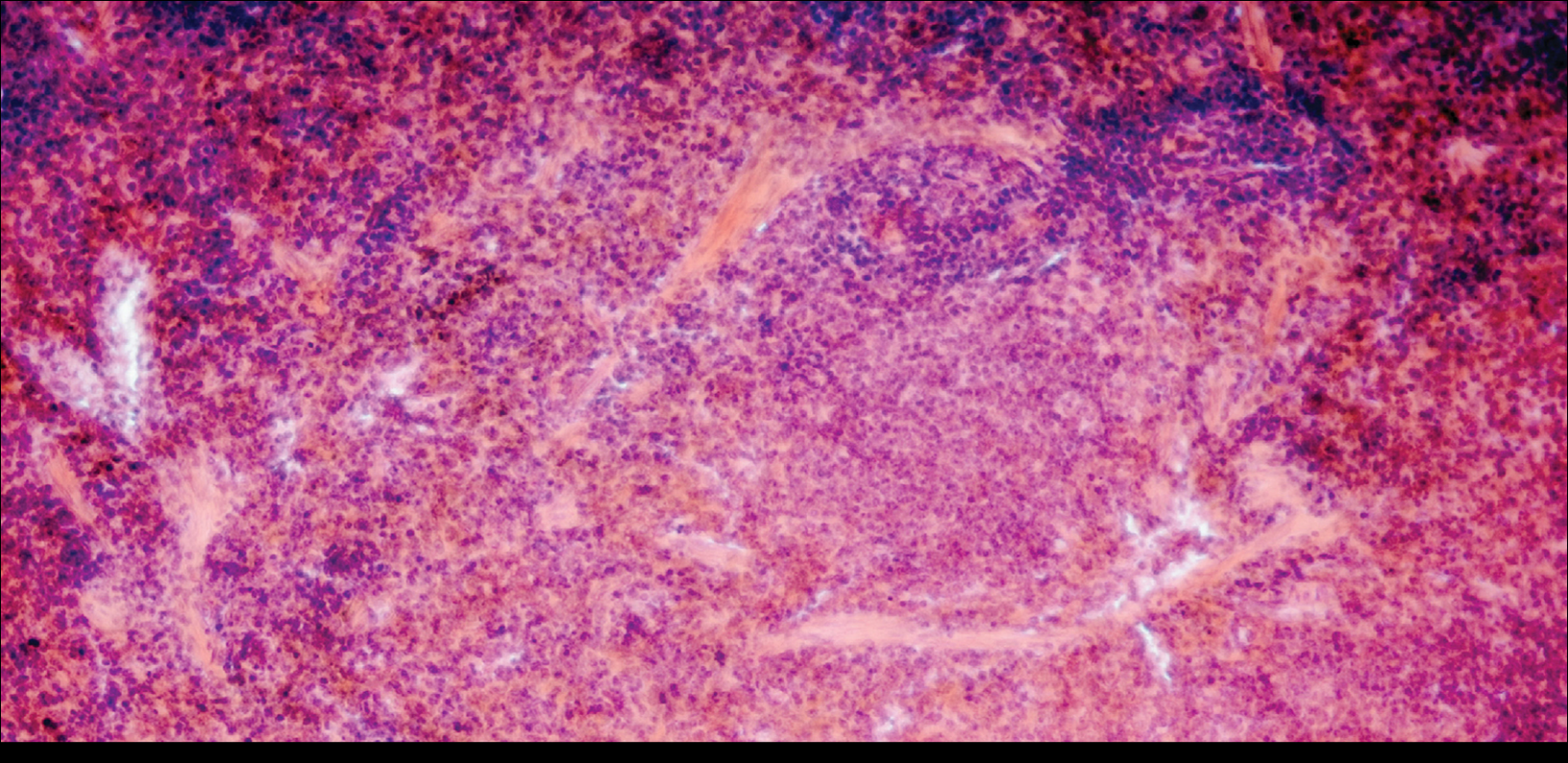

GREENSPAN'S BASIC & CLINICAL ENDOCRINOLOGY

David G. Gardner • Dolores Shoback

10th Edition

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Greenspan's Basic & Clinical Endocrinology

Tenth Edition

Edited by

David G. Gardner, MD, MS

Mount Zion Health Fund Distinguished Professor of Endocrinology and Medicine
Chief, Division of Endocrinology and Metabolism
Department of Medicine and Diabetes Center
University of California, San Francisco

Dolores Shoback, MD

Professor of Medicine
Department of Medicine
University of California, San Francisco
Staff Physician, Endocrine-Metabolism Section, Department of Medicine
San Francisco Veterans Affairs Medical Center

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Milan New Delhi Singapore Sydney Toronto

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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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Authors

Bradley D. Anawalt, MD
Chief of Medicine
University of Washington Medical Center
Professor and Vice Chair
University of Washington Department of Medicine
Seattle, Washington
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David C. Aron, MD, MS
Professor, Department of Medicine and Department of Epidemiology and Biostatistics, Division of Clinical and Molecular Endocrinology, School of Medicine, Case Western Reserve University; Associate Chief of Staff/Education, Louis Stokes Cleveland Department of Veterans Affairs Medical Center, Cleveland, Ohio
david.aron@med.va.gov
Evidence-Based Endocrinology and Clinical Epidemiology
Hypothalamus and Pituitary Gland
Glucocorticoids and Adrenal Androgens

Daniel D. Bikle, MD, PhD
Professor of Medicine and Dermatology, Veterans Affairs Medical Center and University of California, San Francisco
daniel.bikle@ucsf.edu
Metabolic Bone Disease

Glenn D. Braunstein, MD
Professor of Medicine
Cedars-Sinai Medical Center
Emeritus Professor of Medicine
The David Geffen School of Medicine at UCLA
Testes

Ty B. Carroll, MD
Assistant Professor, Endocrinology Center, Department of Medicine, Medical College of Wisconsin, Milwaukee
tcarroll@mcw.edu
Glucocorticoids and Adrenal Androgens

Marcelle I. Cedars, MD
Professor and Director, Division of Reproductive Endocrinology, Department of Obstetrics, Gynecology and Reproductive Sciences, University of California, San Francisco
marcelle.cedars@ucsfmedctr.org
Female Reproductive Endocrinology and Infertility

Orlo H. Clark, MD
Professor Emeritus of Surgery, Department of Surgery, University of California, San Francisco
clarko@surgery.ucsf.edu
Endocrine Surgery

David S. Cooper, MD
Professor of Medicine, Division of Endocrinology and Metabolism, Johns Hopkins University School of Medicine; Baltimore, Maryland
dscooper@jhmi.edu
The Thyroid Gland

James W. Findling, MD
Professor of Medicine, Director of Community Endocrine Services, Medical College of Wisconsin, Milwaukee
jfindling@mcw.edu
Hypothalamus and Pituitary Gland
Glucocorticoids and Adrenal Androgens

Paul A. Fitzgerald, MD
Clinical Professor of Medicine, Division of Endocrinology, Department of Medicine, University of California, San Francisco
paul.fitzgerald@ucsf.edu
Adrenal Medulla and Paraganglia

Janet L. Funk, MD
Associate Professor of Medicine, Division of Endocrinology, Department of Medicine, University of Arizona, Tucson
jfunk@u.arizona.edu
Humoral Manifestations of Malignancy

David G. Gardner, MD, MS
Mount Zion Health Fund Distinguished Professor of Endocrinology and Medicine; Chief, Division of Endocrinology and Metabolism, Department of Medicine and Diabetes Center, University of California, San Francisco
dgardner@diabetes.ucsf.edu
Hormones and Hormone Action
Multiple Endocrine Neoplasia
Endocrine Emergencies

Michael S. German, MD
Professor and Justine K. Schreyer Endowed Chair in Diabetes Research, Department of Medicine, Division of Endocrinology and Diabetes Center, University of California, San Francisco
mgerman@biochem.ucsf.edu
Pancreatic Hormones & Diabetes Mellitus

Stephen E. Gitelman, MD
Professor of Clinical Pediatrics, Chief, Division of Pediatric Endocrinology, Department of Pediatrics, University of California, San Francisco
sgitelma@peds.ucsf.edu
Hypoglycemic Disorders

Carl Grunfeld, MD, PhD
Professor of Medicine, University of California, San Francisco; Associate Chief of Staff for Research and Development; and Chief, Metabolism and Endocrine Sections, Veterans Affairs Medical Center, San Francisco
carl.grunfeld@ucsf.edu
AIDS Endocrinopathies

Wylie C. Hembree, MD
Associate Attending, New York Presbyterian Hospital; Retired Associate Professor of Medicine and of Obstetrics and Gynecology; Special Lecturer, Department of Medicine, Endocrine Division, College of Physicians and Surgeons, Columbia University Medical Center, New York, New York
wch2@columbia.edu
Transgender Endocrinology

Christopher P. Houk, MD
Associate Professor of Pediatrics; Chief, Pediatric Endocrinology, Medical College of Georgia, Georgia Regents University, Augusta, Georgia
chouk@gru.edu
Disorders of Sex Development

Edward C. Hsiao, MD, PhD
Associate Professor in Residence, Division of Endocrinology and Metabolism and Institute of Human Genetics, University of California, San Francisco
edward.hsiao@ucsf.edu
Hormones and Hormone Action

Juan Carlos Jaume, MD
Professor of Medicine; Chief, Division of Endocrinology, Diabetes and Metabolism; and Clinical Director of the Center for Diabetes and Endocrine Research (CeDER), College of Medicine and Life Sciences, University of Toledo, Toledo, Ohio
Juan.Jaume@utoledo.edu
Endocrine Autoimmunity

Bradley R. Javorsky, MD
Assistant Professor of Medicine, Endocrinology Center, Medical College of Wisconsin, Menomonee Falls
bjavorsky@mcw.edu
Hypothalamus and Pituitary Gland

Alka M. Kanaya, MD
Associate Professor of Medicine, Epidemiology & Biostatistics, University of California, San Francisco
alka.kanaya@ucsf.edu
Obesity

John P. Kane, MD, PhD
Professor Emeritus of Medicine, Biochemistry, and Biophysics, and Associate Director, Cardiovascular Research Institute, University of California, San Francisco
john.kane@ucsf.edu
Disorders of Lipoprotein Metabolism

Paul W. Ladenson, MD (Oxon)., MD
John Eager Howard Professor of Endocrinology and Metabolism; Professor of Medicine, Pathology, Oncology, and Radiology and Radiological Sciences; University Distinguished Professor, The Johns Hopkins University School of Medicine, Baltimore, Maryland
ladenson@jhmi.edu
The Thyroid Gland

Geeta Lal, MD, MSc, FRCS(C), FACS
Associate Professor of Surgery; Associate Chief Quality Officer, Adult Inpatient
University of Iowa, Iowa City, Iowa
geeta-lal@uiowa.edu
Endocrine Surgery

Peter A. Lee, MD, PhD
Professor of Pediatrics, Penn State College of Medicine, Hershey Medical Center, Hershey, Pennsylvania
plee@psu.edu
Disorders of Sex Development

Roger K. Long, MD
Associate Clinical Professor of Pediatrics, Division of Pediatric Endocrinology, University of California, San Francisco
Roger.Long@ucsf.edu
Hypoglycemic Disorders

Mary J. Malloy, MD
Professor (Emeritus), Department of Pediatrics and Medicine, Director, Pediatric Lipid Clinic and Co-Director, Adult Lipid Clinic, University of California, San Francisco
mary.malloy@ucsf.edu
Disorders of Lipoprotein Metabolism

Umesh Masharani, MB, BS, MRCP (UK)
Professor of Clinical Medicine, Division of Endocrinology and Metabolism, University of California, San Francisco
umesh.masharani@ucsf.edu
Pancreatic Hormones and Diabetes Mellitus
Hypoglycemic Disorders

Joshua F. Nitsche, MD, PhD
Assistant Professor, Department of Obstetrics and Gynecology, Wake Forest School of Medicine, Winston-Salem, North Carolina
jnitsche@wakehealth.edu
The Endocrinology of Pregnancy

Bansari Patel, MD
Assistant Professor, Wake Forest Baptist Medical Center, Center for Reproductive Medicine, Winston-Salem, North Carolina
bgpatel@wakehealth.edu
The Endocrinology of Pregnancy

Rodolfo A. Rey, MD, PhD
Director, Centro de Investigaciones Endocrinologicas "Dr. Cesar Bergada", CONICET - FEI - Division de Endocrinologia, Hospital de Ninos Ricardo Gutierrez, Buenos Aires, Argentina
rodolforey@cedie.org.ar
Disorders of Sex Development

Alan G. Robinson, MD
Professor of Medicine, Associate Vice Chancellor, Medical Sciences and Executive Associate Dean, David Geffen School of Medicine at UCLA, University of California, Los Angeles
robinson@ucla.edu
The Posterior Pituitary (Neurohypophysis)

Mitchell P. Rosen, MD
Associate Professor, Director, UCSF Fertility Preservation Program and Reproductive Laboratories. Division of Reproductive Endocrinology and Infertility, University of California, San Francisco
Mitchell.Rosen@ucsf.edu
Female Reproductive Endocrinology and Infertility
Transgender Endocrinology

Stephen M. Rosenthal, MD
Professor Emeritus of Pediatrics, Division of Pediatric Endocrinology; Medical Director, Child and Adolescent Gender Center, University of California, San Francisco
stephen.rosenthal@ucsf.edu
Transgender Endocrinology

Anne L. Schafer, MD
Assistant Professor of Medicine, University of California, San Francisco; Staff Physician, San Francisco Veterans Affairs Medical Center, San Francisco, California
anne.schafer@ucsf.edu
Metabolic Bone Disease

Dolores M. Shoback, MD
Professor of Medicine, Department of Medicine, University of California, San Francisco; Staff Physician, Endocrine-Metabolism Section, Department of Medicine, San Francisco Veterans Affairs Medical Center, San Francisco, California
dolores.shoback@ucsf.edu
Metabolic Bone Disease
Humoral Manifestations of Malignancy

Ajay Sood, MD
Chief, Endocrinology Section, and Associate Professor of Medicine, School of Medicine, Case Western Reserve University and Louis Stokes Cleveland Department of Veterans Affairs Medical Center, Cleveland, Ohio
ajay.sood@va.gov
Evidence-Based Endocrinology and Clinical Epidemiology

Dennis Styne, MD
Professor and Rumsey Chair, Department of Pediatrics, Section of Endocrinology, University of California, Davis, Sacramento
dmstyne@ucdavis.edu
Growth, Puberty

Robert N. Taylor, MD, PhD
Professor and Vice Chair for Research, Department of Obstetrics and Gynecology; Co-Director, Molecular Medicine and Translational Sciences Program, Wake Forest School of Medicine, Winston-Salem, North Carolina
rtaylor@wakehealth.edu
The Endocrinology of Pregnancy

J. Blake Tyrrell, MD
Clinical Professor Emeritus of Medicine; Chief, Endocrine Clinic, Division of Endocrinology and Metabolism, University of California, San Francisco
blaket@medicine.ucsf.edu
Hypothalamus and Pituitary Gland
Glucocorticoids and Adrenal Androgens

Christian Vaisse, MD, PhD
Professor of Medicine, Department of Medicine, Diabetes Center, University of California, San Francisco
vaisse@medicine.ucsf.edu
Obesity

Selma Witchel, MD
Director, Pediatric Endocrinology Fellowship Training Program; and Associate Professor with Tenure, Children's Hospital of Pittsburgh and University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania
witchelsf@upmc.edu
Disorders of Sex Development

William F. Young, Jr, MD, MSc
Professor of Medicine, Mayo Clinic College of Medicine, Mayo Clinic, Rochester, Minnesota
young.william@mayo.edu
Endocrine Hypertension

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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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CHAPTER 1

Hormones and Hormone Action

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

ACTH	Adrenocorticotropin hormone
ACVR1	Activin A receptor, type I
AD1	Activation domain 1
AD2	Activation domain 2
AF-1	Activator function-1
AF-2	Activator function-2
Akt	Protein kinase B
AMH	Anti-müllerian hormone
ANP	Atrial natriuretic peptide
AP-1	Activator protein-1
APC	Adenomatous polyposis coli gene
AR	Androgen receptor
β-ARK	β-Adrenergic receptor kinase
β-TrCP	Beta-transducin repeats-containing proteins
BMP	Bone morphogenetic protein
BNP	B-type natriuretic peptide
BXR	Benzoate X receptor
cAMP	Cyclic adenosine-3′,5′-monophosphate
CAR	Constitutive androstane receptor
CARM	Coactivator-associated arginine methyltransferase
CBP	CREB-binding protein
cGMP	Cyclic guanosine-3′,5′-monophosphate
CKI	Casein kinase I
CNP	C-type natriuretic peptide
CREB	cAMP response element-binding protein
DAG	Diacylglycerol
DAN	Differential screening-selected gene in neuroblastoma
DBD	DNA-binding domain
DRIP	Vitamin D receptor–interacting protein
DVL	Dishevelled
EGF	Epidermal growth factor
ER	Estrogen receptor
ERK	Extracellular signal–regulated kinase
FAD	Flavin adenine dinucleotide
FGF	Fibroblast growth factor
FMN	Flavin mononucleotide
FOX A1	Forkhead transcription factor A1
FXR	Farnesoid X-activated receptor
GAP	GTPase-activating protein
GAS	Interferon gamma activated sequences
GDP	Guanosine diphosphate
GH	Growth hormone
GHR	Growth hormone receptor
GLUT4	Glucose transporter type 4
GR	Glucocorticoid receptor
GRB2	Growth factor receptor–bound protein-2
GRE	Glucocorticoid response element
GRIP	Glucocorticoid receptor–interacting protein
GSK3	Glycogen synthase kinase-3
GTF	General transcription factor
GTP	Guanosine triphosphate
HRE	Hormone response element
HSP	Heat shock protein
ID	Receptor–repressor interaction domain
IGF	Insulin-like growth factor
I-κB	Inhibitor of nuclear factor kappa B
IKK	Inhibitor of nuclear factor kappa B kinase
IP_3	Inositol 1,4,5-trisphosphate
IP_4	Inositol 1,3,4,5-tetrakis-phosphate
ISRE	Interferon-stimulated response element
JAK	Janus kinase
KHD	Kinase homology domain
LBD	Ligand-binding domain
LH	Luteinizing hormone
LRP	Lipoprotein receptor related protein
LXR	Liver X receptor
MAPK	Mitogen-activated protein kinase

MEK	MAPK kinase
MR	Mineralocorticoid receptor
MSH	Melanocyte-stimulating hormone
N-Cor	Nuclear receptor corepressor
NF-κB	Nuclear factor kappa B
NO	Nitric oxide
NOS	Nitric oxide synthase
NPR	Natriuretic peptide receptor
NR	Nuclear receptor
NRPTK	Non-receptor protein tyrosine kinase
PAK	p21-activated kinase
P/CAF	p300/CBP-associated factor
P/CIP	p300/CBP cointegrator-associated protein
PDE	Phosphodiesterase
PDGF	Platelet-derived growth factor
PDK	Phosphatidylinositol-3,4,5 trisphosphate-dependent kinase
PHP-1a	Pseudohypoparathyroidism type 1a
PI-3K	Phosphoinositide-3-OH kinase
PIP_2	Phosphatidylinositol-4,5-bisphosphate
PIP_3	Phosphatidylinositol-3,4,5-trisphosphate
PI(3,4)P2	Phosphatidylinositol-3,4-bisphosphate
PKA	Protein kinase A
PKB	Protein kinase B
PKC	Protein kinase C
PKG	cGMP-dependent protein kinase
PLCβ	Phospholipase C beta
PLCγ	Phospholipase C gamma
PLC_{PC}	Phosphatidylcholine-selective phospholipase
POL II	RNA polymerase II
PPAR	Peroxisome proliferator–activated receptor
PR	Progesterone receptor
PTH	Parathyroid hormone
PXR	Pregnane X receptor
RANK	Receptor activator of nuclear factor kappa B
RAR	Retinoic acid receptor
RE	Response element
RGS	Regulators of G protein signaling
RSK	Ribosomal S6 kinase
RXR	Retinoid X receptor
SH2	*src* homology domain type 2
SIE	Sis-inducible element
SMRT	Silencing mediator for RXR and TR
SOCS	Suppressor of cytokine signaling
SOS	Son-of-sevenless
SOST	Sclerostin
SR	Steroid receptor
SRC	Steroid receptor coactivator
SRE	Serum response element
SRF	Serum response factor
STAT	Signal transducer and activator of transcription
SWI/SNF	ATP-dependent chromatin remodeling complex
TAZ	WW domain-containing transcription regulator protein 1
TBP	TATA-binding protein
TCF/LEF	T-cell factor/lymphoid enhancer factor
TGF-β	Transforming growth factor beta
TLE	Transducin-like enhancer protein
TPA	12-*O*-tetradecanoyl-phorbol 13-acetate
TR	Thyroid hormone receptor
TRAF	Tumor necrosis factor receptor–associated factor
TRAP	Thyroid hormone receptor–associated protein
TRE	TPA response element
TSH	Thyroid-stimulating hormone
VDR	Vitamin D receptor
Wnt	int/Wingless family
YAP	Yes-associated protein-1

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

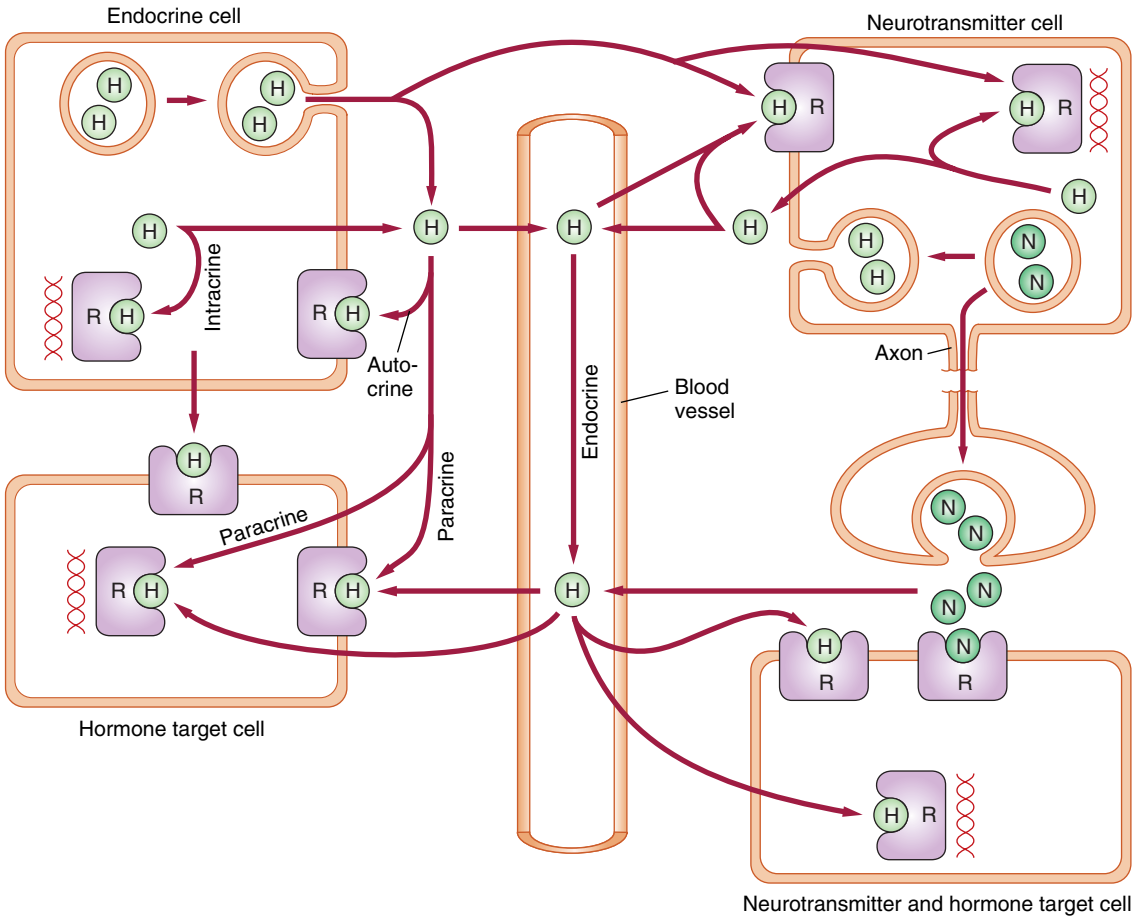

FIGURE 1–1 Actions of hormones and neurotransmitters. Endocrine and neurotransmitter cells synthesize hormones and release them by specialized secretory pathways or by diffusion. Hormones can act at the site of production either following release (autocrine) or without release (intracrine) from the producer 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 nontraditional 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

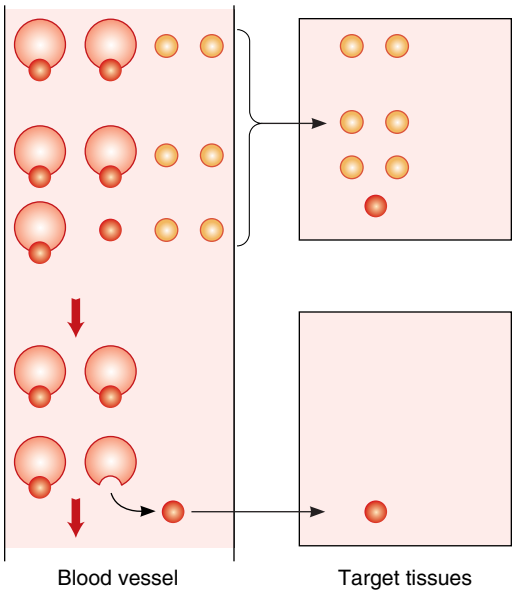

FIGURE 1–2 Role of plasma binding in delivery of hormones to peripheral tissues. Example shows a hormone that is bound (small red circles) to a plasma protein (large circles) and a hormone that is not protein bound (small orange circles). With the bound hormone, only the free fraction is available for 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:

$$[H]+[R]\underset{k_{-1}}{\overset{k_{+1}}{\rightleftharpoons}}[\mathrm{HR}]$$

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,

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

or

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

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 = [HR] + [R], this equation can be rearranged to give

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

This is the Scatchard equation and states that when bound ligand over free ligand (ie, [HR]/[H]) is plotted against bound ligand (ie, [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 [HR] = R_0/2, [H] = K_D; therefore, the K_D is also the concentration of hormone [H] 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.

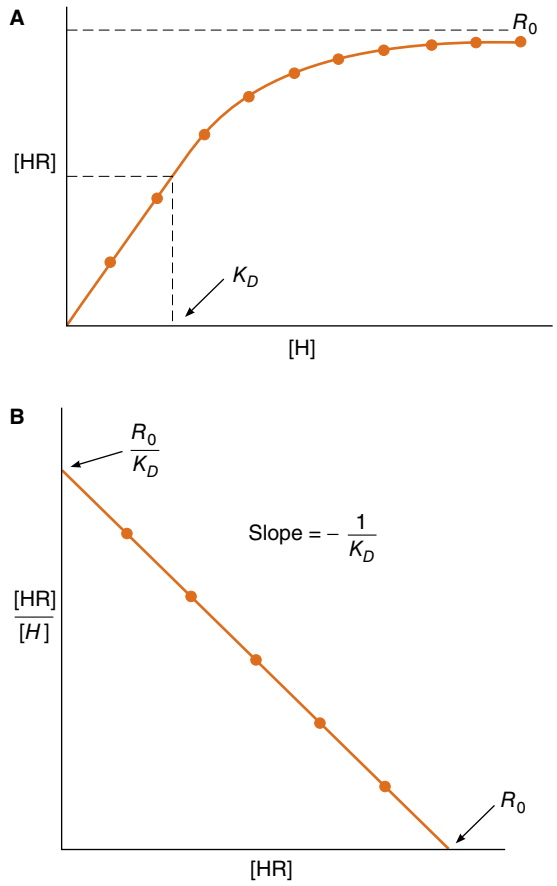

FIGURE 1–3 Ligand saturation **(A)** and Scatchard analysis **(B)** of a hypothetical hormone receptor interaction. K_D represents the dissociation constant; R_0 the total receptor concentration; [HR] and [H] the bound and free ligand, respectively. Note in **(A)** that the K_D is the concentration [H]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

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_{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_{off} of the neurotransmitter–receptor interaction guarantees that the effect is rapid in onset but of short duration, whereas the lower k_{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.[a]

Seven-Transmembrane Domain
β-Adrenergic
PTH
LH
TSH
GRH
TRH
ACTH
MSH
Glucagon
Dopamine
α_2-Adrenergic (–)
Somatostatin (–)
Single-Transmembrane Domain
Growth factor receptors
Insulin
IGF
EGF
PDGF
Cytokine receptors
Growth hormone
Prolactin
Erythropoietin
CSF
Guanylyl cyclase-linked receptors
Natriuretic peptides

[a]Receptors have been subdivided based on shared structural and functional similarities. Minus (–) sign denotes a negative effect on cyclase activity.

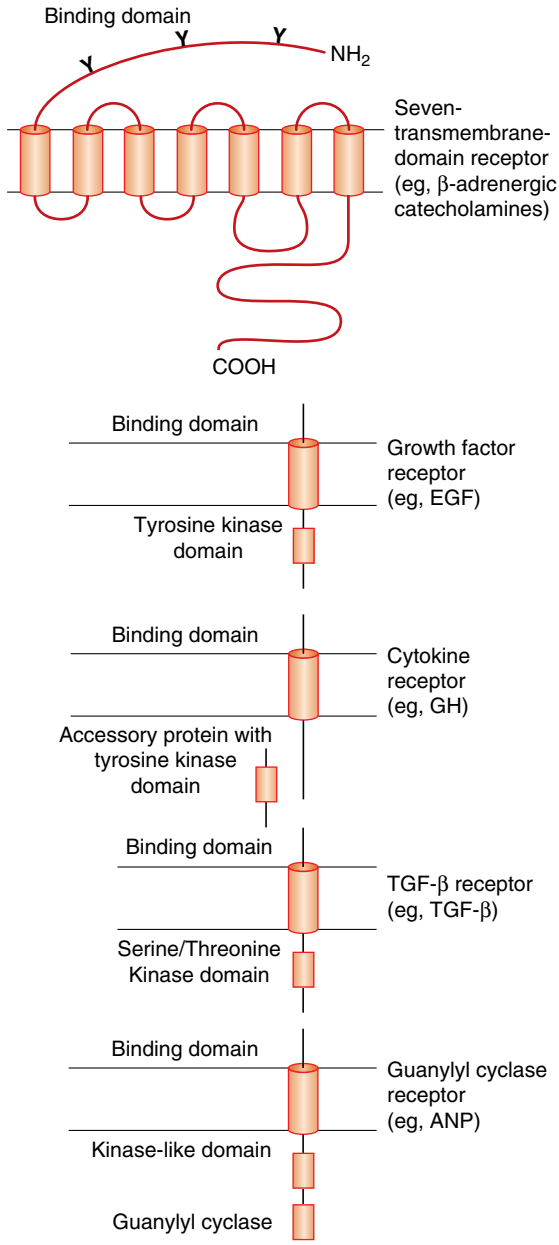

FIGURE 1–4 Structural schematics of different classes of membrane-associated hormone receptors. Representative ligands are presented in parentheses (ANP, atrial natriuretic peptide; EGF, epidermal growth factor; GH, growth hormone; TGF-β, transforming growth factor beta).

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 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 α 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] β). 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 β and γ subunits of G proteins are tightly associated with one another and function as a dimer. In some cases, the βγ 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
α_s	β-Adrenergic TSH Glucagon	Adenylyl cyclase Ca^{2+} channels K^+ channels
α_i	α_2-Adrenergic Muscarinic (type II)	Adenylyl cyclase Ca^{2+} channels K^+ channels
α_q	α_1-Adrenergic	PLCβ
β/γ		Adenylyl cyclase (+ or –) PLC Supports βARK-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 α subunit of the G protein that is critical for receptor signaling. There are about a dozen different G protein α 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 β-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 Gα 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 α 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 α subunit. Dissociation of the GTP-bound α subunit from the βγ 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 α subunit. Hydrolysis of GTP to GDP terminates the activity and promotes reassociation of the αβγ trimer, returning the system to the basal state. The GTPase activity of G protein α 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.

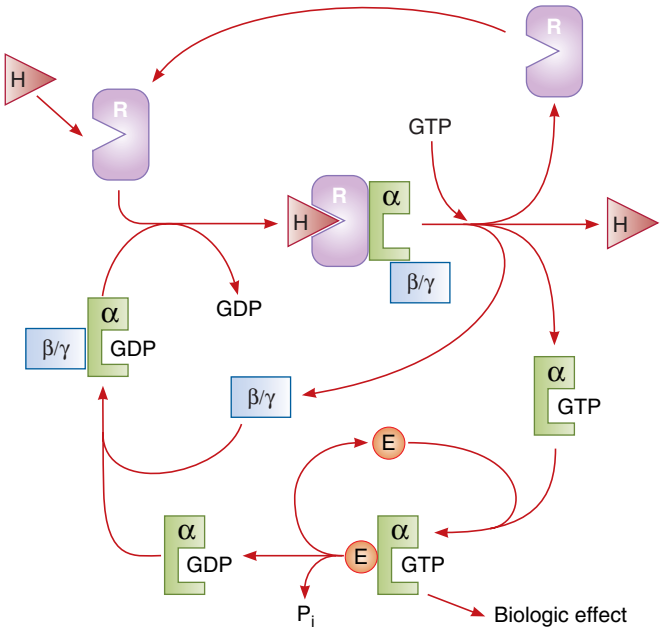

FIGURE 1–5 G protein–mediated signal transduction. α and β/γ subunits of a representative G protein are depicted (see text for details) (E, effector; H, hormonal ligand; R, hormone receptor).

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

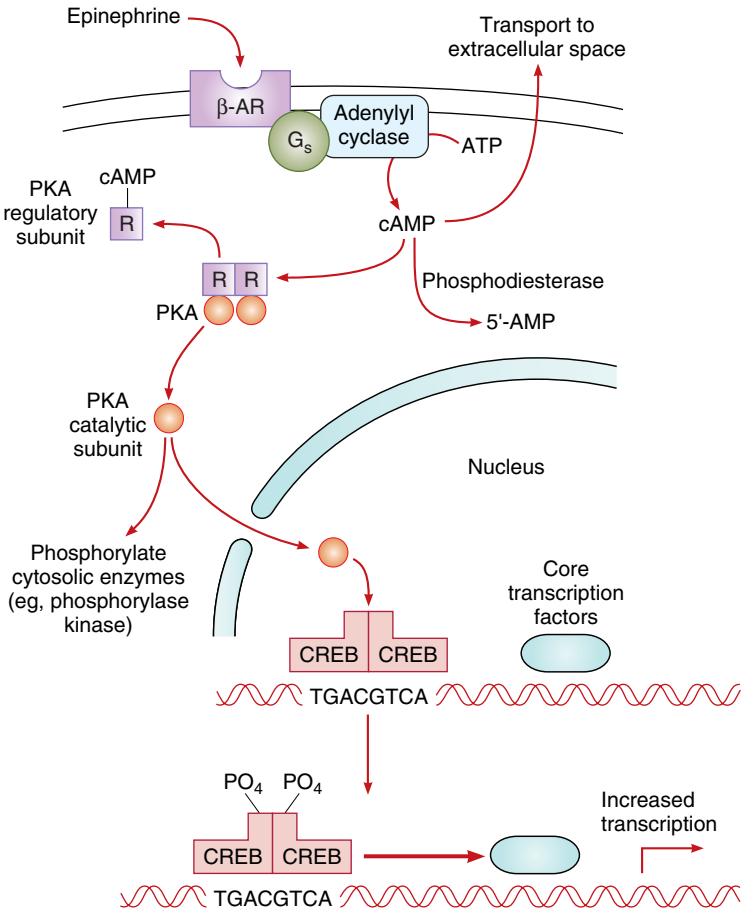

FIGURE 1–6 β-Adrenergic receptor/G_s mediated signaling in the cytoplasmic and nuclear compartments. The cAMP response element–binding protein (CREB) is depicted bound to a consensus CRE in the basal state. Phosphorylation of this protein leads to activation of the juxtaposed core transcriptional machinery.