

CONTENTS

- 1 Introduction to the Endocrine System, 1**
 - Chemical Nature of Hormones, 3
 - Transport of Hormones in the Circulation, 7
 - Cellular Responses to Hormones, 7
 - Summary, 21
- 2 Endocrine Function of the Gastrointestinal Tract, 25**
 - Enteroendocrine Hormone Families and their Receptors, 27
 - Gastrin and the Regulation of Gastric Function, 28
 - Enteroendocrine Regulation of the Exocrine Pancreas and Gallbladder, 32
 - Insulinotropic Actions of Gastrointestinal Peptides (Incretin Action), 35
 - Enterotropic Actions of Gastrointestinal Hormones, 36
 - Summary, 37
- 3 Energy Metabolism, 40**
 - Overview of Energy Metabolism, 40
 - Key Hormones Involved in Metabolic Homeostasis, 43
 - Metabolic Homeostasis: the Integrated Outcome of Hormonal and Substrate/Product Regulation of Metabolic Pathways, 50
 - NADPH Production Through the Pentose Phosphate Pathway, 58
 - Overview of Energy Metabolism During the Fasting Phase, 62
 - Liver Metabolism During the Fasting Phase, 66
 - Adipose Tissue–Derived Hormones and Adipokines, 67
 - Appetite Control and Obesity, 69
 - Summary, 73
- 4 Calcium and Phosphate Homeostasis, 77**
 - Calcium and Phosphorus are Important Dietary Elements That Play Many Crucial Roles in Cellular Physiology, 77
 - Physiologic Regulation of Calcium and Phosphate: Parathyroid Hormone, 1,25-Dihydroxyvitamin D, and Fgf23, 78
 - Small Intestine, Bone, and Kidney Determine Ca^{2+} and Pi Levels, 83
 - Pathologic Disorders of Calcium and Phosphate Balance, 91
 - Summary, 95
- 5 Hypothalamus-Pituitary Complex, 97**
 - Embryology and Anatomy, 97
 - Neurohypophysis, 99
 - Adenohypophysis, 106
 - Summary, 123
- 6 The Thyroid Gland, 125**
 - Anatomy and Histology of the Thyroid Gland, 125
 - Production of Thyroid Hormones, 126
 - Transport and Metabolism of Thyroid Hormones, 131
 - Summary, 140
- 7 The Adrenal Gland, 142**
 - Anatomy, 142
 - Adrenal Medulla, 144
 - Adrenal Cortex, 149
 - Zona Glomerulosa, 159
 - Pathologic Conditions Involving the Adrenal Cortex, 164
 - Summary, 167
- 8 Life Cycle of the Male and Female Reproductive Systems, 170**
 - General Components of a Reproductive System, 170
 - Overview of Meiosis, 170
 - Basic Anatomy of the Reproductive Systems, 172
 - Sexual Development in Utero, 174
 - Female Development, 176
 - Puberty, 177
 - Menopause and Andropause, 182
 - Summary, 183

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- 9 The Male Reproductive System, 186**
Histophysiology of the Testis, 186
Transport, Actions, and Metabolism of Androgens, 193
Hypothalamus-Pituitary-Testis Axis, 195
Male Reproductive Tract, 198
Disorders Involving The Male Reproductive System, 200
Summary, 201
- 10 The Female Reproductive System, 204**
Anatomy and Histology of the Ovary, 204
Growth, Development, and Function of the Ovarian Follicle, 204
The Human Menstrual Cycle, 214
Female Reproductive Tract, 217
Biology of Estradiol and Progesterone, 222
Ovarian Pathophysiology, 223
Summary, 224
- 11 Fertilization, Pregnancy, and Lactation, 227**
Fertilization, Early Embryogenesis, Implantation, and Placentation, 227
Placental Transport, 242
The Fetal Endocrine System, 242
Maternal Endocrine Changes During Pregnancy, 242
Maternal Physiologic Changes During Pregnancy, 244
Parturition, 245
Mammogenesis and Lactation, 246
Contraception, 248
In Vitro Fertilization, 249
Summary, 249
- Appendix A: Answers to Self-Study Problems, 251
Appendix B: Comprehensive Multiple-Choice Examination, 258
Appendix C: Abbreviations and Symbols, 264
Index, 267

Introduction to the Endocrine System

OBJECTIVES

1. List the main endocrine glands of the body.
2. List the chemical nature of the major hormones.
3. Describe how the chemical nature influences hormone synthesis, storage, secretion, transport, clearance, mechanism of action, and appropriate route of exogenous hormone administration.
4. Explain the significance of hormone binding to plasma proteins.
5. Describe the major signal transduction pathways, and their mechanism for termination, for different classes of hormones and provide a specific example of each.

Endocrine glands secrete chemical messengers, called **hormones** (Box 1.1), into the extracellular fluid in a highly regulated manner. Secreted hormones gain access to the circulation, often via fenestrated capillaries, and regulate **target organs** throughout the body. The endocrine system is composed of the **pituitary gland**, the **thyroid gland**, **parathyroid glands**, and **adrenal glands** (Fig. 1.1). The endocrine system also includes the **ovary** and **testis**, which carry out a gametogenic function that is absolutely dependent on their endogenous endocrine function. In addition to dedicated endocrine glands, endocrine cells reside as a minor component (in terms of mass) in other organs, either as groups of cells (the **islets of Langerhans** in the pancreas) or as individual cells spread throughout several glands, including the **gastrointestinal (GI) tract**, **kidney**, **heart**, **adipose tissue**, and **liver**. In addition, there are several types of **hypothalamic neuroendocrine neurons** that produce hormones. The **placenta** serves as a transitory exchange organ, but also functions as an important endocrine structure of pregnancy.

The endocrine system also encompasses a range of specific enzymes, either cell-associated or circulating, that perform the function of **peripheral conversion of hormonal precursors** (see Box 1.1). For example, angiotensinogen from the liver is converted in the circulation to angiotensin I by the renal-derived enzyme renin, followed by conversion to the active hormone angiotensin II by the transmembrane ectoenzyme angiotensin I-converting enzyme (ACE) that is enriched in the endothelia of the lungs (see Chapter 7). Another example of peripheral conversion of a precursor to an active hormone involves the two sequential

hydroxylations of vitamin D in hepatocytes and renal tubular cells.

Numerous extracellular messengers, including prostaglandins, growth factors, neurotransmitters, and cytokines, also regulate cellular function. However, these messengers act predominantly within the context of a microenvironment in an autocrine or paracrine manner, and thus are discussed only to a limited extent where needed.

To function, hormones must bind to specific **receptors** expressed by specific **target cell types** within **target organs**. Hormones are also referred to as **ligands**, in the context of ligand receptor binding, and as **agonists**, in that their binding to the receptor is transduced into a cellular response. Receptor **antagonists** typically bind to a receptor and lock it in an inactive state, unable to induce a cellular response. Drugs that bind to and alter the activity of steroid hormone receptors are referred to as selective receptor modulators. For example, Tamoxifen is a mixed estrogen receptor agonist/antagonist, and thus is referred to as a "**selective estrogen receptor modulator**" or **SERM**. Loss or inactivation of a receptor leads to **hormonal resistance**. **Constitutive activation** of a receptor leads to unregulated, hormone-independent activation of cellular processes.

The widespread delivery of hormones in the blood makes the endocrine system ideal for the functional coordination of multiple organs and cell types in the following contexts:

1. Allowing normal development and growth of the organism
2. Maintaining internal homeostasis

BOX 1.1 A List of Most Hormones and Their Sites of Production**Hormones Synthesized and Secreted by Dedicated Endocrine Glands****Pituitary Gland**

Growth hormone (GH)
Prolactin
Adrenocorticotrophic hormone (ACTH)
Thyroid-stimulating hormone (TSH)
Follicle-stimulating hormone (FSH)
Luteinizing hormone (LH)

Thyroid Gland

Tetraiodothyronine (T_4 ; thyroxine)
Triiodothyronine (T_3)
Calcitonin

Parathyroid Glands

Parathyroid hormone (PTH)

Islets of Langerhans (Endocrine Pancreas)

Insulin
Glucagon
Somatostatin

Adrenal Gland

Epinephrine
Norepinephrine
Cortisol
Aldosterone
Dehydroepiandrosterone sulfate (DHEAS)

Hormones Synthesized by Gonads

Ovaries
Estradiol-17 β
Progesterone
Inhibin
Testes
Testosterone
Antimüllerian hormone (AMH)
Inhibin

Hormones Synthesized in Organs with a Primary Function Other Than Endocrine**Brain (Hypothalamus)**

Antidiuretic hormone (ADH; vasopressin)
Oxytocin
Corticotropin-releasing hormone (CRH)
Thyrotropin-releasing hormone
Gonadotropin-releasing hormone (GnRH)
Growth hormone-releasing hormone (GHRH)
Somatostatin

Dopamine

Brain (Pineal Gland)

Melatonin

Heart

Atrial natriuretic peptide (ANP)

Kidney

Erythropoietin

Adipose Tissue

Leptin
Adiponectin

Stomach

Gastrin
Somatostatin
Ghrelin

Intestines

Secretin
Cholecystokinin
Glucagon-like peptide-1 (GLP-1)
Glucagon-like peptide-2 (GLP-2)
Glucose-dependent insulinotropic peptide (GIP; gastrin inhibitory peptide)
Motilin

Liver

Insulin-like growth factor-I (IGF-I)

Hormones Produced to a Significant Degree by Peripheral Conversion**Lungs**

Angiotensin II

Kidney

1 α ,25-dihydroxyvitamin D

Adipose, Mammary Glands, Other Organs

Estradiol-17 β

Liver, Other Organs

Testosterone

Genital Skin, Prostate, Sebaceous Gland, Other Organs

5-Dihydrotestosterone (DHT)

Many Organs

T_3

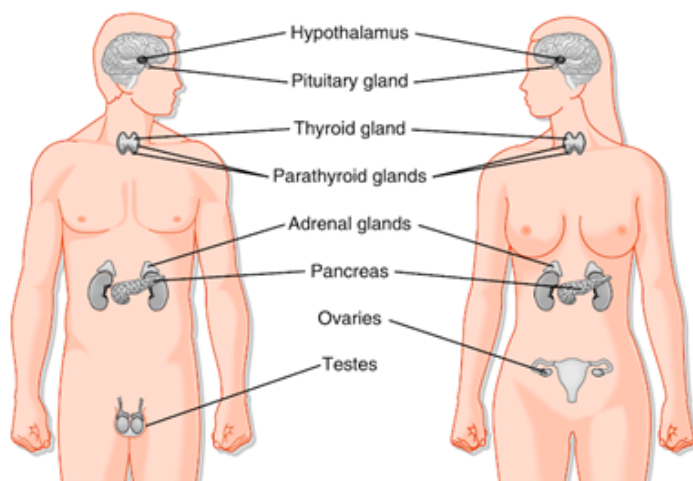


Fig. 1.1 Major glands of the endocrine system. (From Koeppen BM, Stanton BA, editors: *Berne and Levy Physiology*, 6th ed., Philadelphia, 2010, Mosby.)

3. Regulating the onset of reproductive maturity at puberty and the function of the reproductive system in the adult

In the adult, endocrine organs produce and secrete their hormones in response to **feedback control systems** that are tuned to **set-points**, or set ranges, of the levels of circulating hormones. These set-points are genetically determined but may be altered by age, circadian rhythms (24-hour cycles or diurnal rhythms), seasonal cycles, the environment, stress, inflammation, and other influences.

Major forms of endocrine disease are caused by lack of hormone (e.g., hypothyroidism), excess of hormone (e.g., hyperparathyroidism) or dysfunction of receptor (hormonal resistance). It is important to appreciate that hormones often stimulate both the differentiated function and growth of target tissues and organs. This underlies the role of hormones in driving neoplastic transformation and cancer progression (i.e., the existence of hormonally responsive cancers). The pathogenesis of these and other forms of endocrine disease are discussed in the subsequent chapters.

The material in this chapter covers generalizations common to all hormones or to specific groups of hormones. The chemical nature of the hormones and their mechanisms of action are discussed. This presentation provides the generalized information necessary to categorize the hormones and to make predictions about the most likely characteristics of a given hormone. Some of the exceptions to these generalizations are discussed later.

BOX 1.2 Characteristics of Protein/Peptide Hormones

- Synthesized as prehormones or preprohormones
- Stored in membrane-bound secretory vesicles (sometimes called *secretory granules*)
- Regulated at the level of secretion (regulated exocytosis) and synthesis
- Often circulate in blood unbound
- Usually administered by injection
- Hydrophilic and signal through transmembrane receptors

CHEMICAL NATURE OF HORMONES

Hormones are classified biochemically as **proteins/peptides**, **catecholamines**, **steroid hormones**, and **iodothyronines**. The chemical nature of a hormone determines the following:

1. How it is synthesized, stored, and released in a regulated manner
2. How it is carried in the blood
3. Its biologic half-life ($t_{1/2}$) and mode of clearance
4. Its cellular mechanism of action

Proteins/Peptides

The **protein and peptide hormones** can be grouped into structurally related molecules that are encoded by gene families (Box 1.2). Protein/peptide hormones gain their specificity from their primary amino acid sequence, which