

# **GREENSPAN'S BASIC & CLINICAL ENDOCRINOLOGY**

David G. Gardner • Dolores Shoback

10th Edition

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# Greenspan's Basic & Clinical Endocrinology

Tenth Edition

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Francis Sorrel Greenspan, M.D. (1920-2016)

The tenth edition of *Greenspan's Basic & Clinical Endocrinology* is dedicated to the memories of four outstanding endocrinologists—Dr. John Baxter, Dr. Claude Arnaud, Dr. Melvin Grumbach, and, most especially, Dr. Francis Greenspan who was responsible for taking the initial steps to assemble this textbook more than thirty years ago. Each of these individuals was an outstanding endocrine scientist and/or clinical endocrinologist in the global endocrine community, and each contributed enormously to the success of this textbook.

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# Preface

This represents the tenth edition of *Greenspan's Basic & Clinical Endocrinology*—a bittersweet milestone in that it also marks the recent passing of Dr. Francis Greenspan, the originator and namesake of this textbook. Frank's involvement with this textbook will be sorely missed in the years to come. As with each of the previous editions, the individual chapters have been revised and updated to contain the most current information in the field. Our contributors continue to provide comprehensive content in a highly readable format. Chapter 14 (Disorders of Sex Development) has been completely revised and we have added a new chapter dealing with

Transgender Endocrinology (Chapter 23). We trust that you have found previous versions of this text useful and informative and that the current version will continue to serve as a valuable tool for the education of your trainees and management of your endocrine patients.

David G. Gardner, MD, MS  
Dolores Shoback, MD  
San Francisco, CA



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# Hormones and Hormone Action

Edward C. Hsiao, MD, PhD and David G. Gardner, MD, MS

<b>ACTH</b>	Adrenocorticotropin hormone	<b>FAD</b>	Flavin adenine dinucleotide
<b>ACVR1</b>	Activin A receptor, type I	<b>FGF</b>	Fibroblast growth factor
<b>AD1</b>	Activation domain 1	<b>FMN</b>	Flavin mononucleotide
<b>AD2</b>	Activation domain 2	<b>FOX A1</b>	Forkhead transcription factor A1
<b>AF-1</b>	Activator function-1	<b>FXR</b>	Farnesoid X-activated receptor
<b>AF-2</b>	Activator function-2	<b>GAP</b>	GTPase-activating protein
<b>Akt</b>	Protein kinase B	<b>GAS</b>	Interferon gamma activated sequences
<b>AMH</b>	Anti-müllerian hormone	<b>GDP</b>	Guanosine diphosphate
<b>ANP</b>	Atrial natriuretic peptide	<b>GH</b>	Growth hormone
<b>AP-1</b>	Activator protein-1	<b>GHR</b>	Growth hormone receptor
<b>APC</b>	Adenomatous polyposis coli gene	<b>GLUT4</b>	Glucose transporter type 4
<b>AR</b>	Androgen receptor	<b>GR</b>	Glucocorticoid receptor
<b>β-ARK</b>	β-Adrenergic receptor kinase	<b>GRB2</b>	Growth factor receptor-bound protein-2
<b>β-TrCP</b>	Beta-transducin repeats-containing proteins	<b>GRE</b>	Glucocorticoid response element
<b>BMP</b>	Bone morphogenetic protein	<b>GRIP</b>	Glucocorticoid receptor-interacting protein
<b>BNP</b>	B-type natriuretic peptide	<b>GSK3</b>	Glycogen synthase kinase-3
<b>BXR</b>	Benzoate X receptor	<b>GTF</b>	General transcription factor
<b>cAMP</b>	Cyclic adenosine-3',5'-monophosphate	<b>GTP</b>	Guanosine triphosphate
<b>CAR</b>	Constitutive androstane receptor	<b>HRE</b>	Hormone response element
<b>CARM</b>	Coactivator-associated arginine methyltransferase	<b>HSP</b>	Heat shock protein
<b>CBP</b>	CREB-binding protein	<b>ID</b>	Receptor-repressor interaction domain
<b>cGMP</b>	Cyclic guanosine-3',5'-monophosphate	<b>IGF</b>	Insulin-like growth factor
<b>CKI</b>	Casein kinase I	<b>I-κB</b>	Inhibitor of nuclear factor kappa B
<b>CNP</b>	C-type natriuretic peptide	<b>IKK</b>	Inhibitor of nuclear factor kappa B kinase
<b>CREB</b>	cAMP response element-binding protein	<b>IP<sub>3</sub></b>	Inositol 1,4,5-trisphosphate
<b>DAG</b>	Diacylglycerol	<b>IP<sub>4</sub></b>	Inositol 1,3,4,5-tetrakis-phosphate
<b>DAN</b>	Differential screening-selected gene in neuroblastoma	<b>ISRE</b>	Interferon-stimulated response element
<b>DBD</b>	DNA-binding domain	<b>JAK</b>	Janus kinase
<b>DRIP</b>	Vitamin D receptor-interacting protein	<b>KHD</b>	Kinase homology domain
<b>DVL</b>	Dishevelled	<b>LBD</b>	Ligand-binding domain
<b>EGF</b>	Epidermal growth factor	<b>LH</b>	Luteinizing hormone
<b>ER</b>	Estrogen receptor	<b>LRP</b>	Lipoprotein receptor related protein
<b>ERK</b>	Extracellular signal-regulated kinase	<b>LXR</b>	Liver X receptor
		<b>MAPK</b>	Mitogen-activated protein kinase

<b>MEK</b>	MAPK kinase	<b>RAR</b>	Retinoic acid receptor
<b>MR</b>	Mineralocorticoid receptor	<b>RE</b>	Response element
<b>MSH</b>	Melanocyte-stimulating hormone	<b>RGs</b>	Regulators of G protein signaling
<b>N-Cor</b>	Nuclear receptor corepressor	<b>RSK</b>	Ribosomal S6 kinase
<b>NF-<math>\kappa</math>B</b>	Nuclear factor kappa B	<b>RXR</b>	Retinoid X receptor
<b>NO</b>	Nitric oxide	<b>SH2</b>	<i>src</i> homology domain type 2
<b>NOS</b>	Nitric oxide synthase	<b>SIE</b>	Sis-inducible element
<b>NPR</b>	Natriuretic peptide receptor	<b>SMRT</b>	Silencing mediator for RXR and TR
<b>NR</b>	Nuclear receptor	<b>SOCS</b>	Suppressor of cytokine signaling
<b>NRPTK</b>	Non-receptor protein tyrosine kinase	<b>SOS</b>	Son-of-sevenless
<b>PAK</b>	p21-activated kinase	<b>SOST</b>	Sclerostin
<b>P/CAF</b>	p300/CBP-associated factor	<b>SR</b>	Steroid receptor
<b>P/CIP</b>	p300/CBP cointegrator-associated protein	<b>SRC</b>	Steroid receptor coactivator
<b>PDE</b>	Phosphodiesterase	<b>SRE</b>	Serum response element
<b>PDGF</b>	Platelet-derived growth factor	<b>SRF</b>	Serum response factor
<b>PDK</b>	Phosphatidylinositol-3,4,5 trisphosphate-dependent kinase	<b>STAT</b>	Signal transducer and activator of transcription
<b>PHP-1a</b>	Pseudohypoparathyroidism type 1a	<b>SWI/SNF</b>	ATP-dependent chromatin remodeling complex
<b>PI-3K</b>	Phosphoinositide-3-OH kinase	<b>TAZ</b>	WW domain-containing transcription regulator protein 1
<b>PIP<sub>2</sub></b>	Phosphatidylinositol-4,5-bisphosphate	<b>TBP</b>	TATA-binding protein
<b>PIP<sub>3</sub></b>	Phosphatidylinositol-3,4,5-trisphosphate	<b>TCF/LEF</b>	T-cell factor/lymphoid enhancer factor
<b>PI(3,4)P2</b>	Phosphatidylinositol-3,4-bisphosphate	<b>TGF-<math>\beta</math></b>	Transforming growth factor beta
<b>PKA</b>	Protein kinase A	<b>TLE</b>	Transducin-like enhancer protein
<b>PKB</b>	Protein kinase B	<b>TPA</b>	12- <i>O</i> -tetradecanoyl-phorbol 13-acetate
<b>PKC</b>	Protein kinase C	<b>TR</b>	Thyroid hormone receptor
<b>PKG</b>	cGMP-dependent protein kinase	<b>TRAF</b>	Tumor necrosis factor receptor-associated factor
<b>PLC<math>\beta</math></b>	Phospholipase C beta	<b>TRAP</b>	Thyroid hormone receptor-associated protein
<b>PLC<math>\gamma</math></b>	Phospholipase C gamma	<b>TRE</b>	TPA response element
<b>PLC<sub>PC</sub></b>	Phosphatidylcholine-selective phospholipase	<b>TSH</b>	Thyroid-stimulating hormone
<b>POL II</b>	RNA polymerase II	<b>VDR</b>	Vitamin D receptor
<b>PPAR</b>	Peroxisome proliferator-activated receptor	<b>Wnt</b>	int/Wingless family
<b>PR</b>	Progesterone receptor	<b>YAP</b>	Yes-associated protein-1
<b>PTH</b>	Parathyroid hormone		
<b>PXR</b>	Pregnane X receptor		
<b>RANK</b>	Receptor activator of nuclear factor kappa B		

Hormones are signaling molecules that traffic information from one point to another, typically through a soluble medium like the extracellular fluid or blood. Hormones fall into one of a number of different hormonal classes (eg, steroids, monoamines, peptides, proteins, and eicosanoids) and signal through a variety of general (eg, nuclear vs cell surface) and specific (eg, tyrosine kinase vs phosphoinositide turnover) mechanisms in target cells.

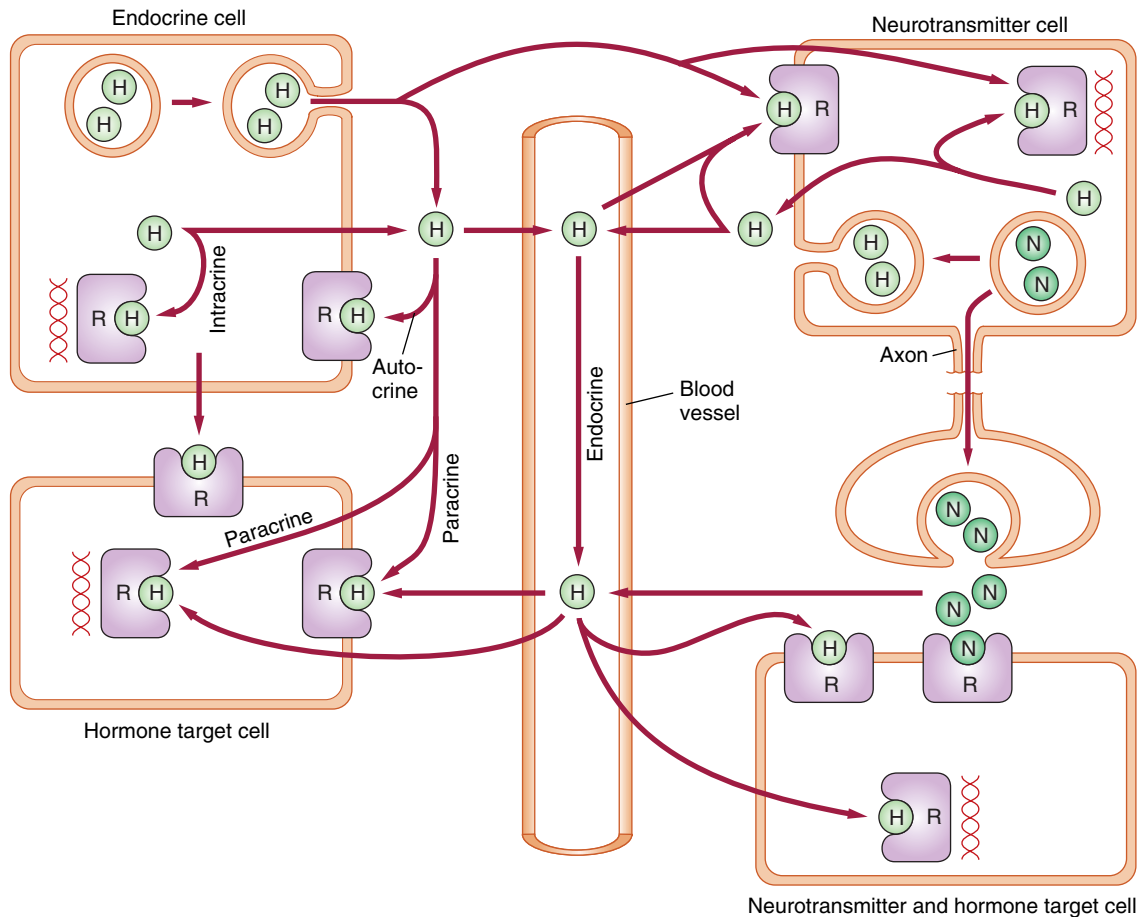
Hormones produced in one tissue may promote activity in a target tissue at some distance from the point of secretion (endocrine effect). In this case the hormone travels through the bloodstream, often bound to a plasma protein, to access the target tissue. In addition, hormones may act locally following secretion; either on a neighboring cell (paracrine effect), on the secretory cell

itself (autocrine effect), or without actually being released from the secretory cell (intracrine effect) (Figure 1–1).

Identification of a tissue as a target for a particular hormone requires the presence of receptors for the hormone in cells of the target tissue. These receptors, in turn, are linked to effector mechanisms that lead to the physiological effects associated with the hormone.

## RELATIONSHIP TO THE NERVOUS SYSTEM

Many features of the endocrine system, such as the use of ligands and receptors to communicate between cells, are also found in the nervous system. In fact, from a functional standpoint, the two



**FIGURE 1–1** Actions of hormones and neurotransmitters. Endocrine and neurotransmitter cells synthesize hormones and release them by specialized secretory pathways or by diffusion. Hormones can act at the site of production either following release (autocrine) or without release (intracrine) from the producer cell. They can also act on neighboring target cells, including neurotransmitter-producing cells, without entering the circulation (paracrine). Finally, they can access target cells through the circulation (endocrine). Neurotransmitters that access the extracellular compartment, including circulating plasma, can act as paracrine or endocrine regulators of target cell activity (H, hormone; N, neurotransmitter; R, receptor).

systems are probably related evolutionarily. However, there are some important differences between the two systems. While the nervous system uses a highly compartmentalized, closed system of axons and dendrites to connect cells at some distance from one another, the endocrine system relies on circulating plasma to carry newly released hormones to their distant targets. As a result, the time constants for signal delivery are quite different between the two—virtually instantaneous for the nervous system but delayed, by virtue of circulation times, for the endocrine system. Thus, while neural responses are typically measured in seconds, endocrine responses are often measured in minutes to hours—thereby accommodating different needs in the organism. A second difference relates to the nature of the ligand–receptor interaction. In the nervous system, the affinity of receptor for ligand tends to be relatively low. This allows for rapid dissociation of ligand from receptor and, if that ligand is degraded locally, a rapid cessation of biological effect. Despite this rapid dissociation, the secretory neuron is able to maintain receptor occupancy by keeping concentrations of the ligand high around the target

neuron. It does this through pulsatile release of secretory granules into an incredibly small volume (ie, that determined by the volume in the synaptic cleft).

The endocrine system, on the other hand, has a very large volume of distribution for many of its ligands (eg, circulating blood volume). Maintaining ligand concentrations analogous to those present in the synaptic cleft would require prodigious secretory capacity. The endocrine system circumvents this problem by using ligand–receptor interactions with 100–10,000 fold higher binding affinity than those used in the nervous system. In effect, the nervous system is structured to deliver high ligand concentrations to relatively low-affinity receptors, allowing it to activate and inactivate biological effects quickly and in a relatively well-defined topography. Its effects are short lived. In contrast, the endocrine system uses high-affinity receptors to extract and retain ligand from a relatively “dilute” pool in circulating plasma. Its biological effects are long lasting. It has sacrificed rapid response to accommodate a wider area of signal distribution and prolongation of the biological effect. Thus, the systems are not only related but

complementary in the respective roles that they play in normal physiological function.

## CHEMICAL NATURE OF HORMONES

Hormones vary widely in terms of their chemical composition. Specific examples include proteins (eg, adrenocorticotrophin), peptides (eg, vasopressin), monoamines (eg, norepinephrine), amino acid derivatives (eg, triiodothyronine), steroids (eg, cortisol), and lipids (eg, prostaglandins). Proteins can be glycosylated (eg, thyroid-stimulating hormone) and/or dimerized (eg, follicle-stimulating hormone) to generate full biological activity. In general, protein, peptide, monoamine, and lipophilic hormones tend to exert their effects primarily through protein receptors at the cell membrane, while thyroid hormone and steroids tend to operate in the cell nucleus. However, exceptions to these rules are being recognized (eg, triiodothyronine activates classic thyroid hormone receptors in the nuclear compartment and the trace amine receptor [TAR1] on the cell surface) and estradiol appears to activate both nuclear and plasma membrane receptors. It is likely that the biological “effect” of a given hormone reflects a composite of receptor activity located in several different cellular compartments.

## ENDOCRINE GLANDS AND TARGET ORGANS

Endocrine glands are traditionally defined as ductless glandular structures that release their hormonal secretions into the extracellular space where they can eventually access circulating plasma. Classic endocrine glands include organs like the pituitary gland, thyroid gland, parathyroid glands, pancreatic islets, adrenal glands, ovaries, and testes. It is now clear that hormones can be secreted from non-traditional endocrine organs and play critical roles in the regulation of physiological homeostasis. Examples of the latter include the heart (natriuretic peptides), kidney (erythropoietin and renin), adipose tissue (leptin and adiponectin), bone (osteocalcin), and gut (cholecystokinin and incretins). Once in the circulation, hormones bind to receptors on target tissues to elicit their biological effects. Target tissues for some hormones (eg, glucocorticoids) are numerous, reflecting the ubiquitous distribution of their receptors, while those for other tissues have a more limited distribution (eg, androgens).

## REGULATION OF HORMONE LEVELS IN PLASMA

Hormone levels in plasma determine the effective ligand concentration at the level of the hormone receptors in peripheral target cells. Thus, regulation of hormone levels plays an important role in the control of the biological effects that the hormone exerts.

### Hormone Biosynthesis

New hormone synthesis is one of the principal mechanisms used to raise hormone levels in circulating plasma. In the case

of protein or peptide hormones this usually reflects increased expression of the gene encoding the hormone (ie, increased production of the mRNA encoding the hormone) with subsequent increases in hormone synthesis. In the case of steroid or thyroid hormones it reflects increased sequestration of precursors for hormone synthesis (eg, cholesterol for steroid hormones or iodide for thyroid hormone) as well as increased activity of enzymatic proteins responsible for executing the individual catalytic events required for hormone production. The latter may involve a rate-limiting step in the synthetic cascade (eg, 1-alpha hydroxylase activity in the synthesis of 1,25-dihydroxyvitamin D).

### Precursor Processing

Processing of hormone precursors contributes to varying degrees in controlling circulating hormone levels. Most peptide and protein hormones require some processing to generate the mature hormonal product (eg, conversion of proinsulin to insulin) and impairment in the processing activity can alter the ratio of precursor to product in plasma. In other cases, a critical processing event is part of the secretory process itself (eg, cleavage of thyroxine from thyroglobulin) and impaired processing can result in a dramatic reduction in immunoreactivity as well as bioactivity of the mature hormone. In addition, protein hormones may require post-translational modification (eg, glycosylation) or assembly (eg, heterodimerization) prior to secretion in order to optimize biological activity.

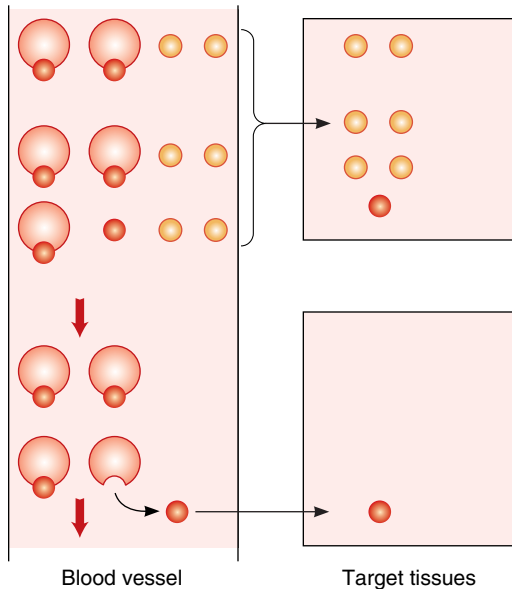
### Hormone Release

Many hormones (eg, peptides, proteins, and monoamines) are stored in secretory granules in endocrine cells. Release of these granules is promoted by signaling events triggered by exogenous regulators termed secretagogues. This often requires activation of a second messenger system (see discussion under Receptors) like cyclic AMP generation or intracellular calcium mobilization in the endocrine cell. Steroid hormones, on the other hand, are not stored to a significant degree in the hormone-producing cells. In this case synthesis rather than hormone release appears to play the dominant role in controlling hormone levels in circulating plasma.

### Hormone Binding in Plasma

Hormones in plasma can circulate either in a free form, uncomplexed with other molecules, or bound to other molecules like plasma proteins. It is the uncomplexed or free form of the hormone that represents the biologically active fraction of hormone in the plasma compartment, and it is this fraction which homeostatic regulatory mechanisms work to preserve.

However, binding of hormone to plasma proteins plays an important role in endocrine physiology. First, it provides a reservoir of hormone that exchanges with the free hormone fraction according to the laws of mass action (see under Receptors). This makes plasma hormone concentrations less dependent on hormone synthesis and release, effectively stabilizing those concentrations over extended periods of time. This also helps guarantee a uniform distribution of hormone concentration in capillary beds



**FIGURE 1–2** Role of plasma binding in delivery of hormones to peripheral tissues. Example shows a hormone that is bound (small red circles) to a plasma protein (large circles) and a hormone that is not protein bound (small orange circles). With the bound hormone, only the free fraction is available for tissue uptake. As the free fraction is depleted, additional hormone dissociates from the plasma-binding protein, making hormone available to more distal portions of the tissue. In contrast, all hormones that are not protein bound are quickly extracted in the proximal part of the tissue.

perfusing target tissues (Figure 1–2). Second, it slows the metabolism or turnover of the hormone by sequestering it away from degradative enzymes or filtration by the kidney.

## Hormone Metabolism

Metabolism of hormones also plays an important role in regulating hormone concentrations. In some cases metabolism is responsible for converting precursors with less hormonal activity to products with greater activity (eg, conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D, or conversion of androstenedione to testosterone). In other cases, metabolism leads to degradation and inactivation of the hormone with a cessation of hormone activity. This type of degradation is often specific to the hormonal class under examination. Steroids, for example, are catalytically converted to inactive metabolites and/or sulfated to promote excretion. Thyroid hormones are subjected to deiodination which strips them of their biological activity. Protein and peptide hormones are internalized by target, as well as nontarget, cells and degraded in intracellular lysosomes. In general, the more avid the degradative mechanisms, the shorter the plasma half-life of the hormone.

## Regulation of Hormone Levels

Hormone levels can be modulated through regulatory factors affecting any of the steps listed earlier; however, the bulk of the acute “fine-tuning” of hormone levels occurs at the level of

hormone secretion and synthesis. Many, if not most, hormone levels are controlled either directly or indirectly by the biological activity that they serve to control. For example, parathyroid hormone (PTH) secretion, which responds to low extracellular calcium levels, mobilizes calcium out of bone which, in turn, signals back to the parathyroid gland to turn off additional PTH secretion. This negative feedback loop is a hallmark of endocrine regulation. The end product or negative regulator can either be an inorganic ion or metabolite (eg, calcium for PTH) or a hormonal product in the endocrine cascade (eg, thyroid hormone for TSH). Not all feedback is negative in nature. Positive feedback loops (eg, mid-cycle estradiol-induced luteinizing hormone secretion) also play important roles in governing physiological homeostasis.

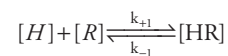
## HORMONE ACTION

Hormones produce their biologic effects through interaction with high-affinity receptors that are, in turn, linked to one or more effector systems within the cell. These effectors involve many different components of the cell’s metabolic machinery, ranging from ion transport at the cell surface to stimulation of the nuclear transcriptional apparatus. Steroids and thyroid hormones exert their effects in the cell nucleus, although regulatory activity in the extranuclear compartment has also been documented. Peptide hormones and neurotransmitters, on the other hand, trigger a plethora of signaling activity in the cytoplasmic and membrane compartments while at the same time exerting parallel effects on the transcriptional apparatus. The discussion that follows will focus on the primary signaling systems employed by selected hormonal agonists and attempt to identify examples where aberrant signaling results in human disease.

## RECEPTORS

The biologic activity of individual hormones is dependent on their interactions with specific high-affinity receptors on the surfaces or in the cytoplasm or nuclei of target cells. The receptors, in turn, are linked to signaling effector systems responsible for generating the observed biologic responses. Receptors, therefore, convey not only specificity of the response (ie, cells lacking receptors lack responsiveness to the hormone) but also the means for activating the effector mechanism. In general, receptors for the peptide hormones and neurotransmitters are aligned on the cell surface and those for the steroid hormones, thyroid hormone, and vitamin D are found in the cytoplasmic or nuclear compartments, although, as noted earlier, exceptions have been identified in both cases.

Interactions between the hormone ligand and its receptor are governed by the laws of mass action:



where  $[H]$  is the hormone concentration,  $[R]$  is the receptor concentration,  $[HR]$  is the concentration of the hormone–receptor

complex, and  $k_{+1}$  and  $k_{-1}$  are the rate constants for [HR] formation and dissociation, respectively. Thus, at equilibrium,

$$k_{+1}[H][R] = k_{-1}[\text{HR}]$$

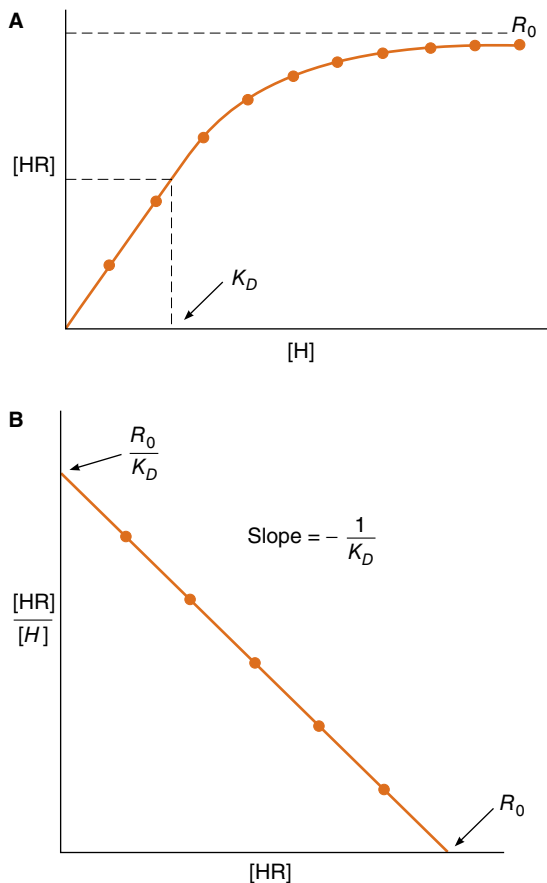
or

$$\frac{[H][R]}{[\text{HR}]} = \frac{k_{-1}}{k_{+1}} = K_D$$

where  $K_D$  is the equilibrium dissociation constant that defines the affinity of the hormone–receptor interaction (ie, lower the dissociation constant, higher the affinity). Assuming that total receptor concentration  $R_0 = [\text{HR}] + [R]$ , this equation can be rearranged to give

$$\frac{[\text{HR}]}{[H]} = -\left(\frac{[\text{HR}]}{K_D}\right) + \frac{R_0}{K_D}$$

This is the Scatchard equation and states that when bound ligand over free ligand (ie,  $[\text{HR}]/[H]$ ) is plotted against bound ligand (ie,  $[\text{HR}]$ ), the slope of the line is defined by  $-1/K_D$ , the  $y$ -intercept by  $R_0/K_D$ , and the  $x$ -intercept by  $R_0$  (Figure 1–3). When  $[\text{HR}] = R_0/2$ ,  $[H] = K_D$ ; therefore, the  $K_D$  is also the concentration of hormone  $[H]$



**FIGURE 1–3** Ligand saturation (A) and Scatchard analysis (B) of a hypothetical hormone receptor interaction.  $K_D$  represents the dissociation constant;  $R_0$  the total receptor concentration;  $[\text{HR}]$  and  $[H]$  the bound and free ligand, respectively. Note in (A) that the  $K_D$  is the concentration  $[H]$  at which half of available receptors are occupied.

at which one-half of the available receptors are occupied. Thus, knowledge of bound and free ligand concentrations, which can be determined experimentally, provides information regarding the affinity of the receptor for its ligand and the total concentration of receptor in the preparation.

Agents that bind to receptors with high affinity are classified as either agonists or antagonists based on the functional outcome of this receptor–ligand interaction. Agonists are ligands that trigger the effector mechanisms and produce biologic effects. Antagonists bind to the receptor but do not activate the effector mechanisms. Because they occupy receptor and block association with the agonist, they antagonize the functional activity of the agonist. Partial agonists bind to the receptor but possess limited ability to activate the effector mechanisms. In different circumstances, partial agonists may demonstrate variable biologic activity. For example, when used alone, they may display weak activating activity, whereas their use together with a full agonist may lead to inhibition of function because the latter is displaced from the receptor molecule by a ligand with lower intrinsic activity.

In some systems, receptors are available in surplus, which may be several-fold higher than that required to elicit a maximal biologic response. Although such spare receptor systems superficially appear redundant, they are designed to rectify a mismatch between low circulating ligand levels and a relatively low-affinity ligand–receptor interaction. Thus, by increasing the number of available receptors, the system is guaranteed a sufficient number of ligand-bound receptor units to activate downstream effector systems fully, despite operating at subsaturating levels of ligand.

## NEUROTRANSMITTER AND PEPTIDE HORMONE RECEPTORS

As mentioned earlier, neurotransmitter and peptide hormones interact predominantly with receptors expressed on the plasma membrane at the cell surface. The  $K_D$  of a neurotransmitter for its receptor is typically higher than that of a hormone for its receptor, reflecting a higher  $k_{\text{off}}$  rate constant (see earlier). Neurotransmitter receptor occupancy is driven by the extraordinarily high concentrations of ligand that can be achieved in the synaptic cleft, and occupancy of the hormone receptor is driven by its high affinity for ligand. The high  $k_{\text{off}}$  of the neurotransmitter–receptor interaction guarantees that the effect is rapid in onset but of short duration, whereas the lower  $k_{\text{off}}$  of the hormone–receptor interaction guarantees that the effect is slow in onset but difficult to extinguish, kinetics that are more appropriate for the hormonal functions of these ligands.

The neurotransmitter and peptide receptors can be divided into several major groups (Table 1–1 and Figure 1–4). The first includes the so-called serpentine or “seven-transmembrane-domain” receptors. These receptors each contain an amino terminal extracellular domain followed by seven hydrophobic amino acid segments, each of which is believed to span the membrane bilayer (see Figure 1–4). The seventh of these, in turn, is followed by a hydrophilic carboxyl terminal domain that resides within the cytoplasmic compartment. As a group, they share a dependence

**TABLE 1–1 Major subdivisions (with examples) of the neurotransmitter-peptide hormone receptor families.<sup>a</sup>**

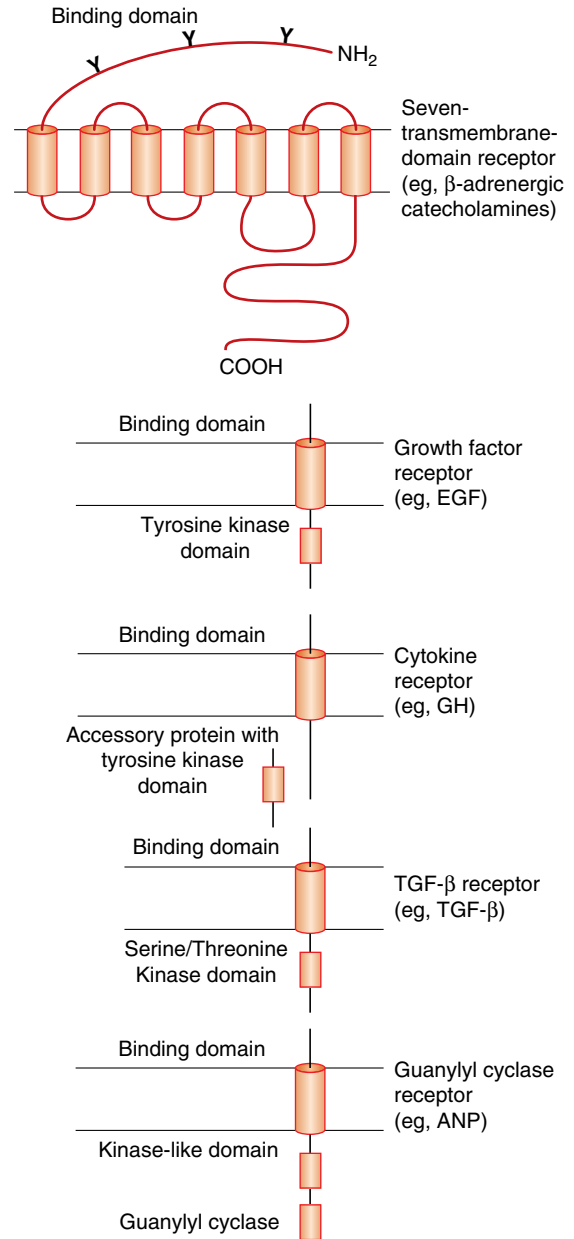
<b>Seven-Transmembrane Domain</b>
β-Adrenergic
PTH
LH
TSH
GRH
TRH
ACTH
MSH
Glucagon
Dopamine
α <sub>2</sub> -Adrenergic (-)
Somatostatin (-)
<b>Single-Transmembrane Domain</b>
Growth factor receptors
Insulin
IGF
EGF
PDGF
Cytokine receptors
Growth hormone
Prolactin
Erythropoietin
CSF
Guanylyl cyclase-linked receptors
Natriuretic peptides

<sup>a</sup>Receptors have been subdivided based on shared structural and functional similarities. Minus (-) sign denotes a negative effect on cyclase activity.

on the G protein transducers (GPCRs discussed later) to execute many of their biologic effects. A second group includes the single-transmembrane-domain receptors that harbor intrinsic tyrosine kinase activity. This includes the insulin, insulin-like growth factor (IGF), and epidermal growth factor (EGF) receptors. A third group, which is functionally similar to the second group, is characterized by a large, extracellular binding domain followed by a single membrane-spanning segment and a cytoplasmic tail. These receptors do not possess intrinsic tyrosine kinase activity but appear to function through interactions with soluble transducer molecules which do possess such activity. Prolactin and growth hormone are included in this group. A fourth group is the transforming growth factor beta (TGF-β) family which signals through serine/threonine kinase domains in their cytoplasmic tails. A fifth group, which includes the natriuretic peptide receptors, operates through activation of a particulate guanylyl cyclase and synthesis of cGMP. The cyclase is covalently attached at the carboxyl terminal portion of the ligand-binding domain (LBD) and thus represents an intrinsic part of the receptor molecule.

## G PROTEIN–COUPLED RECEPTORS

G protein–coupled receptors (GPCRs) constitute a large superfamily of molecules capable of responding to ligands of remarkable structural diversity—ranging from photons to large polypeptide hormones. Because of their diversity, GPCRs are the target of over 40% of modern pharmaceuticals. GPCRs initiate



**FIGURE 1–4** Structural schematics of different classes of membrane-associated hormone receptors. Representative ligands are presented in parentheses (ANP, atrial natriuretic peptide; EGF, epidermal growth factor; GH, growth hormone; TGF-β, transforming growth factor beta).

intracellular signaling by activating one (or in some cases multiple) G proteins resulting in biological responses. These receptors share overall structural features, most notably seven membrane-spanning regions connected by intracellular and extracellular loops (see Figure 1–4). The receptors are oriented such that the amino terminal domain is extracellular, whereas the carboxyl terminal tail is cytoplasmic. The membrane-spanning segments interact with one another, forming an irregular cylindrical bundle around a central cavity within the molecule. GPCRs can assume at least two conformations with differing orientations of the



membrane-spanning segments relative to one another. One orientation is favored in the absence of an agonist ligand. In this orientation the receptor does not activate a G protein (inactive conformation). The second orientation is stabilized by the binding of an appropriate agonist ligand. In this conformation the receptor activates a cognate G protein (active conformation). All GPCRs are thought to undergo a similar conformational switch on agonist binding, producing a structural change in the cytoplasmic domain that promotes G protein activation. Some small agonists, such as catecholamines, are able to enter the cavity formed by the transmembrane segments, thereby directly stabilizing the active receptor conformation. Other agonists, such as large polypeptide hormones, bind primarily to the extracellular domain of their GPCRs. More recently, a number of orphan GPCRs have been found to be activated by hydrophobic ligands including steroids (eg, estrogen binding to GPR30) and lipids (eg, LPA binding to GPR23). Ligand binding indirectly results in movement of the transmembrane region of the receptor and stabilization of the active receptor conformation.

Until recently, it was thought that GPCRs function exclusively as monomers. Many GPCRs are now known to dimerize either with themselves (homodimerization) or with other GPCRs (heterodimerization). In some cases, dimerization is important for efficient receptor biosynthesis and membrane localization. In other cases, dimerization is important for optimal ligand affinity, specificity, or receptor signaling.

Heritable mutations in a variety of GPCRs are known to be associated with disease. Loss-of-function phenotypes can result from mutations that eliminate one or both receptor alleles, or that result in the synthesis of signaling-defective receptors. Gain-of-function phenotypes generally result from point mutations that produce constitutively active receptors (ie, stably assume the active receptor conformation even in the absence of an agonist ligand). Examples of such GPCR disorders relevant to endocrinology are described later and discussed in greater detail elsewhere in this book.

## G PROTEIN TRANSDUCERS

G proteins are a family of heterotrimeric proteins that regulate the activity of effector molecules (eg, enzymes, ion channels) (examples in Table 1–2), ultimately resulting in biological responses. The identity of a G protein is defined by the nature of its  $\alpha$  subunit, which is largely responsible for effector activation. The major G proteins involved in hormone action (and their actions on effectors) are  $G_s$  (stimulation of adenylyl cyclase),  $G_i$  (inhibition of adenylyl cyclase; regulation of calcium and potassium channels), and  $G_{q/11}$  (stimulation of phospholipase C [PLC]  $\beta$ ). Recently, GPCRs linked to  $G_{12/13}$  were identified as key inputs of the Hippo/YAP/TAZ transcriptional regulators, which play a central role in controlling organ size, growth, and integrating extracellular cues. In each of these cases, the  $\beta$  and  $\gamma$  subunits of G proteins are tightly associated with one another and function as a dimer. In some cases, the  $\beta\gamma$  subunit dimer can also regulate effector function.

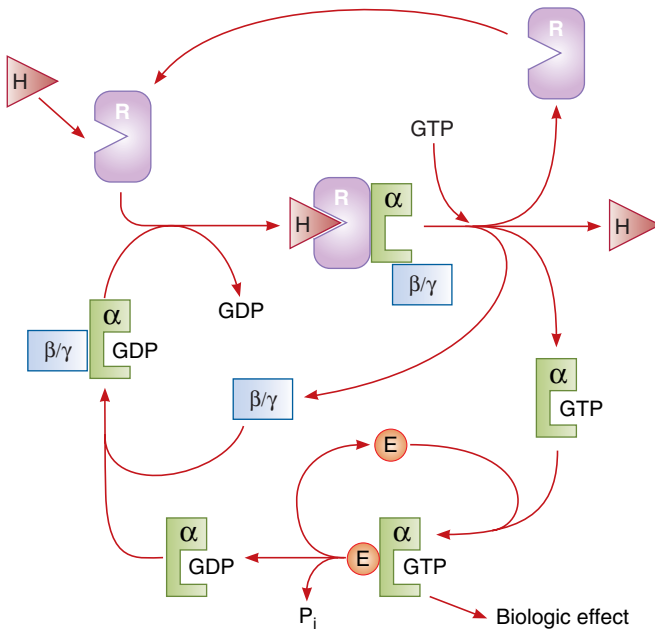
**TABLE 1–2 G protein subunits selectively interact with specific receptor and effector mechanisms.**

G Protein Subunit	Representative Associated Receptors	Effector
$\alpha_s$	$\beta$ -Adrenergic TSH Glucagon	Adenylyl cyclase $Ca^{2+}$ channels $K^+$ channels
$\alpha_i$	$\alpha_2$ -Adrenergic Muscarinic (type II)	Adenylyl cyclase $Ca^{2+}$ channels $K^+$ channels
$\alpha_q$	$\alpha_1$ -Adrenergic	PLC $\beta$
$\beta/\gamma$		Adenylyl cyclase (+ or –) PLC Supports $\beta$ ARK-mediated receptor phosphorylation and desensitization

G proteins are noncovalently tethered to the plasma membrane and are thus proximate to their cognate receptors and to their effector targets. The basis for specificity in receptor–G protein interactions has not been fully defined. It is likely that specific structural determinants presented by the cytoplasmic loops of the GPCR determine the identity of the G proteins that are activated. It is the nature of the  $\alpha$  subunit of the G protein that is critical for receptor signaling. There are about a dozen different G protein  $\alpha$  subunits and hundreds of distinct GPCRs.

Clearly, each specific G protein can be activated by a large number of different receptors. For example,  $G_s$  is activated by receptors for ligands as diverse as  $\beta$ -adrenergic catecholamines and large polypeptide hormones such as luteinizing hormone (LH). LH is thereby able to stimulate adenylyl cyclase and raise intracellular levels of cAMP in cells that express LH receptors (eg, Leydig cells of the testis). In contrast, an individual GPCR can couple to multiple  $G\alpha$  subunits, often in response to different ligands (eg, PTH receptor can activate  $G_s$ ,  $G_i$ , and  $G_q$ ).

Figure 1–5 is a schematic representation of the molecular events associated with activation of G proteins by GPCRs. In the basal, inactive state, the G protein is an intact heterotrimer with guanosine diphosphate (GDP) bound to the  $\alpha$  subunit. Agonist binding to a GPCR promotes the physical interaction between the receptor and its cognate G protein. This produces a conformational change in the G protein, resulting in the dissociation of GDP. This in turn allows the binding of GTP (which is present at a much higher concentration in cells than is GDP) to the  $\alpha$  subunit. Dissociation of the GTP-bound  $\alpha$  subunit from the  $\beta\gamma$  dimer then occurs, allowing these subunits to activate their effector targets. Dissociation of the hormone–receptor complex also occurs. The duration of activation is determined by the intrinsic GTPase activity of the G protein  $\alpha$  subunit. Hydrolysis of GTP to GDP terminates the activity and promotes reassociation of the  $\alpha\beta\gamma$  trimer, returning the system to the basal state. The GTPase activity of G protein  $\alpha$  subunits can be increased by the action of proteins termed “regulators of G protein signaling” (RGS proteins) which act by increasing the speed of GTP cycling.

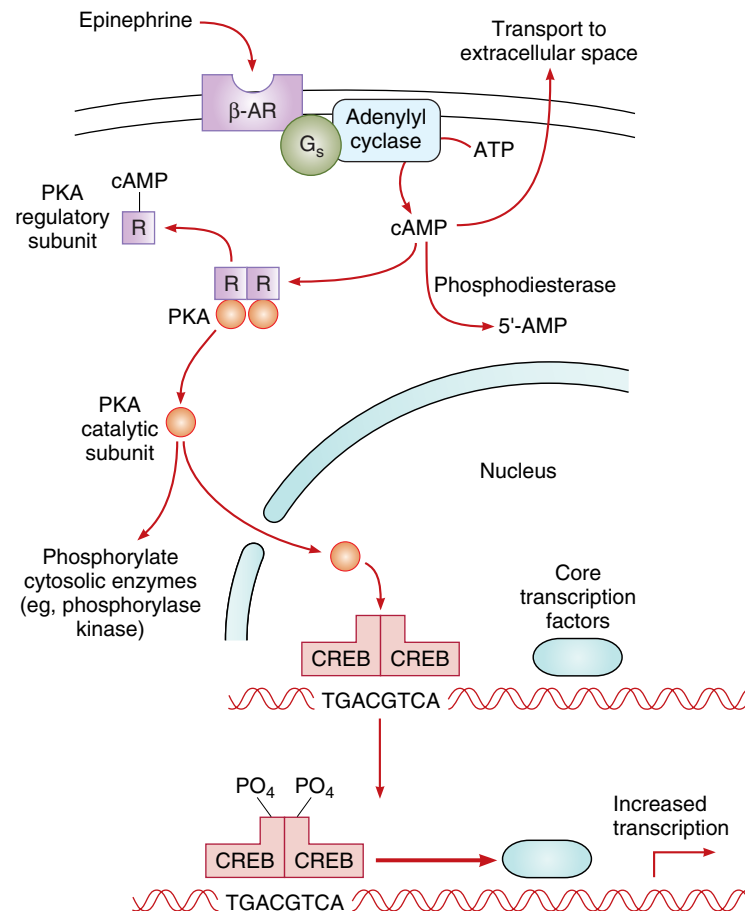


**FIGURE 1-5** G protein-mediated signal transduction.  $\alpha$  and  $\beta/\gamma$  subunits of a representative G protein are depicted (see text for details) (E, effector; H, hormonal ligand; R, hormone receptor).

## EFFECTORS

Numerous effectors have been linked to the GPCRs. A number of these are presented in Table 1-2. A great many other G proteins—not dealt with here—are coupled to physical or biochemical stimuli but have very limited involvement in hormone action. As discussed, adenylyl cyclase, perhaps the best studied of the group, is activated by  $G_s$  (Figure 1-6). This activation results in a transient increase in intracellular cAMP levels. The cAMP binds to the inhibitory regulatory subunit of inactive protein kinase A (PKA) and promotes its dissociation from the complex, thereby permitting enhanced activity of the catalytic subunit. The latter phosphorylates a variety of cellular substrates, among them the hepatic phosphorylase kinase that initiates the enzymatic cascade which results in enhanced glycogenolysis. It also phosphorylates and activates the cAMP response element-binding protein (CREB), which mediates many of the known transcriptional responses to cAMP (and to some extent calcium) in the nuclear compartment. Other transcription factors are also known to be phosphorylated by PKA.

PLC beta (PLC $\beta$ ) is a second effector system that has been studied extensively. The enzyme is activated through  $G_q$ -mediated



**FIGURE 1-6**  $\beta$ -Adrenergic receptor/ $G_s$  mediated signaling in the cytoplasmic and nuclear compartments. The cAMP response element-binding protein (CREB) is depicted bound to a consensus CRE in the basal state. Phosphorylation of this protein leads to activation of the juxtaposed core transcriptional machinery.