref erentially as heterodimers in combination with retinoid X receptors (RXRs). Their DNA half-sites are typically arranged as direct repeats. The carboxy-terminal hormone-binding domains mediate tran scriptional control. For type II receptors such as TR and retinoic acid receptor (RAR), co-repressor proteins bind to the receptor in the absence of ligand and silence gene transcription. Hormone binding induces conformational changes in the receptor, triggering the release of co-repressors and the recruitment of coactivators that stimulate transcription. Thus, these receptors are capable of mediating dynamic changes in the level of gene activity. Disease states can be associated with defective regulation of these events. For example, in promy elocytic leukemia, fusion of RARα to other nuclear proteins causes aberrant gene silencing that prevents normal cellular differentiation. Treatment with retinoic acid reverses this repression and allows cellular differentiation and apoptosis to occur. Most type 1 steroid receptors interact weakly with co-repressors, but ligand binding still induces interactions with an array of coactivators. X-ray crystallography shows that various SERMs induce distinct estrogen receptor conforma tions. The tissue-specific responses caused by these agents in breast, bone, and uterus appear to reflect distinct interactions with various coactivators. The receptor-coactivator complex stimulates gene tran scription by several pathways, including (1) recruitment of enzymes

TABLE 389-2 Genetic Causes of G protein Receptor Disorders RECEPTOR DISORDER GENETICS LH Leydig cell hypoplasia (male) Primary amenorrhea, resistance to LH (female) Familial male precocious puberty (male) Leydig cell adenoma, precocious puberty (male) AR, inactivating AR, inactivating AD, activating Sporadic, activating FSH Hypergonadotropic ovarian failure (female)

Hypospermia (male) Ovarian hyperstimulation (female) AR, inactivating AR, inactivating Sporadic, activating TSH Congenital hypothyroidism, TSH resistance Nonautoimmune familial hyperthyroidism Hyperfunctioning thyroid adenoma AR, AD, inactivating AD, activating Sporadic, activating GnRH Hypogonadotropic hypogonadism AR, inactivating Kisspeptin Hypogonadotropic hypogonadism Precocious puberty AR, inactivating AD, activating Prokineticin Precocious puberty Sporadic, activating TRH Central hypothyroidism AR, inactivating GHRH GH deficiency AR, inactivating PTH Blomstrand chondrodysplasia Jansen metaphyseal chondrodysplasia AR, inactivating AD, activating Calcium sensing receptor Familial hypocalciuric hypercalcemia Neonatal severe hyperparathyroidism Familial hypocalcemic hypercalciura AD, inactivating AR, inactivating AD, activating Arginine vasopressin receptor 2 Nephrogenic diabetes insipidus Nephrogenic SIADH XL, inactivating XL, activating ACTH Familial ACTH resistance ACTH-independent Cushing syndrome AR, inactivating Sporadic, activating Melanocortin 4 Severe obesity Codominant, inactivating Abbreviations: ACTH, adrenocorticotropin hormone; AD, autosomal dominant; AR, autosomal recessive; FSH, follicle-stimulating hormone; GH, growth hormone; GHRH, growth hormone–releasing hormone; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone; PTH, parathyroid hormone; SIADH, syndrome of inappropriate antidiuretic hormone secretion; TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone; XL, X-linked. Homodimer Steroid Heterodimer Receptors Receptors ER, AR, PR, GR Ligands DNA response elements Ligand induces coactivator binding Ligand dissociates corepressors and induces coactivator binding Constitutive activator or repressor binding Gene Expression Activated Activated + – + – + – Basal Hormone Receptor Hormone FIGURE 389-3 Nuclear receptor signaling. AR, androgen receptor; DAX, dosage-sensitive sex-reversal, adrenal hypoplasia congenita, X chromosome; ER, estrogen receptor; GR, glucocorticoid receptor; HNF4α, hepatic nuclear factor 4α; PPAR, peroxisome proliferator activated receptor; PR, progesterone receptor; RAR, retinoic acid receptor; SF-1, steroidogenic factor-1; TR, thyroid hormone receptor; VDR, vitamin D receptor.

(histone acetyl transferases) that modify chromatin structure, (2) inter actions with additional transcription factors on the target gene, and (3) direct interactions with components of the general transcription apparatus to enhance the rate of RNA polymerase II–mediated tran scription. Studies of nuclear receptor–mediated transcription reveal relatively rapid (e.g., 30–60 min) cycling of transcription complexes on any specific target gene.

Nuclear receptor mutations are an important cause of endocrine dis ease. Androgen receptor mutations cause androgen insensitivity syn drome (AIS) (Chap. 402). Because the androgen receptor is located on the X chromosome, phenotypic expression is more commonly manifest than with other nuclear receptor disorders. Affected individuals with AIS are XY phenotypic females with retained testes and male-range testosterone levels. Tissue insensitivity to androgens varies based on the severity of the mutation. Müllerian structures are absent because Sertoli cells of the testis produce AMH during development. Female carriers of androgen receptor mutations are phenotypically normal. Recessive mutations of the estrogen, glucocorticoid, and vitamin D receptors occur but are rare. Mechanisms of Hormone Action CHAPTER 389 Thyroid hormone receptor β (TRβ) mutations have an unusual pathophysiology. They are autosomal dominant and function via a “dominant negative” mechanism to cause resistance to thyroid hor mone (RTH) (Chap. 394). The mutations occur in selected regions of the TRβ hormone-binding domain and preserve the ability of the mutant receptor to heterodimerize with RXR, interact with corepressors, and bind to DNA regulatory sites. The mutant receptors function as antagonists of receptors from

the normal copy of the TRβ gene. Affected patients have high T4 and T3 and inappropriately ele vated (unsuppressed) TSH, reflecting impaired feedback regulation of the hypothalamic-pituitary-thyroid axis. Organ systems are vari ably resistant to thyroid hormones based on the relative expression of TRβ and TRα. Mutations in the genes encoding TRα and PPARγ can also cause disease by functioning in an analogous dominant negative manner. FUNCTIONS OF HORMONES The functions of individual hormones are described in detail in subsequent chapters. Nevertheless, it is useful to illustrate how most biologic responses require the integration of several different hormone pathways. The physiologic functions of hormones can be divided into three general types: (1) growth and differentiation, (2) maintenance of homeostasis, and (3) reproduction. Orphan Receptors SF-1, DAX-1, HNF4α TR, VDR, RAR, PPAR Activated Silenced

■ ■GROWTH Multiple hormones and nutritional factors mediate the complex phe nomenon of growth (Chap. 390). Short stature may be caused by GH deficiency, hypothyroidism, Cushing's syndrome, precocious puberty, malnutrition, chronic illness, or genetic abnormalities that affect the epiphyseal growth plates (e.g., FGFR3 and SHOX mutations). Many factors (GH, IGF1, thyroid hormones) stimulate growth, whereas others (sex steroids) lead to epiphyseal closure. Understanding these hormonal interactions is important in the diagnosis and management of growth disorders. For example, delaying exposure to high levels of sex steroids may enhance the efficacy of GH treatment.

PART 12 Endocrinology and Metabolism ■ ■MAINTENANCE OF HOMEOSTASIS Although virtually all hormones affect homeostasis, the most impor tant among them are the following:

1. Thyroid hormone—controls ~25% of basal metabolism in most tissues.
2. Cortisol—exerts a permissive action for many hormones in addition to its own direct effects.
3. PTH—regulates calcium and phosphorus levels.
4. Vasopressin—regulates serum osmolality by controlling renal freewater clearance.
5. Mineralocorticoids—control vascular volume and serum electrolyte (Na+, K+) concentrations.
6. Insulin—maintains euglycemia in the fed and fasted states. The defense against hypoglycemia is an impressive example of inte grated hormone action (Chap. 418). In response to the fasting state and falling blood glucose, insulin secretion is suppressed, resulting in decreased glucose uptake and enhanced glycogenolysis, lipolysis, proteolysis, and gluconeogenesis to mobilize fuel sources. If hypogly cemia develops (usually from insulin administration or sulfonylureas), an orchestrated counterregulatory response occurs—glucagon and epinephrine rapidly stimulate glycogenolysis and gluconeogenesis, whereas GH and cortisol act over several hours to raise glucose levels and antagonize insulin action. Although free-water clearance is controlled primarily by vasopres sin, cortisol and thyroid hormone are also important for facilitating renal tubular responses to vasopressin (Chap. 393). PTH and vitamin D function in an interdependent manner to control calcium metabo lism (Chap. 421). PTH stimulates renal synthesis of 1,25-dihydroxyvi tamin D, which increases calcium absorption in the gastrointestinal tract and enhances PTH action in bone. Increased calcium, along with vitamin D, feeds back to suppress PTH, thus maintaining calcium balance. Depending on the severity of a specific stress and whether it is acute or chronic, multiple endocrine and cytokine pathways are

activated to mount an appropriate physiologic response. In severe acute stress such as trauma or shock, the sympathetic nervous system is activated, and catecholamines are released, leading to increased cardiac output and a primed musculoskeletal system. Catecholamines also increase mean blood pressure and stimulate glucose production. Multiple stressinduced pathways converge on the hypothalamus, stimulating several hormones, including vasopressin and CRH. These hormones, in addi tion to cytokines (tumor necrosis factor α, interleukin [IL] 2, IL-6), increase ACTH and GH production. ACTH stimulates the adrenal gland, increasing cortisol, which in turn helps sustain blood pressure and dampen the inflammatory response. Increased vasopressin acts to conserve free water. ■ ■REPRODUCTION The stages of reproduction include (1) sex determination during fetal development (Chap. 402); (2) sexual maturation during puberty (Chaps. 403 and 404); (3) conception, pregnancy, lactation, and child rearing (Chap. 404); and (4) cessation of reproductive capability at menopause (Chap. 407). Each of these stages involves an orchestrated interplay of multiple hormones, a phenomenon well illustrated by the dynamic hormonal changes that occur during each 28-day menstrual cycle. In the early follicular phase, pulsatile secretion of LH and FSH

stimulates the progressive maturation of the ovarian follicle. This results in gradually increasing estrogen and progesterone levels, lead ing to enhanced pituitary sensitivity to GnRH, which, when combined with accelerated GnRH secretion, triggers the LH surge and rupture of the mature follicle. Inhibin, a protein produced by the granulosa cells, enhances follicular growth and feeds back to the pituitary to selectively suppress FSH without affecting LH. Growth factors such as EGF and IGF1 modulate follicular responsiveness to gonadotropins. Vascular endothelial growth factor and prostaglandins play a role in follicle vascularization and rupture. During pregnancy, the increased production of PRL, in combina tion with placentally derived steroids (e.g., estrogen and progesterone), prepares the breast for lactation. Estrogens induce the production of progesterone receptors, allowing for increased responsiveness to pro gesterone. In addition to these and other hormones involved in lacta tion, the nervous system and oxytocin mediate the suckling response and milk release. HORMONAL FEEDBACK REGULATORY SYSTEMS Feedback control, both negative and positive, is a fundamental feature of endocrine systems. Each of the major hypothalamic-pituitaryhormone axes is governed by negative feedback, a process that main tains hormone levels within a relatively narrow range (Chap. 390). Examples of hypothalamic-pituitary negative feedback include (1) thy roid hormones on the TRH-TSH axis, (2) cortisol on the CRH-ACTH axis, (3) gonadal steroids on the GnRH-LH/FSH axis, and (4) IGF1 on the GHRH-GH axis (Fig. 389-4). These regulatory loops include both positive (e.g., TRH, TSH) and negative (e.g., T4, T3) components, allowing for exquisite control of hormone levels. As an example, a small reduction of thyroid hormone triggers a rapid increase of TRH and TSH secretion, resulting in thyroid gland stimulation and increased thyroid hormone production. When thyroid hormone reaches a nor mal level, it feeds back to suppress TRH and TSH, and a new steady state is attained. Feedback regulation also occurs for endocrine systems that do not involve the pituitary gland, such as calcium feedback on PTH, glucose inhibition of insulin secretion, and leptin feedback on the hypothalamus. An understanding of feedback regulation provides important insights into endocrine testing paradigms (see below). Hypothalamus CNS Releasing factors – + – Pituitary Target hormone feedback inhibition Trophic hormones + Adrenal Gonads Thyroid FIGURE 389-4 Feedback regulation of endocrine axes. CNS, central nervous system.

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