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1

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
- Adrenocorticotropic 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-17β
- 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
- 1α,25-dihydroxyvitamin D

Adipose, Mammary Glands, Other Organs
- Estradiol-17β

Liver, Other Organs
- Testosterone

Genital Skin, Prostate, Sebaceous Gland, Other Organs
- 5-Dihydrotestosterone (DHT)

Many Organs
- T_3

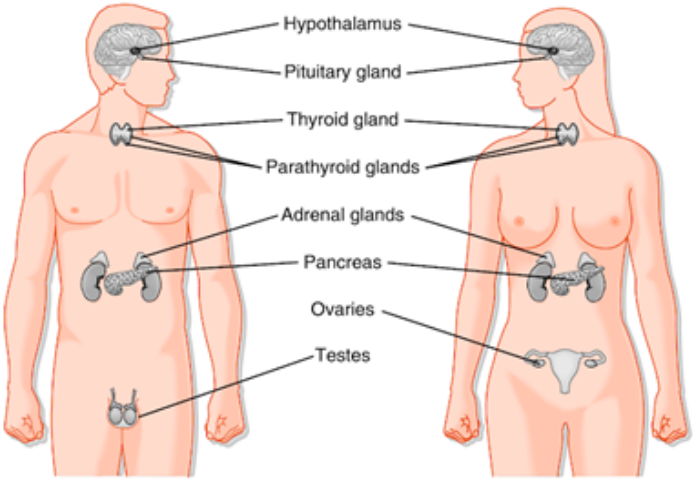

Fig. 1.1 Major glands of the endocrine system. (From Koeppen BM, Stanton BA, editors: *Berne and Levy Physiology,* 6th ed., Philadelphia, 2010, Mosby.)

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