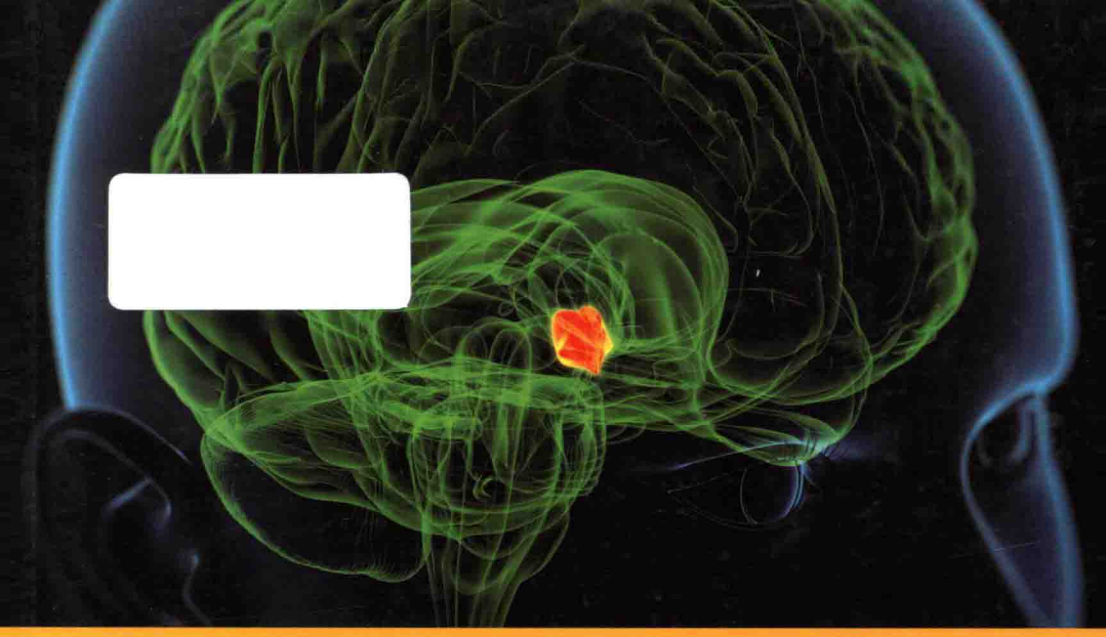

4th edition

Endocrine Physiology

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Endocrine Physiology

fourth edition

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To my friend, colleague, and husband,
Miguel F. Molina, MD, for his
unconditional support and constant
reminder of what is really
important in life.

Contents

Preface

This fourth edition of *Endocrine Physiology* provides comprehensive coverage of the fundamental concepts of hormone biological action. The content has been revised and edited to enhance clarity and understanding, and illustrations have been added and annotated to highlight the principal concepts in each chapter. In addition, the answers to the test questions at the end of the chapter have been expanded to include explanations for the correct answers.

The concepts herein provide the basis by which first- and second-year medical students will better grasp the physiologic mechanisms involved in neuroendocrine regulation of organ function. The information presented is also meant to serve as a reference for residents and fellows. The objectives listed at the beginning of each chapter follow those established and revised in 2012 by the American Physiological Society for each hormone system and are the topics tested in Step I of the United States Medical Licensing Examination (USMLE).

As with any discipline in science and medicine, our understanding of endocrine molecular physiology has changed and continues to evolve to encompass neural, immune, and metabolic regulation and interaction. The suggested readings have been updated to provide guidance for more in-depth understanding of the concepts presented. They are by no means all inclusive, but were found by the author to be of great help in putting the information together.

The first chapter describes the organization of the endocrine system, as well as general concepts of hormone production and release, transport and metabolic fate, and cellular mechanisms of action. Chapters 2–9 discuss specific endocrine systems and describe the specific hormone produced by each system in the context of the regulation of its production and release, the target physiologic actions, and the clinical implications of either its excess or deficiency. Each chapter starts with a short description of the functional anatomy of the organ, highlighting important features pertaining to circulation, location, or cellular composition that have a direct effect on its endocrine function. Understanding the mechanisms underlying normal endocrine physiology is essential in order to understand the transition from health to disease and the rationale involved in pharmacological, surgical, or genetic interventions. Thus, the salient features involved in determination of abnormal hormone production, regulation or function are also described. Each chapter includes simple diagrams illustrating some of the key concepts presented and concludes with sample questions designed to test the overall assimilation of the information given. The key concepts provided in each chapter correspond to the particular section of the chapter that describes them. Chapter 10 illustrates how the individual endocrine systems described throughout the book dynamically interact in maintaining homeostasis.

As with the previous editions of this book; the modifications are driven by the questions raised by my students during lecture or when studying for an

examination. Those questions have been the best way of gauging the clarity of the writing and they have also alerted me when unnecessary description complicated or obscured the understanding of a basic concept. Improved learning and understanding of the concepts by our students continues to be my inspiration. I would like to thank them, as well as all the faculty of the Department of Physiology at LSUHSC for their dedication to the teaching of this discipline.

General Principles of Endocrine Physiology

1

OBJECTIVES

- *Contrast the terms endocrine, paracrine, and autocrine.*
- *Define the terms hormone, target cell, and receptor.*
- *Understand the major differences in mechanisms of action of peptides, steroids, and thyroid hormones.*
- *Compare and contrast hormone actions exerted via plasma membrane receptors with those mediated via intracellular receptors.*
- *Understand the role of hormone-binding proteins.*
- *Understand the feedback control mechanisms of hormone secretion.*
- *Explain the effects of secretion, degradation, and excretion on plasma hormone concentrations.*
- *Understand the basis of hormone measurements and their interpretation.*

The function of the endocrine system is to coordinate and integrate cellular activity within the whole body by regulating cellular and organ function throughout life and maintaining **homeostasis**. Homeostasis, or the maintenance of a constant internal environment, is critical to ensuring appropriate cellular function.

THE ENDOCRINE SYSTEM: PHYSIOLOGIC FUNCTIONS AND COMPONENTS

Some of the key functions of the endocrine system include:

- Regulation of sodium and water balance and control of blood volume and pressure
- Regulation of calcium and phosphate balance to preserve extracellular fluid concentrations required for cell membrane integrity and intracellular signaling
- Regulation of energy balance and control of fuel mobilization, utilization, and storage to ensure that cellular metabolic demands are met

- Coordination of the host hemodynamic and metabolic counterregulatory responses to stress
- Regulation of reproduction, development, growth, and senescence

In the classic description of the endocrine system, a chemical messenger or **hormone** produced by an organ is released into the circulation to produce

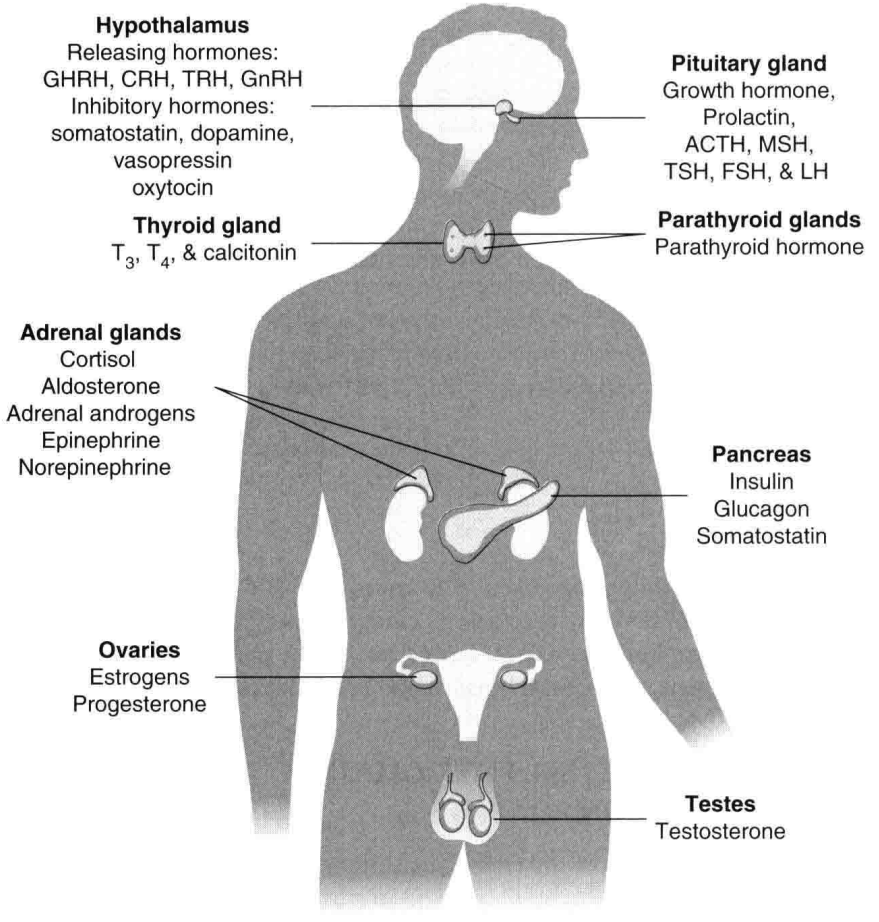

Figure 1–1. The endocrine system. Endocrine organs are located throughout the body, and their function is controlled by hormones delivered through the circulation or produced locally or by direct neuroendocrine stimulation. Integration of hormone production from endocrine organs is regulated by the hypothalamus. ACTH, adrenocorticotropic hormone; CRH, corticotropin-releasing hormone; FSH, follicle-stimulating hormone; GHRH, growth hormone-releasing hormone; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone; MSH, melanocyte-stimulating hormone; TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone; T_3, triiodothyronine; T_4, thyroxine.

an effect on a distant target organ. Currently, the definition of the endocrine system is that of an integrated network of multiple organs derived from different embryologic origins that release hormones ranging from small peptides to glycoproteins, which exert their effects either in neighboring or distant target cells. This endocrine network of organs and mediators does not work in isolation and is closely integrated with the central and peripheral nervous systems as well as with the immune systems, leading to currently used terminology such as "neuroendocrine" or "neuroendocrine-immune" systems for describing their interactions. Three basic components make up the core of the endocrine system.

Endocrine glands—The classic endocrine glands are ductless and secrete their chemical products (hormones) into the interstitial space from where they reach the circulation. Unlike the cardiovascular, renal, and digestive systems, the endocrine glands are not anatomically connected and are scattered throughout the body (Figure 1–1). Communication among the different organs is ensured through the release of hormones or neurotransmitters.

Hormones—Hormones are chemical products, released in very small amounts from the cell, that exert a biologic action on a target cell. Hormones can be released from the endocrine glands (ie, insulin, cortisol); the brain (ie, corticotropin-releasing hormone, oxytocin, and antidiuretic hormone); and other organs such as the heart (atrial natriuretic peptide), liver (insulin-like growth factor 1), and adipose tissue (leptin).

Target organ—The target organ contains cells that express hormone-specific receptors and that respond to hormone binding by a demonstrable biologic response.

HORMONE CHEMISTRY AND MECHANISMS OF ACTION

Based on their chemical structure, hormones can be classified into proteins (or peptides), steroids, and amino acid derivatives (amines). Hormone structure, to a great extent, dictates the location of the hormone receptor, with amines and peptide hormones binding to receptors in the cell surface and steroid hormones being able to cross plasma membranes and bind to intracellular receptors. An exception to this generalization is thyroid hormone, an amino acid–derived hormone that is transported into the cell in order to bind to its nuclear receptor. Hormone structure influences the half-life of the hormone as well. Amines have the shortest half-life (2–3 minutes), followed by polypeptides (4–40 minutes), steroids and proteins (4–170 minutes), and thyroid hormones (0.75–6.7 days).

Protein or Peptide Hormones

Protein or peptide hormones constitute the majority of hormones. These are molecules ranging from 3 to 200 amino acid residues. They are synthesized as preprohormones and undergo post-translational processing. They are stored in secretory granules before being released by exocytosis (Figure 1–2), in a

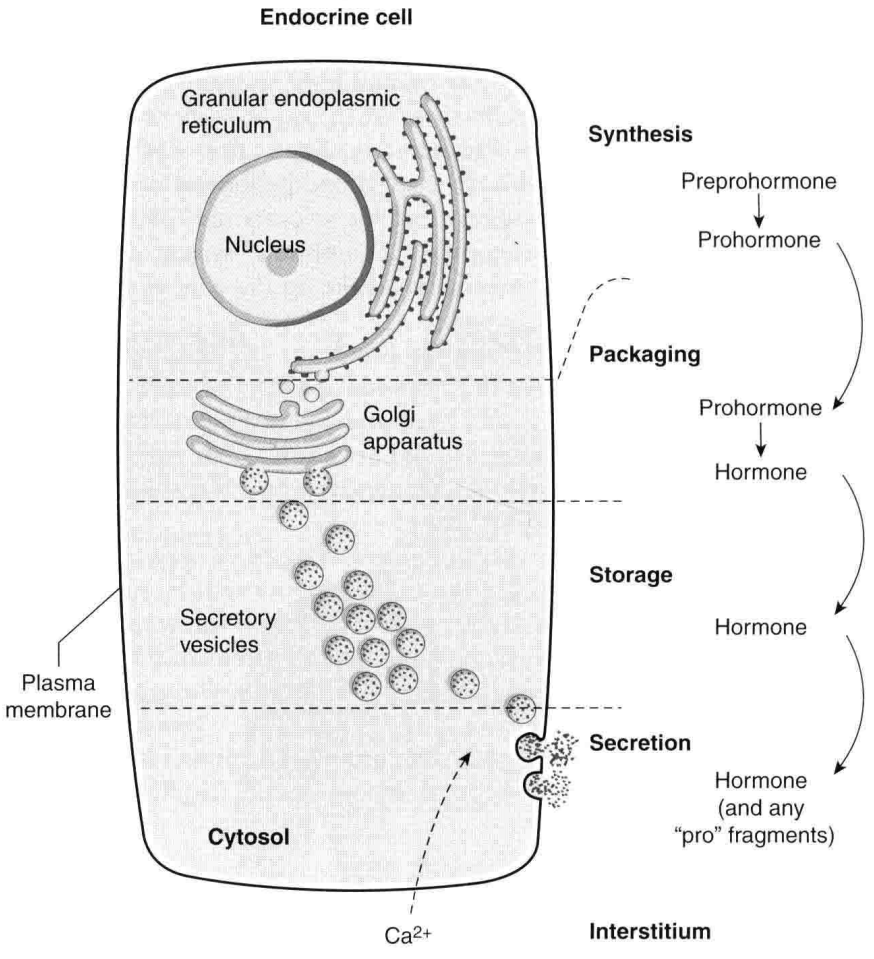

Figure 1–2. Peptide hormone synthesis. Peptide hormones are synthesized as preprohormones in the ribosomes and processed to prohormones in the endoplasmic reticulum (ER). In the Golgi apparatus, the hormone or prohormone is packaged in secretory vesicles, which are released from the cell in response to an influx of Ca^{2+}. The increase in cytoplasmic Ca^{2+} is required for docking of the secretory vesicles in the plasma membrane and for exocytosis of the vesicular contents. The hormone and the products of the post-translational processing that occurs inside the secretory vesicles are released into the extracellular space. Examples of peptide hormones are adrenocorticotropic hormone (ACTH), insulin, growth hormone, and glucagon.

manner reminiscent of how neurotransmitters are released from nerve terminals. Examples of peptide hormones include insulin, glucagon, and adrenocorticotropic hormone (ACTH). Some hormones in this category, such as the gonadotropic hormone, luteinizing hormone, and follicle-stimulating hormone, together with thyroid-stimulating hormone (TSH) and human chorionic gonadotropin, contain

carbohydrate moieties, leading to their designation as glycoproteins. The carbohydrate moieties play important roles in determining the biologic activities and circulating clearance rates of glycoprotein hormones.

Steroid Hormones

Steroid hormones are derived from cholesterol and are synthesized in the adrenal cortex, gonads, and placenta. They are lipid soluble, circulate bound to binding proteins in plasma, and cross the plasma membrane to bind to intracellular cytosolic or nuclear receptors. Vitamin D and its metabolites are also considered steroid hormones. Steroid hormone synthesis is described in Chapters 5 and 6.

Amino Acid–Derived Hormones

Amino acid–derived hormones are those hormones that are synthesized from the amino acid tyrosine and include the catecholamines norepinephrine, epinephrine, and dopamine; as well as the thyroid hormones, derived from the combination of 2 iodinated tyrosine amino acid residues. The synthesis of thyroid hormone and catecholamines is described in Chapters 4 and 6, respectively.

Hormone Effects

Depending on where the biologic effect of a hormone is elicited in relation to where the hormone was released, its effects can be classified in 1 of 3 ways (Figure 1–3). The effect is **endocrine** when a hormone is released into the circulation and then travels in the blood to produce a biologic effect on distant target cells. The effect is **paracrine** when a hormone released from 1 cell produces a biologic effect on a neighboring cell, which is frequently a cell in the same organ or tissue. The effect is **autocrine** when a hormone produces a biologic effect on the same cell that released it.

Recently, an additional mechanism of hormone action has been proposed in which a hormone is synthesized and acts intracellularly in the same cell. This mechanism has been termed **intracrine** and has been identified to be involved in the effects of parathyroid hormone–related peptide in malignant cells and in some of the effects of androgen-derived estrogen (see Chapter 9).

Hormone Transport

Hormones released into the circulation can circulate either freely or bound to carrier proteins, also known as *binding proteins*. The binding proteins serve as a reservoir for the hormone and prolong the hormone's **half-life**, the time during which the concentration of a hormone decreases to 50% of its initial concentration. The free or unbound hormone is the active form of the hormone, which binds to the specific hormone receptor. Thus, hormone binding to its carrier protein serves to regulate the activity of the hormone by determining how much hormone is free to exert a biologic action. Most carrier proteins are globulins and are synthesized in the liver. Some of the binding proteins are specific for a given protein, such as cortisol-binding proteins. However, proteins such as

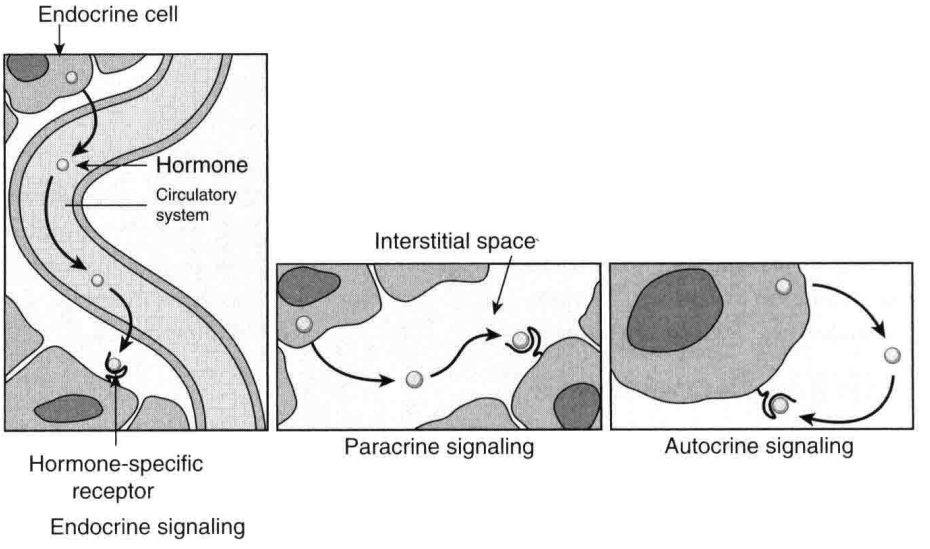

Figure 1–3. Mechanisms of hormone action. Depending on where hormones exert their effects, they can be classified into endocrine, paracrine, and autocrine mediators. Hormones that enter the bloodstream and bind to hormone receptors in target cells in distant organs mediate endocrine effects. Hormones that bind to cells near the cell that released them mediate paracrine effects. Hormones that produce their physiologic effects by binding to receptors on the same cell that produced them mediate autocrine effects.

globulins and albumin are known to bind hormones as well. Because for the most part these proteins are synthesized in the liver, alterations in hepatic function may result in abnormalities in binding-protein levels and may indirectly affect total hormone levels. In general, the majority of amines, peptides, and protein (hydrophilic) hormones circulate in their free form. However, a notable exception to this rule is the binding of the insulin-like growth factors to 1 of 6 different high-affinity binding proteins. Steroid and thyroid (lipophilic) hormones circulate bound to specific transport proteins.

The interaction between a given hormone and its carrier protein is in a **dynamic equilibrium** and allows adjustments that prevent clinical manifestations of hormone deficiency or excess. Secretion of the hormone is adjusted rapidly following changes in the levels of carrier proteins. For example, plasma levels of cortisol-binding protein increase during pregnancy. Cortisol is a steroid hormone produced by the adrenal cortex (see Chapter 6). The increase in circulating levels of cortisol-binding protein leads to an increased binding capacity for cortisol and a resulting decrease in free cortisol levels. This decrease in free cortisol stimulates the hypothalamic release of corticotropin-releasing hormone, which stimulates ACTH release from the anterior pituitary and consequently cortisol synthesis and release from the adrenal glands. The cortisol, released

in greater amounts, restores free cortisol levels and prevents manifestation of cortisol deficiency.

As already mentioned, the binding of a hormone to a binding protein prolongs its half-life. The half-life of a hormone is inversely related to its removal from the circulation. Removal of hormones from the circulation is also known as the **metabolic clearance rate**: the volume of plasma cleared of the hormone per unit of time. Once hormones are released into the circulation, they can bind to their specific receptor in a target organ, they can undergo metabolic transformation by the liver, or they can undergo urinary excretion (Figure 1–4). In the liver, hormones can be inactivated through phase I (hydroxylation or oxidation) and/or phase II (glucuronidation, sulfation, or reduction with glutathione) reactions, and then excreted by the liver through the bile or by the kidney. In some instances, the liver can actually activate a hormone precursor, as is the case for vitamin D synthesis, discussed in Chapter 5. Hormones can be degraded at their

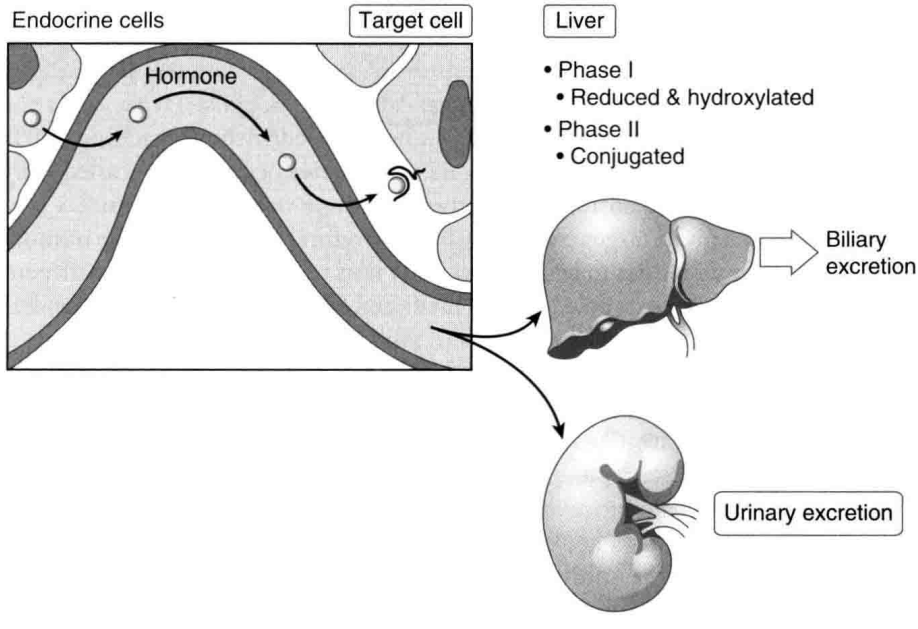

Figure 1–4. Hormone metabolic fate. The removal of hormones from the organism is the result of metabolic degradation, which occurs mainly in the liver through enzymatic processes that include proteolysis, oxidation, reduction, hydroxylation, decarboxylation (phase I), and methylation or glucuronidation (phase II) among others. Excretion can be achieved by bile or urinary excretion following glucuronidation and sulfation (phase II). In addition, the target cell may internalize the hormone and degrade it. The role of the kidney in eliminating hormone and its degradation products from the body is important. In some cases urinary determinations of a hormone or its metabolite are used to assess function of a particular endocrine organ based on the assumption that renal function and handling of the hormone are normal.

target cell through internalization of the hormone-receptor complex followed by lysosomal degradation of the hormone. Only a very small fraction of total hormone production is excreted intact in the urine and feces.

HORMONE CELLULAR EFFECTS

The biologic response to hormones is elicited through binding to hormone-specific receptors at the target organ. Hormones circulate in very low concentrations ($10^{-7} - 10^{-12}$ M), so the receptor must have high affinity and specificity for the hormone to produce a biologic response.

Affinity is determined by the rates of dissociation and association for the hormone-receptor complex under equilibrium conditions. The equilibrium dissociation constant (K_d) is defined as the hormone concentration required for binding 50% of the receptor sites. The lower the K_d, the higher the affinity of binding. Basically, affinity is a reflection of how tight the hormone-receptor interaction is. **Specificity** is the ability of a hormone receptor to discriminate among hormones with related structures. This is a key concept that has clinical relevance as will be discussed in Chapter 6 as it pertains to cortisol and aldosterone receptors.

The binding of hormones to their receptors is saturable, with a finite number of hormone receptors to which a hormone can bind. In most target cells, the maximal biologic response to a hormone can be achieved without reaching 100% hormone-receptor occupancy. The receptors that are not occupied are called *spare receptors*. Frequently, the hormone-receptor occupancy needed to produce a biologic response in a given target cell is very low; therefore, a decrease in the number of receptors in target tissues may not necessarily lead to an immediate impairment in hormone action. For example, insulin-mediated cellular effects occur when less than 3% of the total number of receptors in adipocytes is occupied.

Abnormal endocrine function is the result of either excess or deficiency in hormone action. This can result from abnormal production of a given hormone (either in excess or in insufficient amounts) or from decreased receptor number or function. Hormone-receptor agonists and antagonists are widely used clinically to restore endocrine function in patients with hormone deficiency or excess. Hormone-receptor agonists are molecules that bind the hormone receptor and produce a biologic effect similar to that elicited by the hormone. Hormone-receptor antagonists are molecules that bind to the hormone receptor and inhibit the biologic effects of a particular hormone.

HORMONE RECEPTORS AND SIGNAL TRANSDUCTION

As mentioned previously, hormones produce their biologic effects by binding to specific hormone receptors in target cells, and the type of receptor to which they bind is largely determined by the hormone's chemical structure. Hormone receptors are classified depending on their cellular localization, as **cell membrane** or **intracellular receptors**. Peptides and catecholamines are unable to cross the cell membrane lipid bilayer and in general bind to cell

membrane receptors, with the exception of thyroid hormones as mentioned above. Thyroid hormones are transported into the cell and bind to nuclear receptors. Steroid hormones are lipid soluble, cross the plasma membrane, and bind to intracellular receptors.

Cell Membrane Receptors

These receptor proteins are located within the phospholipid bilayer of the cell membrane of target cells (Figure 1–5). Binding of hormones (ie, catecholamines, peptide and protein hormones) to cell membrane receptors and formation of the

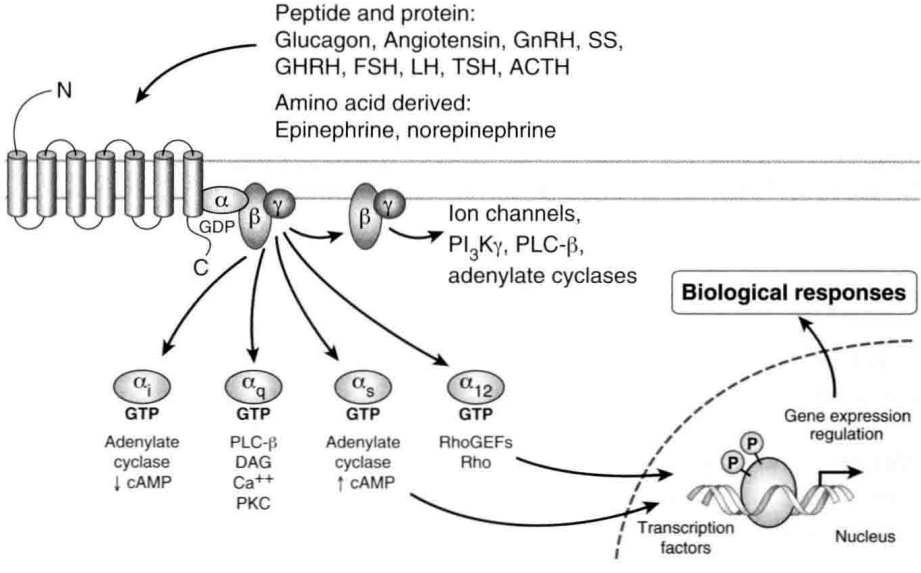

Figure 1–5. G protein–coupled receptors. Peptide and protein hormones bind to cell surface receptors coupled to G proteins. Binding of the hormone to the receptor produces a conformational change that allows the receptor to interact with the G proteins. This results in the exchange of guanosine diphosphate (GDP) for guanosine triphosphate (GTP) and activation of the G protein. The second-messenger systems that are activated vary depending on the specific receptor, the α-subunit of the G protein associated with the receptor, and the ligand it binds. Examples of hormones that bind to G protein–coupled receptors are thyroid hormone, arginine vasopressin, parathyroid hormone, epinephrine, and glucagon. ACTH, adrenocorticotropic hormone; ADP, adenosine diphosphate; cAMP, cyclic 3′,5′-adenosine monophosphate; DAG, diacylglycerol; FSH, follicle-stimulating hormone; GHRH, growth hormone-releasing hormone; GnRh, gonadotropin-releasing hormone; IP_3, inositol trisphosphate; LH, luteinizing hormone; $PI_3K\gamma$, phosphatidyl-3-kinase; PIP_2, phosphatidylinositol bisphosphate; PKC, protein kinase C; PLC-β, phospholipase C; RhoGEFs, Rho guanine-nucleotide exchange factors; SS, somatostatin; TSH, thyroid-stimulating hormone.