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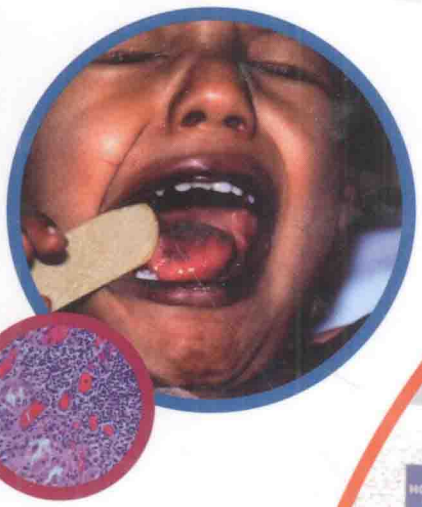

Michael S. Kappy
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PEDIATRIC PRACTICE

Endocrinology

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Pediatric Practice: Endocrinology

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Preface

Of the many attractive qualities of pediatric endocrinology, two in particular—its diversity of disorders and its intrinsically pediatric focus on growth and physical development—amplify the importance of practical knowledge of this specialty for the primary care provider. In the past, apart from type 1 diabetes, endocrine problems in clinical practice were relatively rare; they required a pediatric health care expert to differentiate their distinguishing features from the breadth of normal variations in ruling such disorders *out* much more often than *in*. During the past 20 years, however, as the incidence of type 1 diabetes mellitus has increased, other diseases that were virtually unseen in children—obesity-associated insulin resistance, type 2 diabetes mellitus, and ovarian androgen excess—have emerged as common occurrences in pediatric primary care. Ethnic demographic changes, growth and puberty acceleration due to excess nutrition, and other factors have reduced the mean age of appearance of first puberty signs so that normal variations must now be distinguished more frequently from pathologic causes of precocious puberty. The expanded availability and variety of (often controversial) growth-promoting and puberty-altering treatments have created therapeutic options for a broadening spectrum of children, for whom critical evaluation of benefit, cost, and risk is required. Further, in most states of the United States, every new baby is now screened for congenital adrenal hyperplasia as well as for congenital hypothyroidism. Because of these changes among others, the primary child health care provider ponders possible endocrine diagnoses or therapeutics virtually every day.

With these thoughts in mind, the editors set out to create a pediatric endocrinology text that, first and foremost, would be an outstanding clinical analysis and decision-making resource. Since an understanding of the clinical manifestations and treatments of endocrine disorders begins with knowledge of concepts of hormone action and principles of feedback control, the first chapter, "General Concepts and Physiology," links genetics, cell biology, and physiology with pathophysiology to provide a clear and approachable overview of endocrine systems. Subsequent chapters are traditional in title—disorders of growth, water homeostasis, thyroid and adrenal glands, calcium and bone metabolism, puberty, sex differentiation, and carbohydrate metabolism—but innovative in organization and emphasis. Problem-oriented rather than diagnosis-oriented frameworks are emphasized so as to capture conceptual and practical approaches to clinical dilemmas of current general practice. Integration of pathophysiology with clinical management is emphasized, with extensive use of figures to illustrate principles of normal and abnormal physiology and treatment rationale and effects. Attention is paid to guiding readers in "how to think about" the evaluation of clinical problems and "when to refer" complex or worrisome patients. Through this approach, the editors' objective is to achieve a subspecialty text that, true to its inclusion in the "Pediatric Practice" series, is distinguished not only by its effective description of state-of-the-art science, but by its clinical utility as well.

It is our added hope that this text is an equally valuable education resource for pediatric endocrinology. Talented educators have a gift for making complex phenomena understandable, a gift that cannot be displaced by the unlimited and instant access to information now provided by web-based journals and databases. The task placed before our group of internationally recognized senior authors was daunting: concisely yet comprehensively review current knowledge, link these concepts with analysis of clinical situations suggesting endocrine system problems, and provide practical recommendations for rational and efficient evaluation and treatment of children with endocrine disorders. The skill with which

they accomplished this synthesis is a testament to their far-reaching experience and thoughtful analysis and makes these chapters exceptional examples for young subspecialists developing their own conceptual approaches, and to all pediatric endocrinologists engaged in teaching others. It is the editors' hope that well-worn covers with many dog-eared pages will signify that this book has adeptly filled an important niche.

The editors wish to thank Alyssa Fried of McGraw-Hill for her expert assistance and firm yet always friendly prodding to remain on task and on time.

Michael S. Kappy, MD, PhD
David B. Allen, MD
Mitchell E. Geffner, MD

Acknowledgments

Once again, we get to acknowledge those family members, friends, and colleagues whose influence in our lives is inestimable. I would like to begin by expressing my gratitude for the support given to me over many years by my parents, Jack and Lil; my wife, Peggy; my sons, Doug and Greg; my granddaughters, Samantha and Summer; my brother, David; and my sister, Ellen. Other family members to thank are my brothers-in-law, Joe Suckiel and Jay Markson, and the entire Markson family. I am particularly saddened by the recent loss of my great-cousin, Ralph Kaplowitz, a member of the first NBA Championship team—the 1946-47 Philadelphia Warriors—and a good friend.

Of the many wonderful colleagues with whom I have worked for 50 years, I particularly thank the following for guidance and support at various times in my life: Lennie Licara, Saul Chavkin, Yvonne Brackbill, Kenneth Monty, Harry Harlow, Harry Waisman, Robert Metzenberg, Willam Middleton, Henry Kempe, Henry Silver, Vince Fulginiti, Grant Morrow, Claude Migeon, Bob Blizzard, Harold and Helen Harrison, and Elmer "Whitey" Lightner. A special thanks to Jules Amer, Irwin Redlener, Lew Barness, and Enid Gilbert-Barness for their guidance and friendship.

It goes without saying that this book and our previous one, "Principles and Practice of Pediatric Endocrinology," would not have been possible without the incredibly valuable collaboration and support given freely by Dave Allen and Mitch Geffner. There are many other colleagues and friends whom I would like to acknowledge, but space limitations do exist. To all of you, you know who you are, thank you.

Michael S. Kappy, MD, PhD

The work of this book has stimulated much positive personal and professional reflection—on the complexity, advancement, and expansion of our field of pediatric endocrinology, on the insights of countless brilliant contributors to this progress, on the joy and privilege of caring for children, and on the satisfaction of collaborating with such wonderful and talented colleagues: Michael Kappy, Mitch Geffner, and our contributing authors.

For inspiration, I am most indebted to my father, Rich Allen, a dedicated pediatrician in the truest and most profound sense of the word. In spite of my efforts to take a different path, the example he provided in caring for children brought me back to medicine, and then to pediatrics. For whatever perspective and humility I do have, I give thanks to my mother, Joyce, the most centered and loving individual I have ever known. And for everything else, I thank my wife, Sally, who has unselfishly and constantly supported and encouraged me for over 35 years; and my children, Brittany, Doug, and Nick, who provide immeasurable love and joy and the motivation always to do my best.

Professionally, I first acknowledge the generous spirit of Dr. Robert Blizzard for his invaluable advice and support early in my career. I also thank Ann Johanson, Ron Rosenfeld, Ed Reiter, Alan Rogol, Barbara Lippe, Margaret MacGillivray, and Ken Copeland, who have inspired and encouraged me to seek academic and leadership challenges. I am indebted to my University of Wisconsin mentors and colleagues Norm Fost and Aaron Friedman, who instilled in me a love for critical thinking and the importance of challenging conventional wisdom. And finally, a sincere thank you to my UW Endocrine Division co-workers—Michael MacDonald, Ellen Connor, Aaron Carrel, and Tracy Bekx—who make work in the real world so much fun, and without whose patience and support I could not have pursued so many opportunities.

Twenty-five years ago, the specialty of pediatric endocrinology captivated my interest because of its elegance, diversity, mystery, and intrinsically pediatric focus on the changes of childhood and adolescence. My hope for this book is that it both captures and conveys these qualities for the reader.

David B. Allen, MD

I have once again had a professional thrill ride working with my close friends, Mike Kappy and Dave Allen, on our second endeavor into the world of textbook writing. Their endless knowledge, work ethic, and unyielding camaraderie are unmatched.

For the second time, I can see that editing and language are key essentials to the art of creating a textbook, talents for which my father (high school chemistry teacher and review book writer) and mother (high school French teacher) must be commended for providing the impetus (and genetics).

In my preface in our previous book, I acknowledged the many mentors, colleagues, and trainees who had inspired me to that point. That list is still true to this day, but I would like to expand it to make up for one inadvertent omission, Alan Morris, former fellow and longstanding friend, and to acknowledge my most recent fellow graduates: Josh May, Lily Chao, Christine Burt Solorzano, Avni Shah, and Nina Ma. I also can't say enough about Rob Rapaport, who is such a superb physician, scientist, and, most importantly, friend.

I must also pay special tribute to three people from my prior list who, tragically, met untimely deaths and who had major impacts in my professional life: Dave Golde, Joao Antunes, and Alan Herschenfeld.

But not to dwell on the obvious, I would never have had the opportunity to write this book or to have had any professional success were it not for the unwavering support of my family. My wife, Andrea, has been my rock and my children, Jenny and Eric, have always been there for me. I also want to acknowledge my soon-to-be daughter-in-law, Ashley King. I am so fortunate to have them all in my life.

Mitchell E. Geffner, MD

Contents

CHAPTER 1

General Concepts and Physiology

Kathleen Bethin and John S. Fuqua

INTRODUCTION

There are broad principles and concepts in endocrinology that the reader must understand. Familiarity with concepts such as negative feedback loops, hormone-receptor function, and hormone replacement therapy allows the physician to generalize what is learned in one area and apply it to others. This gives the ability to predict the effects of an endocrine abnormality or perturbation on downstream hormones and its subsequent clinical effects. Conversely, it also allows the clinician to consider a set of symptoms, work backward to develop a differential diagnosis, and test this by looking for laboratory abnormalities that are diagnostic for an endocrine disease. This chapter will review many of these basic principles that are applicable across the field in order to provide groundwork for later chapters. Following a discussion of general hormone function and integration of endocrine systems, we will discuss the classification of hormones. Reviews of hormone synthesis, processing, and transport follow, and then we will outline the regulation of hormone secretion. Following this, we will examine the evolving field of hormone receptors and discuss nontraditional endocrine systems. The clinical relevance of the preceding material is apparent in the section covering principles of endocrine disease. Finally, we will summarize important principles in endocrine testing.

HORMONE FUNCTION

The endocrine system consists of a dizzying number of hormones, and newly discovered ones are added to the list on a regular basis. The word "hormone" comes from the Greek word "ormaein" meaning to set in motion or to spur on. This is an apt derivation, because hormones are chemicals secreted by one tissue that produce effects in distant tissues, leading to an array of physiological responses. In children, we can categorize hormones by the systems they affect, including growth, reproduction, homeostasis, and energy regulation. Many hormones play roles in multiple categories, emphasizing the complex network of interactions and the redundancy built into these processes. Table 1-1 shows how selected endocrine systems fit into this categorization, illustrating this redundancy

Growth

Growth is an exceedingly complex process that is unique to pediatric medicine. When considering the endocrine control of growth, many think first of growth hormone (GH), but growth involves many other hormones as well. For example, thyroid hormone and sex steroids are permissive for growth hormone secretion, and in the presence of hypothyroidism or hypogonadism, growth hormone is not secreted normally. Growth hormone itself is critical for the secretion of insulin-like growth factor-1 (IGF-1), a hormone that is responsible for many of the effects of GH on linear growth and other metabolic processes, both in fetal life and in childhood and beyond. Before birth, growth hormone's effects are less noticeable, and insulin serves an active role in promoting fetal growth. Insulin-like growth factor-2 (IGF-2), which is not under the regulation of GH, is also an important endocrine mediator of fetal growth. Each of the above hormones have their own sets of regulatory hormones and factors, such as growth-hormone-releasing hormone (GHRH) and somatostatin for GH and thyrotropin-releasing hormone (TRH) and thyroid-stimulating hormone (TSH) for thyroid hormone.

Table 1-1.

Classes of Hormone Function with Selected Examples of Endocrine Systems

Hormone Function	Regulatory Hormones	Effector Hormones
Growth	GHRH	GH
	Somatostatin	IGF-1
	TRH	T_4
	TSH	T_3
	LH	Estradiol
	FSH	Testosterone
		Insulin
Reproduction	GnRH	Estradiol
	LH	Testosterone
	FSH	MIS
		Prolactin
Homeostasis	TRH	T_4
	TSH	T_3
	CRH	
	ACTH	Cortisol
	GnRH	
	LH	Estradiol
	FSH	Testosterone
		ADH
		Renin
		Angiotensin
		Aldosterone
		PTH
		Vitamin D
		Insulin
		Epinephrine
		Leptin
Energy Balance	TRH	T_4
	TSH	T_3
	GHRH	GH
	Somatostatin	IGF-1
	CRH	Cortisol
	ACTH	
		Leptin
		Glucagon
		Insulin

ACTH, adrenocorticotrophic hormone; ADH, antidiuretic hormone; CRH, corticotrophin-releasing hormone; FSH, follicle-stimulating hormone; GH, growth hormone; GHRH, GH -releasing hormone; GnRH, gonadotropin-releasing hormone; IGF-1, insulin-like growth factor-1; LH, luteinizing hormone; MIS, Mullerian-inhibiting hormone; PTH, parathyroid hormone; T_3, triiodothyronine; T_4, L-thyroxine; TRH, thyrotropin-releasing hormone; TSH, thyroid -stimulating hormone

Deficiencies of the regulatory hormones have much the same effects on growth as deficiencies of the primary hormones. Some hormones also play less direct roles, primarily promoting processes important for homeostasis, but without which growth cannot proceed. Examples of these include the hormones required for normal calcium and bone mineralization such as parathyroid hormone (PTH), 25-hydroxy- and 1,25-dihydroxyvitamin D, and fibroblast growth factor-23 (FGF-23). Hormones, particularly estrogens, also actively mediate the physiologic cessation of growth during adolescence, as indicated by the failure of growth plate fusion in an individual with an estrogen receptor mutation and in those patients carrying mutations in the gene for the aromatase enzyme, critical for the synthesis of estrogen.[1,2]

Reproduction

Reproduction is an essential function of every species, and the endocrine system plays critical roles in both the reproductive process itself and in the anatomic and physiological development essential for reproduction to occur in both males and females. Developmental defects of the internal and external genitalia and errors of puberty are also unique to pediatric endocrinology and comprise a significant percentage of patients seen in clinical practice. In the area of reproduction, as in other endocrine systems, there is a large degree of cross talk between different hormones and their receptors. Beginning with sexual differentiation, a coordinated network of genetic events results in the synthesis and secretion of testosterone and Müllerian inhibiting substance (MIS) that, interacting with their specific receptors, initiate the differentiation of nonspecific or bi-potential reproductive structures into either typical male or female features. Participating in this process are regulatory hormones such as chorionic gonadotropin, luteinizing hormone (LH), follicle-stimulating hormone (FSH), and inhibins.

The reproductive system is typically quiescent during the mid-childhood years, but at the time of puberty, gonadal activity restarts in both males and females under regulatory mechanisms involving the central nervous system as well as the gonadotropins LH and FSH. While MIS appears to be less critical for normal gonadal function in postnatal life, other gonadal factors such as the inhibins remain important. In the male, testosterone secretion during puberty causes various secondary sex characteristics such as muscularity, body hair, and voice deepening, and estrogen secretion in females causes breast development and the establishment of a female body habitus. In the case of the reproductive system then, across the life of a developing child a given hormone may have very different effects, depending on the physiological and developmental state of the individual, be it fetus or adolescent.

Although regulatory mechanisms are generally fixed, the reproductive system features one of the few feedback loops that changes. While gonadotropin secretion in sexually mature females causes ovarian estrogen secretion that leads to suppression of gonadotropin production by negative feedback, at the midpoint of the menstrual cycle this changes to a positive feedback system and results in the LH surge that causes ovulation.

Homeostasis

Homeostasis refers to the maintenance of the metabolic milieu of the individual at steady state, and this is arguably the most important function of endocrine systems in general. Homeostasis is not a single process; it consists of many very different aspects. Hormones tightly regulate diverse physiological features such as maintenance of normal serum osmolality, normal bone mineral content, normoglycemia, metabolic rate, and many others.

Osmoreceptors in the vasculature in part control the release of vasopressin (antidiuretic hormone [ADH]) from the posterior pituitary gland, which subsequently controls free water excretion and regulates water balance and serum osmolality. The renin-angiotensin-aldosterone system provides separate but overlapping regulation of sodium and potassium balance.

PTH and 1,25-dihydroxyvitamin D, the activated form of vitamin D, maintain bone mineral content, serum calcium, and phosphorus concentrations at a steady state. Other endocrine factors directly influencing this system include FGF-23, PTH-related protein (PTHrP), and calcitonin.

Glucose availability is critical for energy homeostasis, and a far-reaching system of apparently unconnected hormones (see the "Glucose Control" section later in the chapter) controls serum glucose levels. Basal metabolic rate, defined as the rate of oxygen consumption at rest, is partially under the influence of thyroid hormones, including the regulatory hormones TRH and TSH and the effector hormones L-thyroxine (T_4) and its activated or active form, triiodothyronine (T_3). It is T_3 that binds to the intracellular thyroid hormone receptor to alter the transcription of genes controlling metabolic rate.

Energy Production

Endocrine regulation is essential for handling of the body's energy needs, including the immediate use and storage of nutrients such as glucose, proteins, and lipids. Insulin permits the uptake of glucose into muscle cells where it is converted to energy in the form of adenosine triphosphate (ATP). At the same time, insulin suppresses the oxidation of fatty acids and promotes energy storage. Deficiency of insulin, as is seen in type 1 diabetes, leads to hyperglycemia, with lack of normal glucose utilization, as well as excessive lipolysis, fatty acid oxidation, and protein breakdown, resulting in the polyuria, polydipsia, weight loss, and ketoacidosis seen in untreated diabetes. Other hormones also influence energy storage and delivery, including cortisol and growth hormone. A complex neuroendocrine system controls food intake with remarkably fine regulation of body weight over years using leptin as the primary adipocyte-derived endocrine hormone leading to satiety.[3]

INTEGRATION OF HORMONE SYSTEMS

As seen from the above discussion, endocrine control of physiologic processes often features a rich interweaving of hormone systems, with a great deal of redundancy. Table 1-1 and Figure 1-1 illustrate this overlap, with several of the hormone systems, such as the growth and thyroid axes, being involved in more than one aspect of endocrine function. Such integration of multiple hormone systems in the regulation of a body process increases the robustness and stability of the system and

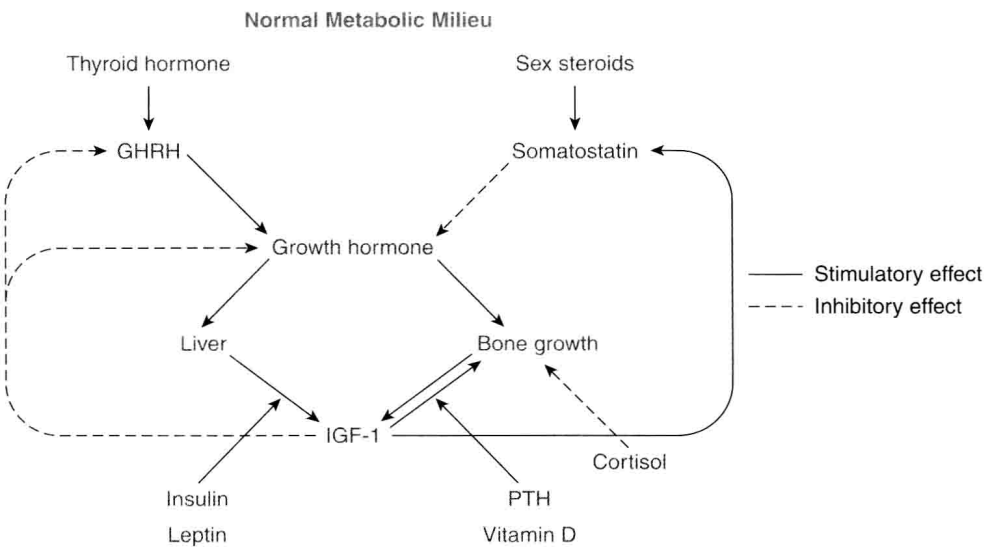

FIGURE 1-1 ■ There are many different endocrine influences in the process of growth, including the GH/IGF-1, thyroid, adrenal, insulin, and PTH/vitamin D axes, illustrating the integration of many systems in the regulation of complex physiologic processes.

allows for smoother and finer regulation. Two examples of this hormone integration are growth and the regulation of serum glucose levels.

Growth

Human growth involves not only the classic growth hormone axis, consisting of the hypothalamic regulatory hormones GHRH and somatostatin, GH itself, IGF-1, and various binding hormones, carrier proteins, and receptors, but also an array of other axes[4] (Figure 1-1). Thyroid hormone is essential for normal GH secretion and efficacy. During adolescence, the hypothalamic-pituitary-gonadal axis is also essential for normal growth. Delivery of adequate amounts of glucose, amino acids, and lipids to cells is clearly necessary for normal metabolism, and insulin, cortisol, and leptin are required for this to occur. Bone metabolism also needs to flourish for proper skeletal development, and this requires multiple steps of endocrine input, including PTH and vitamin D metabolites as well as input from GH and IGF-1. All of this must occur on a background of normal electrolyte balance and normal serum osmolality.

Glucose Control

Plasma glucose concentration is finely regulated within a relatively narrow range, and this also occurs through a complex interaction of numerous endocrine processes. Insulin provides the primary regulation within the normal physiologic range. If a large influx of glucose occurs, putting upward pressure on glucose concentration, insulin secretion also increases, promoting entry of glucose into muscle cells, glycogen synthesis, and lipogenesis. Serum glucose levels declining into the hypoglycemic range, however, suppress insulin secretion, leading to lipolysis and fatty acid oxidation which provide additional substrate for energy. Hypoglycemia also activates counter-regulatory hormone secretion. These counter-regulatory hormones consist of GH, epinephrine, glucagon, and cortisol, and cause increased hepatic glycogen breakdown and gluconeogenesis. Proteolysis releases amino acids for use in gluconeogenesis, again providing for system redundancy.

HORMONE TYPES

The signal transduction pathways of the endocrine system are very elaborate.[5] However, the processes are actually based on a simple concept. Hormone binding to its receptor causes a conformational change of the receptor, which transmits a signal that initiates the physiological response. The specificity of the receptor for its hormone, the specific cell type, and the specific signaling system in the cell all contribute to the specific response that is seen. There are three major classifications of hormones based on chemical structure: proteins or peptides, steroids, and amines (Table 1-2). The structure of the hormone determines both the location of the hormone receptor (membrane or nuclear) and the half-life of the hormone in circulation. Since peptide hormones are water soluble, peptide hormones bind to membrane receptors. Most amine hormones also bind membrane receptors, except for thyroid hormone, which binds nuclear receptors. Steroid hormones also bind nuclear receptors. Thyroid hormones have the longest half-life, which is measured in days, but other amine hormones have the shortest half-life of only a few minutes. Peptide and steroid hormones fall in the middle, with half-lives ranging from a few minutes to several hours. Hormones that circulate in low concentrations rapidly associate and dissociate from the receptor, such that receptor occupancy is a function of both hormone concentration and receptor affinity.

Table 1-2.

Classification of Some Known Hormones

Peptide Hormones	Steroid Hormones	Amine Hormones
GHRH	Cortisol	Epinephrine
Somatostatin	Estradiol	Norepinephrine
GH	Testosterone	Dopamine
IGF-1	25-hydroxyvitamin D	T_4
TRH	1,25-dihydroxyvitamin D	T_3
TSH		
GnRH		
LH		
FSH		
hCG		
MIS		
Prolactin		
Insulin		
ACTH		
CRH		
MSH		
PTH		
PTHrP		
ADH		

ACTH, adrenocorticotrophic hormone; ADH, antidiuretic hormone; CRH, corticotrophin releasing hormone; FSH, follicle stimulating hormone; GH, growth hormone; GHRH, G H-releasing hormone; hCG, human chorionic gonadotropin; IGF-1, insulin-like growth factor-1; LH, luteinizing hormone; MIS, Mullerian-inhibiting hormone; MSH, melanocyte-stimulating hormone; PTH, parathyroid hormone; PTHrP, PTH-related peptide ; T_3, triiodothyronine; T_4, L-thyroxine; TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone

Peptide

The majority of hormones are peptide hormones.[5] Peptide hormones vary greatly in size from as small as three peptides to large multi-subunit glycoproteins. Examples of peptide hormones are listed in Tables 1-2 and 1-3.

Table 1-3.

Membrane Receptor Families and Signaling Pathways

Receptors	Effectors	Signaling Pathways
G protein–coupled-seven transmembrane (GPCR)		
β-Adrenergic	$G_s\alpha$, adenylate cyclase	Stimulation of cyclic AMP
LH, FSH, TSH	Ca^{2+} channels	production, protein kinase A
Glucagon		
PTH, PTHrP		Calmodulin, Ca^{2+}-dependent kinases
ACTH, MSH		
GHRH, CRH		
α-Adrenergic	$G_i\alpha$	Inhibition of cyclic AMP production
Somatostatin		Activation of K^+, Ca^{2+} channels
TRH, GnRH	G_q, G_{11}	Phospholipase C, diacylglycerol-IP_3, protein kinase C, voltage-dependent Ca^{2+} channels
Receptor tyrosine kinase		
Insulin, JGF-1	Tyrosine kinases, IRS-1 to IRS-4	MAP kinases, PI 3-kinase, RSK
EGF, NGF	Tyrosine kinases, ras	Raf, MAP kinases, RSK
Cytokine receptor-linked kinase		
GH, PRL	JAK, tyrosine kinases	STAT, MAP kinase, PI 3-kinase, IRS-1, IRS-2
Serine kinase		
Activin, TGF-β, MIS	Serine kinase	Smads

IP_3, inostol triphosphate; IRS, insulin receptor substrates; MAP, mitogen-activated protein; MSH, metanocyte-stimulating hormone, NGF, nerve growth factor, PI, phosphatidylinostol, RSK, ribosconal S6 kinase; TGF-β, transforming growth factor β. For all other abbreviations, see text.
Reproduced from Jameson JL. Principles of endocrinology. In: Jameson JL, ed. Harrison's Endocrinology. *New York, NY: McGraw-Hill; 2006:1-15.*

Since peptide hormones are not fat soluble, they do not easily cross the cell membrane and thus bind membrane receptors. When protein hormones bind their receptors, there is an immediate induction of the intracellular signaling pathway associated with that particular receptor. Depending on the specific receptor, the signaling cascades may activate or inhibit cAMP production, activate calcium or potassium channels, or regulate other proteins by phosphorylation. The signaling pathways for many membrane receptors are depicted in Figure 1-2.

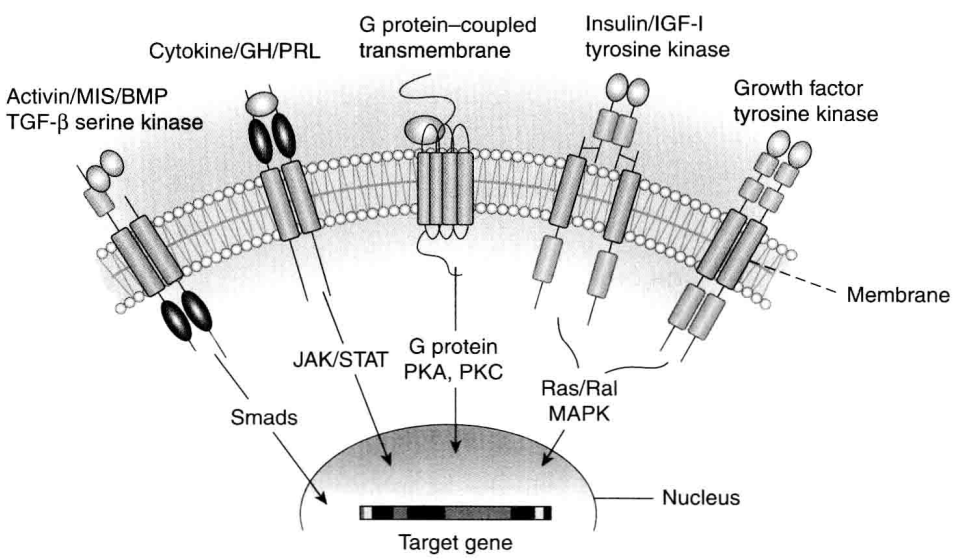

FIGURE 1-2 ■ Membrane receptor signaling. MAPK, mitogen-activated protein kinase; PKA, -C, protein kinase A, C; TGF, transforming growth factor. For other abbreviations, see text. (*From Jameson JL. Principles of endocrinology. In: Jameson JL, ed.* Harrison's Endocrinology. *New York, NY: McGraw-Hill; 2006:1-15.*)

The membrane receptor families and their associated signaling pathways are shown in Table 1-3.

The glycoproteins are structurally the most complex group of peptide hormones.[6] The carbohydrate moiety constitutes 15% to 35% of the hormone by weight. These hormones include: LH, FSH, TSH, and human chorionic gonadotropin (hCG). Glycoprotein hormones are composed of 2 subunits joined by noncovalent forces. They share a common α subunit and a hormone-specific β subunit. Although the β subunits are unique, they are homologous, with the β subunits of hCG and LH sharing the most homology. In order for hormones to affect the target organ, they must bind and activate their specific receptors. In the physiological state, hormones bind only their specific receptor. However, in the case of hormone excess, a hormone may bind to its receptor as well as closely related receptors. This is demonstrated by the use of synthetic hCG by endocrinologists to stimulate the LH receptor during testing of testicular function in prepubertal boys.[7] This also may be demonstrated in cases of severe hypothyroidism. At very high TSH levels may bind to the FSH receptor, activating the gonads, causing testicular enlargement in boys and ovarian stimulation in girls (van Wyk-Grumbach syndrome).[8] The receptors for the glycoprotein hormones are G protein–coupled receptors (GPCRs) that activate the adenylate cyclase and inositol triphosphate diacylglycerol pathways.[5,9]

Steroid

Steroid hormones are derived from cholesterol (Figure 1-3).[5] Steroid hormones include estrogen, testosterone, cortisol, vitamin D, and retinoids. Because of their lipophilic nature, steroid hormones readily cross the cell membrane and bind nuclear receptors. Once hormone is bound to its nuclear receptor, the receptor binds the DNA response element, usually as a dimer. Steroid hormone binding to its receptor results in activation or repression of gene transcription (Figure 1-4). Thus, the effects of steroid hormones are delayed compared to peptide hormones. However, since gene transcription is altered, the effect of steroid hormones is sustained.

Amines

Amine hormones are derived from the amino acid tyrosine.[9] This class includes dopamine, catecholamines, and thyroid hormone. Like the peptide hormones, the amine hormones usually bind membrane receptors. Thyroid hormone, however, binds nuclear receptors. Similar to steroid hormones, it takes longer to see the effects of increases in thyroid hormone, but the effects are sustained. Epinephrine, norepinephrine, and dopamine induce rapid- and short-lived changes, even more rapidly than seen with the peptide hormones.

HORMONE PRECURSORS AND PROCESSING

There are numerous steps involved in the production of the active hormone. Some hormones are directly synthesized in the active form and others require further processing to the active hormone, or more active form.

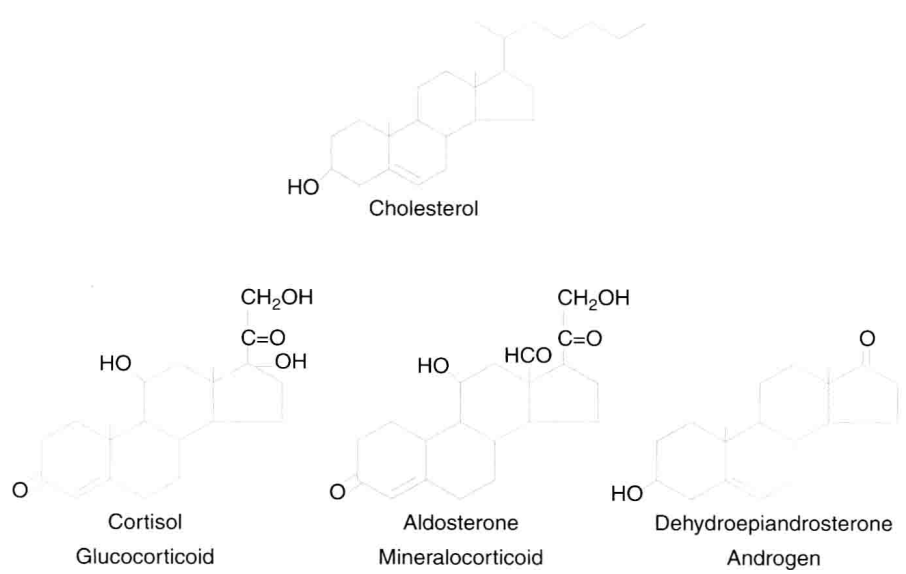

FIGURE 1-3 ■ Hormones of the adrenal cortex. The principal hormones synthesized and released by the adrenal cortex are the glucocorticoid (cortisol), the mineralocorticoid (aldosterone), and the androgen (dehydroepiandrosterone). These steroid hormones are derived from cholesterol. (*From Molina PE. Adrenal gland. In: Molina PE.* Endocrine Physiology. 2nd ed. *New York, NY: McGraw-Hill; 2006:123-156*)

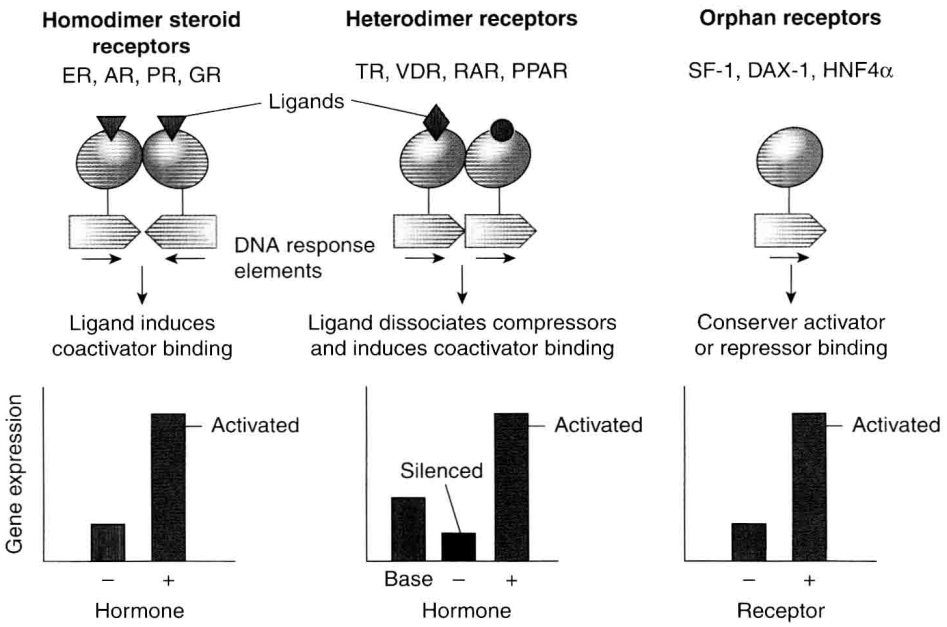

FIGURE 1-4 ■ Nuclear receptor signaling. ER, estrogen receptor; AR, androgen receptor; PR, progesterone receptor; GR, glucocorticoid receptor; TR, thyroid hormone receptor; VDR, vitamin D receptor; RAR, retinoic acid receptor; PPAR, peroxisome proliferator activated receptor; SF-1, steroidogenic factor-1; DAX, *d*osage sensitive sex-reversal, *a*drenal hypoplasia congenita, *X*-chromosome; HNF4α, hepatic nuclear factor 4α. *(From Jameson JL. Principles of endocrinology. In: Jameson JL, ed.* Harrison's Endocrinology. *New York, NY: McGraw-Hill; 2006:1-15.)*

Hormone Synthesis

No matter which class a hormone belongs to, the rate-limiting step in hormone activation is usually the synthesis of the hormone.

Protein/peptide hormones

The synthesis of peptide hormones is dependent on classical gene expression.[5] The gene for a peptide hormone is transcribed into mRNA which is then translated into a protein. The protein is further modified by post-translational processing. Synthesis of peptide hormones is regulated by DNA regulatory elements found on many genes. However, the peptide hormone genes also contain specific hormone response elements, resulting in very precise control of synthesis. This is exemplified by direct repression of TSH synthesis by binding of thyroid hormone to a thyroid hormone response element on the TSH gene. Peptide hormones are synthesized in the endoplasmic reticulum and then transferred to the Golgi apparatus, where they are packaged into secretory granules (Figure 1-5). Mature secretory granules sit immediately beneath the plasma membrane. Typically, the signal for granule release causes a change in intracellular calcium, resulting in fusion of the granule to the plasma membrane and, finally, release of its contents.

Steroid hormones

Steroid hormones are derived from cholesterol.[10] The first and rate-limiting step in hormone synthesis is the cleavage of cholesterol to pregnenolone in the inner mitochondrial membrane by the enzyme CYP11A1 (cholesterol side-chain cleavage). The hormone precursors are shuttled back and forth between the endoplasmic reticulum and the mitochondria until the final product is produced. The basic steroid backbone is depicted in Figure 1-3. There is very little storage of steroid hormones, with the finished product usually diffusing into circulation after synthesis.

Amines

The amine hormones are derived from tyrosine.[9] Thyroid hormone synthesis is critically dependent on iodine ingestion.[11] Thyroglobulin is a large glycoprotein that contains multiple tyrosine residues. It is synthesized in thyroid follicular epithelial cells. Thyroglobulin is secreted into the follicular lumen where it undergoes posttranslational modification. TSH binding to its receptor on the basolateral membrane of thyroid follicular epithelial cells results in stimulation of the enzymatic steps involved in thyroid hormone synthesis, thyroid hormone release, and growth of the thyroid gland.[11] In hypothyroidism, the high levels of TSH stimulate thyroid growth, resulting in a goiter. In hyperthyroidism, stimulation of the TSH receptor by the thyroid antibodies results in thyroid growth and development of a goiter. The thyroid hormones, T_4 and T_3, are both secreted from the thyroid gland. However, T_4 is produced in far excess compared to T_3.

Catecholamines are synthesized from tyrosine in the adrenal medulla.[10] Tyrosine is actively transported into the cell, where the first and rate-limiting step is catalyzed by tyrosine hydroxylase. A total of four enzymatic