

CHAPTER 9

Endocrine Physiology

The endocrine system, in concert with the nervous system, is responsible for homeostasis. Growth, development, reproduction, blood pressure, concentrations of ions and other substances in blood, and even behavior are all regulated by the endocrine system. Endocrine physiology involves the secretion of hormones and their subsequent actions on target tissues.

A hormone is a chemical substance that is classified as a peptide, a steroid, or an amine. Hormones are secreted into the circulation in small amounts and delivered to target tissues, where they produce physiologic responses. Hormones are synthesized and secreted by endocrine cells usually found in endocrine glands. [Table 9.1](#) is a list of hormones and their abbreviations, which are used throughout Chapters 9 and 10.

The classic endocrine glands are the hypothalamus, anterior and posterior lobes of the pituitary, thyroid, parathyroid, adrenal cortex, adrenal medulla, gonads, placenta, and pancreas. The kidney also is considered to be an endocrine gland, and endocrine cells are found throughout the gastrointestinal tract. [Table 9.2](#) summarizes the major hormones, their glands of origin, their chemical nature, and their major actions. Its companion, [Figure 9.1](#), is a pictorial summary of the endocrine glands and their hormonal secretions.

HORMONE SYNTHESIS

Hormones are categorized in one of three classes: peptides and proteins, steroids, or amines. Each class differs in its biosynthetic pathway: Peptide and protein hormones are synthesized from amino acids; steroid hormones are derivatives of cholesterol; and amine hormones are derivatives of tyrosine.

Peptide and Protein Hormone Synthesis

Most hormones are peptide or protein in nature. The biosynthetic pathways are familiar from biochemistry. The primary amino acid sequence of the peptide is dictated by a specific messenger ribonucleotide (mRNA), which has been transcribed from the gene for that hormone. The biosynthetic pathway for peptide hormones is summarized in

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TABLE 9.1 Commonly Used Abbreviations in Endocrine Physiology

Abbreviation	Hormone	Abbreviation	Hormone
ACTH	Adrenocorticotrophic hormone	LH	Luteinizing hormone
ADH	Antidiuretic hormone	MIT	Monoiodotyrosine
CRH	Corticotropin-releasing hormone	MSH	Melanocyte-stimulating hormone
DHEA	Dehydroepiandrosterone	PIF	Prolactin-inhibiting factor (dopamine)
DIT	Diiodotyrosine	POMC	Pro-opiomelanocortin
DOC	11-Deoxycorticosterone	PTH	Parathyroid hormone
FSH	Follicle-stimulating hormone	PTU	Propylthiouracil
GHRH	Growth hormone-releasing hormone	SRIF	Somatotropin release-inhibiting factor
GnRH	Gonadotropin-releasing hormone	T ₃	Triiodothyronine
HCG	Human chorionic gonadotropin	T ₄	Thyroxine
HGH	Human growth hormone	TBG	Thyroxine-binding globulin
hPL	Human placental lactogen	TRH	Thyrotropin-releasing hormone
IGF	Insulin-like growth factor	TSH	Thyroid-stimulating hormone

TABLE 9.2 Summary of Endocrine Glands and Actions of Hormones

Gland of Origin	Hormones ^a	Chemical Classification ^b	Major Actions
Hypothalamus	Thyrotropin-releasing hormone (TRH)	Peptide	Stimulates secretion of TSH and prolactin
	Corticotropin-releasing hormone (CRH)	Peptide	Stimulates secretion of ACTH
	Gonadotropin-releasing hormone (GnRH)	Peptide	Stimulates secretion of LH and FSH
	Somatostatin or somatotropin release-inhibiting hormone (SRIF)	Peptide	Inhibits secretion of growth hormone
	Dopamine or prolactin-inhibiting factor (PIF)	Amine	Inhibits secretion of prolactin
	Growth hormone-releasing hormone (GHRH)	Peptide	Stimulates secretion of growth hormone
Anterior Pituitary	Thyroid-stimulating hormone (TSH)	Peptide	Stimulates synthesis and secretion of thyroid hormones
	Follicle-stimulating hormone (FSH)	Peptide	Stimulates sperm maturation in Sertoli cells of testes Stimulates follicular development and estrogen synthesis in ovaries
	Luteinizing hormone (LH)	Peptide	Stimulates testosterone synthesis in Leydig cells of testes Stimulates ovulation, formation of corpus luteum, estrogen and progesterone synthesis in ovaries
	Growth hormone	Peptide	Stimulates protein synthesis and overall growth
	Prolactin	Peptide	Stimulates milk production and secretion in breast
	Adrenocorticotrophic hormone (ACTH)	Peptide	Stimulates synthesis and secretion of adrenal cortical hormones (cortisol, androgens, and aldosterone)
	Melanocyte-stimulating hormone (MSH)	Peptide	Stimulates melanin synthesis (? humans)

TABLE 9.2 Summary of Endocrine Glands and Actions of Hormones—cont'd

Gland of Origin	Hormones ^a	Chemical Classification ^b	Major Actions
Posterior Pituitary	Oxytocin	Peptide	Stimulates milk ejection from breasts and uterine contractions
	Vasopressin or antidiuretic hormone (ADH)	Peptide	Stimulates water reabsorption in principal cells of collecting ducts and constriction of arterioles
Thyroid	Triiodothyronine (T ₃) and L-thyroxine (T ₄)	Amine	Stimulates skeletal growth; oxygen consumption; heat production; protein, fat, and carbohydrate utilization; perinatal maturation of the central nervous system
	Calcitonin	Peptide	Decreases serum [Ca ²⁺]
Parathyroid	Parathyroid hormone (PTH)	Peptide	Increases serum [Ca ²⁺]
Adrenal Cortex	Cortisol (glucocorticoid)	Steroid	Stimulates gluconeogenesis; inhibits inflammatory response; suppresses immune response; enhances vascular responsiveness to catecholamines
	Aldosterone (mineralocorticoid)	Steroid	Increases renal Na ⁺ reabsorption, K ⁺ secretion, and H ⁺ secretion
	Dehydroepiandrosterone (DHEA) and androstenedione (adrenal androgens)	Steroid	See actions of testosterone from testes (see later)
Testes	Testosterone	Steroid	Stimulates spermatogenesis; stimulates male secondary sex characteristics
Ovaries	Estradiol	Steroid	Stimulates growth and development of female reproductive system, follicular phase of menstrual cycle, development of breasts, prolactin secretion; maintains pregnancy
	Progesterone	Steroid	Stimulates luteal phase of menstrual cycle; maintains pregnancy
Corpus Luteum	Estradiol and progesterone	Steroid	See actions of estradiol and progesterone from ovaries (see earlier)
Placenta	Human chorionic gonadotropin (HCG)	Peptide	Stimulates estrogen and progesterone synthesis in corpus luteum of early pregnancy
	Human placental lactogen (hPL), or human chorionic somatomammotropin	Peptide	Has growth hormone-like and prolactin-like actions during pregnancy
	Estriol	Steroid	See actions of estradiol from ovaries (see earlier)
	Progesterone	Steroid	See actions of progesterone from ovaries (see earlier)
Pancreas	Insulin (β cells)	Peptide	Decreases blood [glucose]
	Glucagon (α cells)	Peptide	Increases blood [glucose]
Kidney	Renin	Peptide	Catalyzes conversion of angiotensinogen to angiotensin I
	1,25-Dihydroxycholecalciferol	Steroid	Increases intestinal absorption of Ca ²⁺ ; bone mineralization
Adrenal Medulla	Norepinephrine, epinephrine	Amine	See actions of sympathetic nervous system (see Chapter 2)

^aStandard abbreviations for hormones are given in parentheses.

^bPeptide refers to both peptides and proteins.

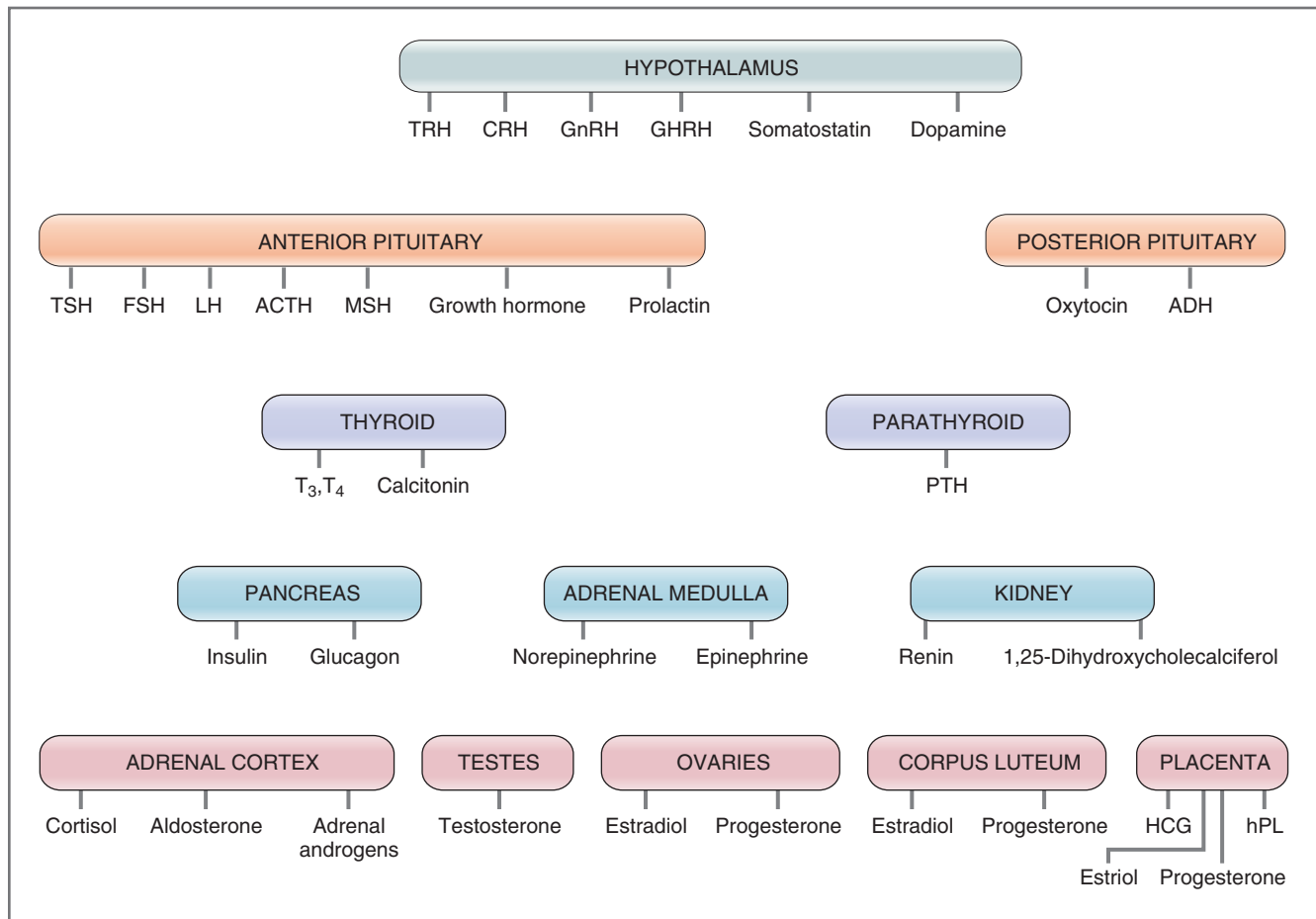


Fig. 9.1 Endocrine glands and the hormones secreted by each gland. Refer to Table 9.1 for abbreviations used in this figure.

Figure 9.2. The circled numbers in the figure correspond to the following steps:

1. In the **nucleus**, the gene for the hormone is transcribed into an **mRNA**. Generally, a single gene is responsible for directing the primary structure of each peptide hormone. (Because the genes for almost all peptide hormones have been cloned, recombinant DNA technology makes it possible to synthesize human peptide hormones.)
2. The mRNA is transferred to the cytoplasm and translated on the **ribosomes** to the first protein product, a **preprohormone**. Translation of the mRNA begins with a signal peptide at the N terminus. Translation ceases, and the signal peptide attaches to receptors on the endoplasmic reticulum via “docking proteins.” Translation then continues on the endoplasmic reticulum until the entire peptide sequence is produced (i.e., the preprohormone).
3. The signal peptide is removed in the **endoplasmic reticulum**, converting the preprohormone to a **prohormone**. The prohormone contains the complete hormone sequence plus other peptide sequences, which will be removed in a final step. Some of the “other” peptide sequences in the prohormone are necessary for proper folding of the hormone (e.g., formation of intramolecular linkages).
4. The prohormone is transferred to the **Golgi apparatus**, where it is packaged in secretory vesicles. In the secretory vesicles, proteolytic enzymes cleave peptide sequences from the prohormone to produce the final **hormone**. Other functions of the Golgi apparatus include glycosylation and phosphorylation of the hormone.
5. The final hormone is stored in **secretory vesicles** until the endocrine cell is stimulated. For example, parathyroid hormone (PTH) is synthesized and stored in vesicles in the chief cells of the parathyroid gland. The stimulus for secretion of PTH is low-extracellular calcium (Ca^{2+}) concentration. When sensors on the parathyroid gland detect a low-extracellular Ca^{2+} concentration, the secretory vesicles are translocated to the cell membrane, where they extrude PTH into the blood by exocytosis. The other constituents of

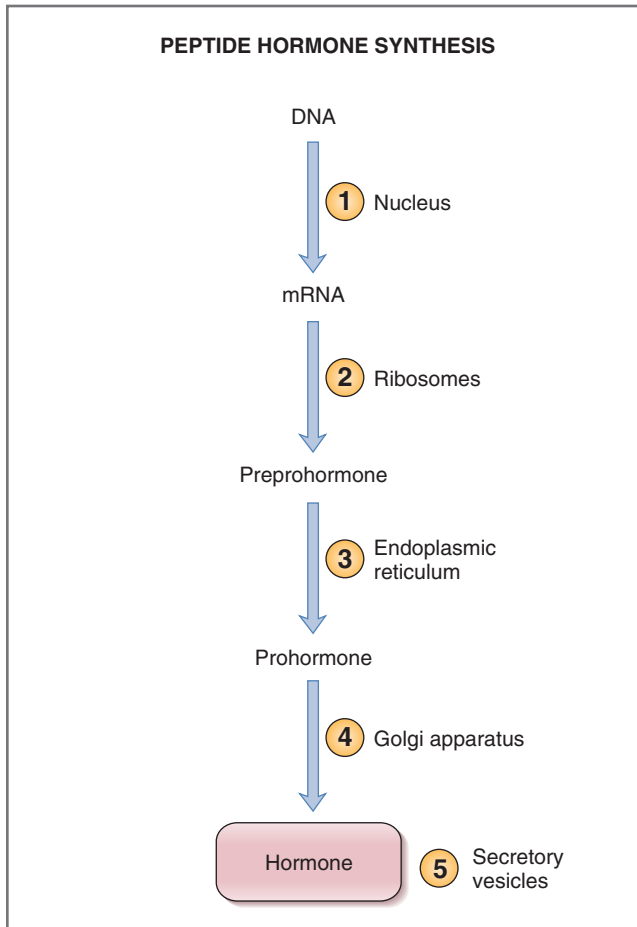


Fig. 9.2 Steps involved in the synthesis of peptide hormones. See the text for an explanation of the circled numbers. *DNA*, Deoxyribonucleic acid; *mRNA*, messenger ribonucleic acid.

the secretory vesicles, including copeptides and cleavage enzymes, are extruded with PTH.

Steroid Hormone Synthesis

Steroid hormones are synthesized and secreted by the adrenal cortex, gonads, corpus luteum, and placenta. The steroid hormones are cortisol, aldosterone, estradiol and estriol, progesterone, testosterone, and 1,25-dihydroxycholecalciferol. All steroid hormones are derivatives of **cholesterol**, which is modified by removal or addition of side chains, hydroxylation, or aromatization of the steroid nucleus. The biosynthetic pathways for the adrenocortical hormones and for 1,25-dihydroxycholecalciferol are discussed in this chapter. The pathways for the sex steroid hormones are discussed in Chapter 10.

Amine Hormone Synthesis

The amine hormones are catecholamines (epinephrine, norepinephrine, and dopamine) and thyroid hormones.

The amine hormones are derivatives of the amino acid **tyrosine**. The biosynthetic pathway for catecholamines is discussed in Chapter 1. The pathway for thyroid hormones is discussed in this chapter.

REGULATION OF HORMONE SECRETION

To maintain homeostasis, the secretion of hormones must be turned on and off as needed. Adjustments in secretory rates may be accomplished by neural mechanisms or by feedback mechanisms. **Neural mechanisms** are illustrated by the secretion of catecholamines, where preganglionic sympathetic nerves synapse on the adrenal medulla and, when stimulated, cause secretion of catecholamines into the circulation. **Feedback mechanisms** are more common than neural mechanisms. The term “feedback” means that some element of the physiologic response to a hormone “feeds back,” either directly or indirectly, on the endocrine gland that secreted the hormone, changing its secretion rate. Feedback can be negative or positive. Negative feedback is the more important and common mechanism for regulating hormone secretion; positive feedback is rare.

Negative Feedback

The principles of negative feedback underlie the homeostatic regulation of virtually all organ systems. For example, in Chapter 4, negative feedback is discussed in the regulation of arterial blood pressure in which small changes in blood pressure turn on, or activate, mechanisms that will restore blood pressure back to normal. A decrease in arterial blood pressure is detected by baroreceptors, which activate coordinated mechanisms that increase blood pressure. As blood pressure returns to normal, a disturbance is no longer sensed by the baroreceptors and those mechanisms previously activated will be turned off. The more sensitive the feedback mechanism, the smaller the “excursions” of blood pressure above or below normal.

In endocrine systems, negative feedback means that *some feature of hormone action, directly or indirectly, inhibits further secretion of the hormone*. Negative feedback loops are illustrated in Figure 9.3. For illustrative purposes, the hypothalamus is shown in relation to the anterior pituitary, which is shown in relation to a peripheral endocrine gland. In the figure, the hypothalamus secretes a releasing hormone, which stimulates secretion of an anterior pituitary hormone. The anterior pituitary hormone then acts on a peripheral endocrine gland (e.g., the testis) to cause secretion of the hormone (e.g., testosterone), which acts on target

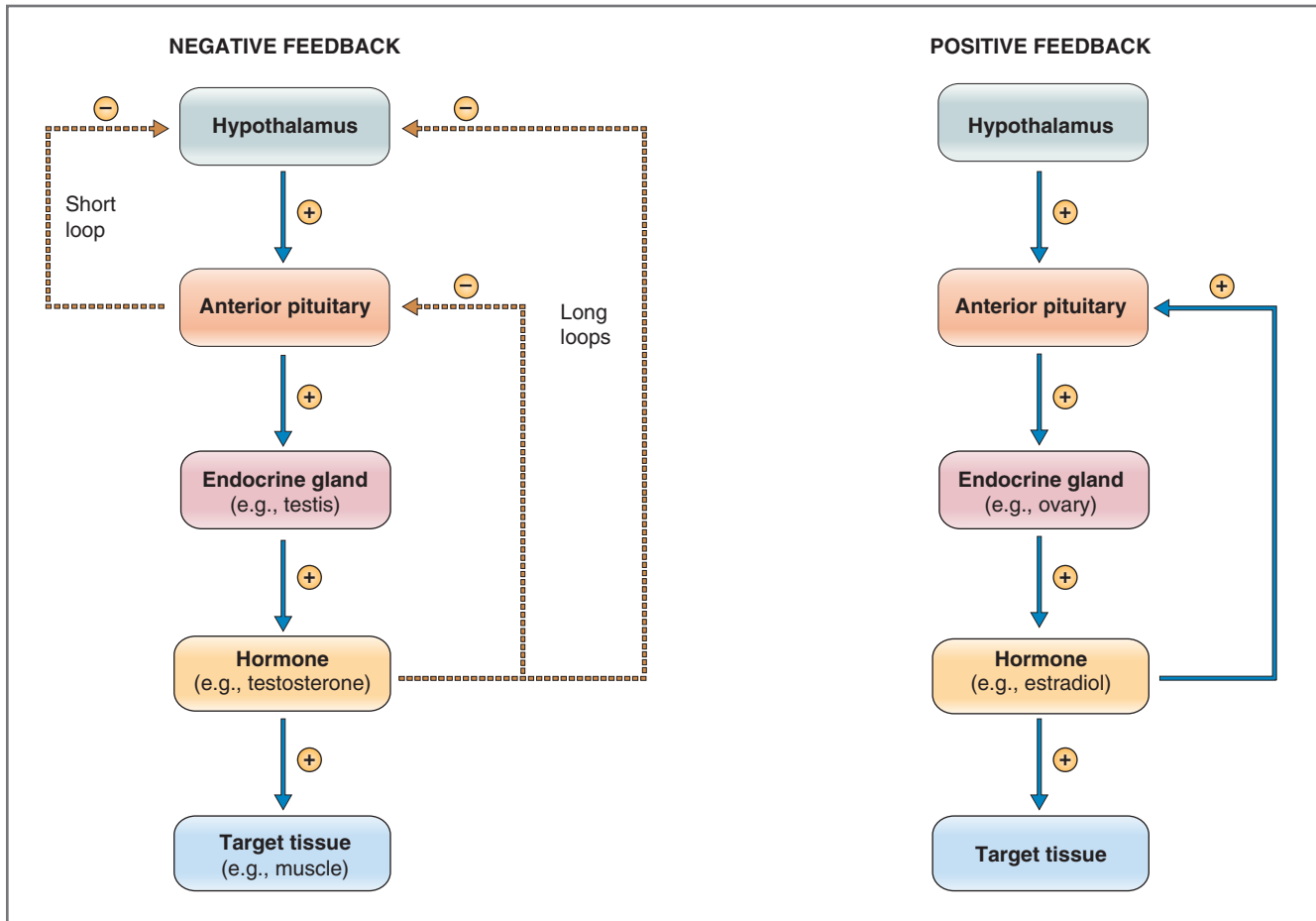


Fig. 9.3 Negative and positive feedback mechanisms. The hypothalamic-pituitary axis is used as an example in this illustration. Solid lines and plus signs (+) indicate stimulation; dashed lines and minus signs (–) indicate inhibition.

tissues (e.g., skeletal muscle) to produce physiologic actions. The hormones “feed back” on the anterior pituitary and the hypothalamus to inhibit their hormonal secretions. **Long-loop feedback** means that the hormone feeds back *all the way* to the hypothalamic-pituitary axis. **Short-loop feedback** means that the anterior pituitary hormone feeds back on the hypothalamus to inhibit secretion of hypothalamic-releasing hormone. Not shown in the figure is a third possibility called **ultrashort-loop feedback**, in which the hypothalamic hormone inhibits its own secretion (e.g., growth hormone-releasing hormone [GHRH] inhibits GHRH secretion).

The net result of any version of negative feedback is that when hormone levels are judged (by their physiologic actions) to be adequate or high, further secretion of the hormone is inhibited. When hormone levels are judged to be inadequate or low, secretion of the hormone is stimulated.

There are other examples of negative feedback that do not utilize the hypothalamic-pituitary axis. For example, **insulin** regulates blood glucose concentration.

In turn, insulin secretion is turned on or off by changes in the blood glucose concentration. Thus when blood glucose concentration is high, insulin secretion from the pancreas is turned on; insulin then acts on its target tissues (liver, muscle, and adipose) to decrease the blood glucose concentration back toward normal. When the glucose concentration is sensed as being low enough, insulin is no longer needed and its secretion is turned off.

Positive Feedback

Positive feedback is uncommon. With positive feedback, some feature of hormone action causes *more* secretion of the hormone (see Fig. 9.3). When compared with negative feedback, which is self-limiting, positive feedback is self-augmenting. Although rare in biologic systems, when positive feedback does occur, it leads to an explosive event.

A nonhormonal example of positive feedback is the opening of nerve sodium (Na^+) channels during the **upstroke of the action potential**. Depolarization opens

voltage-sensitive Na^+ channels and causes Na^+ entry into the cell, which leads to more depolarization and more Na^+ entry. This self-reinforcing process produces the rapid, explosive upstroke.

In hormonal systems, the primary example of positive feedback is the effect of **estrogen** on the secretion of follicle-stimulating hormone (**FSH**) and luteinizing hormone (**LH**) by the anterior pituitary at the midpoint of the menstrual cycle. During the follicular phase of the menstrual cycle, the ovaries secrete estrogen, which acts on the anterior pituitary to produce a rapid burst of FSH and LH secretion. FSH and LH have two effects on the ovaries: ovulation *and* stimulation of estrogen secretion. Thus estrogen secreted from the ovaries acts on the anterior pituitary to cause secretion of FSH and LH, and these anterior pituitary hormones cause *more* estrogen secretion. In this example, the explosive event is the burst of FSH and LH that precedes ovulation.

A second example of hormonal positive feedback is **oxytocin**. Dilation of the cervix causes the posterior pituitary to secrete oxytocin. In turn, oxytocin stimulates uterine contraction, which causes further dilation of the cervix. In this example, the explosive event is parturition, the delivery of the fetus.

REGULATION OF HORMONE RECEPTORS

The previous section describes the mechanisms that regulate circulating levels of hormones, usually by negative feedback. Although circulating hormone levels are important, they are *not* the only determinant of the response of a target tissue. To respond, a target tissue must possess specific receptors that recognize the hormone. Those receptors are coupled to cellular mechanisms that produce the physiologic response. (The coupling mechanisms are discussed in the section on mechanisms of hormone action.)

The responsiveness of a target tissue to a hormone is expressed in the **dose-response relationship** in which the magnitude of response is correlated with hormone concentration. As the hormone concentration increases, the response usually increases and then levels off. **Sensitivity** is defined as the hormone concentration that produces 50% of the maximal response. If more hormone is required to produce 50% of the maximal response, then there has been a decrease in sensitivity of the target tissue. If less hormone is required, there has been an increase in sensitivity of the target tissue.

The responsiveness or sensitivity of a target tissue can be changed in one of two ways: by changing the *number* of receptors or by changing the *affinity* of the receptors for the hormone. The greater the

number of receptors for a hormone, the greater the maximal response. The higher the affinity of the receptor for the hormone, the greater the likelihood of a response.

A change in the number or affinity of receptors is called down-regulation or up-regulation. **Down-regulation** means that the number of receptors or the affinity of the receptors for the hormone has decreased. **Up-regulation** means that the number or the affinity of the receptors has increased. Hormones may down-regulate or up-regulate their own receptors in target tissues and even may regulate receptors for other hormones.

Down-Regulation

Down-regulation is a mechanism in which a hormone *decreases* the number or affinity of its receptors in a target tissue. Down-regulation may occur by decreasing the synthesis of new receptors, by increasing the degradation of existing receptors, or by inactivating receptors. The purpose of down-regulation is to reduce the sensitivity of the target tissue when hormone levels are high for an extended period of time. As down-regulation occurs, the response to hormone declines, although hormone levels remain high. An example of down-regulation is the effect of **progesterone** on its own receptor in the uterus (see Chapter 10).

Down-regulation can also refer to a hormone's effect on receptors for other related hormones. This type of down-regulation also is illustrated by progesterone. In the uterus, progesterone down-regulates its own receptor *and* down-regulates the receptors for estrogen. A second example of this type of down-regulation is seen in the thyroid system: Triiodothyronine, or **T₃**, decreases the sensitivity of thyrotropin-releasing hormone (TRH) receptors in the anterior pituitary. The overall effect is that chronically high levels of T₃ reduce the overall responsiveness of the hypothalamic-pituitary-thyroid axis.

Up-Regulation

Up-regulation of receptors is a mechanism in which a hormone *increases* the number or affinity of its receptors. Up-regulation may occur by increasing synthesis of new receptors, decreasing degradation of existing receptors, or activating receptors. For example, **prolactin** increases the number of its receptors in the breast, **growth hormone** increases the number of its receptors in skeletal muscle and liver, and **estrogen** increases the number of its receptors in the uterus.

A hormone also can up-regulate the receptors for other hormones. For example, estrogen not only up-regulates its own receptor in the uterus, but it also up-regulates the receptors for LH in the ovaries.

MECHANISMS OF HORMONE ACTION AND SECOND MESSENGERS

Hormone actions on target cells begin when the hormone binds to a membrane receptor, forming a hormone-receptor complex. In many hormonal systems, the hormone-receptor complex is coupled to effector proteins by guanosine triphosphate (GTP)-binding proteins (G proteins). The effector proteins usually are enzymes, either adenylyl cyclase or phospholipase C. When the effector proteins are activated, a second messenger, either cyclic adenosine monophosphate (cAMP) or inositol 1,4,5-triphosphate (IP_3), is produced, which amplifies the original hormonal signal and orchestrates the physiologic actions.

The major mechanisms of hormone action on target cells are the **adenylyl cyclase** mechanism, in which cAMP is the second messenger; the **phospholipase C** mechanism, in which IP_3/Ca^{2+} is the second messenger; and the **steroid hormone** mechanism. In addition, insulin and insulin-like growth factors (IGFs) act on their target cells through a **tyrosine kinase** mechanism. Finally, several hormones activate **guanylate cyclase**, in which cyclic guanosine monophosphate (cyclic GMP, or cGMP) is the second messenger. The mechanisms of action of the major hormones are summarized in [Table 9.3](#).

G Proteins

G proteins are discussed in Chapter 2 in the context of autonomic receptors. Briefly, G proteins are a family of membrane-bound proteins that couple hormone receptors to effector enzymes (e.g., adenylyl cyclase). Thus G proteins serve as “molecular switches” that decide whether the hormone action can proceed.

At the molecular level, G proteins are heterotrimeric proteins (i.e., they have three subunits). The three subunits are designated alpha (α), beta (β), and gamma (γ). The α subunit can bind either guanosine diphosphate (GDP) or GTP, and it contains GTPase activity. When GDP is bound to the α subunit, the G protein is inactive; when GTP is bound, the G protein is active and can perform its coupling function. Guanosine nucleotide-releasing factors (GRFs) facilitate dissociation of GDP so that GTP binds more rapidly, whereas GTPase-activating factors (GAPs) facilitate hydrolysis of GTP. Thus the relative activity of GRFs and GAPs influences the overall rate of G protein activation.

G proteins can be either stimulatory or inhibitory and are called, accordingly, **G_s** or **G_i**. Stimulatory or inhibitory activity resides in the α subunit (α_s or α_i). Thus when GTP is bound to the α_s subunit of a G_s protein, the G_s protein *stimulates* the effector enzyme (e.g., adenylyl cyclase). When GTP is bound to the α_i subunit of a G_i protein, the G_i protein *inhibits* the effector enzyme.

Adenylyl Cyclase Mechanism

The adenylyl cyclase/cAMP mechanism is utilized by many hormonal systems (see [Table 9.3](#)). This mechanism involves binding of a hormone to a receptor, coupling by a G_s or G_i protein, and then activation or inhibition of adenylyl cyclase, leading to increases or decreases in intracellular cAMP. cAMP, the second messenger, then amplifies the hormonal signal to produce the final physiologic actions.

The steps in the adenylyl cyclase/cAMP mechanism are shown in [Figure 9.4](#). In this example, the hormone utilizes a G_s protein (rather than a G_i protein). The receptor–G_s–adenylyl cyclase complex is embedded in the cell membrane. When no hormone is bound to the

TABLE 9.3 Mechanisms of Hormone Action

Adenylyl Cyclase Mechanism (cAMP)	Phospholipase C Mechanism (IP_3/Ca^{2+})	Steroid Hormone Mechanism	Tyrosine Kinase Mechanism	Guanylate Cyclase Mechanism (cGMP)
ACTH	GnRH	Glucocorticoids	Insulin	Atrial natriuretic peptide (ANP)
LH	TRH	Estrogen	IGF-1	Nitric oxide (NO)
FSH	GHRH	Progesterone	Growth hormone	
TSH	Angiotensin II	Testosterone	Prolactin	
ADH (V_2 receptor)	ADH (V_1 receptor)	Aldosterone		
HCG	Oxytocin	1,25-		
MSH	α_1 Receptors	Dihydroxycholecalciferol		
CRH		Thyroid hormones		
Calcitonin				
PTH				
Glucagon				
β_1 and β_2 receptors				

cAMP, Cyclic adenosine monophosphate; cGMP, cyclic guanosine monophosphate; IP_3 , inositol 1,4,5-triphosphate.

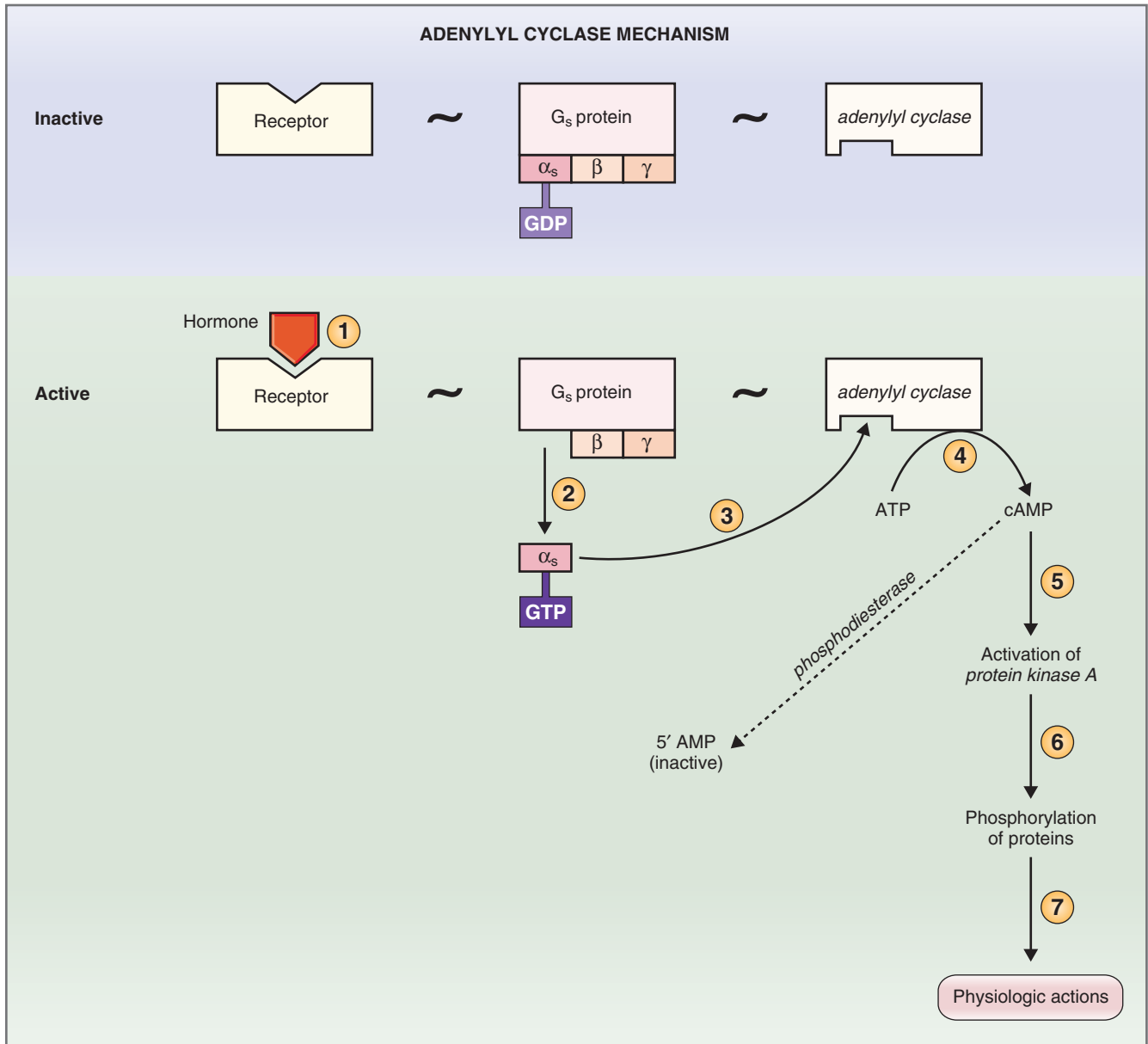


Fig. 9.4 Steps involved in the adenylyl cyclase (cAMP) mechanism of action. See the text for an explanation of the circled numbers. AMP, Adenosine monophosphate; ATP, adenosine triphosphate; cAMP, cyclic adenosine monophosphate; GDP, guanosine diphosphate; GTP, guanosine triphosphate.

receptor, the α_s subunit of the G_s protein binds GDP. In this configuration, the G_s protein is **inactive**. When hormone binds to its receptor, the following steps (see Fig. 9.4) occur:

1. Hormone binds to its **receptor** in the cell membrane, producing a conformational change in the α_s subunit (Step 1), which produces two changes: GDP is released from the α_s subunit and is replaced by GTP, and the α_s subunit detaches from the G_s protein (Step 2).
2. The **α_s -GTP complex** migrates within the cell membrane and binds to and activates adenylyl cyclase (Step 3). Activated **adenylyl cyclase** catalyzes the conversion of adenosine triphosphate (ATP) to cAMP, which serves as the second messenger (Step 4). Although not shown, intrinsic GTPase activity in the G protein converts GTP back to GDP, and the α_s subunit returns to its inactive state.
3. **cAMP**, via a series of steps involving activation of **protein kinase A**, phosphorylates intracellular proteins (Steps 5 and 6). These phosphorylated proteins then execute the final physiologic actions (Step 7).
4. Intracellular cAMP is degraded to an inactive metabolite, 5' adenosine monophosphate (**5' AMP**),

by the enzyme **phosphodiesterase**, thereby turning off the action of the second messenger.

Phospholipase C Mechanism

Hormones that utilize the phospholipase C ($\text{IP}_3/\text{Ca}^{2+}$) mechanism also are listed in Table 9.3. The mechanism involves binding of hormone to a receptor and coupling via a G_q protein to phospholipase C. Intracellular levels of IP_3 and Ca^{2+} are increased, producing the final physiologic actions. The steps in the phospholipase C ($\text{IP}_3/\text{Ca}^{2+}$) mechanism are shown in Figure 9.5.

The receptor- G_q -phospholipase C complex is embedded in the cell membrane. With no hormone bound to the receptor, the α_q subunit binds GDP. In this configuration, the G_q protein is **inactive**. When the hormone binds to the receptor, G_q is activated, which activates phospholipase C, in the following steps (see Fig. 9.5):

1. Hormone binds to its receptor in the cell membrane, producing a conformational change in the α_q subunit (Step 1). GDP is released from the α_q subunit and is replaced by GTP, and the α_q subunit detaches from the G_q protein (Step 2).
2. The **α_q -GTP complex** migrates within the cell membrane and binds to and activates phospholipase C (Step 3). Activated **phospholipase C** catalyzes the liberation of diacylglycerol and IP_3 from phosphatidylinositol 4,5-diphosphate (PIP_2), a membrane phospholipid (Step 4). The IP_3 generated causes the release of Ca^{2+} from intracellular stores in the endoplasmic or sarcoplasmic reticulum, resulting in an increase in intracellular Ca^{2+} concentration (Step 5).
3. Together, Ca^{2+} and diacylglycerol activate **protein kinase C** (Step 6), which phosphorylates proteins and produces the final physiologic actions (Step 7).

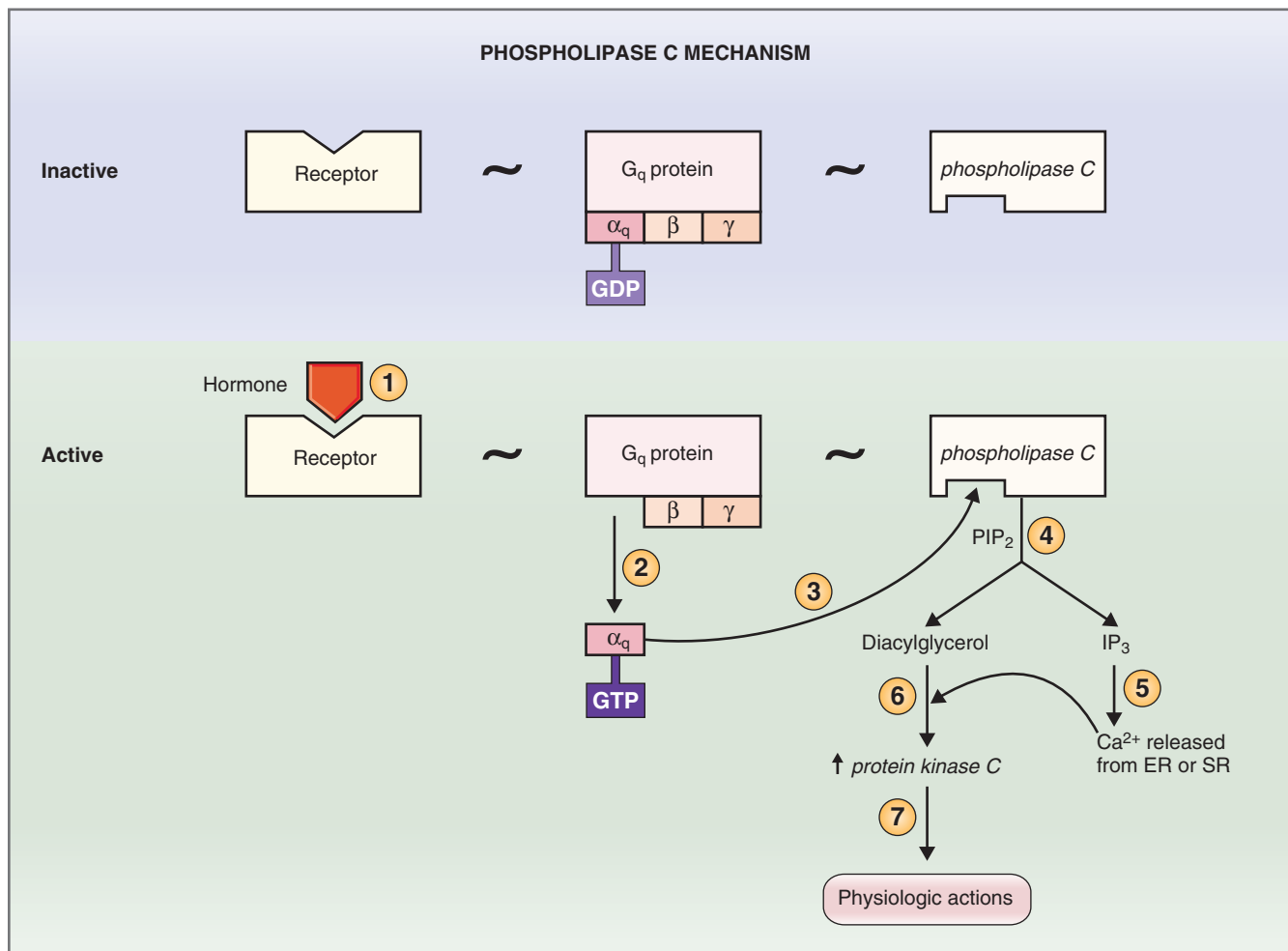


Fig. 9.5 Steps involved in the phospholipase C ($\text{IP}_3/\text{Ca}^{2+}$) mechanism of action. See the text for an explanation of the circled numbers. ER, Endoplasmic reticulum; GDP, guanosine diphosphate; GTP, guanosine triphosphate; IP_3 , inositol 1,4,5-triphosphate; PIP_2 , phosphatidylinositol 4,5-diphosphate; SR, sarcoplasmic reticulum.

Catalytic Receptor Mechanisms

Some hormones bind to cell surface receptors that have, or are associated with, enzymatic activity on the intracellular side of the cell membrane. These so-called **catalytic receptors** include guanylyl cyclase, serine/threonine kinases, tyrosine kinases, and tyrosine kinase–associated receptors. Guanylyl cyclase catalyzes the generation of cGMP from GTP. The kinases phosphorylate serine, threonine, or tyrosine on proteins and thus add negative charge in the form of the phosphate group; phosphorylation of target proteins results in conformational changes that are responsible for the hormone's physiologic actions.

Guanylyl Cyclase

Hormones acting through the guanylyl cyclase mechanism are also listed in [Table 9.3](#). **Atrial natriuretic peptide (ANP)** and related natriuretic peptides act through a *receptor* guanylyl cyclase mechanism as follows (see Chapters 4 and 6). The extracellular domain of the receptor has a binding site for ANP, while the intracellular domain of the receptor has guanylyl cyclase activity. Binding of ANP causes activation of guanylyl cyclase and conversion of GTP to cGMP. cGMP then activates cGMP-dependent kinase, which phosphorylates the proteins responsible for ANP's physiologic actions.

Nitric oxide (NO) acts through a *cytosolic* guanylyl cyclase as follows (see Chapter 4). NO synthase in vascular endothelial cells cleaves arginine into citrulline and NO. The just-synthesized NO diffuses out of

the endothelial cells into nearby vascular smooth muscle cells, where it binds to and activates soluble, or cytosolic, guanylyl cyclase. GTP is converted to cGMP, which relaxes vascular smooth muscle.

Serine/Threonine Kinases

As previously discussed, numerous hormones utilize G protein–linked receptors as part of the **adenylyl cyclase** and **phospholipase C** mechanisms (see [Table 9.3](#)). In these mechanisms, the cascade of events ultimately activates protein kinase A or protein kinase C, respectively. The activated kinases then phosphorylate serine and threonine moieties on proteins that execute the hormone's physiologic actions. In addition, **Ca²⁺-calmodulin-dependent protein kinase (CaMK)** and **mitogen-activated protein kinases (MAPKs)** phosphorylate serine and threonine in the cascade of events leading to their biologic actions.

Tyrosine Kinases

Tyrosine kinases phosphorylate tyrosine moieties on proteins and fall in two major categories. **Receptor tyrosine kinases** have *intrinsic* tyrosine kinase activity within the receptor molecule. **Tyrosine kinase–associated receptors** do not have intrinsic tyrosine kinase activity but *associate* noncovalently with proteins that do ([Fig. 9.6](#)).

- ◆ **Receptor tyrosine kinases** have an extracellular binding domain that binds the hormone or ligand, a hydrophobic transmembrane domain, and an intracellular domain that contains tyrosine kinase

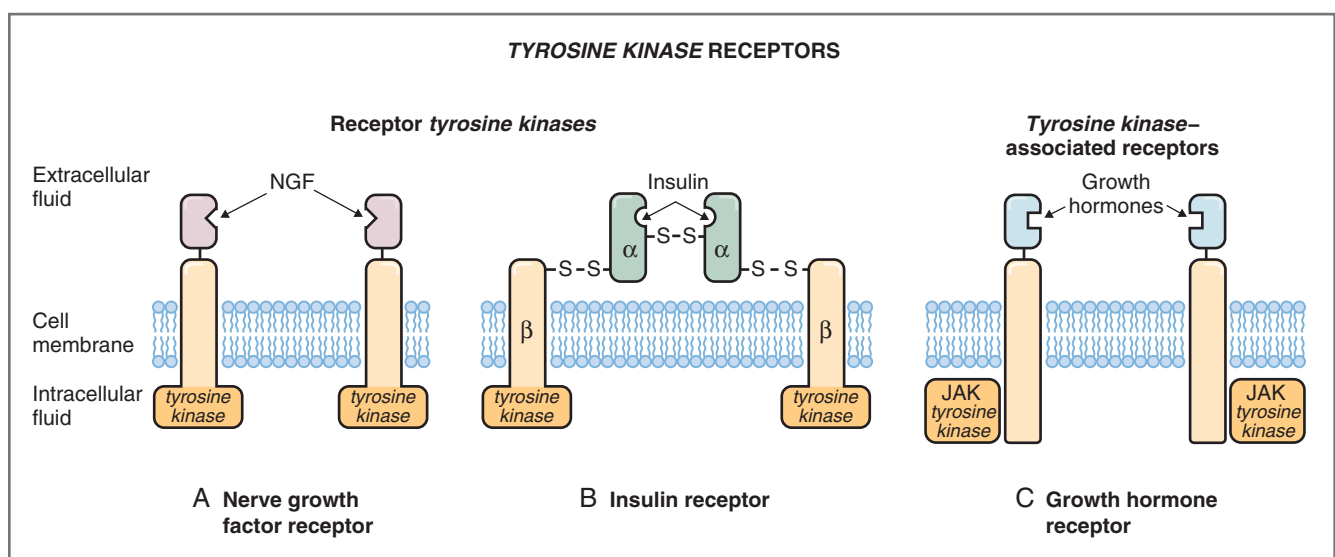


Fig. 9.6 Tyrosine kinase receptors. Nerve growth factor (A) and insulin (B) utilize receptor tyrosine kinases that have intrinsic tyrosine kinase activity. Growth hormone (C) utilizes a tyrosine kinase–associated receptor. *JAK*, Janus family of receptor-associated tyrosine kinase; *NGF*, nerve growth factor.

activity. When activated by hormone or ligand, the intrinsic tyrosine kinase phosphorylates itself and other proteins.

One type of receptor tyrosine kinase is a monomer (e.g., **nerve growth factor [NGF] and epidermal growth factor receptors**, see Fig. 9.6A). In this monomeric type, binding of ligand to the extracellular domain results in dimerization of the receptor, activation of intrinsic tyrosine kinase, and phosphorylation of tyrosine moieties on itself and other proteins, leading to its physiologic actions.

Another type of receptor tyrosine kinase is already a dimer (e.g., **insulin and insulin-like growth factor [IGF] receptors**, see Fig. 9.6B). In this dimeric type, binding of the ligand (e.g., insulin) activates intrinsic tyrosine kinase and leads to phosphorylation of itself and other proteins and ultimately the hormone's physiologic actions. The mechanism of the insulin receptor is also discussed later in the chapter.

- ◆ **Tyrosine kinase–associated receptors** (e.g., **growth hormone receptors**, see Fig. 9.6C) also have an extracellular domain, a hydrophobic transmembrane domain, and an intracellular domain. However, unlike the receptor tyrosine kinases, the intracellular domain does not have tyrosine kinase activity but is noncovalently “associated” with tyrosine kinase such as those in the Janus kinase family (**JAK**, Janus family of receptor-associated tyrosine kinase, or “just another kinase”). Hormone binds to the extracellular domain, leading to receptor dimerization and activation of tyrosine kinase in the associated protein (e.g., JAK). The associated tyrosine kinase phosphorylates tyrosine moieties on itself, the hormone receptor, and other proteins. Downstream targets of JAK include members of the **STAT** (signal transducers and activators of transcription) family, which cause transcription of mRNAs and ultimately new proteins involved in the hormone's physiologic actions.

Steroid and Thyroid Hormone Mechanism

Steroid hormones and thyroid hormones have the same mechanism of action. In contrast to the adenylyl cyclase and phospholipase C mechanisms utilized by peptide hormones and involving cell membrane receptors and generation of intracellular second messengers, the steroid hormone mechanism involves binding to cytosolic (or nuclear) receptors (Fig. 9.7) that initiate DNA transcription and synthesis of new proteins. In further contrast to peptide hormones, which act quickly on their target cells (within minutes), steroid hormones **act slowly** (taking hours).

The steps in the steroid hormone mechanism (shown in Fig. 9.8) are described as follows:

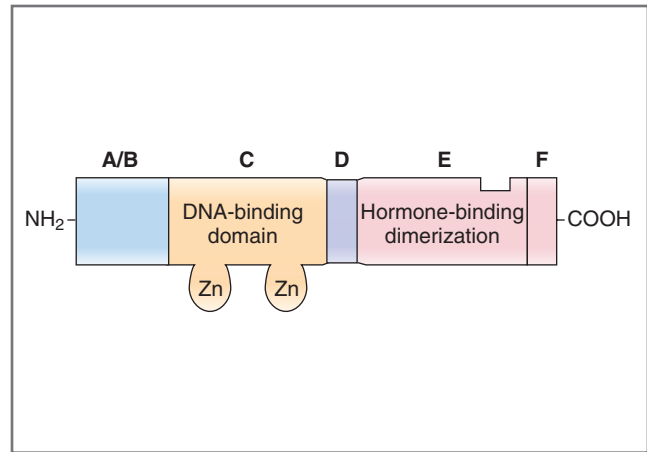


Fig. 9.7 Structure of cytosolic (or nuclear) steroid hormone receptor. Letters A–F represent the six domains of the receptor.

1. The steroid hormone diffuses across the cell membrane and enters its target cell (Step 1), where it binds to a specific **receptor protein** (Step 2) that is located in either the cytosol (as shown in Fig. 9.8) or nucleus. Steroid hormone receptors are monomeric phosphoproteins that are part of a gene superfamily of intracellular receptors. Each receptor has six domains (see Fig. 9.7). The steroid hormone binds in the **E domain** located near the C terminus. The central **C domain** is highly conserved among different steroid hormone receptors, has two zinc fingers, and is responsible for DNA binding. With hormone bound, the receptor undergoes a conformational change and the activated hormone-receptor complex enters the nucleus of the target cell.
2. The hormone-receptor complex **dimerizes** and binds (at its C domain) via the zinc fingers to specific DNA sequences, called **steroid-responsive elements (SREs)** located in the 5' region of target genes (Step 3).
3. The hormone-receptor complex has now become a **transcription factor** that regulates the rate of transcription of that gene (Step 4). New **messenger RNA (mRNA)** is transcribed (Step 5), leaves the nucleus (Step 6), and is translated to new proteins (Step 7) that have specific physiologic actions (Step 8). The nature of the **new proteins** is specific to the hormone and accounts for the specificity of the hormone's actions. For example, 1,25-dihydroxycholecalciferol induces the synthesis of a Ca^{2+} -binding protein that promotes Ca^{2+} absorption from the intestine; aldosterone induces synthesis of Na^+ channels (ENaC) in the renal principal cells that promote Na^+ reabsorption in the kidney; and testosterone induces synthesis of skeletal muscle proteins.

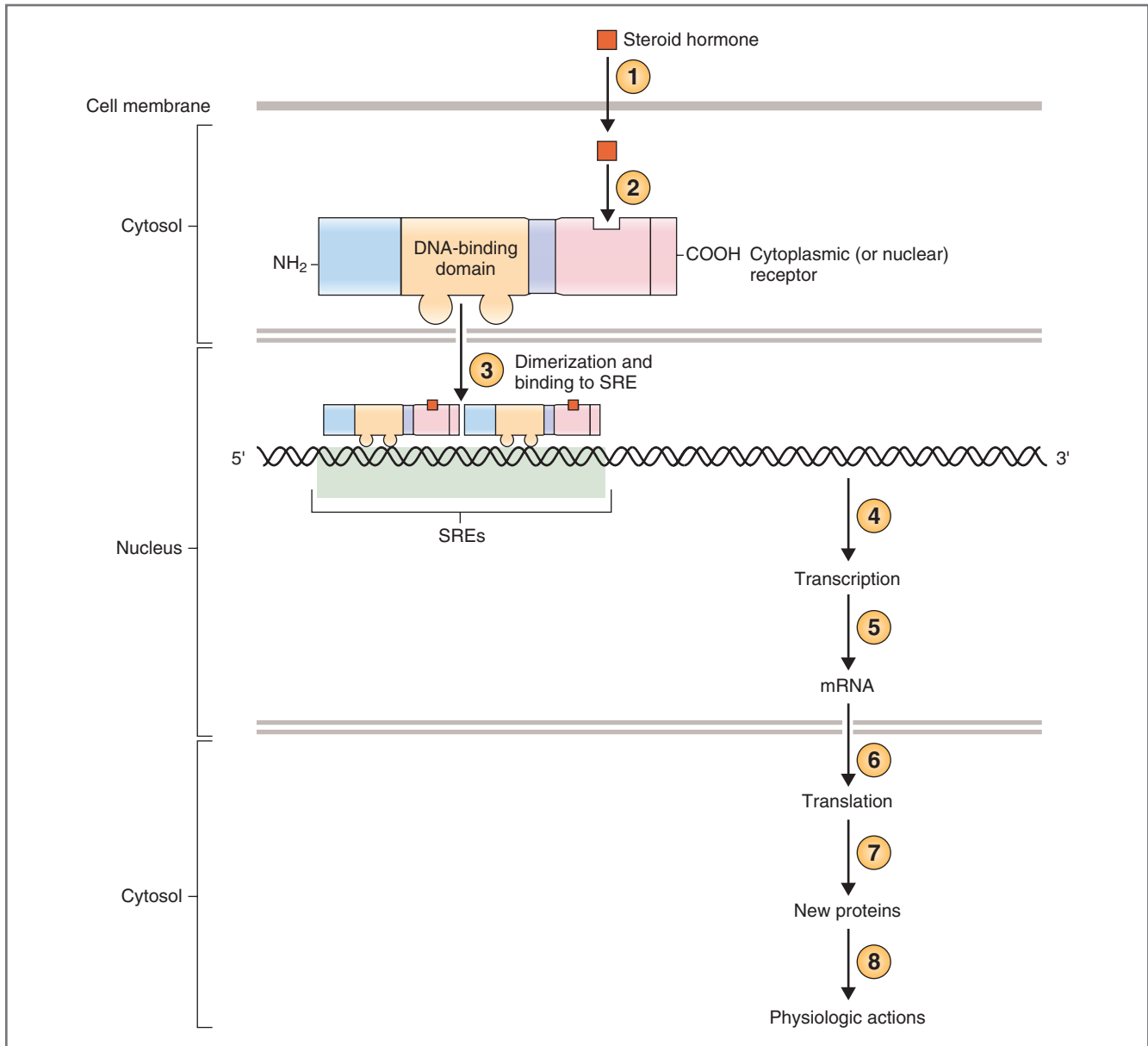


Fig. 9.8 Steps involved in the steroid hormone mechanism of action. See the text for an explanation of the circled numbers. *mRNA*, Messenger ribonucleic acid; *SREs*, steroid-responsive elements.

HYPOTHALAMIC-PITUITARY RELATIONSHIPS

The hypothalamus and pituitary gland function in a coordinated fashion to orchestrate many of the endocrine systems. The hypothalamic-pituitary unit regulates the functions of the thyroid, adrenal, and reproductive glands and also controls growth, milk production and ejection, and osmoregulation. It is important to visualize the anatomic relationships between the hypothalamus

and the pituitary because these relationships underlie the functional connections between the glands.

The pituitary gland, which also is called the hypophysis, consists of a posterior lobe and an anterior lobe. The **posterior lobe** (or posterior pituitary) is also called the neurohypophysis. The **anterior lobe** (or anterior pituitary) is also called the adenohypophysis. The hypothalamus is connected to the pituitary gland by a thin stalk called the **infundibulum**. Functionally, the hypothalamus controls the pituitary gland by both neural and hormonal mechanisms (Fig. 9.9).

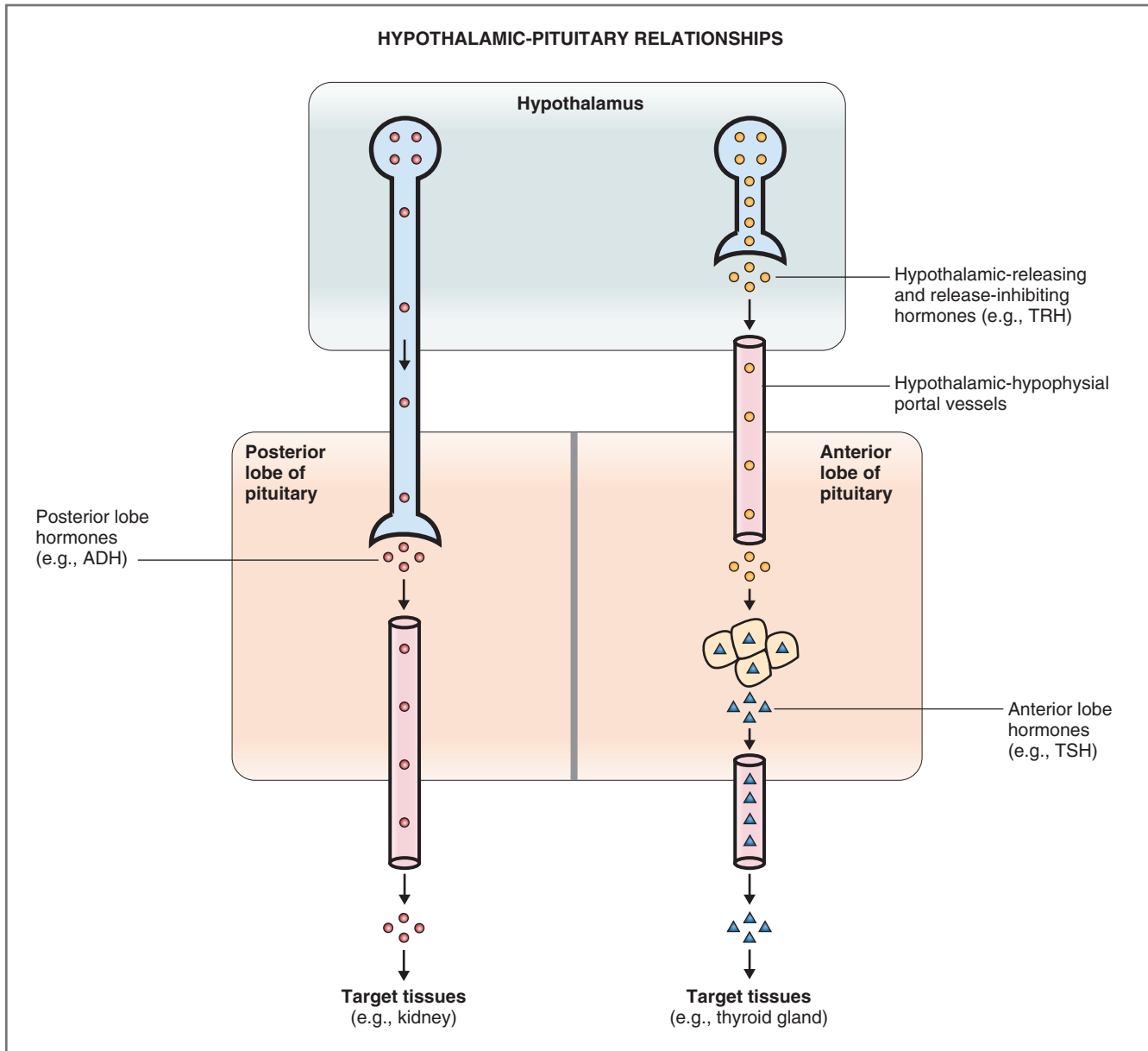


Fig. 9.9 Schematic figure showing the relationship between the hypothalamus and the posterior and anterior lobes of the pituitary gland. Pink circles are posterior pituitary hormones; yellow circles are hypothalamic hormones; triangles are anterior pituitary hormones. ADH, Antidiuretic hormone; TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone.

Relationship of the Hypothalamus to the Posterior Pituitary

The posterior lobe of the pituitary gland is derived from neural tissue. It secretes two peptide hormones, antidiuretic hormone (ADH) and oxytocin, which act on their respective target tissues—the kidney and arterioles (ADH) and the breast and uterus (oxytocin).

The connections between the hypothalamus and the posterior lobe of the pituitary are neural. In fact, the posterior pituitary is a collection of nerve axons whose cell bodies are located in the hypothalamus. Thus the hormones secreted by the posterior lobe (ADH and

oxytocin) are actually **neuropeptides**; in other words, they are peptides released from neurons.

The cell bodies of ADH- and oxytocin-secreting neurons are located in supraoptic and paraventricular nuclei within the hypothalamus. Although both hormones are synthesized in both nuclei, **ADH** is primarily associated with **supraoptic** nuclei and **oxytocin** is primarily associated with **paraventricular** nuclei.

Once synthesized in the cell bodies, the hormones (i.e., neuropeptides) are transported down the axons in neurosecretory vesicles and stored in bulbous nerve terminals in the posterior pituitary. When the cell body

is stimulated, the neurosecretory vesicles are released from the nerve terminals by exocytosis and the secreted hormone enters nearby fenestrated capillaries. Venous blood from the posterior pituitary enters the systemic circulation, which delivers the hormones to their target tissues.

In summary, the relationship between the hypothalamus and the posterior pituitary is straightforward—a hormone-secreting neuron has its cell body in the hypothalamus and its axons in the posterior lobe of the pituitary.

Relationship of the Hypothalamus to the Anterior Pituitary

The anterior lobe of the pituitary gland is derived from primitive foregut. Unlike the posterior lobe, which is neural tissue, the anterior lobe is primarily a collection of endocrine cells. The anterior pituitary secretes six peptide hormones: thyroid-stimulating hormone (TSH), FSH, LH, growth hormone, prolactin, and adrenocorticotropic hormone (ACTH).

The nature of the relationship between the hypothalamus and the anterior pituitary is both neural and endocrine (in contrast to the posterior lobe, which is only neural). The hypothalamus and anterior pituitary are linked directly by the **hypothalamic-hypophysial portal blood vessels**, which provide most of the blood supply of the anterior lobe.

There are both long and short hypophysial portal vessels, which are distinguished as follows: Arterial blood is delivered to the hypothalamus via the superior hypophysial arteries, which distribute the blood in a capillary network in the median eminence, called the primary capillary plexuses. These primary capillary plexuses converge to form the **long hypophysial portal vessels**, which travel down the infundibulum to deliver hypothalamic venous blood to the anterior lobe of the pituitary. A parallel capillary plexus forms from the inferior hypophysial arteries in the lower portion of the infundibular stem. These capillaries converge to form the **short hypophysial portal vessels**, which deliver blood to the anterior lobe of the pituitary. In summary, the blood supply of the anterior pituitary differs from that of other organs: Most of its blood supply is *venous* blood from the hypothalamus, supplied by the long and short hypophysial portal vessels.

There are two important physiologic implications of the portal blood supply to the anterior lobe of the pituitary: (1) The hypothalamic hormones can be delivered to the anterior pituitary directly and in high concentration, and (2) the hypothalamic hormones do not appear in the systemic circulation in high concentrations. The cells of the anterior pituitary, therefore, are the only cells in the body to receive high concentrations of the hypothalamic hormones.

The *functional* connections between the hypothalamus and the anterior lobe of the pituitary now can be understood in the context of the *anatomic* connections. Hypothalamic-releasing hormones and release-inhibiting hormones are synthesized in the cell bodies of hypothalamic neurons and travel down the axons of these neurons to the median eminence of the hypothalamus. Upon stimulation of these neurons, the hormones are secreted into the surrounding hypothalamic tissue and enter the nearby capillary plexus. The blood from these capillaries (now venous blood) drains into the hypophysial portal vessels and is delivered directly to the anterior lobe of the pituitary. There, the hypothalamic hormones act on the cells of the anterior lobe, where they stimulate or inhibit the release of the anterior pituitary hormones. The anterior pituitary hormones then enter the systemic circulation, which delivers them to their target tissues.

The hypothalamic-anterior pituitary relationship can be illustrated by considering the TRH-TSH-thyroid hormone system. **TRH** is synthesized in hypothalamic neurons and secreted in the median eminence of the hypothalamus, where it enters capillaries and then hypophysial portal vessels. It is delivered in this portal blood to the anterior lobe of the pituitary, where it stimulates TSH secretion. **TSH** enters the systemic circulation and is delivered to its target tissue, the thyroid gland, where it stimulates secretion of **thyroid hormones**.

ANTERIOR LOBE HORMONES

Six major hormones are secreted by the anterior lobe of the pituitary: TSH, FSH, LH, ACTH, growth hormone, and prolactin. Each hormone is secreted by a different cell type (except FSH and LH, which are secreted by the same cell type). The cell types are denoted by the suffix “troph,” meaning nutritive. Thus TSH is secreted by **thyrotrophs** (5%), FSH and LH by **gonadotrophs** (15%), ACTH by **corticotrophs** (15%), growth hormone by **somatotrophs** (20%), and prolactin by **lactotrophs** (15%). (The percentages give the representation of each cell type in the anterior pituitary gland.)

Each of the anterior pituitary hormones is a peptide or polypeptide. As described, the synthesis of peptide hormones includes the following steps: transcription of DNA to mRNA in the nucleus; translation of mRNA to a preprohormone on the ribosomes; and post-translational modification of the preprohormone on the endoplasmic reticulum and the Golgi apparatus to produce the final hormone. The hormone is stored in membrane-bound secretory granules for subsequent release. When the anterior pituitary is stimulated by a hypothalamic-releasing hormone or a release-inhibiting hormone (e.g., thyrotrophs are stimulated by TRH to

secrete TSH), there is exocytosis of the secretory granules; the anterior pituitary hormone (e.g., TSH) enters capillary blood and is delivered by the systemic circulation to the target tissue (e.g., thyroid gland).

The hormones of the anterior lobe are organized in “families” according to their structural and functional homology. TSH, FSH, and LH are structurally related and constitute one family, ACTH is part of a second family, and growth hormone and prolactin constitute a third family.

TSH, FSH, LH, and ACTH are discussed briefly in this section and later in the chapter in the context of their actions. (TSH is discussed within the context of the thyroid gland. ACTH is discussed in the context of the adrenal cortex. FSH and LH are discussed in Chapter 10 with male and female reproductive physiology.) Growth hormone and prolactin are discussed in this section.

TSH, FSH, and LH Family

TSH, FSH, and LH are all **glycoproteins** with sugar moieties covalently linked to asparagine residues in their polypeptide chains. Each hormone consists of two subunits, α and β , which are not covalently linked; none of the subunits alone is biologically active. The **α subunits** of TSH, FSH, and LH are identical and are synthesized from the same mRNA. The **β subunits** for each hormone are different and therefore confer the biologic specificity (although the β subunits have a high degree of homology among the different hormones). During the biosynthetic process, pairing of the

α and β subunits begins in the endoplasmic reticulum and continues in the Golgi apparatus. In the secretory granules, the paired molecules are refolded into more stable forms prior to secretion.

The placental hormone **human chorionic gonadotropin (HCG)** is structurally related to the TSH-FSH-LH family. Thus HCG is a glycoprotein with the identical α chain and its own β chain, which confers its biologic specificity.

ACTH Family

The ACTH family is derived from a single precursor, **pro-opiomelanocortin (POMC)**. The ACTH family includes ACTH, γ - and β -lipotropin, β -endorphin, and melanocyte-stimulating hormone (MSH). ACTH is the only hormone in this family with well-established physiologic actions in humans. MSH is involved in pigmentation in lower vertebrates but has some activity in humans. β -Endorphin is an endogenous opiate.

The prohormone for this group, **prepro-opiomelanocortin**, is transcribed from a single gene. The signal peptide is cleaved in the endoplasmic reticulum, yielding POMC, the precursor to the ACTH family. Endopeptidases then hydrolyze peptide bonds in POMC and intermediates to produce the members of the ACTH family (Fig. 9.10). The anterior pituitary in humans produces mainly ACTH, γ -lipotropin, and β -endorphin.

It is noteworthy that MSH activity is found in POMC and in several of its products: The “fragment,” which is left over from hydrolysis of the ACTH intermediate, contains γ -MSH; ACTH contains α -MSH; and γ -lipotropin

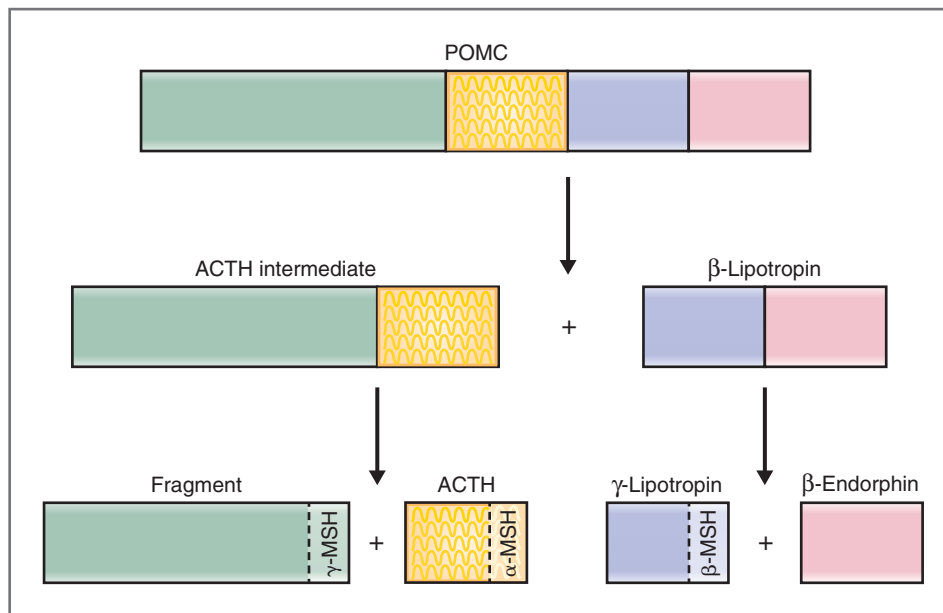


Fig. 9.10 The hormones derived from pro-opiomelanocortin (POMC). The fragment contains γ -MSH; ACTH contains α -MSH; and γ -lipotropin contains β -MSH. ACTH, Adrenocorticotropic hormone; MSH, melanocyte-stimulating hormone.

contains β -MSH. These MSH-containing fragments can cause skin pigmentation in humans if their blood levels are increased. For example, in **Addison disease** (primary adrenal insufficiency), POMC and ACTH levels are increased by negative feedback. Because POMC and ACTH contain MSH activity, skin pigmentation is a symptom of this disorder.

Growth Hormone

Growth hormone is secreted throughout life. It is the single most important hormone for **normal growth** to adult stature. Considering the broad nature of this task (growth), it is not surprising that growth hormone has profound effects on protein, carbohydrate, and fat metabolism.

Chemistry of Growth Hormone

Growth hormone is synthesized in the somatotrophs of the anterior lobe of the pituitary and also is called somatotropin or somatotrophic hormone. Human growth hormone contains **191 amino acids** in a straight-chain polypeptide with **2 internal disulfide bridges**. The gene for growth hormone is a member of a family of genes for related peptides, prolactin and human placental lactogen. The synthesis of growth hormone is stimulated by GHRH, its hypothalamic-releasing hormone.

Human growth hormone is structurally similar to prolactin, which is synthesized by lactotrophs in the anterior lobe, and to human placental lactogen, which is synthesized in the placenta. Prolactin, a 198-amino acid straight-chain polypeptide with 3 disulfide bridges, has 75% homology with growth hormone. Human placental lactogen, a 191-amino acid straight-chain polypeptide with 2 disulfide bridges, has 80% homology.

Regulation of Growth Hormone Secretion

Growth hormone is secreted in a **pulsatile** pattern, with bursts of secretion occurring approximately every 2 hours. The largest secretory burst occurs within 1 hour of falling asleep (during sleep stages III and IV). The bursting pattern, in terms of both frequency and magnitude, is affected by several agents that alter the overall level of growth hormone secretion (Table 9.4).

Growth hormone secretory rates are not constant over a lifetime. The rate of secretion increases steadily from birth into early childhood. During childhood, secretion remains relatively stable. At **puberty**, there is an enormous secretory burst, induced in females by estrogen and in males by testosterone. The high pubertal levels of growth hormone are associated with both increased frequency and increased magnitude of the secretory pulses and are responsible for the **growth spurt** of puberty. After puberty, the rate of growth hormone secretion declines to a stable level. Finally, in

TABLE 9.4 Factors Affecting Growth Hormone Secretion

Stimulatory Factors	Inhibitory Factors
Decreased glucose concentration	Increased glucose concentration
Decreased free fatty acid concentration	Increased free fatty acid concentration
Arginine	Obesity
Fasting or starvation	Senescence
Hormones of puberty (estrogen, testosterone)	Somatostatin
Exercise	Somatomedins
Stress	Growth hormone
Stage III and IV sleep	β -Adrenergic agonists
α -Adrenergic agonists	Pregnancy

senescence, growth hormone secretory rates and pulsatility decline to their lowest levels.

The major factors that alter growth hormone secretion are summarized in Table 9.4. **Hypoglycemia** (a decrease in blood glucose concentration) and **starvation** are potent stimuli for growth hormone secretion. Other stimuli for secretion are exercise and various forms of stress including trauma, fever, and anesthesia. The highest rates of growth hormone secretion occur during puberty, and the lowest rates occur in senescence.

Regulation of growth hormone secretion is illustrated in Figure 9.11, which shows the relationship between the hypothalamus, the anterior lobe of the pituitary, and the target tissues for growth hormone. Secretion of growth hormone by the anterior pituitary is controlled by two pathways from the hypothalamus, one stimulatory (GHRH) and the other inhibitory (somatostatin, also known as somatotropin release-inhibiting factor [SRIF]).

- ◆ **GHRH** acts directly on somatotrophs of the anterior pituitary to induce transcription of the growth hormone gene and thereby to stimulate both synthesis and secretion of growth hormone. In initiating its action on the somatotroph, GHRH binds to a membrane receptor, which is coupled through a G_s protein to *both* adenylyl cyclase and phospholipase C. Thus GHRH stimulates growth hormone secretion by utilizing both cAMP and IP_3/Ca^{2+} as second messengers.
- ◆ **Somatostatin (somatotropin release-inhibiting hormone [SRIF])** is also secreted by the hypothalamus and acts on the somatotrophs to inhibit growth hormone secretion. Somatostatin inhibits growth hormone secretion by blocking the action of GHRH on the somatotroph. Somatostatin binds to its own membrane receptor, which is coupled to adenylyl cyclase by a G_i protein, inhibiting the generation of cAMP and decreasing growth hormone secretion.

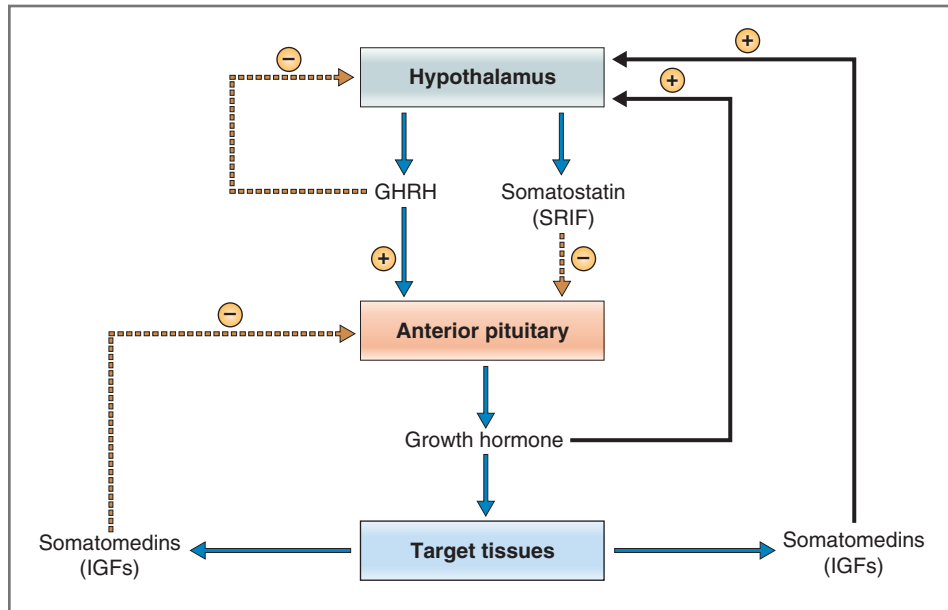


Fig. 9.11 Regulation of growth hormone secretion. *GHRH*, Growth hormone-releasing hormone; *IGF*, insulin-like growth factor; *SRIF*, somatotropin release-inhibiting factor.

Growth hormone secretion is regulated by negative feedback (see Fig. 9.11). Three feedback loops including both long and short loops are involved. (1) GHRH inhibits its own secretion from the hypothalamus via an ultrashort-loop feedback. (2) Somatomedins, which are byproducts of the growth hormone action on target tissues, inhibit secretion of growth hormone by the anterior pituitary. (3) Both growth hormone and somatomedins stimulate the secretion of somatostatin by the hypothalamus. The overall effect of this third loop is *inhibitory* (i.e., negative feedback) because somatostatin inhibits growth hormone secretion by the anterior pituitary.

Actions of Growth Hormone

Growth hormone has multiple metabolic actions on liver, muscle, adipose tissue, and bone, as well as growth-promoting actions in virtually every other organ. The actions of growth hormone include effects on linear growth, protein synthesis and organ growth, carbohydrate metabolism, and lipid metabolism.

Some of the actions of growth hormone result from the hormone's *direct* effect on target tissues such as skeletal muscle, the liver, or adipose tissue. These direct actions are mediated by **tyrosine kinase-associated receptors**. Other actions of growth hormone are mediated *indirectly* through the production of **somatomedins** (or IGFs) in the liver. The most important of the somatomedins is somatomedin C or **IGF-1**. Somatomedins act on target tissues through IGF receptors that are similar to the insulin receptor, having **intrinsic tyrosine kinase activity** and exhibiting

autophosphorylation. The growth-promoting effects of growth hormone are mediated largely through production of somatomedins.

The actions of growth hormone are described as follows:

- ◆ **Diabetogenic or anti-insulin effect.** Growth hormone causes **insulin resistance** and decreases glucose uptake and utilization by target tissues such as muscle and adipose tissue. These effects are called “diabetogenic” because they produce an increase in blood glucose concentration, as occurs when insulin is lacking or when tissues are resistant to insulin (e.g., diabetes mellitus). Growth hormone also increases lipolysis in adipose tissue. As a consequence of these metabolic effects, growth hormone causes an increase in blood insulin levels.
- ◆ **Increased protein synthesis and organ growth.** In virtually all organs, growth hormone increases the uptake of amino acids and stimulates the synthesis of DNA, RNA, and protein. These effects account for the hormone’s growth-promoting actions: increased lean body mass and increased organ size. As noted, many of the growth effects of growth hormone are mediated by somatomedins.
- ◆ **Increased linear growth.** The most striking effect of growth hormone is its ability to increase linear growth. Mediated by the somatomedins, growth hormone alters every aspect of cartilage metabolism: stimulation of DNA synthesis, RNA synthesis, and protein synthesis. In growing bones, the epiphyseal

plates widen and more bone is laid down at the ends of long bones. There also is increased metabolism in cartilage-forming cells and proliferation of chondrocytes.

Pathophysiology of Growth Hormone

The pathophysiology of growth hormone includes deficiency or excess of the hormone, with predictable effects on linear growth, organ growth, and carbohydrate and lipid metabolism.

Growth hormone deficiency in children causes **dwarfism**, including failure to grow, short stature, mild obesity, and delayed puberty. The causes of growth hormone deficiency include defects at every step in the hypothalamic–anterior pituitary–target tissue axis: decreased secretion of GHRH due to hypothalamic dysfunction; primary deficiencies of growth hormone secretion from the anterior pituitary; failure to generate somatomedins in the liver; and deficiency of growth hormone or somatomedin receptors in target tissues (growth hormone resistance). Growth hormone deficiency in children is treated with human growth hormone replacement. One variant of dwarfism is **Laron dwarfism**, in which growth hormone levels are elevated and treatment with growth hormone is ineffective. In these individuals, growth hormone receptors are defective; thus growth hormone cannot cause production of IGFs in target tissues.

Growth hormone excess causes **acromegaly** and is most often due to a growth hormone–secreting pituitary adenoma. The consequences of excess growth hormone differ, depending on whether the excess occurs before or after puberty. Before puberty, excessive levels of growth hormone cause **gigantism** (increased linear growth) because of intense hormonal stimulation at the epiphyseal plates. After puberty, when linear growth is complete and can no longer be influenced, excess levels of growth hormone cause increased periosteal bone growth, increased organ size, increased hand and foot size, enlargement of the tongue, coarsening of facial features, insulin resistance, and glucose intolerance. Conditions with excess secretion of growth hormone are treated with **somatostatin analogues** (e.g., **octreotide**), which, like endogenous somatostatin, inhibit growth hormone secretion by the anterior pituitary.

Prolactin

Prolactin is the major hormone responsible for **milk production** and also participates in the development of the breasts. In nonpregnant, nonlactating females and in males, blood levels of prolactin are low. However, during pregnancy and lactation, blood levels of prolactin increase, consistent with the hormone's role in breast development and lactogenesis (milk production).

Chemistry of Prolactin

Prolactin is synthesized by the lactotrophs, which represent approximately 15% of the tissue in the anterior lobe of the pituitary. The number of lactotrophs increases during pregnancy and lactation when the demand for prolactin is increased. Chemically, prolactin is related to growth hormone, having **198 amino acids** in a **single-chain polypeptide** with 3 internal disulfide bridges.

Stimuli that increase or decrease prolactin secretion do so by altering transcription of the prolactin gene. Thus TRH, a stimulant of prolactin secretion, increases transcription of the prolactin gene, whereas dopamine, an inhibitor of prolactin secretion, decreases transcription of the gene.

Regulation of Prolactin Secretion

Figure 9.12 illustrates the hypothalamic control of prolactin secretion. There are two regulatory paths from the hypothalamus, one inhibitory (via dopamine, which acts by decreasing cAMP levels) and the other stimulatory (via TRH).

In persons who are not pregnant or lactating, prolactin secretion is **tonically inhibited by dopamine** (prolactin-inhibiting factor [PIF]) from the hypothalamus. In other words, the inhibitory effect of dopamine dominates and overrides the stimulatory effect of TRH. In contrast to other hypothalamic-releasing or release-inhibiting hormones, which are peptides, dopamine is a catecholamine.

Two questions arise regarding this inhibitory action of dopamine: *What is the source of hypothalamic*

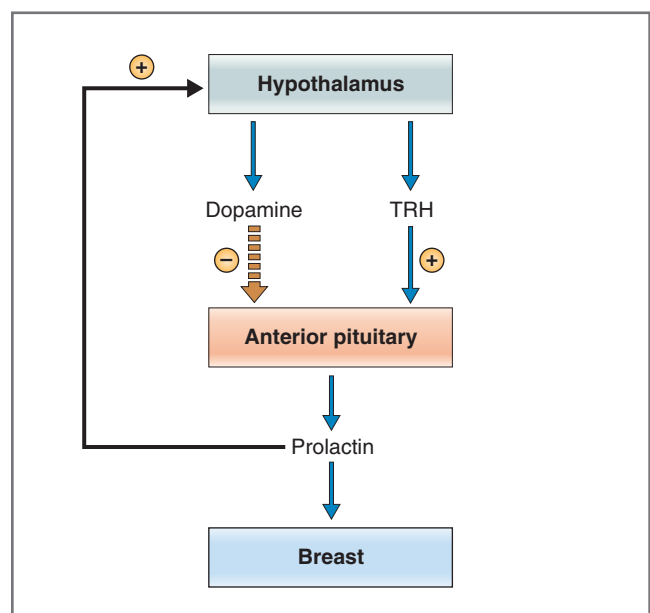


Fig. 9.12 Regulation of prolactin secretion. TRH, Thyrotropin-releasing hormone.

dopamine? How does dopamine reach the anterior lobe? There are three sources and three routes: (1) The major source of dopamine is dopaminergic neurons in the hypothalamus, which synthesize and secrete dopamine into the median eminence. This dopamine enters capillaries that drain into the hypothalamic-hypophysial portal vessels and deliver dopamine directly and in high concentration to the anterior pituitary, where it inhibits prolactin secretion. (2) Dopamine also is secreted by dopaminergic neurons of the posterior lobe of the pituitary, reaching the anterior lobe by short connecting portal veins. (3) Finally, nonlactotroph cells of the anterior pituitary secrete a small amount of dopamine that diffuses a short distance to the lactotrophs and inhibits prolactin secretion by a paracrine mechanism.

The factors that alter prolactin secretion are summarized in [Table 9.5](#). **Prolactin** inhibits its own secretion by increasing the synthesis and secretion of dopamine from the hypothalamus (see [Fig. 9.12](#)). This action of prolactin constitutes negative feedback because *stimulation* of dopamine secretion causes *inhibition* of prolactin secretion. **Pregnancy** and **breast-feeding** (suckling) are the most important stimuli for prolactin secretion. For example, during breast-feeding, serum prolactin levels can increase to more than 10-fold the basal levels. During suckling, afferent fibers from the nipple carry information to the hypothalamus and inhibit dopamine secretion; by releasing the inhibitory effect of dopamine, prolactin secretion is increased. The effects of dopamine, dopamine agonists, and dopamine antagonists on prolactin secretion are predictable, based on feedback regulation (see [Fig. 9.12](#)). Thus dopamine itself and dopamine agonists such as **bromocriptine** inhibit prolactin secretion, whereas dopamine antagonists stimulate prolactin secretion by “inhibiting the inhibition” by dopamine.

Actions of Prolactin

Prolactin, in a supportive role with estrogen and progesterone, stimulates development of the breasts, promotes milk secretion from the breasts during lactation, and suppresses ovulation.

TABLE 9.5 Factors Affecting Prolactin Secretion

Stimulatory Factors	Inhibitory Factors
Pregnancy (estrogen)	Dopamine
Breast-feeding	Bromocriptine (dopamine agonist)
Sleep	Somatostatin
Stress	Prolactin (negative feedback)
TRH	
Dopamine antagonists	

TRH, Thyrotropin-releasing hormone.

◆ **Breast development.** At puberty, prolactin, with estrogen and progesterone, stimulates proliferation and branching of the mammary ducts. During pregnancy, prolactin (again with estrogen and progesterone) stimulates growth and development of the mammary alveoli, which will produce milk once parturition occurs.

◆ **Lactogenesis (milk production).** The major action of prolactin is stimulation of milk production and secretion in response to suckling. (Interestingly, pregnancy *does not* have to occur for lactation to be possible; if there is sufficient stimulation of the nipple, prolactin is secreted and milk is produced.) Prolactin stimulates milk production by inducing the synthesis of the components of milk including **lactose** (the carbohydrate of milk), **casein** (the protein of milk), and **lipids**. The mechanism of action of prolactin on the breast involves binding of prolactin to a cell membrane receptor and, via an unknown second messenger, inducing transcription of the genes for enzymes in the biosynthetic pathways for lactose, casein, and lipid.

Although prolactin levels are high during pregnancy, lactation does not occur because the high levels of estrogen and progesterone down-regulate prolactin receptors in the breast and block the action of prolactin. At parturition, estrogen and progesterone levels drop precipitously and their inhibitory actions cease. Prolactin can then stimulate lactogenesis, and lactation can occur.

◆ **Inhibition of ovulation.** In females, prolactin inhibits ovulation by inhibiting the synthesis and release of gonadotropin-releasing hormone (GnRH) (see Chapter 10). Inhibition of GnRH secretion and, secondarily, inhibition of ovulation account for the decreased fertility during breast-feeding. In males with high prolactin levels (e.g., due to a prolactinoma), there is a parallel inhibitory effect on GnRH secretion and spermatogenesis, resulting in infertility.

Pathophysiology of Prolactin

The pathophysiology of prolactin can involve either a deficiency of prolactin, which results in the inability to lactate, or an excess of prolactin, which causes galactorrhea (excessive milk production).

◆ **Prolactin deficiency** can be caused by either destruction of the entire anterior lobe of the pituitary or selective destruction of the lactotrophs. Prolactin deficiency results, predictably, in a failure to lactate.

◆ **Prolactin excess** can be caused by destruction of the hypothalamus, interruption of the hypothalamic-hypophysial tract, or prolactinomas

(prolactin-secreting tumors). In cases of hypothalamic destruction or interruption of the hypothalamic-hypophysial tract, increased prolactin secretion occurs because of the *loss of tonic inhibition by dopamine*. The major symptoms of excess prolactin secretion are **galactorrhea** and **infertility** (which is caused by inhibition of GnRH secretion by the high-prolactin levels). Whether the result of hypothalamic failure or a prolactinoma, prolactin excess can be treated by administration of **bromocriptine**, a dopamine agonist. Like dopamine, bromocriptine inhibits prolactin secretion by the anterior pituitary.

POSTERIOR LOBE HORMONES

The posterior lobe of the pituitary secretes ADH and oxytocin. Both ADH and oxytocin are neuropeptides,

synthesized in cell bodies of hypothalamic neurons and secreted from nerve terminals in the posterior pituitary.

Synthesis and Secretion of Antidiuretic Hormone and Oxytocin

Synthesis and Processing

ADH and oxytocin are homologous **nonapeptides** (containing nine amino acids) (Figs. 9.13 and 9.14) that are synthesized in the supraoptic and paraventricular nuclei of the hypothalamus. The **ADH** neurons have their cell bodies primarily in the **supraoptic nuclei** of the hypothalamus. The **oxytocin** neurons have their cell bodies primarily in **paraventricular nuclei**. While primarily dedicated to producing ADH or oxytocin, each nucleus also produces the “other” hormone. Similar genes located in close proximity on the chromosome

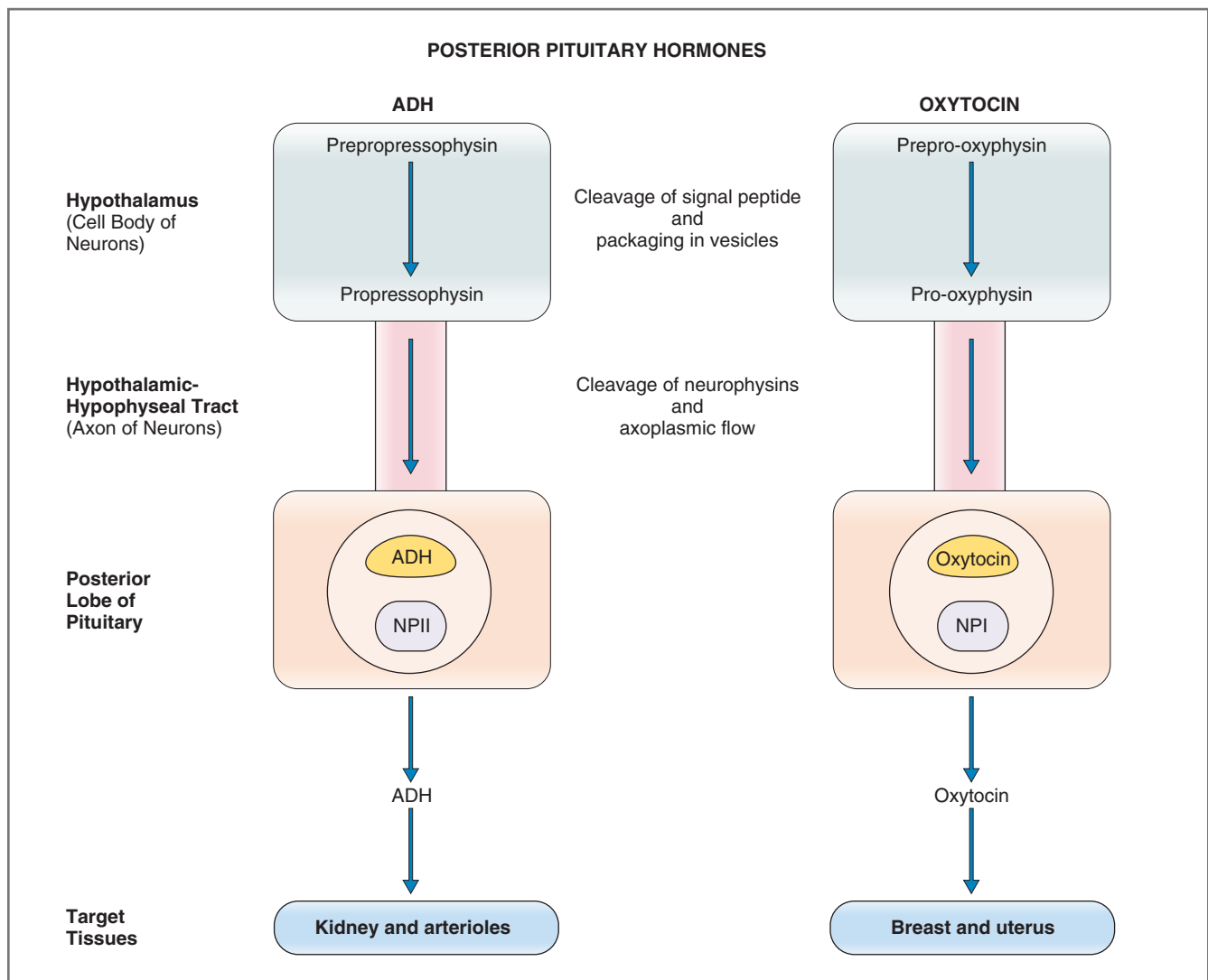


Fig. 9.13 Synthesis, processing, and secretion of antidiuretic hormone (ADH) and oxytocin. *NPI*, Neurophysin I; *NPII*, neurophysin II.

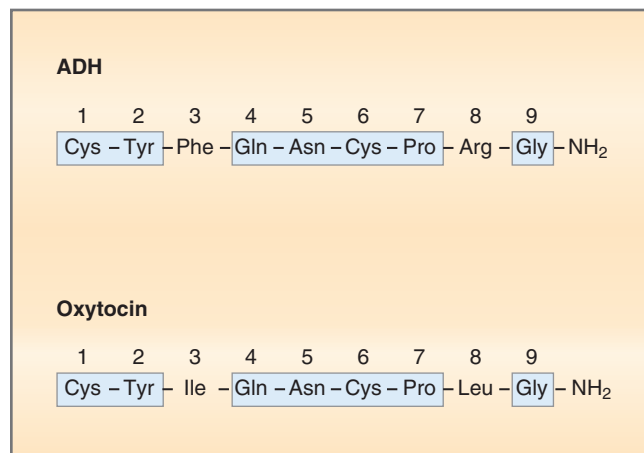


Fig. 9.14 Structures of antidiuretic hormone (ADH) and oxytocin. Homologous amino acid sequences are shown within the shaded boxes.

direct synthesis of the prohormones for ADH and oxytocin. The peptide precursor for ADH is **prepro-pressophysin**, which comprises a signal peptide, ADH, neurophysin II, and a glycoprotein. The precursor for oxytocin is **prepro-oxyphysin**, which comprises a signal peptide, oxytocin, and neurophysin I. In the Golgi apparatus, the signal peptides are removed from the *preprohormones* to form the *prohormones*, *propresophysin* and *pro-oxyphysin*, and the prohormones are packaged in secretory vesicles. The secretory vesicles, containing the prohormones, then travel down the axon of the neuron, through the hypothalamic-hypophysial tract, to the posterior pituitary. En route to the posterior pituitary, the neurophysins are cleaved from their respective prohormones within the secretory vesicles.

Secretion

The secretory vesicles that arrive at the posterior pituitary contain either ADH, neurophysin II, and glycoprotein *or* oxytocin and neurophysin I. Secretion is initiated when an action potential is transmitted from the cell body in the hypothalamus, down the axon to the nerve terminal in the posterior pituitary. When the nerve terminal is depolarized by the action potential, Ca²⁺ enters the terminal, causing exocytosis of the secretory granules containing ADH or oxytocin and their neurophysins. The secreted hormones enter nearby fenestrated capillaries and are carried to the systemic circulation, which delivers the hormones to their target tissues.

Antidiuretic Hormone

ADH (or vasopressin) is the major hormone concerned with regulation of body fluid osmolarity. ADH is secreted by the posterior pituitary in response to an increase in serum osmolarity. ADH then acts on the

TABLE 9.6 Factors Affecting Antidiuretic Hormone Secretion

Stimulatory Factors	Inhibitory Factors
Increased serum osmolarity	Decreased serum osmolarity
Decreased ECF volume	Ethanol
Angiotensin II	α -Adrenergic agonists
Pain	ANP
Nausea	
Hypoglycemia	
Nicotine	
Opiates	
Antineoplastic drugs	

ANP, Atrial natriuretic peptide; ECF, extracellular fluid.

principal cells of the late distal tubule and collecting duct to increase water reabsorption, thus decreasing body fluid osmolarity back toward normal. Osmoregulation and the actions of ADH on the kidney are discussed in Chapter 6.

Regulation of Antidiuretic Hormone Secretion

The factors that stimulate or inhibit the secretion of ADH by the posterior pituitary are summarized in Table 9.6.

Increased plasma osmolarity is the most important physiologic stimulus for increasing ADH secretion (Fig. 9.15). For example, when a person is deprived of water, serum osmolarity increases. The increase is sensed by osmoreceptors in the anterior hypothalamus. Action potentials are initiated in cell bodies of the nearby ADH neurons and propagated down the axons, causing the secretion of ADH from nerve terminals in the posterior pituitary. Conversely, decreases in serum osmolarity signal the hypothalamic osmoreceptors to inhibit the secretion of ADH.

Hypovolemia, or volume contraction (e.g., due to hemorrhage), is also a potent stimulus for ADH secretion. Decreases in extracellular fluid (ECF) volume of 10% or more cause a decrease in arterial blood pressure that is sensed by baroreceptors in the left atrium, carotid artery, and aortic arch. This information about blood pressure is transmitted via the vagus nerve to the hypothalamus, which directs an increase in ADH secretion. ADH then stimulates water reabsorption in the collecting ducts, attempting to restore ECF volume. Importantly, hypovolemia stimulates ADH secretion, even when plasma osmolarity is lower than normal (see Fig. 9.15). Conversely, hypervolemia (volume expansion) inhibits ADH secretion, even when plasma osmolarity is higher than normal.

Pain, nausea, hypoglycemia, and various drugs (e.g., nicotine, opiates, antineoplastic agents) all stimulate the secretion of ADH. Ethanol, α -adrenergic agonists, and ANP inhibit secretion of ADH.

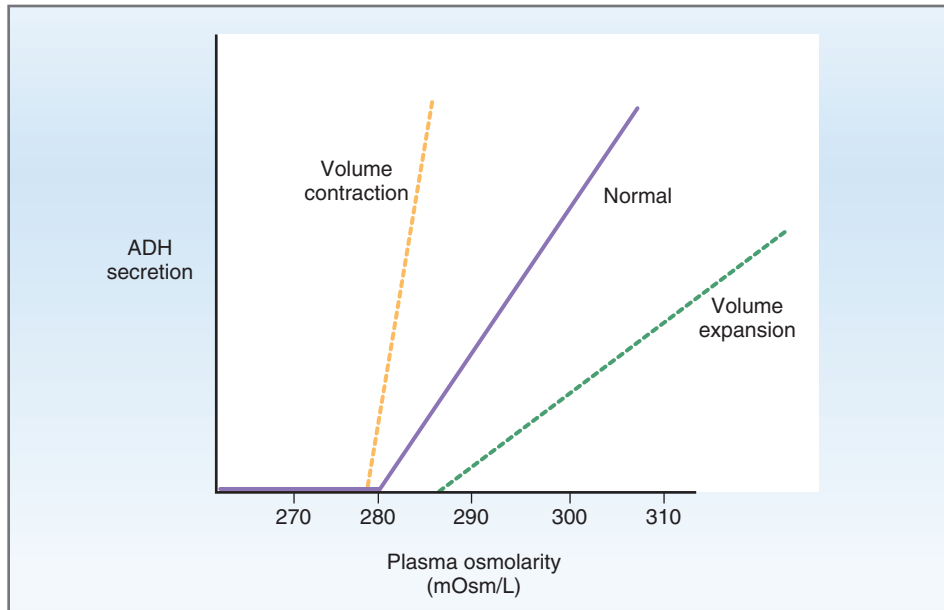


Fig. 9.15 Control of antidiuretic hormone (ADH) secretion by osmolarity and extracellular fluid volume.

Actions of Antidiuretic Hormone

ADH (vasopressin) has two actions, one on the kidney and the other on vascular smooth muscle. These actions are mediated by different receptors, different intracellular mechanisms, and different second messengers.

- ◆ **Increase in water permeability.** The major action of ADH is to increase the water permeability of principal cells in the late distal tubule and collecting duct. The receptor for ADH on the principal cells is a **V₂ receptor**, which is coupled to adenylyl cyclase via a G_s protein. The second messenger is **cAMP**, which, via phosphorylation steps, directs the insertion of water channels, **aquaporin 2 (AQP2)**, in the luminal membranes. The increased water permeability of the principal cells allows water to be reabsorbed by the collecting ducts and makes the urine concentrated, or hyperosmotic (see Chapter 6).
- ◆ **Contraction of vascular smooth muscle.** The second action of ADH is to cause contraction of vascular smooth muscle (as implied by its other name, vasopressin). The receptor for ADH on vascular smooth muscle is a **V₁ receptor**, which is coupled to phospholipase C via a G_q protein. The second messenger for this action is **IP₃/Ca²⁺**, which produces contraction of vascular smooth muscle, constriction of arterioles, and increased total peripheral resistance.

Pathophysiology of Antidiuretic Hormone

The pathophysiology of ADH is discussed in detail in Chapter 6 and is summarized here.

Central diabetes insipidus is caused by failure of the posterior pituitary to secrete ADH. In this disorder, circulating levels of ADH are low, the collecting ducts are impermeable to water, and the urine cannot be concentrated. Thus persons with central diabetes insipidus produce large volumes of dilute urine, and their body fluids become concentrated (e.g., increased serum osmolarity, increased serum Na⁺ concentration). Central diabetes insipidus is treated with an ADH analogue, **dDAVP**.

In **nephrogenic diabetes insipidus**, the posterior pituitary is normal but the principal cells of the collecting duct are unresponsive to ADH due to a defect in the V₂ receptor, G_s protein, or adenylyl cyclase. As in central diabetes insipidus, water is not reabsorbed in the collecting ducts and the urine cannot be concentrated, resulting in excretion of large volumes of dilute urine. As a result, the body fluids become concentrated and the serum osmolarity increases. In contrast to central diabetes insipidus, however, ADH levels are elevated in nephrogenic diabetes insipidus due to stimulation of secretion by the increased serum osmolarity. Nephrogenic diabetes insipidus is treated with **thiazide diuretics**. The usefulness of thiazide diuretics in treating nephrogenic diabetes insipidus is explained as follows: (1) Thiazide diuretics inhibit Na⁺ reabsorption in the early distal tubule. By preventing dilution of the urine at that site, the final, excreted urine is less dilute (than it would be without treatment). (2) Thiazide diuretics decrease glomerular filtration rate (GFR); because less water is filtered, less water is excreted. (3) Thiazide diuretics, by increasing Na⁺

excretion, can cause a secondary ECF volume contraction. In response to volume contraction, proximal reabsorption of solutes and water is increased; because more water is reabsorbed, less water is excreted.

In **syndrome of inappropriate ADH (SIADH)**, excess ADH is secreted from an autonomous site (e.g., oat cell carcinoma of the lung; **Box 9.1**). High levels of ADH cause excess water reabsorption by the collecting ducts, which dilutes the body fluids (e.g., decreases plasma osmolarity and Na^+ concentration). The urine is *inappropriately concentrated* (i.e., too concentrated for the serum osmolarity). SIADH is treated with an ADH antagonist such as **demeclocycline** or **water restriction**.

Oxytocin

Oxytocin produces milk “letdown” or milk ejection from the lactating breast by stimulating contraction of myoepithelial cells lining the milk ducts.

Regulation of Oxytocin Secretion

Several factors cause the secretion of oxytocin from the posterior pituitary including suckling; the sight, sound, or smell of the infant; and dilation of the cervix (**Table 9.7**).

The major stimulus for oxytocin secretion is **suckling** of the breast. Sensory receptors in the nipple transmit impulses to the spinal cord via afferent neurons. This information then ascends in the

TABLE 9.7 Factors Affecting Oxytocin Secretion

Stimulatory Factors	Inhibitory Factors
Suckling	Opioids (endorphins)
Sight, sound, or smell of the infant	
Dilation of the cervix	
Orgasm	

BOX 9.1 Clinical Physiology: Syndrome of Inappropriate ADH

DESCRIPTION OF CASE. A 56-year-old man with oat cell carcinoma of the lung is admitted to the hospital after having a grand mal seizure. Laboratory studies yield the following information:

Serum	Urine
$[\text{Na}^+]$, 110 mEq/L	Osmolarity, 650 mOsm/L
Osmolarity, 225 mOsm/L	

The man’s lung tumor is diagnosed as inoperable. He is treated with an intravenous infusion of hypertonic NaCl and is stabilized and discharged. He is given demeclocycline, an ADH antagonist, and is ordered to severely limit his water intake.

EXPLANATION OF CASE. Upon his admission to the hospital, the man’s serum $[\text{Na}^+]$ and serum osmolarity are severely depressed (normal serum $[\text{Na}^+]$, 140 mEq/L; normal serum osmolarity, 290 mOsm/L). Simultaneously, his urine is hyperosmotic, with a measured osmolarity of 650 mOsm/L. In other words, his urine is *inappropriately* concentrated, given his very dilute serum osmolarity.

Independent of the posterior pituitary, the oat cell carcinoma synthesized and secreted ADH and caused the abnormal urine and serum values. Normally, ADH is secreted by the posterior lobe of the pituitary, which is under negative-feedback regulation by serum osmolarity. When the serum osmolarity decreases below normal, ADH secretion by the posterior pituitary is inhibited. However, ADH secretion by the tumor is not under such negative feedback regulation, and ADH secretion continues unabated (no matter how low the serum osmolarity) and causes SIADH.

The man’s serum and urine values are explained as follows: The tumor is secreting large amounts of ADH (inappropriately). This ADH circulates to the kidney and acts on the principal cells of the late distal tubule and collecting duct to increase water reabsorption. The reabsorbed water is added to the total body water, diluting the solutes. Thus serum $[\text{Na}^+]$ and serum osmolarity are diluted by the excess water reabsorbed by the kidney. Although this dilution of serum osmolarity turns off ADH secretion by the posterior pituitary, it does not turn off ADH secretion by the tumor cells.

The man’s grand mal seizure was caused by swelling of brain cells. The excess water reabsorbed by the kidney was distributed throughout the total body water including intracellular fluid (ICF). As water flowed into the cells, their volume increased. For brain cells, this swelling was catastrophic because the brain is encased in a fixed cavity, the skull.

TREATMENT. The man is treated promptly with an infusion of hypertonic NaCl to raise the osmolarity of his ECF. As extracellular osmolarity becomes higher than intracellular osmolarity, water flows out of the cells, driven by the osmotic gradient, and decreases ICF volume. For brain cells, the reduction in cell volume decreases the probability of another seizure.

The man’s lung tumor is inoperable and will continue to secrete large quantities of ADH. His treatment includes water restriction and administration of demeclocycline, an ADH antagonist that blocks the effect of ADH on water reabsorption in the principal cells.

spinothalamic tract to the brain stem and, finally, to the paraventricular nuclei of the hypothalamus. Within seconds of suckling, oxytocin is secreted from nerve terminals in the posterior pituitary. If suckling continues, new oxytocin is synthesized in the hypothalamic cell bodies, travels down the axons, and replenishes the oxytocin that was secreted.

Suckling is *not required* for oxytocin secretion; **conditioned responses** to the sight, sound, or smell of the infant also cause milk letdown. Oxytocin also is secreted in response to dilation of the cervix during labor and orgasm.

Actions of Oxytocin

- ◆ **Milk ejection.** Prolactin stimulates lactogenesis. The milk is stored in mammary alveoli and small milk ducts. The major action of oxytocin is to cause milk letdown. When oxytocin is secreted in response to suckling or to conditioned responses, it causes contraction of myoepithelial cells lining these small ducts, forcing the milk into large ducts. The milk collects in cisterns and then flows out through the nipple.
- ◆ **Uterine contraction.** At a very low concentration, oxytocin also causes powerful rhythmic contractions of uterine smooth muscle. Although it is tempting to speculate that oxytocin is the critical hormone involved in parturition, it is unclear whether oxytocin plays a physiologic role in either the initiation of or the normal course of labor. However, this action of oxytocin is the basis for its use in **inducing labor** and in **reducing postpartum bleeding**.

THYROID HORMONES

Thyroid hormones are synthesized and secreted by epithelial cells of the thyroid gland. They have effects

on virtually every organ system in the body including those involved in normal growth and development. The thyroid gland was the first of the endocrine organs to be described by a deficiency disorder. In 1850, patients without thyroid glands were described as having a form of mental and growth retardation called **cretinism**. In 1891, such patients were treated by administering crude thyroid extracts (i.e., hormone replacement therapy). Disorders of thyroid deficiency and excess are among the most common of the endocrinopathies (disorders of the endocrine glands), affecting 4% to 5% of the population in the United States and an even greater percentage of people in regions of the world where there is iodine deficiency.

Synthesis and Transport of Thyroid Hormones

The two active thyroid hormones are triiodothyronine (T_3) and tetraiodothyronine, or thyroxine (T_4). The structures of T_3 and T_4 differ only by a single atom of iodine, as shown in Figure 9.16. Although T_3 is more active than T_4 , almost all hormonal output of the thyroid gland is T_4 . This “problem” of secreting the less active form is solved by the target tissues, which convert T_4 to T_3 . A third compound, reverse T_3 (rT_3 ; *not shown in Fig. 9.16*), has no biologic activity.

Synthesis of Thyroid Hormones

Thyroid hormones are synthesized by the **follicular epithelial cells** of the thyroid gland. The follicular epithelial cells are arranged in circular follicles 200–300 μm in diameter, as shown in Figure 9.17. The cells have a basal membrane facing the blood and an apical membrane facing the follicular lumen. The material in the lumen of the follicles is **colloid**, which is composed of newly synthesized thyroid hormones attached to **thyroglobulin (TG)**. When the thyroid gland is stimulated, this colloidal thyroid hormone is absorbed into the follicular cells by endocytosis.

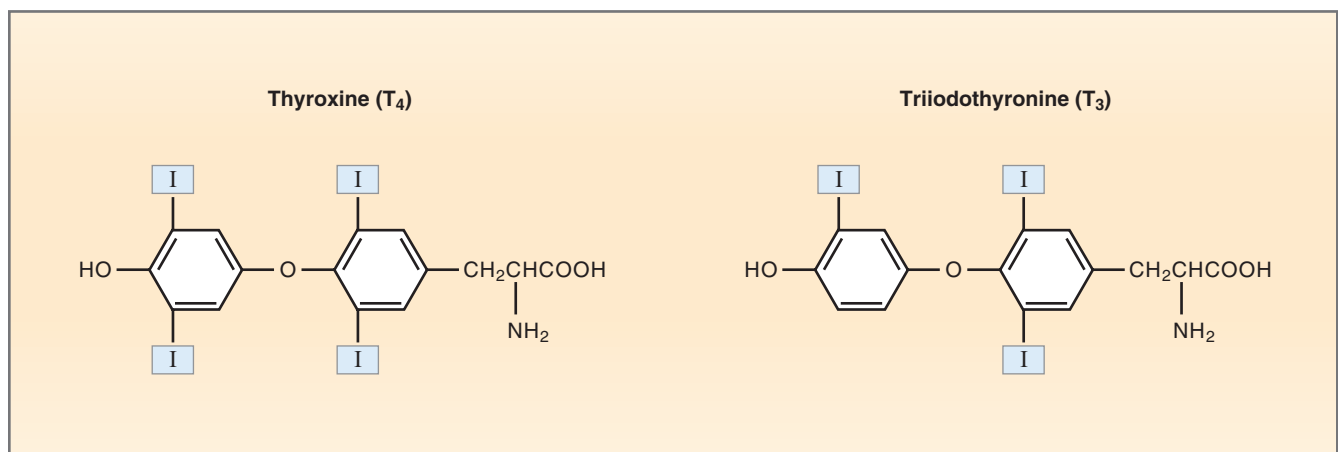


Fig. 9.16 Structures of the thyroid hormones thyroxine (T_4) and triiodothyronine (T_3).

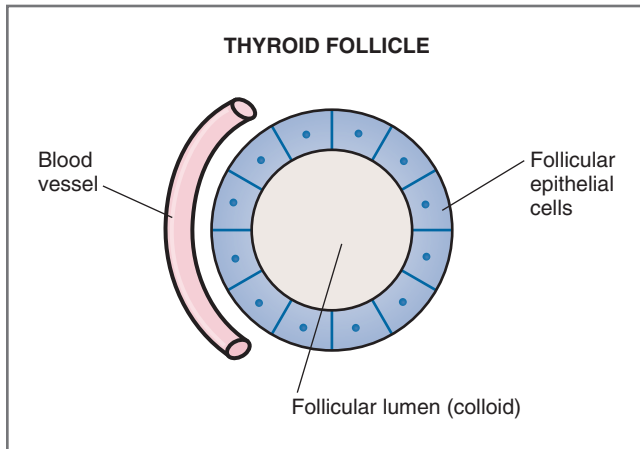


Fig. 9.17 Schematic drawing of a thyroid follicle. Colloid is present in the follicular lumen.

The synthesis of thyroid hormones is more complex than that of most hormones. There are three unusual features of the synthetic process: (1) Thyroid hormones contain large amounts of iodine, which must be adequately supplied in the diet. (2) Synthesis of thyroid hormones is partially intracellular and partially extracellular, with the completed hormones stored extracellularly in the follicular lumen until the thyroid gland is stimulated to secrete. (3) As noted, although T_4 is the major secretory product of the thyroid gland, it is not the most active form of the hormone.

The steps in thyroid hormone biosynthesis in follicular epithelial cells are illustrated in Figure 9.18. The circled numbers in the figure correlate with the following steps:

1. **Thyroglobulin (TG)**, a glycoprotein containing large quantities of **tyrosine**, is synthesized on the rough endoplasmic reticulum and the Golgi apparatus of the thyroid follicular cells. TG is then incorporated into secretory vesicles and extruded across the apical membrane into the follicular lumen. Later, the tyrosine residues of TG will be iodinated to form the precursors of thyroid hormones.
2. **Na^+I^- cotransport, or “I-trap.”** I^- is actively transported from blood into the follicular epithelial cells against both chemical and electrical gradients. The activity of this pump is regulated by I^- levels in the body. For example, low levels of I^- stimulate the pump. When there is a dietary deficiency of I^- , the Na^+I^- cotransport increases its activity, attempting to compensate for the deficiency. If the dietary deficiency is severe, however, even Na^+I^- cotransport cannot compensate and the synthesis of thyroid hormones will be decreased.

There are several competitive inhibitors of Na^+I^- cotransport including the anions **thiocyanate** and **perchlorate**, which block I^- uptake into follicular

cells and interfere with the synthesis of thyroid hormones.

3. **Oxidation of I^- to I_2 .** Once I^- is pumped into the cell, it traverses the cell to the apical membrane, where it is oxidized to I_2 by the enzyme **thyroid peroxidase**. Thyroid peroxidase catalyzes this oxidation step and the next two steps (i.e., organification of I_2 into TG and the coupling reactions).

Thyroid peroxidase is inhibited by **propylthiouracil (PTU)**, which blocks the synthesis of thyroid hormones by blocking *all* of the steps catalyzed by thyroid peroxidase. Thus administration of PTU is an effective treatment for hyperthyroidism.

4. **Organification of I_2 .** At the apical membrane, just inside the lumen of the follicle, I_2 combines with the tyrosine moieties of TG, catalyzed by thyroid peroxidase, to form **monoiodotyrosine (MIT)** and **diiodotyrosine (DIT)**. *MIT and DIT remain attached to TG* in the follicular lumen until the thyroid gland is stimulated to secrete its hormones. High levels of I^- inhibit organification and synthesis of thyroid hormones, which is known as the **Wolff-Chaikoff effect**.
5. **Coupling reaction.** While still part of TG, two separate coupling reactions occur between MIT and DIT, again catalyzed by thyroid peroxidase. In one reaction, two molecules of DIT combine to form **T_4** . In the other reaction, one molecule of DIT combines with one molecule of MIT to form **T_3** . The first reaction is faster, and as a result, approximately 10 times more T_4 is produced than T_3 . A portion of MIT and DIT does not couple (is “left over”) and simply remains attached to TG. After the coupling reactions occur, TG contains T_4 , T_3 , and leftover MIT and DIT. This iodinated TG is stored in the follicular lumen as **colloid** until the thyroid gland is stimulated to secrete its hormones (e.g., by TSH).
6. **Endocytosis of thyroglobulin.** When the thyroid gland is stimulated, iodinated TG (with its attached T_4 , T_3 , MIT, and DIT) is endocytosed into the follicular epithelial cells. Pseudopods are pinched off the apical cell membrane, engulf a portion of colloid, and absorb it into the cell. Once inside the cell, TG is transported in the direction of the basal membrane by microtubular action.
7. **Hydrolysis of T_4 and T_3 from TG by lysosomal enzymes.** TG droplets fuse with lysosomal membranes. Lysosomal proteases then hydrolyze peptide bonds to release T_4 , T_3 , MIT, and DIT from TG. T_4 and T_3 are transported across the basal membrane into nearby capillaries to be delivered to the systemic circulation; the gland secretes 90% of its thyroid hormone as T_4 and 10% as T_3 . MIT and DIT remain

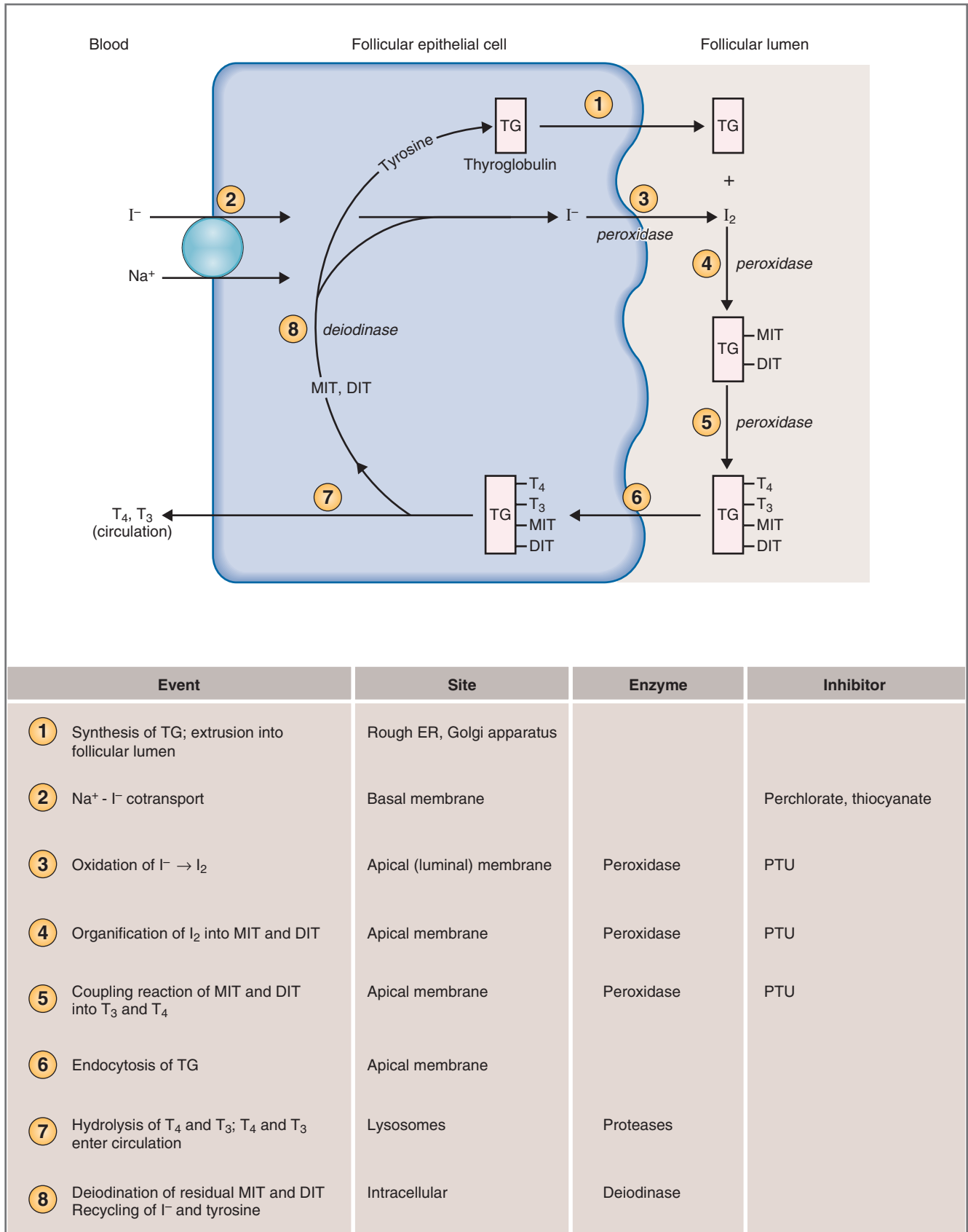


Fig. 9.18 Steps involved in the synthesis of thyroid hormones in thyroid follicular cells. Also see the text for an explanation of the circled numbers. *DIT*, Diiodotyrosine; *ER*, endoplasmic reticulum; *MIT*, monoiodotyrosine; *PTU*, propylthiouracil; T_3 , triiodothyronine; T_4 , thyroxine; *TG*, thyroglobulin.

in the follicular cell and are recycled into the synthesis of new TG.

8. **Deiodination of MIT and DIT.** MIT and DIT are deiodinated inside the follicular cell by the enzyme **thyroid deiodinase**. The I^- generated by this step is recycled into the intracellular pool and added to the I^- transported by the pump. The tyrosine molecules are incorporated into the synthesis of new TG to begin another cycle. Thus both I^- and tyrosine are “salvaged” by the deiodinase enzyme. A deficiency of thyroid deiodinase therefore mimics dietary I^- deficiency.

Binding of Thyroid Hormones in the Circulation

Thyroid hormones (T_4 and T_3) circulate in the bloodstream either bound to plasma proteins or free (unbound). Most T_4 and T_3 circulates bound to **thyroxine-binding globulin (TBG)**. Smaller amounts circulate bound to T_4 -binding prealbumin and albumin. Still smaller amounts circulate in the free, unbound form. Because only *free* thyroid hormones are physiologically active, the role of TBG is to provide a large reservoir of circulating thyroid hormones, which can be released and added to the pool of free hormone.

Changes in the blood levels of TBG alter the fraction of free (physiologically active) thyroid hormones. For example, in **hepatic failure**, blood levels of TBG decrease because there is decreased hepatic protein synthesis. The decrease in TBG levels results in a transient increase in the level of free thyroid hormones; a consequence of increased free thyroid hormone is inhibition of synthesis of thyroid hormones (by negative feedback). In contrast, during **pregnancy**, the high level of estrogen inhibits hepatic breakdown of TBG and increases TBG levels. With a higher level of TBG, more thyroid hormone is bound to TBG and less thyroid hormone is free and unbound. The transiently decreased level of free hormone causes, by negative feedback, increased synthesis and secretion of thyroid hormones by the thyroid gland. In pregnancy, as a consequence of all these changes, levels of *total* T_4 and T_3 are increased (due to the increased level of TBG), but levels of *free*, physiologically active, thyroid hormones are normal and the person is said to be “clinically euthyroid.”

Circulating levels of TBG can be indirectly assessed with the **T_3 resin uptake test**, which measures the binding of radioactive T_3 to a synthetic resin. In the test, a standard amount of radioactive T_3 is added to an assay system that contains a sample of the patient’s serum and the T_3 -binding resin. The rationale is that radioactive T_3 will first bind to unoccupied sites on the patient’s TBG and any “leftover” radioactive T_3 will bind to the resin. Thus T_3 resin uptake is increased when circulating levels of TBG are decreased (e.g.,

hepatic failure) or when endogenous T_3 levels are increased (i.e., endogenous hormone occupies more sites than usual on TBG). Conversely, T_3 resin uptake is decreased when circulating levels of TBG are increased (e.g., during pregnancy) or when endogenous T_3 levels are decreased (i.e., endogenous hormone occupies fewer sites than usual on TBG).

Activation of T_4 in Target Tissues

As noted, the major secretory product of the thyroid gland is T_4 , which is the less active form of thyroid hormone. This “problem” is solved in the target tissues by the enzyme **5′-iodinase**, which converts T_4 to T_3 by removing one atom of I_2 from the outer ring of the molecule. The target tissues also convert a portion of the T_4 to **reverse T_3 (r T_3)** by removing one atom of I_2 from the inner ring of the molecule; r T_3 is inactive. Essentially, T_4 serves as a precursor for T_3 , and the relative amounts of T_4 converted to T_3 and r T_3 determine how much *active* hormone is produced in the target tissue.

In **starvation** (fasting), target tissue 5′-iodinase plays an interesting role. Starvation inhibits 5′-iodinase in tissues such as skeletal muscle, thus lowering O_2 consumption and basal metabolic rate (BMR) during periods of caloric deprivation. However, brain 5′-iodinase differs from the 5′-iodinase in other tissues and is therefore not inhibited in starvation; in this way, brain levels of T_3 are protected even during caloric deprivation.

Regulation of Thyroid Hormone Secretion

The factors that increase or decrease the secretion of thyroid hormones are summarized in [Table 9.8](#). Major control of the synthesis and secretion of thyroid hormones is via the hypothalamic-pituitary axis ([Fig. 9.19](#)). TRH is secreted by the hypothalamus and acts on the thyrotrophs of the anterior pituitary to cause

TABLE 9.8 Factors Affecting Thyroid Hormone Secretion

Stimulatory Factors	Inhibitory Factors
TSH	I^- deficiency
Thyroid-stimulating immunoglobulins	Deiodinase deficiency
Increased TBG levels (e.g., pregnancy)	Excessive I^- intake (Wolff-Chaikoff effect)
	Perchlorate, thiocyanate (inhibit Na^+I^- cotransport)
	Propylthiouracil (inhibits peroxidase enzyme)
	Decreased TBG levels (e.g., liver disease)

TBG, Thyroxine-binding globulin; TSH, thyroid-stimulating hormone.

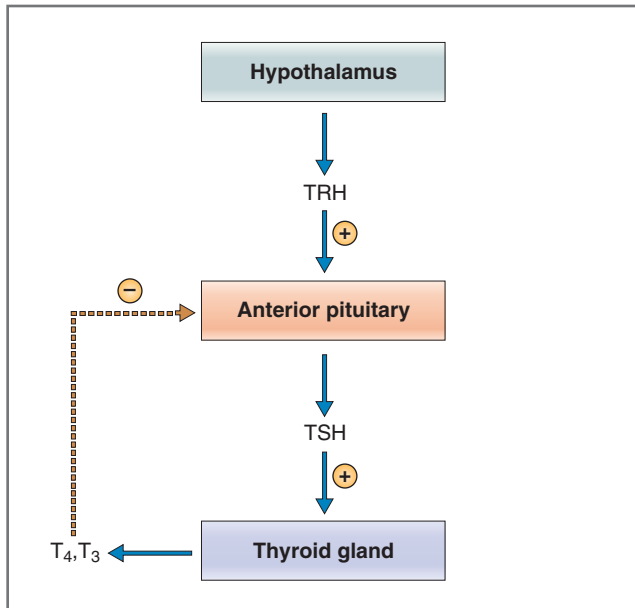


Fig. 9.19 Regulation of thyroid hormone secretion. T_3 , Triiodothyronine; T_4 , thyroxine; *TRH*, thyrotropin-releasing hormone; *TSH*, thyroid-stimulating hormone.

secretion of TSH. TSH then acts on the thyroid gland to stimulate the synthesis and secretion of thyroid hormones.

- ◆ **TRH**, a tripeptide, is secreted by the paraventricular nuclei of the hypothalamus. TRH then acts on the thyrotrophs of the anterior pituitary to stimulate both transcription of the *TSH* gene and secretion of TSH. (Recall that the other action of TRH is to stimulate the secretion of prolactin by the anterior pituitary.)
- ◆ **TSH**, a glycoprotein, is secreted by the anterior lobe of the pituitary in response to stimulation by TRH. The role of TSH is to regulate the growth of the thyroid gland (i.e., a trophic effect) and the secretion of thyroid hormones by influencing several steps in the biosynthetic pathway. The thyrotrophs of the anterior pituitary develop and begin secreting TSH at approximately gestational week 13, the same time that the fetal thyroid gland begins secreting thyroid hormones.

TSH secretion is regulated by two reciprocal factors. (1) TRH from the hypothalamus stimulates the secretion of TSH. (2) Thyroid hormones inhibit the secretion of TSH by down-regulating the TRH receptor on the thyrotrophs, thus decreasing their sensitivity to stimulation by TRH. This negative feedback effect of thyroid hormones is mediated by **free T_3** , which is possible because the anterior lobe contains thyroid deiodinase (converting T_4 to T_3). The reciprocal regulation of TSH secretion by TRH and negative feedback by free T_3 results in a

relatively steady rate of TSH secretion, which in turn produces a steady rate of secretion of thyroid hormones (in contrast to growth hormone secretion, whose secretion is pulsatile).

- ◆ The **actions of TSH on the thyroid gland** are initiated when TSH binds to a membrane receptor, which is coupled to adenylyl cyclase via a G_s protein. Activation of adenylyl cyclase generates **cAMP**, which serves as the second messenger for TSH. TSH has two types of actions on the thyroid gland. (1) It increases the synthesis and secretion of thyroid hormones by stimulating *every* step in the biosynthetic pathway: I^- uptake and oxidation, organification of I_2 into MIT and DIT, coupling of MIT and DIT to form T_4 and T_3 , endocytosis, and proteolysis of TG to release T_4 and T_3 for secretion. (2) TSH has a trophic effect on the thyroid gland. This trophic effect is exhibited when TSH levels are elevated for a sustained period of time and leads to hypertrophy and hyperplasia of thyroid follicular cells and increased thyroidal blood flow.
- ◆ The TSH receptor on the thyroid cells also is activated by **thyroid-stimulating immunoglobulins**, which are antibodies to the TSH receptor. Thyroid-stimulating immunoglobulins are components of the immunoglobulin G (IgG) fraction of plasma proteins. When these immunoglobulins bind to the TSH receptor, they produce the same response in thyroid cells as TSH: stimulation of thyroid hormone synthesis and secretion and hypertrophy and hyperplasia of the gland (i.e., hyperthyroidism). **Graves disease**, a common form of hyperthyroidism, is caused by increased circulating levels of thyroid-stimulating immunoglobulins. In this disorder, the thyroid gland is intensely stimulated by the antibodies, causing circulating levels of thyroid hormones to be increased. In Graves disease, TSH levels are actually lower than normal because the high-circulating levels of thyroid hormones inhibit TSH secretion by negative feedback.

Actions of Thyroid Hormones

Thyroid hormones act on virtually every organ system in the human body (Fig. 9.20): Thyroid hormones act synergistically with growth hormone and somatomedins to promote bone formation; they increase BMR, heat production, and oxygen consumption; and they alter the cardiovascular and respiratory systems to increase blood flow and oxygen delivery to the tissues.

The first step in the action of thyroid hormones in target tissues is **conversion of T_4 to T_3** by **5'-iodinase**. (Recall that T_4 is secreted in far greater amounts than T_3 , but it also is much less active.) In an alternate pathway, T_4 can be converted to rT_3 , which is

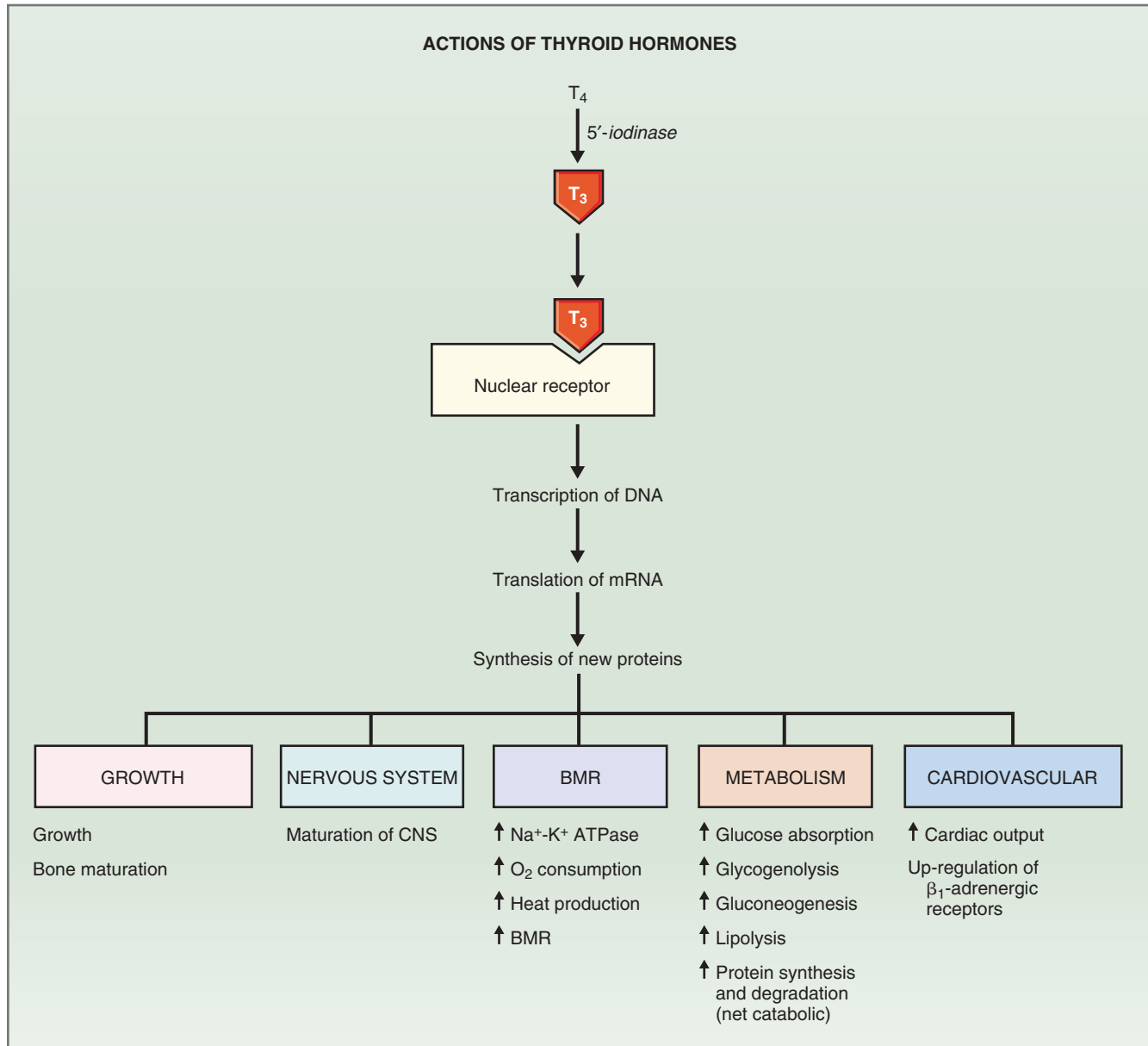


Fig. 9.20 Mechanism of action of thyroid hormones. Thyroxine (T_4) is converted to triiodothyronine (T_3) in target tissues. The actions of T_3 on several organ systems are shown. *BMR*, Basal metabolic rate; *CNS*, central nervous system; *DNA*, deoxyribonucleic acid; *mRNA*, messenger ribonucleic acid.

physiologically inactive. Normally, the tissues produce T_3 and rT_3 in approximately equal amounts (T_3 , 45% and rT_3 , 55%). However, under certain conditions the relative amounts may change. For example, pregnancy, fasting, stress, hepatic and renal failure, and β -adrenergic blocking agents all decrease the conversion of T_4 to T_3 (and increase conversion to rT_3), thus decreasing the amount of the active hormone. Obesity increases the conversion of T_4 to T_3 , increasing the amount of the active hormone.

Once T_3 is produced inside the target cells, it enters the nucleus and binds to a **nuclear receptor**. The T_3 -receptor complex then binds to a thyroid-regulatory

element on DNA, where it stimulates **DNA transcription**. The newly transcribed mRNAs are translated, and new proteins are synthesized. These new proteins are responsible for the multiple actions of thyroid hormones. Other T_3 receptors located in ribosomes and mitochondria mediate post-transcriptional and post-translational events.

A vast array of **new proteins** are synthesized under the direction of thyroid hormones, including $\text{Na}^+\text{-K}^+$ ATPase, transport proteins, β_1 -adrenergic receptors, lysosomal enzymes, proteolytic proteins, and structural proteins. The nature of the protein induced is specific to the target tissue. In most tissues, $\text{Na}^+\text{-K}^+$ ATPase

synthesis is induced, which leads to increased oxygen consumption, BMR, and heat production. In myocardial cells, myosin, β_1 -adrenergic receptors, and Ca^{2+} ATPase are induced, accounting for thyroid hormone-induced increases in heart rate and contractility. In liver and adipose tissue, key metabolic enzymes are induced, leading to alterations in carbohydrate, fat, and protein metabolism.

The effects of thyroid hormone (T_3) on various organ systems are as follows:

- ◆ **Basal metabolic rate (BMR).** One of the most significant and pronounced effects of thyroid hormone is **increased oxygen consumption** and a resulting increase in **BMR** and **body temperature**. Thyroid hormones increase oxygen consumption in all tissues *except brain, gonads, and spleen* by inducing the synthesis and increasing the activity of the **$\text{Na}^+\text{-K}^+$ ATPase**. The $\text{Na}^+\text{-K}^+$ ATPase is responsible for primary active transport of Na^+ and K^+ in all cells; this activity is highly correlated with and accounts for a large percentage of the total oxygen consumption and heat production in the body. Thus when thyroid hormones increase $\text{Na}^+\text{-K}^+$ ATPase activity, they also increase oxygen consumption, BMR, and heat production.
- ◆ **Metabolism.** Ultimately, increased oxygen consumption depends on increased availability of substrates for oxidative metabolism. Thyroid hormones increase glucose absorption from the gastrointestinal tract and potentiate the effects of other hormones (e.g., catecholamines, glucagon, growth hormone) on gluconeogenesis, lipolysis, and proteolysis. Thyroid hormones increase both protein synthesis and degradation, but overall their effect is *catabolic* (i.e., net degradation), which results in decreased muscle mass. These metabolic effects occur because thyroid hormones induce the synthesis of key metabolic enzymes including cytochrome oxidase, NADPH cytochrome C reductase, α -glycerophosphate dehydrogenase, malic enzyme, and several proteolytic enzymes.
- ◆ **Cardiovascular and respiratory.** Because thyroid hormones increase O_2 consumption, they create a higher demand for O_2 in the tissues. Increased O_2 delivery to the tissues is possible because thyroid hormones produce an increase in cardiac output and ventilation. The **increase in cardiac output** is the result of a combination of increased heart rate and increased stroke volume (increased contractility). These cardiac effects are explained by the fact that thyroid hormones induce the synthesis of (i.e., up-regulate) cardiac β_1 -adrenergic receptors. Recall that these β_1 receptors mediate the effects of the sympathetic nervous system to increase heart rate and contractility. Thus when thyroid hormone levels are high, the myocardium has an increased number of β_1 receptors and is more sensitive to stimulation by the sympathetic nervous system. (In complementary actions, thyroid hormones also induce the synthesis of cardiac myosin and sarcoplasmic reticulum Ca^{2+} ATPase.)
- ◆ **Growth.** Thyroid hormone is required for growth to adult stature. Thyroid hormones act synergistically with growth hormone and somatomedins to promote bone formation. Thyroid hormones promote ossification and fusion of bone plates and bone maturation. In hypothyroidism, bone age is less than chronologic age.
- ◆ **Central nervous system (CNS).** Thyroid hormones have multiple effects on the CNS, and the impact of these effects is age dependent. In the **perinatal period**, thyroid hormone is *essential for normal maturation of the CNS*. Hypothyroidism in the perinatal period causes irreversible mental retardation. For this reason, screening of newborns for hypothyroidism is mandated; if it is detected in the newborn, thyroid hormone replacement can reverse the CNS effects. In **adults**, hypothyroidism causes listlessness, slowed movement, somnolence, impaired memory, and decreased mental capacity. Hyperthyroidism causes hyperexcitability, hyperreflexia, and irritability.
- ◆ **Autonomic nervous system.** Thyroid hormones interact with the **sympathetic nervous system** in ways that are not fully understood. Many of the effects of thyroid hormones on BMR, heat production, heart rate, and stroke volume are similar to those produced by catecholamines via **β -adrenergic receptors**. The effects of thyroid hormones and catecholamines on heat production, cardiac output, lipolysis, and gluconeogenesis appear to be synergistic. The significance of this synergism is illustrated by the effectiveness of **β -adrenergic blocking agents** (e.g., propranolol) in treating many of the symptoms of hyperthyroidism.

Pathophysiology of Thyroid Hormone

The most common endocrine abnormalities are disturbances of thyroid hormones. The constellation of signs and symptoms produced by an excess or a deficiency of thyroid hormones is predictable on the basis of the hormones' physiologic actions. Thus disturbances of thyroid hormones will affect growth, CNS function, BMR and heat production, nutrient metabolism, and the cardiovascular system. The symptoms of hyperthyroidism and hypothyroidism, common etiologies, TSH levels, and treatments are summarized in [Table 9.9](#).

TABLE 9.9 Pathophysiology of Thyroid Hormones

	Hyperthyroidism	Hypothyroidism
Symptoms	Increased basal metabolic rate Weight loss Negative nitrogen balance Increased heat production Sweating Increased cardiac output Dyspnea (shortness of breath) Tremor, muscle weakness Exophthalmos Goiter	Decreased basal metabolic rate Weight gain Positive nitrogen balance Decreased heat production Cold sensitivity Decreased cardiac output Hypoventilation Lethargy, mental slowness Drooping eyelids Myxedema Growth retardation Mental retardation (perinatal) Goiter
Causes	Graves disease (increased thyroid-stimulating immunoglobulins) Thyroid neoplasm Excess TSH secretion Exogenous T ₃ or T ₄ (factitious)	Thyroiditis (autoimmune or Hashimoto thyroiditis) Surgery for hyperthyroidism I ⁻ deficiency Congenital (cretinism) Decreased TRH or TSH
TSH Levels	Decreased (feedback inhibition of T ₃ on the anterior lobe) Increased (if defect is in anterior pituitary)	Increased (by negative feedback if primary defect is in thyroid gland) Decreased (if defect is in hypothalamus or anterior pituitary)
Treatment	Propylthiouracil (inhibits peroxidase enzyme and thyroid hormone synthesis) Thyroidectomy ¹³¹ I ⁻ (destroys thyroid) β-Adrenergic blocking agents (adjunct therapy)	Thyroid hormone replacement therapy

TRH, Thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone.

Hyperthyroidism

The most common form of hyperthyroidism is **Graves disease**, an autoimmune disorder characterized by increased circulating levels of **thyroid-stimulating immunoglobulins**. These immunoglobulins are antibodies to TSH receptors on thyroid follicular cells. When present, the antibodies intensely stimulate the thyroid gland, resulting in increased secretion of thyroid hormones and hypertrophy of the gland. Other causes of hyperthyroidism are thyroid neoplasm, excessive secretion of TRH or TSH, and administration of excessive amounts of exogenous thyroid hormones.

The **diagnosis of hyperthyroidism** is based on symptoms and measurement of increased levels of T₃ and T₄. TSH levels may be decreased or increased, depending on the cause of the hyperthyroidism. If the *cause* of hyperthyroidism is Graves disease, thyroid neoplasm (i.e., the disorder is in the thyroid gland), or exogenous administration of thyroid hormones (factitious hyperthyroidism), then TSH levels will be decreased by negative feedback of the high levels of T₃ on the anterior pituitary. However, if the *cause* of hyperthyroidism is increased secretion of TRH or TSH

(i.e., the disorder is in the hypothalamus or anterior pituitary), then TSH levels will be increased.

The **symptoms of hyperthyroidism** are dramatic and include weight loss accompanied by increased food intake due to the increased metabolic rate; excessive heat production and sweating secondary to increased oxygen consumption; rapid heart rate due to up-regulation of β₁ receptors in the heart; breathlessness on exertion; and tremor, nervousness, and weakness due to the CNS effects of thyroid hormones. The increased activity of the thyroid gland causes it to enlarge, called **goiter**. The goiter may compress the esophagus and cause difficulty in swallowing.

Treatment of hyperthyroidism includes administration of drugs such as **propylthiouracil**, which inhibit the synthesis of thyroid hormones; surgical removal of the gland; or radioactive ablation of the thyroid gland with ¹³¹I⁻.

Hypothyroidism

The most common cause of hypothyroidism is **auto-immune destruction of the thyroid gland** (thyroiditis)

in which antibodies may either frankly destroy the gland or block thyroid hormone synthesis. Other causes of hypothyroidism are surgical removal of the thyroid as treatment for hyperthyroidism, hypothalamic or pituitary failure, and Γ deficiency. Rarely, hypothyroidism is the result of target tissue resistance caused by down-regulation of thyroid-hormone receptors.

The **diagnosis of hypothyroidism** is based on symptoms and a finding of decreased levels of T_3 and T_4 . Depending on the cause of the hypothyroidism, TSH levels may be increased or decreased. If the defect is in the thyroid gland (e.g., thyroiditis), TSH levels will be increased by negative feedback; the low circulating levels of T_3 stimulate TSH secretion. If the defect is in the hypothalamus or pituitary, then TSH levels will be decreased.

The **symptoms of hypothyroidism** are opposite those seen in hyperthyroidism and include decreased metabolic rate and weight gain without increased food intake; decreased heat production and cold intolerance; decreased heart rate; slowing of movement, slurred speech, slowed mental activity, lethargy, and somnolence; periorbital puffiness; constipation; hair loss; and menstrual dysfunction. In some cases, **myxedema** develops, in which there is increased filtration of fluid out of the capillaries and edema due to accumulation of osmotically active mucopolysaccharides in interstitial fluid. When the cause of hypothyroidism is a defect in the thyroid, a **goiter** develops from the unrelenting stimulation of the thyroid gland by the high circulating levels of TSH. Finally, and of critical importance, if hypothyroidism occurs in the **perinatal period** and is untreated, it results in an irreversible form of growth and mental retardation called **cretinism**.

Treatment of hypothyroidism involves thyroid hormone replacement therapy, usually T_4 . Like endogenous hormone, exogenous T_4 is converted to its active form, T_3 , in the target tissues.

Goiter

Goiter (i.e., enlarged thyroid) can be associated with certain causes of hyperthyroidism and also, perhaps surprisingly, with certain causes of hypothyroidism and euthyroidism. The terms hyperthyroid, hypothyroid, and euthyroid describe, respectively, the *clinical states* of excess thyroid hormone, deficiency of thyroid hormone, and normal levels of thyroid hormone. Thus they describe blood levels of thyroid hormone, *not* the size of the thyroid gland. The presence or absence of goiter can be understood only by analyzing the etiology of the various thyroid disorders. The central principle in understanding goiter is that high levels of TSH and substances that act like TSH (e.g., thyroid-stimulating immunoglobulins) have a trophic (growth) effect on the thyroid and cause it to enlarge.

- ◆ **Graves disease.** In Graves disease, the most common cause of hyperthyroidism, the high levels of thyroid-stimulating immunoglobulins drive excess secretion of T_4 and T_3 and also have a trophic effect on the thyroid gland to produce **goiter**. Although TSH levels are decreased (by negative feedback) in Graves disease, the trophic effect is due to the TSH-like effect of the immunoglobulins.
- ◆ **TSH-secreting tumor.** TSH-secreting tumors are an uncommon cause of hyperthyroidism. Increased levels of TSH drive the thyroid to secrete excess T_4 and T_3 and have a trophic effect on the thyroid gland to produce **goiter**.
- ◆ **Ingestion of T_4 .** Ingestion of exogenous thyroid hormones, or factitious hyperthyroidism, is associated with increased levels of thyroid hormone (from the ingestion), which causes decreased levels of TSH (by negative feedback). Because TSH levels are low there is **no goiter**; in fact, with time, the thyroid gland shrinks, or involutes.
- ◆ **Autoimmune thyroiditis.** Autoimmune thyroiditis is a common cause of hypothyroidism, in which thyroid hormone synthesis is impaired by antibodies to peroxidase, leading to decreased T_4 and T_3 secretion. TSH levels are increased (by negative feedback), and the resulting high levels of TSH have a trophic effect on the thyroid gland to produce **goiter**. That's right! The gland enlarges even though it is not effectively synthesizing thyroid hormones.
- ◆ **TSH deficiency (anterior pituitary failure).** TSH deficiency is an uncommon cause of hypothyroidism, where the decreased levels of TSH cause decreased thyroid hormone secretion and **no goiter**.
- ◆ **Γ deficiency.** Deficiency of Γ leads to transiently decreased synthesis of T_4 and T_3 , which increases TSH secretion by negative feedback. Increased TSH levels then have a trophic effect on the gland, causing **goiter**. The enlarged gland (which is otherwise normal) can often maintain normal blood levels of thyroid hormone (due to the high TSH levels); in that case, the person will be clinically euthyroid and asymptomatic. If the gland cannot maintain normal blood levels of thyroid hormone, then the person will be clinically hypothyroid.

ADRENAL MEDULLA AND CORTEX

The adrenal glands are located in the retroperitoneal cavity above each kidney. The adrenal glands are actually two separate glands, the adrenal medulla and the adrenal cortex, whose secretions are essential for life.

When corrected for weight, these glands receive among the highest blood flow of any organ in the body.

The **adrenal medulla**, which is in the inner zone of the gland, composes approximately 20% of the tissue. The adrenal medulla is of neuroectodermal origin and secretes the catecholamines epinephrine and norepinephrine (see Chapter 2).

The **adrenal cortex**, which is in the outer zone of the gland, is of mesodermal origin and has three distinct layers. It composes 80% of the adrenal tissue and secretes adrenocortical steroid hormones. The adrenal cortex differentiates by gestational week 8 and is responsible for the production of fetal adrenal steroids throughout intrauterine life (see Chapter 10). Soon after birth, the fetal adrenal cortex begins to involute, eventually disappears, and is replaced by the three-layered adult adrenal cortex.

Synthesis of Adrenocortical Steroid Hormones

The adrenal cortex secretes three classes of steroid hormones: glucocorticoids, mineralocorticoids, and androgens. Figure 9.21 shows the three layers of the adrenal cortex in relation to the adrenal medulla. The innermost zone of the cortex, called the **zona reticularis**, and the middle (and widest) zone, called the **zona fasciculata**, synthesize and secrete glucocorticoids and adrenal androgens. The outermost zone, called the **zona glomerulosa**, secretes mineralocorticoids.

Structures of Adrenocortical Steroids

The structures of the major adrenocortical steroids are shown in Figure 9.22, which should be used as a reference throughout this section. All of the steroids of the adrenal cortex are chemical modifications of a basic steroid nucleus, which is illustrated in the structure of **cholesterol**. The basic nucleus is a carbon skeleton, with carbons numbered from 1 through 21 and four labeled rings: A, B, C, and D. (Cholesterol is called, therefore, a 21-carbon steroid.) The **glucocorticoids**, represented by cortisol, have a ketone group at carbon 3 (C3) and hydroxyl groups at C11 and C21. The **mineralocorticoids**, represented by aldosterone, have a double-bond oxygen at C18. The **androgens**, represented in the adrenal cortex by dehydroepiandrosterone (DHEA) and androstenedione, have a double-bond oxygen at C17; androgens do not have the C20,21 side chain that is present in glucocorticoids and mineralocorticoids. Another androgen, testosterone (*not shown in Fig. 9.22*), is produced primarily in the testes. Estrogens (*not shown*), which are aromatized in the A ring and are lacking C19, are produced primarily in the ovaries.

In summary, cholesterol, progesterone, the glucocorticoids, and the mineralocorticoids are 21-carbon steroids; androgens are 19-carbon steroids; and estrogens (produced primarily in the ovaries) are 18-carbon steroids.

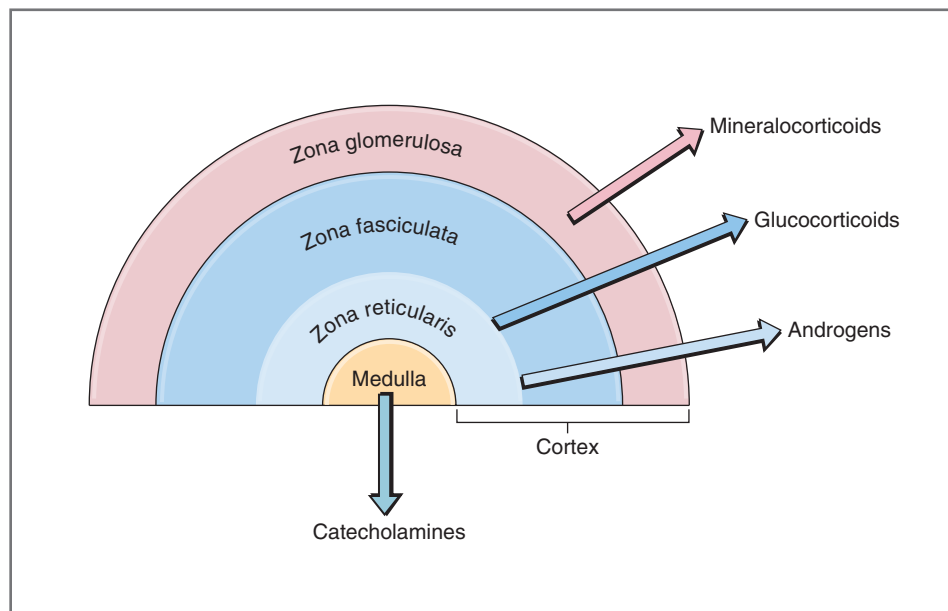


Fig. 9.21 Secretions of the adrenal medulla and adrenal cortex. The zonae fasciculata and reticularis secrete glucocorticoids and androgens; the zona glomerulosa secretes mineralocorticoids.

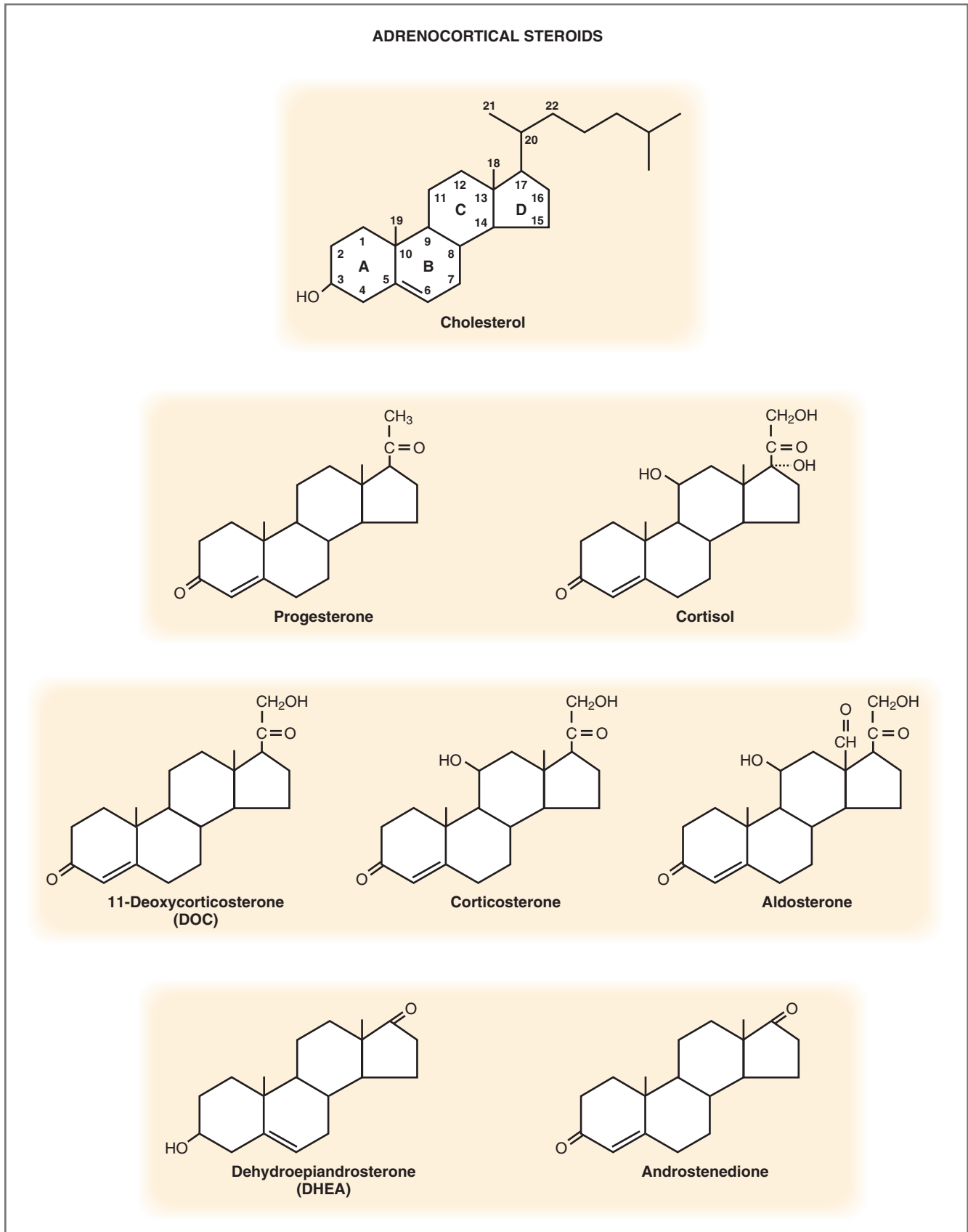


Fig. 9.22 Structures of adrenocortical steroids. In the structure of cholesterol, the four rings of the steroid molecules are labeled A, B, C, and D, and the carbon atoms are numbered.

Biosynthetic Pathways in the Adrenal Cortex

Figure 9.23 is a schematic diagram of the biosynthetic pathways of the adrenocortical steroids. As noted earlier, the layers of the adrenal cortex are specialized to synthesize and secrete particular steroid hormones: either glucocorticoids and androgens or mineralocorticoids. The *basis for this specialization* is the presence or absence of the enzymes that catalyze various modifications of the steroid nucleus. For example, the *zonae reticularis/fasciculata* produce androgenic ste-

roids because they contain 17,20-lyase; on the other hand, the *zona glomerulosa* produces aldosterone because it contains aldosterone synthase.

The precursor for all adrenocortical steroids is **cholesterol**. Most of the cholesterol is provided to the adrenal cortex via the circulation, and small amounts are synthesized *de novo* within the adrenal cortical cells. Cholesterol circulates bound to low-density lipoproteins. There are receptors for these lipoproteins in the membranes of adrenocortical cells; the lipoprotein-cholesterol complex binds and is transferred into the

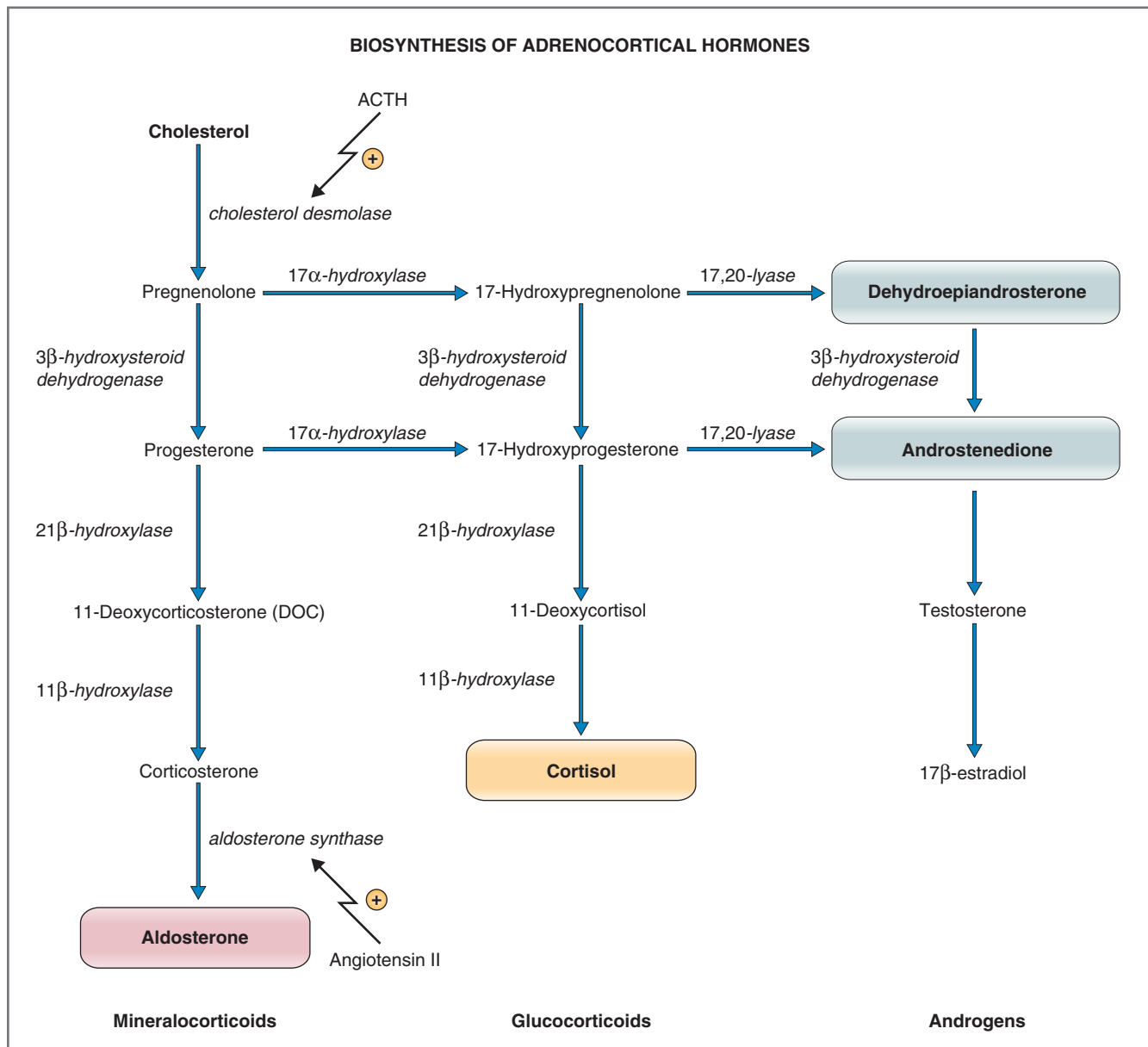


Fig. 9.23 Biosynthetic pathways for glucocorticoids, mineralocorticoids, and androgens in the adrenal cortex. The major secretory products of the adrenal cortex are shown in colored boxes. ACTH, Adrenocorticotrophic hormone.

cell by endocytosis. Inside the cells, cholesterol is esterified and stored in cytoplasmic vesicles until it is needed for synthesis of steroid hormones.

The enzymes catalyzing the conversion of cholesterol to active steroid hormones require **cytochrome P-450**, molecular oxygen, and NADPH, which serves as the hydrogen donor for the reducing steps. A flavo-protein enzyme called **adrenodoxin reductase** and an iron-containing protein called **adrenodoxin** are intermediates in the transfer of hydrogen from NADPH to the cytochrome P-450 enzymes.

For purposes of illustration, all of the biosynthetic pathways in the adrenal cortex are shown in [Figure 9.23](#). Remember, however, that not all layers of the cortex contain all of the steps in the pathway: Each layer has that portion of the pathway necessary to produce its primary hormones (i.e., glucocorticoids and androgens or mineralocorticoids).

The first step in each pathway is catalyzed by **cholesterol desmolase**. In this step, the long side chain of cholesterol is removed (i.e., side-chain cleavage) and cholesterol is converted to pregnenolone. Thus all layers of the adrenal cortex contain cholesterol desmolase. Cholesterol desmolase is the rate-limiting enzyme in the pathway, and it is stimulated by **ACTH** (see further discussion concerning regulation of cortisol secretion). Follow the pathways for the synthesis of cortisol, aldosterone, and DHEA and androstenedione:

◆ **Glucocorticoids (cortisol).** The major glucocorticoid produced in humans is **cortisol** (hydrocortisone), which is synthesized in the **zonae fasciculata/reticularis**. Thus the zona fasciculata contains all of the enzymes required to convert cholesterol to cortisol: cholesterol desmolase, which converts cholesterol to pregnenolone; 17α -hydroxylase, which hydroxylates pregnenolone to form 17-hydroxypregnenolone; 3β -hydroxysteroid dehydrogenase, which converts 17-hydroxypregnenolone to 17-hydroxyprogesterone; and 21β -hydroxylase and 11β -hydroxylase, which hydroxylate at C11 and C21 to produce the final product, cortisol. Interestingly, some steps in the cortisol biosynthetic pathway can occur in a different order; for example, hydroxylation at C17 can occur before or after the action of 3β -hydroxysteroid dehydrogenase.

Cortisol is not the only steroid in the pathway with glucocorticoid activity; **corticosterone** is also a glucocorticoid. For example, if the 17α -hydroxylase step is blocked, the zona fasciculata still can produce corticosterone without deleterious effect. Thus cortisol is not absolutely necessary to sustain life as long as corticosterone is being synthesized. Blocks at the cholesterol desmolase, 3β -hydroxysteroid dehydrogenase, 21β -hydroxylase, or 11β -hydroxylase steps

are devastating because they prevent the production of cortisol *and* corticosterone; in these cases, death will ensue without appropriate hormone replacement therapy.

Metyrapone and ketoconazole are drugs that inhibit glucocorticoid biosynthesis. **Metyrapone** inhibits 11β -hydroxylase, the last step in cortisol synthesis. **Ketoconazole** inhibits several steps in the pathway including cholesterol desmolase, the first step.

◆ **Adrenal androgens (DHEA and androstenedione).** DHEA and androstenedione are androgenic steroids produced by the **zonae fasciculata/reticularis**. These compounds have weak androgenic activity, but in the testes they are converted to testosterone, a more potent androgen. The precursors for the adrenal androgens are 17-hydroxypregnenolone and 17-hydroxyprogesterone, which are converted to androgens by removal of the C20,21 side chain. In males, adrenal androgens are of little significance; the testes produce their own testosterone from cholesterol and do not require the adrenal precursors (see Chapter 10). In females, however, the adrenal cortex is the major source of androgenic compounds.

Adrenal androgens have a ketone group at C17 that distinguishes them from cortisol, aldosterone, and testosterone. (Cortisol and aldosterone have side chains at C17. Testosterone has a hydroxyl group at C17.) Thus the major adrenal androgens are called **17-ketosteroids**, which can be measured in the urine.

The zona fasciculata/reticularis also produce small amounts of testosterone and 17β -estradiol, although the major sources for these hormones are the testes and ovaries, respectively (see Chapter 10).

◆ **Mineralocorticoids (aldosterone).** The major mineralocorticoid in the body is **aldosterone**, which is synthesized only in the **zona glomerulosa**. The steps required to convert cholesterol to corticosterone are identical to those in the zona fasciculata, and the addition of **aldosterone synthase** in the zona glomerulosa converts corticosterone to aldosterone. The zona glomerulosa *does not* produce glucocorticoids for two reasons: (1) Corticosterone, a glucocorticoid, is converted to aldosterone because this zone contains aldosterone synthase, and (2) the zona glomerulosa lacks 17α -hydroxylase and therefore is unable to produce cortisol from progesterone.

Aldosterone is not the only steroid with mineralocorticoid activity; **11-deoxycorticosterone (DOC)** and **corticosterone** also have mineralocorticoid activity. Thus if the mineralocorticoid pathway is blocked *below the level of DOC* (e.g., absence of

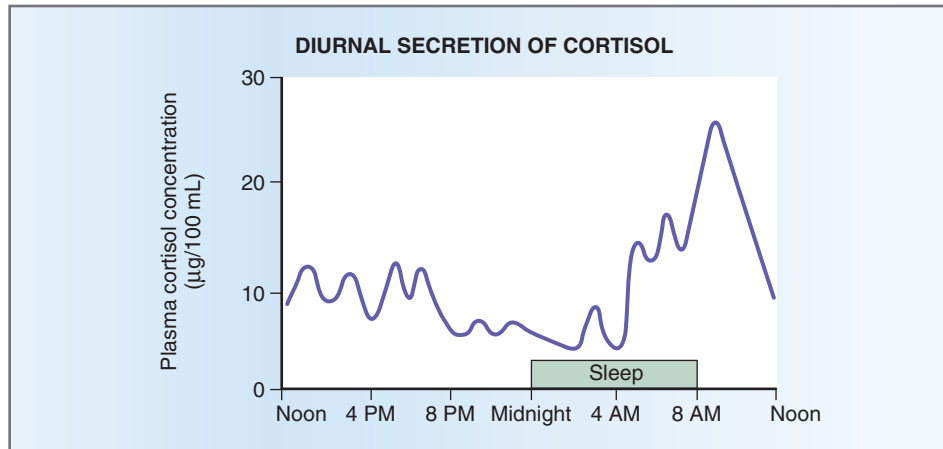


Fig. 9.24 Diurnal pattern of cortisol secretion.

11 β -hydroxylase or aldosterone synthase), mineralocorticoids will continue to be produced. However, if the pathway is blocked *above the level of DOC* (e.g., absence of 21 β -hydroxylase), then no mineralocorticoids will be produced.

Regulation of Secretion of Adrenocortical Steroids

As discussed previously, the synthesis and secretion of steroid hormones by the adrenal cortex depend on the stimulation of cholesterol desmolase (the first step) by **ACTH**. In the absence of ACTH, biosynthesis of adrenocortical steroid hormones ceases. Two questions arise, therefore: *What regulates the secretion of ACTH? What special regulatory factors control the functions of the zonae reticularis, fasciculata, and glomerulosa?*

- ◆ The **zonae fasciculata/reticularis**, which secrete glucocorticoids and androgens, are under the exclusive control of the hypothalamic-pituitary axis. The hypothalamic hormone is corticotropin-releasing hormone (CRH), and the anterior pituitary hormone is ACTH.
- ◆ The **zona glomerulosa**, which secretes mineralocorticoids, depends on ACTH for the first step in steroid biosynthesis, but otherwise it is controlled separately via the renin-angiotensin-aldosterone system.

Control of the zonae fasciculata and reticularis will be discussed together, and control of the zona glomerulosa will be discussed separately.

Regulation of Glucocorticoid and Adrenal Androgen Secretion

An impressive feature of the regulation of cortisol secretion is its **pulsatile** nature and its **diurnal** (daily) pattern (Fig. 9.24). The daily profile of blood cortisol levels is characterized by an average of 10 secretory

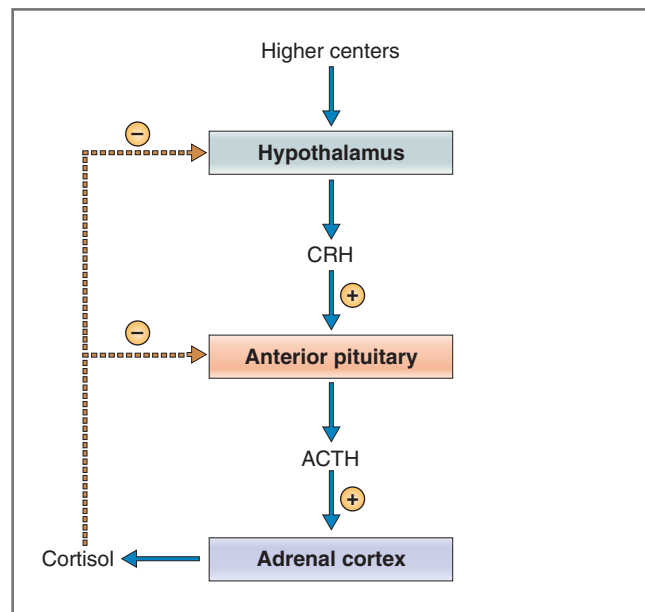


Fig. 9.25 Regulation of cortisol secretion. ACTH, Adrenocorticotrophic hormone; CRH, corticotropin-releasing hormone.

bursts during a 24-hour period. The lowest secretory rates occur during the evening hours and just after falling asleep (e.g., midnight), and the highest secretory rates occur just before awakening in the morning (e.g., 8 AM). The major burst of cortisol secretion before awakening accounts for one-half of the total daily cortisol secretion. Other adrenal steroids (e.g., adrenal androgens) are secreted in similar bursting diurnal patterns. ACTH secretion also exhibits the same diurnal pattern; in fact, it is the pattern of ACTH secretion that drives the diurnal pattern of steroid hormone secretion.

The secretion of glucocorticoids by the zonae fasciculata/reticularis is regulated exclusively by the **hypothalamic-pituitary axis** (Fig. 9.25). CRH is secreted by the hypothalamus and acts on the corticotrophs of

the anterior pituitary to cause secretion of ACTH. In turn, ACTH acts on the cells of the adrenal cortex to stimulate the synthesis and secretion of adrenocortical hormones.

- ◆ **CRH** is a polypeptide containing 41 amino acids. It is secreted by cells of the paraventricular nuclei of the hypothalamus. Like other hypothalamic hormones that act on the anterior pituitary, CRH travels to the pituitary in the hypothalamic-hypophysial portal blood. In the anterior lobe, it acts on the corticotrophs by an adenyl cyclase/cAMP mechanism to cause secretion of ACTH into the bloodstream.
- ◆ **ACTH**, the anterior pituitary hormone, has several effects on the adrenal cortex. The immediate effects of ACTH are to stimulate transfer of stored cholesterol to the mitochondria, to stimulate binding of cholesterol to cytochrome P-450, and to activate cholesterol desmolase. Long-term effects of ACTH include stimulation of transcription of the genes for cytochrome P-450 and adrenodoxin and up-regulation of ACTH receptors. Chronic effects of elevated ACTH levels include hypertrophy and hyperplasia of the adrenal cortical cells, mediated by local growth factors (e.g., IGF-2).

As noted, ACTH has a **pulsatile** and **diurnal** secretory pattern that drives a parallel pattern of cortisol secretion. The nocturnal peak of ACTH (i.e., preceding awakening) is driven, in turn, by a burst of CRH secretion. The “internal clock” that drives the diurnal pattern can be shifted by alternating the sleep-wake cycle (e.g., varying the time of going to sleep and awakening). The diurnal pattern is abolished by coma, blindness, or constant exposure to either light or dark.

- ◆ **Negative feedback** is exerted by cortisol at three points in the hypothalamic-pituitary axis. (1) Cortisol directly inhibits secretion of CRH from the hypothalamus. (2) Cortisol indirectly inhibits CRH secretion by effects on hippocampal neurons, which synapse on the hypothalamus. (3) Cortisol inhibits the action of CRH on the anterior pituitary, resulting in inhibition of ACTH secretion. Thus chronic *deficiency* of cortisol leads to stimulation of the CRH-ACTH axis and to increased ACTH levels; chronic *excess* of cortisol leads to inhibition (suppression) of the CRH-ACTH axis and decreased ACTH levels.
- ◆ The **dexamethasone suppression test** is based on the negative feedback effects of cortisol on the CRH-ACTH axis. Dexamethasone is a synthetic glucocorticoid that has all of the actions of cortisol including the negative feedback effect on ACTH secretion. When a low dose of dexamethasone is given to a **healthy person**, it inhibits (or “suppresses”) ACTH secretion, just as cortisol, the natural glucocorticoid,

does. The decreased level of ACTH then causes decreased cortisol secretion, which is measured in the test. The major use of the dexamethasone suppression test is in persons with **hypercortisolism** (high levels of cortisol). The test is used to determine whether the hypercortisolism is due to an ACTH-secreting tumor or a cortisol-secreting tumor of the adrenal cortex. If the cause of hypercortisolism is an **ACTH-secreting tumor** of the anterior pituitary, a low dose of dexamethasone does not suppress cortisol secretion but a high dose of dexamethasone does. (The tumor’s ACTH secretion is less sensitive to negative feedback by glucocorticoids than is normal anterior pituitary tissue.) If the cause of hypercortisolism is an **adrenal cortical tumor**, then neither low-dose nor high-dose dexamethasone suppresses cortisol secretion. (The tumor’s secretion of cortisol is autonomous and is not affected by changes in the ACTH level.)

In addition to negative feedback control by the CRH-ACTH axis, other factors alter ACTH and cortisol secretion (Table 9.10). Many of these factors alter ACTH secretion via effects of higher brain centers on the hypothalamus.

Regulation of Aldosterone Secretion

The regulation of aldosterone secretion by the zona glomerulosa is different from the regulation of the secretion of cortisol and adrenal androgens. Naturally, ACTH remains essential in this process because it stimulates cholesterol desmolase, the first step in the biosynthetic pathway. (Thus ACTH has a tonic effect on aldosterone secretion.) Like the other adrenal steroid hormones, aldosterone exhibits a diurnal pattern, with the lowest levels occurring at midnight and the highest levels occurring just before awakening. However, the primary regulation of aldosterone secretion occurs not by ACTH but through changes in ECF volume via the renin-angiotensin II-aldosterone system and through changes in serum potassium (K^+) levels.

TABLE 9.10 Factors Affecting ACTH Secretion

Stimulatory Factors	Inhibitory Factors
Decreased blood cortisol levels	Increased blood cortisol levels
Sleep-wake transition	Opioids
Stress; hypoglycemia; surgery; trauma	Somatostatin
Psychiatric disturbances	
ADH	
α -Adrenergic agonists	
β -Adrenergic antagonists	
Serotonin	

ADH, Antidiuretic hormone.

◆ **Renin–angiotensin II–aldosterone.** The major control of aldosterone secretion is via the renin–angiotensin II–aldosterone system. The mediator of this regulation is **angiotensin II**, which increases the synthesis and secretion of aldosterone by stimulating cholesterol desmolase and aldosterone synthase, the first and last steps in the pathway (see Fig. 9.23). In the zona glomerulosa, angiotensin II binds to AT₁ receptors that are coupled to phospholipase C via a G_q protein. Thus the second messengers for the action of angiotensin II are IP₃/Ca²⁺.

Regulation of the renin–angiotensin II–aldosterone axis is described in Chapter 4. Briefly, a decrease in ECF volume (e.g., due to hemorrhage or Na⁺ depletion) causes a decrease in renal perfusion pressure, which increases renin secretion by the juxtaglomerular cells of the kidney. **Renin**, an enzyme, catalyzes the conversion of angiotensinogen to angiotensin I, which is inactive. **Angiotensin-converting enzyme (ACE)** catalyzes the conversion of angiotensin I to **angiotensin II**, which then acts on the zona glomerulosa to stimulate **aldosterone** synthesis.

In light of the role that aldosterone plays in maintaining ECF volume, the control of aldosterone secretion by the renin–angiotensin II–aldosterone system is logical. For example, decreases in ECF volume stimulate aldosterone secretion, and aldosterone stimulates Na⁺ reabsorption by the kidney to help restore ECF Na⁺ content and ECF volume.

◆ **Serum K⁺ concentration.** The other factor that controls aldosterone secretion is the serum K⁺ concentration. Increases in serum K⁺ concentration increase aldosterone secretion, and decreases in serum K⁺ concentration decrease aldosterone secretion. For example, an increase in serum K⁺ concentration acts on adrenal cells by depolarizing them and opening voltage-sensitive Ca²⁺ channels. When Ca²⁺ channels open, intracellular Ca²⁺ concentration increases

and stimulates aldosterone secretion. In light of the major role that aldosterone plays in maintaining K⁺ balance, the control of aldosterone secretion by serum K⁺ concentration also is logical. For example, increases in serum K⁺ stimulate aldosterone secretion, and aldosterone increases K⁺ secretion by the kidney, thereby decreasing serum K⁺ concentration toward normal.

Actions of Adrenocortical Steroids

Adrenocortical steroids have diverse actions, and the actions are classified as glucocorticoid (cortisol), mineralocorticoid (aldosterone), or androgenic (DHEA and androstenedione). As steroid hormones, these actions first require transcription of DNA, synthesis of specific mRNAs, and induction of new protein synthesis. These new proteins confer specificity to the steroid hormone actions in target tissues (Table 9.11).

Actions of Glucocorticoids

Glucocorticoids are essential for life. If the adrenal cortex is removed or is not functioning, exogenous glucocorticoids must be administered or death will ensue. The actions of glucocorticoids (e.g., cortisol) are essential for gluconeogenesis, vascular responsiveness to catecholamines, suppression of inflammatory and immune responses, and modulation of CNS function.

◆ **Stimulation of gluconeogenesis.** A major action of cortisol is to promote gluconeogenesis and storage of glycogen. Overall, the effects of cortisol are **catabolic** and **diabetogenic**. Cortisol affects protein, fat, and carbohydrate metabolism in a coordinated fashion to increase glucose synthesis as follows: Cortisol increases protein catabolism in muscle and decreases new protein synthesis, thereby providing additional amino acids to the liver for gluconeogenesis. Cortisol increases lipolysis, which provides additional

TABLE 9.11 Actions of Adrenocortical Steroids

Actions of Glucocorticoids	Actions of Mineralocorticoids	Actions of Adrenal Androgens
Increase gluconeogenesis	Increase Na ⁺ reabsorption	Females: stimulate growth of pubic and axillary hair; stimulate libido
Increase proteolysis (catabolic)	Increase K ⁺ secretion	Males: same as testosterone
Increase lipolysis	Increase H ⁺ secretion	
Decrease glucose utilization		
Decrease insulin sensitivity		
Inhibit inflammatory response		
Suppress immune response		
Enhance vascular responsiveness to catecholamines		
Inhibit bone formation		
Increase GFR		
Decrease REM sleep		

GFR, Glomerular filtration rate; REM, rapid eye movement.

glycerol to the liver for gluconeogenesis. Finally, cortisol decreases glucose utilization by tissues and decreases the insulin sensitivity of adipose tissue. Glucocorticoids are essential for **survival during fasting** because they stimulate these gluconeogenic routes. In hypocortisolism (e.g., primary adrenal insufficiency, Addison disease), there is hypoglycemia. In hypercortisolism (e.g., Cushing syndrome), there is hyperglycemia.

- ◆ **Anti-inflammatory effects.** Cortisol has three actions that interfere with the body's inflammatory response to trauma and irritants. (1) Cortisol induces the synthesis of **lipocortin**, an inhibitor of the enzyme phospholipase A₂. Phospholipase A₂ liberates arachidonic acid from membrane phospholipids and provides the precursor for the prostaglandins and leukotrienes that mediate the inflammatory response. Therefore this component of the anti-inflammatory effect of cortisol is based on inhibiting the synthesis of the precursor to prostaglandins and leukotrienes. (2) Cortisol inhibits the production of **interleukin-2 (IL-2)** and the proliferation of T lymphocytes. (3) Cortisol inhibits the release of **histamine** and **serotonin** from mast cells and platelets.
- ◆ **Suppression of immune response.** As previously noted, cortisol inhibits the production of IL-2 and the proliferation of T lymphocytes, which also are critical for cellular immunity. Exogenous glucocorticoids can be administered therapeutically to suppress the immune response and prevent the rejection of transplanted organs.
- ◆ **Maintenance of vascular responsiveness to catecholamines.** Cortisol is necessary for the maintenance of normal blood pressure and plays a permissive role in the arterioles by up-regulating α_1 -adrenergic receptors. In this way, cortisol is required for the vasoconstrictive response of the arterioles to catecholamines. In hypocortisolism, there is hypotension; in hypercortisolism, there is hypertension.
- ◆ **Inhibition of bone formation.** Cortisol inhibits bone formation by decreasing the synthesis of type I collagen, the major component of bone matrix; by decreasing formation of new bone by osteoblasts; and by decreasing intestinal Ca²⁺ absorption.
- ◆ **Increases in glomerular filtration rate (GFR).** Cortisol increases GFR by causing vasodilation of afferent arterioles, thereby increasing renal blood flow and GFR.
- ◆ **Effects on CNS.** Glucocorticoid receptors are found in the brain, particularly in the limbic system. Cortisol decreases REM sleep, increases slow-wave sleep, and increases awake time. (Recall that the

largest bursts of ACTH and cortisol occur just before awakening.)

Actions of Mineralocorticoids

The actions of mineralocorticoids (e.g., aldosterone) are described in detail in Chapter 6. Briefly, aldosterone has three actions on the late distal tubule and collecting ducts of the kidney: It increases **Na⁺ reabsorption**, it increases **K⁺ secretion**, and it increases **H⁺ secretion**. Its effects on Na⁺ reabsorption and K⁺ secretion are on the principal cells, and its effect on H⁺ secretion is on the α -intercalated cells. Thus when aldosterone levels are increased (e.g., due to an aldosterone-secreting tumor), Na⁺ reabsorption, K⁺ secretion, and H⁺ secretion all are increased. These changes in renal transport result in ECF volume expansion and hypertension, hypokalemia, and metabolic alkalosis. Conversely, when aldosterone levels are decreased (e.g., due to adrenal insufficiency), Na⁺ reabsorption, K⁺ secretion, and H⁺ secretion all are decreased. These changes produce ECF volume contraction and hypotension, hyperkalemia, and metabolic acidosis.

An interesting “problem” arises with respect to the actions of mineralocorticoids in their target tissues (i.e., late distal tubule and collecting ducts of the kidney). That is, the affinity of mineralocorticoid receptors for cortisol is, surprisingly, just as high as their affinity for aldosterone. Because circulating levels of cortisol are much higher than circulating levels of aldosterone, it seems that cortisol would overwhelm and dominate the mineralocorticoid receptors. How would the kidneys know that a change in aldosterone concentration had occurred and that mineralocorticoid actions are desired? The “problem” is solved by the renal cells themselves. They contain the enzyme **11 β -hydroxysteroid dehydrogenase**, which converts cortisol to cortisone; in contrast to cortisol, cortisone has a low affinity for mineralocorticoid receptors. In this way, cortisol is effectively inactivated in mineralocorticoid target tissues. This unique solution allows changes in blood levels of aldosterone to be “seen” by the renal cells and not be overshadowed by the high-circulating levels of cortisol. This inactivation of cortisol in mineralocorticoid target tissues also explains why, when circulating levels of cortisol are high, the cortisol has only weak mineralocorticoid activity (despite its high affinity for mineralocorticoid receptors).

Actions of Adrenal Androgens

The adrenal cortex produces the androgenic compounds, DHEA and androstenedione, which are converted to testosterone primarily in the testes. In males, adrenal androgens play only a minor role because de novo synthesis of testosterone from cholesterol in the testes is much greater than testosterone synthesis from adrenal androgenic precursors. In females, however,

adrenal androgens are the *major* androgens, and they are responsible for the development of pubic and axillary hair and for libido.

In conditions such as **adrenogenital syndrome**, in which there is increased synthesis of adrenal androgens, the high levels of DHEA and androstenedione lead to masculinization in females, early development of axillary and pubic hair, and suppression of gonadal function in both males and females. Also, in the adrenogenital syndromes, due to the overproduction of adrenal androgens, there will be increased urinary levels of **17-ketosteroids**.

Pathophysiology of the Adrenal Cortex

Disorders involving the adrenal cortex are characterized by either an excess or a deficiency of adrenocortical hormones. When evaluating the pathophysiology of these disorders, it is helpful to consider the following issues:

1. What are the symptoms and signs? Are the signs and symptoms consistent with an excess or a deficiency of one or more of the adrenocortical hormones? The normal physiologic effects of each of the adrenocortical hormones can be used to predict the effects of hormonal excess or deficiency (see [Table 9.11](#)). A few examples are cited here.

Cortisol promotes gluconeogenesis, and therefore, excess levels of cortisol will produce hyperglycemia; deficits of cortisol will produce hypoglycemia upon fasting. **Aldosterone** causes increased K^+ secretion by the renal principal cells; thus excess aldosterone will cause increased K^+ secretion and hypokalemia, and deficiency of aldosterone will cause decreased K^+ secretion and hyperkalemia. Aldosterone also causes increased Na^+ reabsorption by the principal cells; thus excess aldosterone causes ECF volume expansion and hypertension, and deficiency of aldosterone causes ECF volume contraction and hypotension. Because **adrenal androgens** have testosterone-like effects, overproduction causes masculinization in females (e.g., hirsutism); deficits of adrenal androgens result in loss of pubic and axillary hair and decreased libido in females.

2. *What is the etiology of the disorder?* Disorders of the adrenal cortex can be caused by a primary defect in the adrenal cortex or by a primary defect in the hypothalamic-pituitary axis. Or, in the case of aldosterone, the defect may be in the renin-angiotensin II axis. For example, symptoms consistent with overproduction of an adrenocortical hormone (e.g., hypercortisolism) may be caused by a primary defect in the adrenal cortex. Or, the symptoms may be caused by a primary defect in the anterior pituitary or the hypothalamus, which then produces a

secondary effect on the adrenal cortex. The etiology of the disorder may not be deduced until circulating levels of CRH and ACTH are measured and the feedback regulation of the CRH-ACTH axis is evaluated.

For disorders caused by enzyme deficiencies in the steroid hormone biosynthetic pathway, the pathways can be visualized to predict the effects of a given enzyme block (see [Fig. 9.23](#)). For example, a woman with masculinization also has symptoms consistent with aldosterone deficiency (e.g., hyperkalemia) and cortisol deficiency (e.g., hypoglycemia). This constellation of symptoms suggests that there is an enzyme block preventing the synthesis of all mineralocorticoids and all glucocorticoids (e.g., deficiency of 21β -hydroxylase). Because of the block, steroid intermediates are “shunted” toward androgen production and the increased adrenal androgen levels cause masculinization. To understand the pathophysiology of the adrenal cortex, use the biosynthetic pathway shown in [Figure 9.23](#) in combination with the actions of the steroid hormones summarized in [Table 9.11](#). The features of each disorder are summarized in [Table 9.12](#).

Addison Disease

Addison disease, or **primary adrenocortical insufficiency**, is commonly caused by autoimmune destruction of all zones of the adrenal cortex ([Box 9.2](#)). In this disease, there is decreased synthesis of all adrenocortical hormones, resulting in decreased circulating levels of cortisol, aldosterone, and adrenal androgens. The symptoms of Addison disease can be predicted on the basis of the known physiologic effects of these hormones. The loss of glucocorticoids (cortisol) produces hypoglycemia, anorexia, weight loss, nausea and vomiting, and weakness. The loss of mineralocorticoids (aldosterone) produces hyperkalemia, metabolic acidosis, and hypotension (due to decreased ECF volume). In women, the loss of the adrenal androgens, DHEA and androstenedione, results in decreased pubic and axillary hair and decreased libido.

Addison disease also is characterized by **hyperpigmentation** of the skin, particularly of the elbows, knees, nail beds, nipples, and areolae and on recent scars. Hyperpigmentation is a result of **increased levels of ACTH** (which contains the α -MSH fragment). Hyperpigmentation therefore provides an important clue about the etiology of Addison disease: ACTH levels must be high, not low, and the cause of the hypocortisolism must *not* be a primary defect in ACTH secretion from the anterior pituitary. Rather, the hypocortisolism of Addison disease must be due to a primary defect in the adrenal cortex itself (i.e., primary adrenal insufficiency), with low levels of cortisol then causing an

TABLE 9.12 Pathophysiology of the Adrenal Cortex

Disease	Clinical Features	ACTH Levels	Treatment
Addison Disease (Primary Adrenocortical Insufficiency)	Hypoglycemia Anorexia, weight loss, nausea, vomiting Weakness Hypotension Hyperkalemia Metabolic acidosis Decreased pubic and axillary hair in females Hyperpigmentation	Increased (negative feedback effect of decreased cortisol)	Replacement of glucocorticoids and mineralocorticoids
Cushing Syndrome (e.g., Primary Adrenal Hyperplasia)	Hyperglycemia Muscle wasting Central obesity Round face, supraclavicular fat, buffalo hump Osteoporosis Striae Virilization and menstrual disorders in females Hypertension	Decreased (negative feedback effect of increased cortisol)	Ketoconazole Metyrapone
Cushing Disease (Excess ACTH)	Same as Cushing syndrome (see earlier)	Increased	Surgical removal of ACTH-secreting tumor
Conn Syndrome (Aldosterone-Secreting Tumor)	Hypertension Hypokalemia Metabolic alkalosis Decreased renin levels	—	Aldosterone antagonist (e.g., spironolactone) Surgery
21β-Hydroxylase Deficiency	Virilization in females Early acceleration of linear growth Early appearance of pubic and axillary hair Symptoms of deficiency of glucocorticoids and mineralocorticoids	Increased (negative feedback effect of decreased cortisol)	Replacement of glucocorticoids and mineralocorticoids
17α-Hydroxylase Deficiency	Lack of pubic and axillary hair in females Symptoms of deficiency of glucocorticoids Symptoms of excess mineralocorticoids	Increased (negative feedback effect of decreased cortisol)	Replacement of glucocorticoids Aldosterone antagonist (e.g., spironolactone)

ACTH, Adrenocorticotropic hormone.

increase in ACTH secretion by negative feedback (see Fig. 9.25).

Treatment of Addison disease includes glucocorticoid and mineralocorticoid replacement.

Secondary Adrenocortical Insufficiency

Conditions of secondary adrenocortical insufficiency occur when there is insufficient CRH (uncommon) or insufficient ACTH (resulting from failure of corticotrophs in the anterior pituitary to secrete ACTH). In either case, there is decreased ACTH, which then

decreases cortisol secretion by the adrenal cortex. The cortisol deficiency then produces many of the symptoms that occur in primary adrenocortical insufficiency (e.g., hypoglycemia). There are, however, several distinctions between primary and secondary adrenocortical insufficiency. (1) In secondary adrenocortical insufficiency, ACTH levels are low, not high. (2) In secondary adrenocortical insufficiency, aldosterone levels usually are normal because aldosterone synthesis by the zona glomerulosa requires only tonic levels of ACTH. If aldosterone levels are normal, hyperkalemia,

BOX 9.2 Clinical Physiology: Addison Disease

DESCRIPTION OF CASE. A 45-year-old woman is admitted to the hospital with a history of progressive weakness and weight loss, occasional nausea, and darkening skin pigmentation. On physical examination, she is thin, has dark skin creases, and has diminished axillary and pubic hair. Her blood pressure is 120/80 when supine and 106/50 when standing. Her pulse rate is 100/minute when supine and 120/minute when standing. Laboratory studies yield the following values:

Serum	Urine
[Na ⁺], 120 mEq/L	Na ⁺ , increased
[K ⁺], 5.8 mEq/L	K ⁺ , decreased
[HCO ₃ ⁻], 120 mEq/L	pH, increased
Osmolarity, 254 mOsm/L	Osmolarity, 450 mOsm/L

Arterial blood gases are consistent with metabolic acidosis. Blood urea nitrogen (BUN) and serum creatinine are increased. Her blood glucose concentration is low-normal, and she becomes hypoglycemic upon fasting. Serum levels of ACTH are elevated. An ACTH stimulation test shows a “flat” cortisol response (i.e., the adrenal cortex *did not* respond to ACTH).

The woman is treated with cortisol, taken twice daily, early morning and late afternoon, and fludrocortisone, a synthetic mineralocorticoid.

EXPLANATION OF CASE. The woman has primary adrenocortical insufficiency (Addison disease), in which all layers of the adrenal cortex are destroyed. None of the adrenocortical hormones, glucocorticoids, mineralocorticoids, and adrenal androgens are secreted in adequate amounts. Decreased blood levels of cortisol, via negative feedback mechanisms, then cause increased secretion of ACTH by the anterior lobe of the pituitary. The woman’s abnormal serum and urine values, orthostatic hypotension, hypoglycemia, decreased body hair, and hyperpigmentation can be explained by decreased circulating levels of adrenocortical steroids as follows:

The woman has increased serum [K⁺] (hyperkalemia) and metabolic acidosis. Simultaneously, urinary excretion of K⁺ is decreased, and urine pH is increased. These disturbances of K⁺ and acid-base balance are caused by the loss of the adrenocortical hormone aldosterone. Normally, aldosterone stimulates K⁺ and H⁺ secretion in the renal distal tubule and collecting duct. Therefore when there is a deficiency of aldosterone, the kidney secretes inadequate amounts of K⁺ and H⁺, elevating their respective blood levels and causing hyperkalemia and metabolic acidosis. (Accordingly, the excretion of K⁺ and H⁺ in urine is decreased.)

When the woman moves from a supine to a standing position, her blood pressure decreases and her pulse

rate increases. Orthostatic hypotension, the decrease in blood pressure upon standing, is explained by a deficiency of aldosterone and a deficiency of cortisol. In addition to its effects on K⁺ and H⁺ secretion, aldosterone stimulates renal Na⁺ reabsorption. When aldosterone is deficient, there is inadequate renal Na⁺ reabsorption, which results in decreased body Na⁺ content, decreased ECF volume and blood volume, and decreased arterial blood pressure (especially when standing). Lack of cortisol contributes to her hypotension by reducing vascular responsiveness to catecholamines. The increased pulse rate upon standing reflects the response of the baroreceptor reflex to this orthostatic decrease in blood pressure. A component of the baroreceptor reflex response is increased heart rate, which attempts to restore blood pressure back to normal. The woman’s elevated BUN and serum creatinine reflect a decreased GFR, which is consistent with decreased ECF volume (i.e., prerenal azotemia).

The woman’s decreased serum [Na⁺] and serum osmolarity are secondary to the ECF volume contraction. When ECF volume decreases by 10% or more, ADH secretion is stimulated. ADH then circulates to the kidney, stimulating water reabsorption, as reflected in the hyperosmotic urine. The reabsorbed water is added to the body fluids, diluting them, as reflected in the decreased [Na⁺] and osmolarity. ADH secreted under such hypovolemic conditions is quite appropriate for her volume status but inappropriate for her serum osmolarity.

Hypoglycemia, nausea, weight loss, and weakness are caused by a deficiency of glucocorticoids. The decreased body Na⁺ content and decreased ECF volume also contribute to weight loss because a large percentage of body weight is water.

Hyperpigmentation resulted from negative feedback on the anterior pituitary by the low circulating cortisol levels. The decreased levels of cortisol stimulate secretion of ACTH, which contains the α -MSH fragment. When circulating levels of ACTH are elevated, as in Addison disease, the α -MSH component of the molecule produces darkening skin pigmentation.

The woman has decreased pubic and axillary hair from the loss of the adrenal androgens, DHEA and androstenedione. (In females, adrenal androgens are the major source of androgens.)

TREATMENT. Treatment of this patient consists of replacing the missing adrenocortical steroid hormones, which are necessary for life. She is given a synthetic mineralocorticoid (fludrocortisone) and a glucocorticoid (cortisol). Cortisol is administered twice daily, a large dose in early morning and a smaller dose in late afternoon, to simulate the normal diurnal pattern of cortisol secretion.

metabolic acidosis, and ECF volume contraction are not present. (3) In secondary adrenocortical insufficiency, hyperpigmentation does not occur because levels of ACTH (containing the α -MSH fragment) are low, not high as occurs in Addison disease.

Cushing Syndrome

Cushing syndrome is the result of chronic excess of glucocorticoids. It can be caused by spontaneous overproduction of cortisol by the adrenal cortex or from the administration of pharmacologic doses of exogenous glucocorticoids. **Cushing disease** is a separate entity, also characterized by excess glucocorticoids, in which the cause is hypersecretion of ACTH from a pituitary adenoma (which then drives the adrenal cortex to secrete excess cortisol).

The symptoms of either Cushing syndrome or Cushing disease are the result of excessive glucocorticoids and adrenal androgens (Fig. 9.26). Excess cortisol causes hyperglycemia, increased proteolysis and muscle wasting, increased lipolysis and thin extremities, central obesity, round face, supraclavicular fat, buffalo hump,

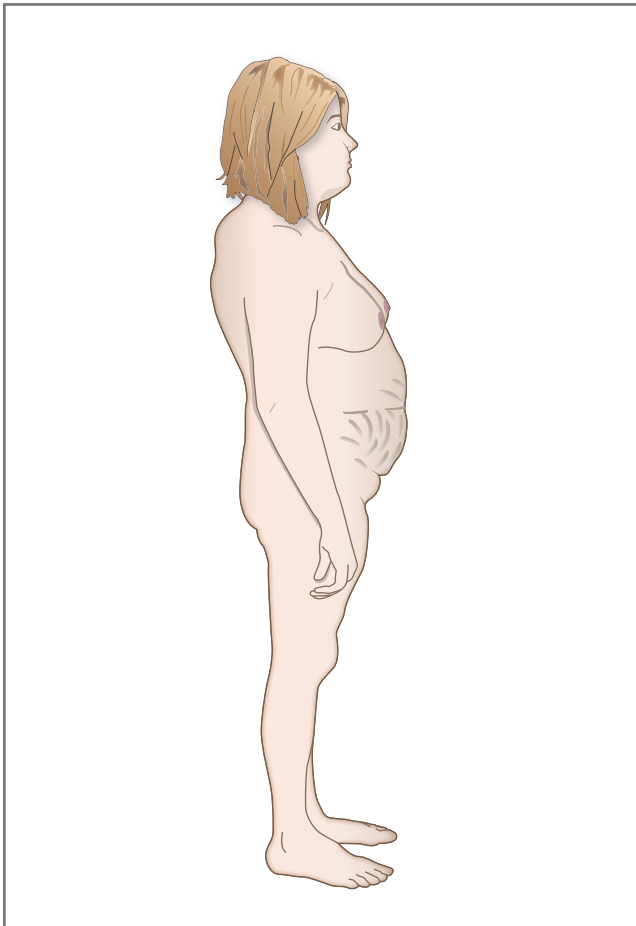


Fig. 9.26 Drawing of a woman with Cushing disease. Note the central obesity, buffalo hump, muscle wasting, and striae.

poor wound healing, osteoporosis, and striae (caused by a loss of connective tissue). Hypertension occurs because cortisol has weak mineralocorticoid activity and because cortisol increases the responsiveness of arterioles to catecholamines (by up-regulating α_1 receptors). Excess androgens cause virilization and menstrual disorders in females.

Cushing syndrome and Cushing disease exhibit similar clinical features, but they differ in the circulating levels of ACTH. In *Cushing syndrome*, the primary defect is in the adrenal cortex, which is overproducing cortisol. Accordingly, ACTH levels are low because the high cortisol levels feed back on the anterior pituitary and inhibit ACTH secretion. In *Cushing disease*, the primary defect is in the anterior pituitary, which is overproducing ACTH; ACTH levels are elevated. As already described, the **dexamethasone suppression test**, in which a synthetic glucocorticoid is administered, can distinguish between the two disorders. In Cushing syndrome (primary adrenal defect with a normal CRH-ACTH axis), because the adrenal tumor functions autonomously, cortisol secretion is not suppressed by either low- or high-dose dexamethasone. In Cushing disease, ACTH and cortisol secretion are suppressed by high-dose dexamethasone but not by low-dose dexamethasone.

Treatment of *Cushing syndrome* includes administration of drugs such as **ketoconazole** or **metyrapone**, which block steroid hormone biosynthesis. If drug treatment is ineffective, then bilateral adrenalectomy coupled with steroid hormone replacement may be required. Because of its different etiology, treatment of *Cushing disease* involves surgical removal of the ACTH-secreting tumor.

Conn Syndrome

Conn syndrome, or **primary hyperaldosteronism**, is caused by an aldosterone-secreting tumor. The symptoms of Conn syndrome are explainable by the known physiologic actions of aldosterone: Na^+ reabsorption, K^+ secretion, and H^+ secretion. The effects of excess aldosterone are increased ECF volume and hypertension (due to increased Na^+ reabsorption), hypokalemia (due to increased K^+ secretion), and metabolic alkalosis (due to increased H^+ secretion). In Conn syndrome, circulating renin levels are decreased because the increased ECF volume (caused by high levels of aldosterone) increases renal perfusion pressure, which inhibits renin secretion. Treatment of Conn syndrome consists of administration of an aldosterone antagonist such as **spironolactone**, followed by surgical removal of the aldosterone-secreting tumor.

21 β -Hydroxylase Deficiency

Several congenital abnormalities are associated with enzyme defects in the steroid hormone biosynthetic

pathways. The most common enzymatic defect is deficiency of 21 β -hydroxylase, which belongs to a group of disorders called **adrenogenital syndrome**. Review [Figure 9.23](#) to understand the consequences of this enzyme deficiency. Without 21 β -hydroxylase, the adrenal cortex is unable to convert progesterone to DOC or to convert 17-hydroxyprogesterone to 11-deoxycortisol. In other words, the adrenal cortex does not synthesize mineralocorticoids or glucocorticoids, resulting in predictable symptoms (as previously discussed). Steroid intermediates will accumulate *above* the enzyme block and be shunted toward production of the adrenal androgens, DHEA and androstenedione, which then cause virilization in females. There will be increased urinary levels of 17-ketosteroids. If the defect is present in utero in a female fetus, the excess androgens cause masculinization of the external genitalia, with a penis-like clitoris and scrotum-like labia. If untreated in childhood, the androgen excess will cause an acceleration of linear growth, the early appearance of pubic and axillary hair, and suppression of gonadal function. ACTH levels will be elevated because of negative feedback on the anterior pituitary by the low cortisol levels, and these high ACTH levels will have a trophic effect on the adrenal cortex and cause adrenocortical hyperplasia. (Thus the other name for this group of disorders is **congenital adrenal hyperplasia**.) Treatment of 21 β -hydroxylase deficiency consists of replacement of both glucocorticoids and mineralocorticoids.

17 α -Hydroxylase Deficiency

A less common congenital abnormality of the steroid hormone biosynthetic pathway is deficiency of 17 α -hydroxylase. The consequences of this defect differ from those of 21 β -hydroxylase deficiency. Examination of [Figure 9.23](#) shows that without 17 α -hydroxylase, pregnenolone cannot be converted to 17-hydroxypregnenolone and progesterone cannot be converted to 17-hydroxyprogesterone. As a result, neither glucocorticoids nor adrenal androgens will be produced by the adrenal cortex. The absence of cortisol will cause predictable effects (e.g., hypoglycemia), and the absence of adrenal androgens will result in the lack of pubic and axillary hair in females. In this disorder, steroid intermediates accumulate to the *left* of the enzyme block and will be shunted toward mineralocorticoids; there will be overproduction of DOC and corticosterone, both of which have mineralocorticoid activity. The resulting high levels of mineralocorticoids then cause hypertension, hypokalemia, and metabolic alkalosis.

Interestingly, the levels of aldosterone itself are actually *decreased* in 17 α -hydroxylase deficiency. Why would this be so, if steroid intermediates are shunted toward the production of mineralocorticoids? The

answer lies in the feedback regulation of the renin-angiotensin II-aldosterone system. The increased levels of DOC and corticosterone cause symptoms of mineralocorticoid excess: hypertension, metabolic alkalosis, and hypokalemia. Hypertension inhibits renin secretion, thus leading to decreased levels of angiotensin II and aldosterone; hypokalemia also inhibits aldosterone secretion directly.

ENDOCRINE PANCREAS

The endocrine pancreas secretes two major peptide hormones, insulin and glucagon, whose coordinated functions are to regulate glucose, fatty acid, and amino acid metabolism. The endocrine pancreas also secretes somatostatin and pancreatic polypeptide, whose functions are less well established.

The endocrine cells of the pancreas are arranged in clusters called the **islets of Langerhans**, which compose 1% to 2% of the pancreatic mass. There are approximately 1 million islets of Langerhans, each containing about 2500 cells. The islets of Langerhans contain four cell types, and each cell secretes a different hormone or peptide ([Fig. 9.27](#)). The **β cells** compose 65% of the islet and secrete **insulin**. The **α cells** compose 20% of the islet and secrete **glucagon**. The **delta (δ) cells** compose 10% of the islet and secrete **somatostatin**. The remaining cells (*not shown in [Fig. 9.27](#)*) secrete **pancreatic polypeptide** or other peptides.

The central core of the islet of Langerhans contains mostly β cells, with α cells distributed around the outer rim. The δ cells are interposed between α and β cells,

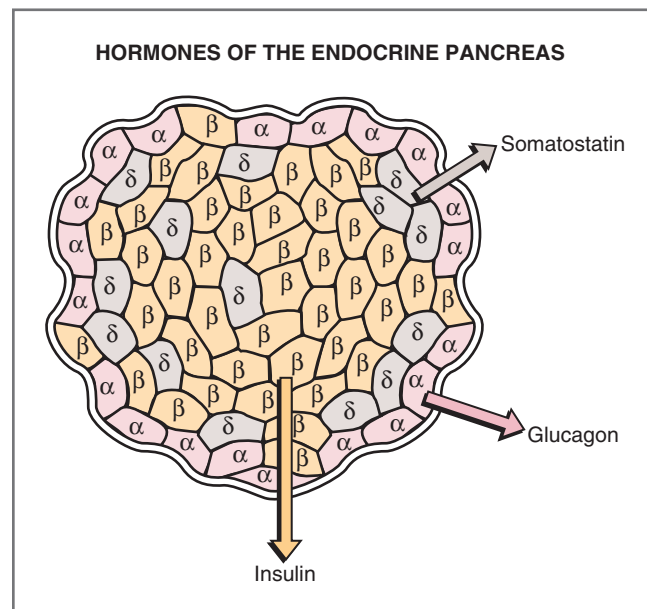


Fig. 9.27 Schematic drawing showing the arrangement of cell types and the hormones they secrete in an islet of Langerhans.

and their intimate contact with the other cell types suggests a paracrine function.

There are three ways in which cells of the islets of Langerhans communicate with each other and thereby alter each other's secretion (i.e., paracrine mechanisms). (1) Gap junctions connect α cells to each other, β cells to each other, and α cells to β cells. These gap junctions permit rapid cell-to-cell communication via either ionic current flow or transfer of molecules (up to 1000 molecular weight). (2) The islets receive about 10% of the total pancreatic blood flow. The **blood supply** of the endocrine pancreas is arranged so that venous blood from one cell type bathes the other cell types. Small arteries enter the core of the islet, distributing blood through a network of fenestrated capillaries and then converging into venules that carry the blood to the rim of the islet. Thus venous blood from the β cells carries insulin to the α and δ cells. (3) The islets are innervated by adrenergic, cholinergic, and peptidergic neurons. The δ cells even have a "neuronal" appearance and send dendrite-like processes onto the β cells, suggesting intraislet neural communication.

Insulin

Insulin, which is synthesized and secreted by the **β cells**, boasts an impressive array of "firsts." It was the *first* hormone to be isolated from animal sources in a form that could be administered therapeutically to humans; the *first* hormone to have its primary and tertiary structure determined; the *first* hormone to have its mechanism of action elucidated; the *first* hormone to be measured by radioimmunoassay; the *first* hormone known to be synthesized from a larger precursor (prohormone); and the *first* hormone to be synthesized with recombinant DNA technology.

Structure and Synthesis of Insulin

Insulin is a peptide hormone consisting of two straight chains, an **A chain** (21 amino acids) and a **B chain** (30 amino acids). Two disulfide bridges link the A chain to the B chain, and a third disulfide bridge is located within the A chain.

The synthesis of insulin is directed by a gene on **chromosome 11**, a member of a superfamily of genes that encode related growth factors. The mRNA directs ribosomal synthesis of **preproinsulin**, which contains four peptides: a signal peptide, the A and B chains of insulin, and a connecting peptide (C peptide). The signal peptide is cleaved early in the biosynthetic process (while the peptide chains are still being assembled), yielding **proinsulin** (Fig. 9.28). Proinsulin is then shuttled to the endoplasmic reticulum, where, with the connecting peptide still attached, disulfide bridges form to yield a "folded" form of insulin. Proinsulin is packaged in secretory granules on the Golgi apparatus.

During this packaging process, proteases cleave the connecting peptide, yielding **insulin**.

Insulin and the cleaved connecting peptide are packaged together in secretory granules, and when the β cell is stimulated, they are released in equimolar quantities into the blood. The secretion of **connecting peptide (C peptide)** is the basis of a test for β cell function in persons with type I diabetes mellitus who are receiving injections of exogenous insulin. (In these persons, serum insulin levels do not reflect endogenous secretory rates.)

Insulin is metabolized in the liver and kidney by enzymes that break disulfide bonds. The A chains and B chains are released, now inactive, and are excreted in the urine.

Regulation of Insulin Secretion

Table 9.13 summarizes the factors that influence the secretion of insulin by β cells. Of these factors, the most important is **glucose**. Increases in blood glucose concentration rapidly stimulate the secretion of insulin. Because of the preeminence of glucose as a stimulant, it is used to describe the mechanism of insulin secretion by the β cell, as illustrated in Figure 9.29. The circled numbers in the figure correlate with the steps described as follows:

1. **Transport of glucose into the β cell.** The β cell membrane contains **GLUT2**, a specific transporter for glucose that moves glucose from the blood into the cell by facilitated diffusion (Step 1).
2. **Metabolism of glucose inside the β cell.** Once inside the cell, glucose is phosphorylated to glucose-6-phosphate by glucokinase (Step 2), and glucose-6-phosphate is subsequently oxidized (Step 3). ATP,

TABLE 9.13 Factors Affecting Insulin Secretion

Stimulatory Factors	Inhibitory Factors
Increased glucose concentration	Decreased blood glucose
Increased amino acid concentration	Fasting
Increased fatty acid and ketoacid concentration	Exercise
Glucagon	Somatostatin
Cortisol	α -Adrenergic agonists
Glucose-dependent insulinotropic peptide (GIP)	Diazoxide
Potassium	
Vagal stimulation; acetylcholine	
Sulfonylurea drugs (e.g., tolbutamide, glyburide)	
Obesity	

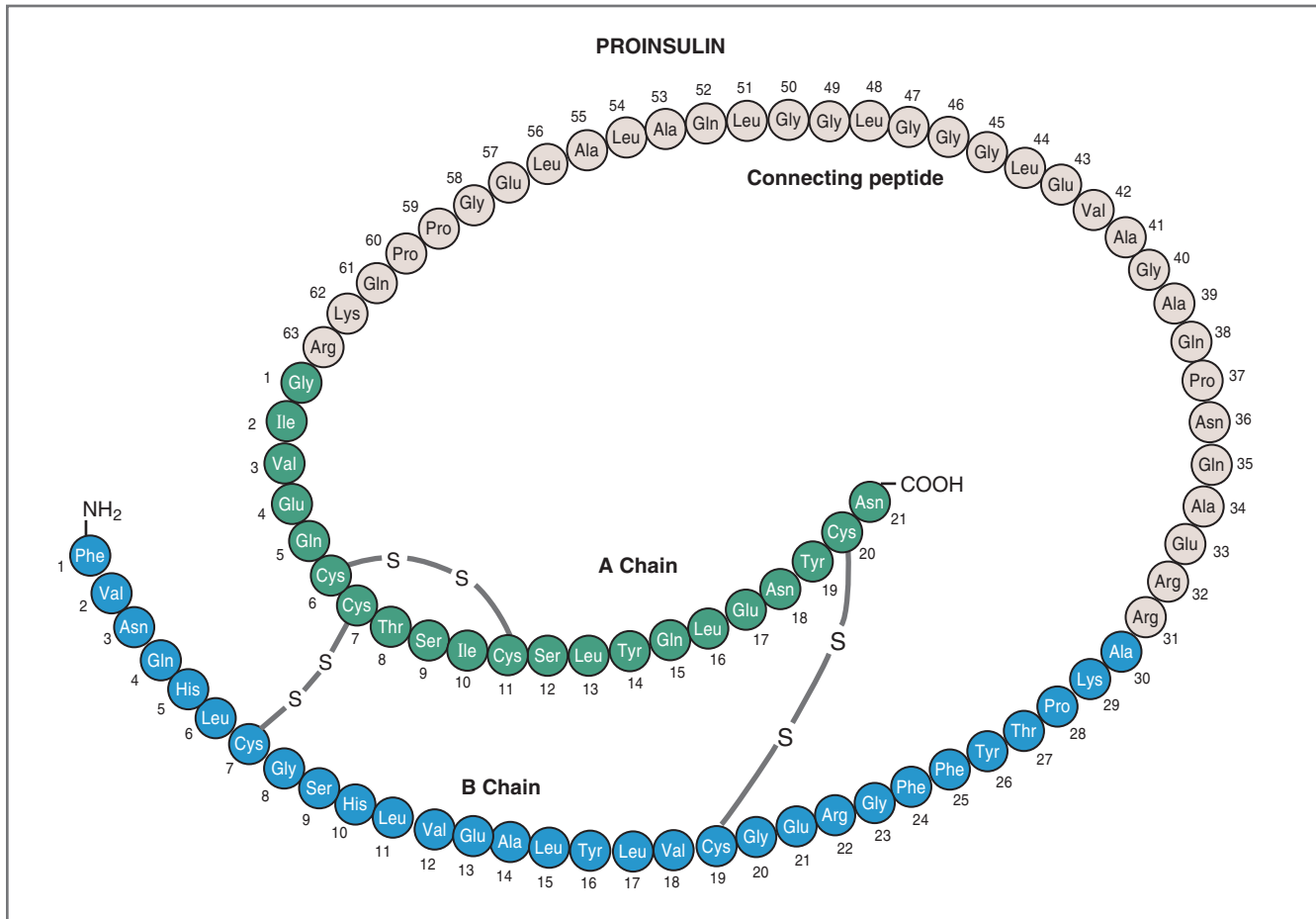


Fig. 9.28 Structure of porcine proinsulin. The connecting peptide (C peptide) is cleaved to form insulin. (Modified from Shaw WN, Chance RR: Effect of porcine proinsulin in vitro on adipose tissue and diaphragm of the normal rat. *Diabetes* 17:737, 1968.)

one of the products of this oxidation step, appears to be the key factor that regulates insulin secretion.

- ATP closes ATP-sensitive K^+ channels.** K^+ channels in the β cell membrane are regulated (i.e., opened or closed) by changes in ATP levels. When ATP levels inside the β cell increase, the K^+ channels close (Step 4), which depolarizes the β cell membrane (Step 5). (Refer to Chapter 1 for the complete discussion of why closing the K^+ channels depolarizes the cell. Briefly, when the K^+ channels close, K^+ conductance decreases and the membrane potential moves away from the K^+ equilibrium potential and is depolarized.)
- Depolarization opens voltage-sensitive Ca^{2+} channels.** Ca^{2+} channels, also in the β cell membrane, are regulated by changes in voltage; they are opened by depolarization and closed by hyperpolarization. The depolarization caused by ATP opens these Ca^{2+} channels (Step 6). Ca^{2+} flows into the β cell down its electrochemical gradient and the intracellular Ca^{2+} concentration increases (Step 7).

- Increased intracellular Ca^{2+} causes insulin secretion.** Increases in intracellular Ca^{2+} concentration cause exocytosis of the insulin-containing secretory granules (Step 8). Insulin is secreted into pancreatic venous blood and then delivered to the systemic circulation. C peptide is secreted in equimolar amounts with insulin and is excreted unchanged in the urine. Therefore the excretion rate of C peptide can be used to assess and monitor endogenous β cell function.

Recall from Chapter 8 that oral glucose is a more powerful stimulant for insulin secretion than intravenous glucose. The reason for this difference is that oral glucose stimulates the secretion of **glucose-dependent insulinotropic peptide (GIP)**, a gastrointestinal hormone that has an independent stimulatory effect on insulin secretion (adding to the direct effect of glucose on the β cells). Intravenous glucose does not cause the release of GIP and thus only acts directly.

Many of the other factors that affect insulin secretion do so by altering one or more steps in this basic

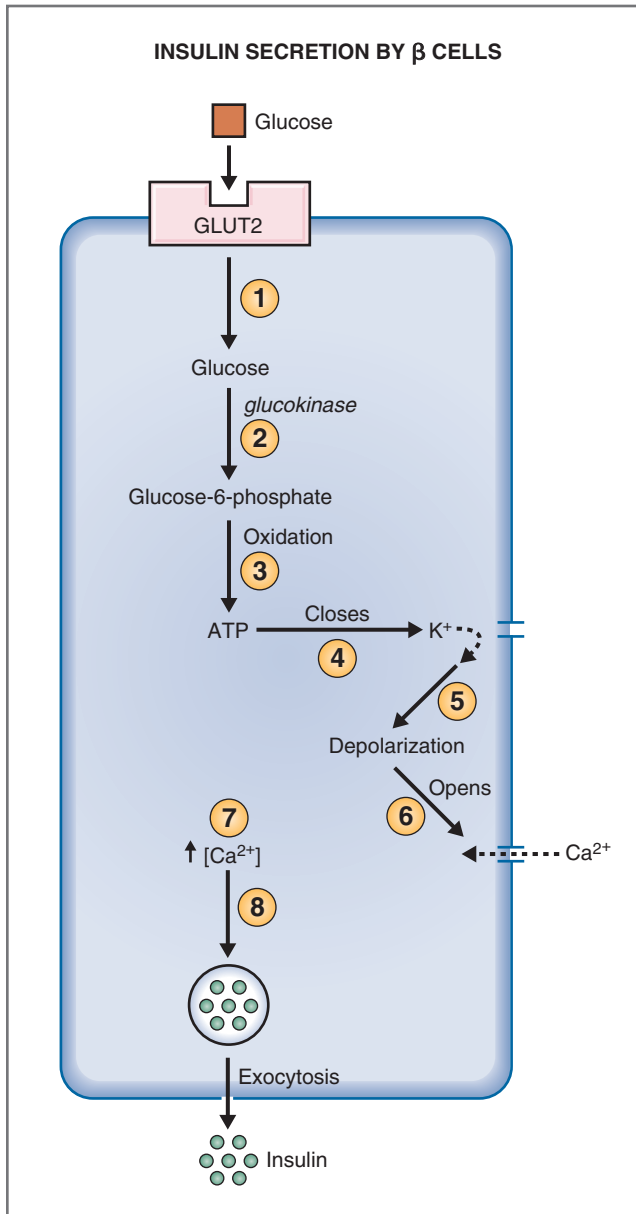


Fig. 9.29 Mechanism of insulin secretion by pancreatic β cells stimulated by glucose. See the text for an explanation of the circled numbers. *ATP*, Adenosine triphosphate; *GLUT2*, glucose transporter.

mechanism. For example, the stimulatory effects of amino acids and fatty acids on insulin secretion utilize metabolic pathways parallel to those utilized by glucose. **Glucagon** activates a G_q protein coupled to phospholipase C, which leads to a rise in intracellular Ca^{2+} (i.e., IP_3/Ca^{2+}), causing exocytosis of insulin. **Somatostatin** inhibits the mechanism that glucagon stimulates. The **sulfonylurea drugs** (e.g., tolbutamide, glyburide) that are used to treat type II (non-insulin-dependent) diabetes mellitus stimulate insulin release from β cells by closing the ATP-dependent K^+ channels, depolarizing the cell, and mimicking the depolarization induced by glucose.

Mechanism of Action of Insulin

The action of insulin on target cells begins when the hormone binds to its receptor in the cell membrane. The **insulin receptor** is a tetramer composed of **two α subunits** and **two β subunits** (Fig. 9.30). The α subunits lie in the extracellular domain, and the β subunits span the cell membrane. A disulfide bond connects the two α subunits, and each α subunit is connected to a β subunit by a disulfide bond. The β subunits have **intrinsic tyrosine kinase activity**.

Insulin acts on its target cells, as described in the following steps:

1. **Insulin binds to the α subunits** of the tetrameric insulin receptor, producing a conformational change in the receptor. The conformational change activates tyrosine kinase in the β subunits, which phosphorylate themselves in the presence of ATP. In other words, the β subunits **autophosphorylate**.
2. Activated **tyrosine kinase** phosphorylates several other proteins or enzymes that are involved in the physiologic actions of insulin including protein kinases, phosphatases, phospholipases, and G proteins. Phosphorylation either activates or inhibits these proteins to produce the various metabolic actions of insulin.
3. The **insulin-receptor complex is internalized** (i.e., taken in) by its target cell by endocytosis. The insulin receptor is either degraded by intracellular proteases, stored, or recycled to the cell membrane to be used again. Insulin **down-regulates** its own receptor by decreasing the rate of synthesis and increasing the rate of degradation of the receptor. Down-regulation of the insulin receptor is in part responsible for the decreased insulin sensitivity of target tissues in obesity and type II diabetes mellitus.

In addition to the previously described actions, insulin also binds to elements in the nucleus, the Golgi apparatus, and the endoplasmic reticulum. Thus insulin stimulates **gene transcription**, similar to the actions of somatomedins, IGF-1 and IGF-2.

Actions of Insulin

Insulin is known as the hormone of “**abundance**” or plenty. When the availability of nutrients exceeds the demands of the body, insulin ensures that excess nutrients are stored as glycogen in the liver, as fat in adipose tissue, and as protein in muscle. These stored nutrients are then available during subsequent periods of fasting to maintain glucose delivery to the brain, muscle, and other organs. The effects of insulin on nutrient flow and the resulting changes in blood levels are summarized in Table 9.14 and shown in Figure 9.31.

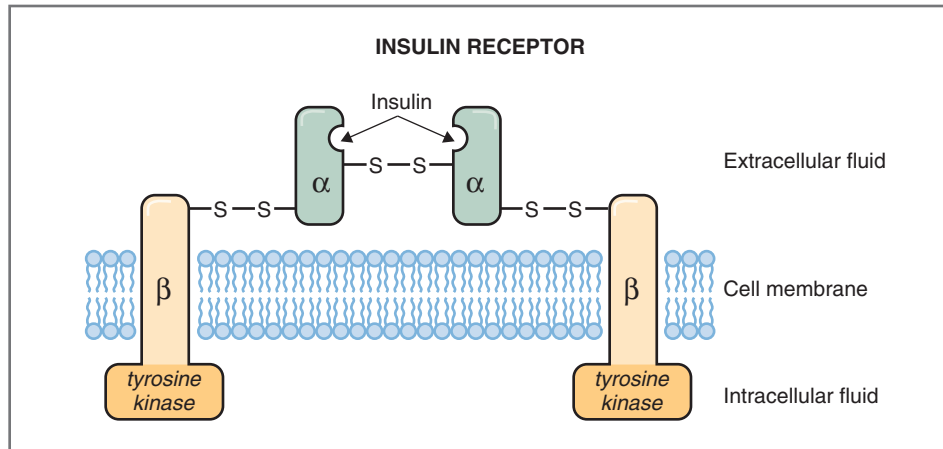


Fig. 9.30 Structure of the insulin receptor. The two α subunits are connected by disulfide bonds; each α subunit is connected to a β subunit by a disulfide bond. The β subunits have intrinsic tyrosine kinase activity.

TABLE 9.14 Major Actions of Insulin and the Effect on Blood Levels

Action of Insulin	Effect on Blood Level
Increases glucose uptake into cells	Decreases blood [glucose]
Increases glycogen formation	
Decreases glycogenolysis	
Decreases gluconeogenesis	
Increases protein synthesis (anabolic)	Decreases blood [amino acid]
Increases fat deposition	Decreases blood [fatty acid]
Decreases lipolysis	Decreases blood [ketoacid]
Increases K^+ uptake into cells	Decreases blood [K^+]

Insulin has the following actions on liver, muscle, and adipose tissue:

- ◆ **Decreases blood glucose concentration.** The hypoglycemic action of insulin can be described in two ways: Insulin causes a frank decrease in blood glucose concentration, *and* insulin limits the rise in blood glucose that occurs after ingestion of carbohydrates. The hypoglycemic action of insulin is the result of coordinated responses that simultaneously stimulate glucose oxidation and inhibit gluconeogenesis as follows: (1) Insulin **increases glucose transport** into target cells such as muscle and adipose by directing the insertion of glucose transporters (**GLUT4**) into the cell membranes. As glucose enters the cells, the blood glucose concentration decreases. (2) Insulin **promotes the formation of glycogen** from glucose in the liver and in muscle and, simultaneously,

inhibits glycogenolysis (glycogen breakdown). (3) Insulin **inhibits gluconeogenesis** (synthesis of glucose) by increasing the production of fructose 2,6-bisphosphate, which increases phosphofruktokinase activity. In effect, substrates are directed *away from* the formation of glucose.

- ◆ **Decreases blood fatty acid and ketoacid concentrations.** The overall effect of insulin on fat metabolism is to inhibit the mobilization and oxidation of fatty acids and, simultaneously, to increase the storage of fatty acids. As a result, insulin decreases the circulating levels of fatty acids and ketoacids. In adipose tissue, insulin **stimulates fat deposition** and **inhibits lipolysis**. Simultaneously, insulin inhibits ketoacid (β -hydroxybutyric acid and acetoacetic acid) formation in liver because decreased fatty acid degradation means that less acetyl coenzyme A (acetyl CoA) substrate will be available for the formation of ketoacids.
- ◆ **Decreases blood amino acid concentration.** The overall effect of insulin on protein metabolism is **anabolic**. Insulin increases amino acid and protein uptake by tissues, thereby decreasing blood levels of amino acids. Insulin stimulates amino acid uptake into target cells (e.g., muscle), increases protein synthesis, and inhibits protein degradation.
- ◆ **Other actions.** In addition to major actions on carbohydrate, fat, and protein metabolism, insulin has several additional effects. Insulin promotes **K^+ uptake into cells** (at the same time that it promotes glucose uptake) by increasing the activity of the Na^+K^+ ATPase. This action of insulin can be viewed as “protecting” against an increase in serum K^+ concentration. When K^+ is ingested in the diet, insulin ensures that ingested K^+ will be taken into the cells with glucose and other nutrients. Insulin

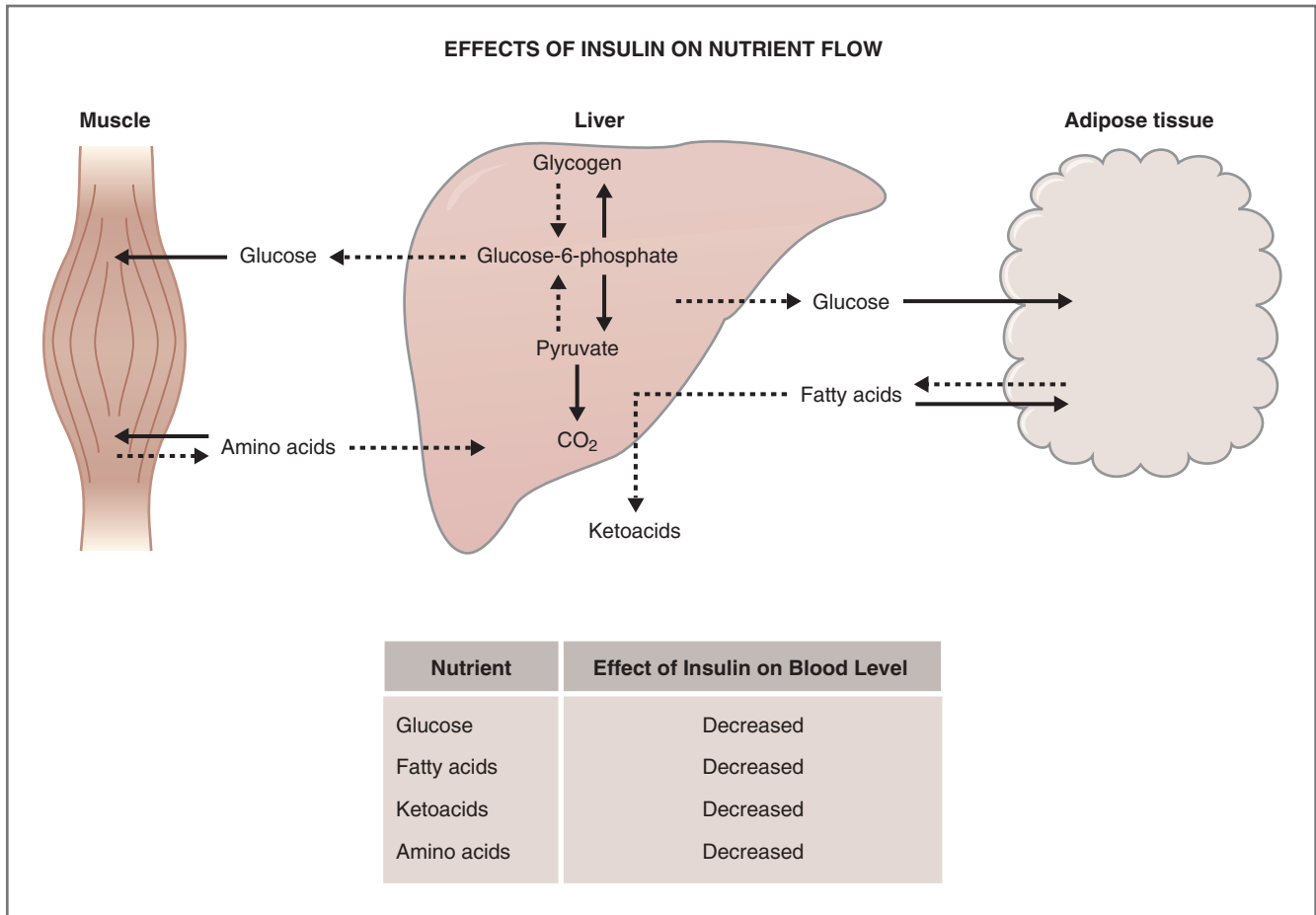


Fig. 9.31 Effects of insulin on nutrient flow in muscle, liver, and adipose tissue and resulting effects on blood levels of nutrients. *Solid arrows* indicate that the step is stimulated; *dashed arrows* indicate that the step is inhibited.

also appears to have a direct effect on the **hypothalamic satiety center** independent of the changes it produces in blood glucose concentration.

Pathophysiology of Insulin

The major disorder involving insulin is diabetes mellitus. In one form of diabetes mellitus (type I), there is inadequate insulin secretion; in another form (type II), there is insulin resistance of target tissues.

◆ **Insulin-dependent diabetes mellitus**, or type I diabetes mellitus, is caused by destruction of β cells, often as a result of an autoimmune process. When pancreatic β cells do not secrete adequate amounts of insulin, there are serious metabolic consequences: Carbohydrate, fat, and protein metabolism all will be disturbed.

Type I diabetes mellitus is characterized by the following changes: **increased blood glucose concentration** from decreased uptake of glucose into cells, decreased glucose utilization, and increased gluconeogenesis; **increased blood fatty acid and**

ketoacid concentration from increased lipolysis of fat, increased conversion of fatty acids to ketoacids, and decreased utilization of ketoacids by tissues; and **increased blood amino acid concentration** from increased breakdown of protein to amino acids. There also is loss of lean body mass (i.e., a catabolic state) and loss of adipose tissue.

Disturbances of fluid and electrolyte balance are present in type I diabetes mellitus. The increased levels of ketoacids cause a form of metabolic acidosis called **diabetic ketoacidosis (DKA)**. The increased blood glucose concentration results in an increased filtered load of glucose, which exceeds the reabsorptive capacity of the proximal tubule. The nonreabsorbed glucose then acts as an osmotic solute in urine, producing an **osmotic diuresis**, polyuria, and thirst. The polyuria produces ECF volume contraction and hypotension. Lack of insulin also causes a shift of K^+ out of cells (recall that insulin promotes K^+ uptake), resulting in **hyperkalemia**.

Treatment of type I diabetes mellitus consists of insulin replacement therapy, which restores the

ability of the body to store carbohydrates, lipids, and proteins and returns the blood values of nutrients and electrolytes to normal.

- ◆ **Non-insulin-dependent diabetes mellitus**, or type II diabetes mellitus, is often associated with obesity. It exhibits some, but not all, of the metabolic derangements seen in type I diabetes mellitus. Type II diabetes mellitus is caused by down-regulation of insulin receptors in target tissues and **insulin resistance**. Insulin is secreted normally by the β cells, but at normal concentrations, it cannot activate its receptors on muscle, liver, and adipose tissue; thus insulin is unable to produce its usual metabolic effects. Typically, the blood glucose concentration is elevated in both fasting and postprandial (after eating) states. Treatment of type II diabetes mellitus includes caloric restriction and weight reduction; treatment with **sulfonylurea drugs** (e.g., tolbutamide or glyburide), which stimulate pancreatic insulin secretion; and treatment with biguanide drugs (e.g., **metformin**), which up-regulate insulin receptors on target tissues.

Glucagon

Glucagon is synthesized and secreted by the α cells of the islets of Langerhans. In most respects (i.e., regulation of secretion, actions, and effect on blood levels), glucagon is the “mirror image” of insulin. Thus while insulin is the hormone of “abundance,” glucagon is the hormone of “starvation.” In contrast to insulin, which promotes storage of metabolic fuels, glucagon promotes their mobilization and utilization.

Structure and Synthesis of Glucagon

Glucagon is a single straight-chain polypeptide with 29 amino acids. It is a member of a family of peptides that includes the gastrointestinal hormones secretin and GIP. All of the peptides in the family share structural features and overlap in their physiologic actions (see Chapter 8, Fig. 8.6).

As with other peptide hormones, glucagon is synthesized as preproglucagon. The signal peptide and other peptide sequences are removed to produce glucagon, which then is stored in dense granules until it is secreted by the α cells. Both glucose and insulin inhibit the synthesis of glucagon; insulin-sensitive and cAMP-sensitive elements are present on the gene for preproglucagon.

Regulation of Glucagon Secretion

The actions of glucagon are coordinated to increase and maintain the blood glucose concentration. Thus the factors that cause stimulation of glucagon secretion are those that inform the α cells that a decrease in blood glucose has occurred (Table 9.15).

TABLE 9.15 Factors Affecting Glucagon Secretion

Stimulatory Factors	Inhibitory Factors
Fasting	Insulin
Decreased glucose concentration	Somatostatin
Increased amino acid concentration (especially arginine)	Increased fatty acid and ketoacid concentration
Cholecystokinin (CCK)	
β -Adrenergic agonists	
Acetylcholine	

The major factor stimulating the secretion of glucagon is **decreased blood glucose concentration**. Coordinating with this stimulatory effect of low blood glucose is a separate inhibitory action of insulin. Thus the presence of insulin reduces or *modulates* the effect of low blood glucose concentration to stimulate glucagon secretion. In the absence of insulin (i.e., type I diabetes mellitus), however, the glucagon response to hypoglycemia is exaggerated and may lead to severe, perpetuated hyperglycemia.

Glucagon secretion also is stimulated by the ingestion of protein, specifically by the amino acids **arginine** and **alanine**. The response of the α cells to amino acids is blunted if glucose is administered simultaneously (partially mediated by the inhibitory effect of insulin on glucagon secretion). Thus glucose and amino acids have offsetting or opposite effects on glucagon secretion (in contrast to their effects on insulin secretion, which are complementary).

Other factors stimulating glucagon secretion are **cholecystokinin** (CCK), which is secreted from the gastrointestinal tract when protein or fat is ingested, and **fasting** and **intense exercise**. Some of the stimulatory effects on glucagon secretion are mediated by activation of sympathetic α -adrenergic receptors.

Actions of Glucagon

The **mechanism of action** of glucagon on its target cells begins with hormone binding to a cell membrane receptor, which is coupled to **adenylyl cyclase** via a G_s protein. The second messenger is **cAMP**, which activates protein kinases that phosphorylate various enzymes; the phosphorylated enzymes then mediate the physiologic actions of glucagon.

As the hormone of starvation, glucagon promotes mobilization and utilization of stored nutrients to maintain the blood glucose concentration in the fasting state. The major actions of glucagon are on the liver (in contrast to insulin, which acts on liver, adipose, and muscle tissue). The effects of glucagon on the flow of nutrients are illustrated in Figure 9.32. Glucagon has

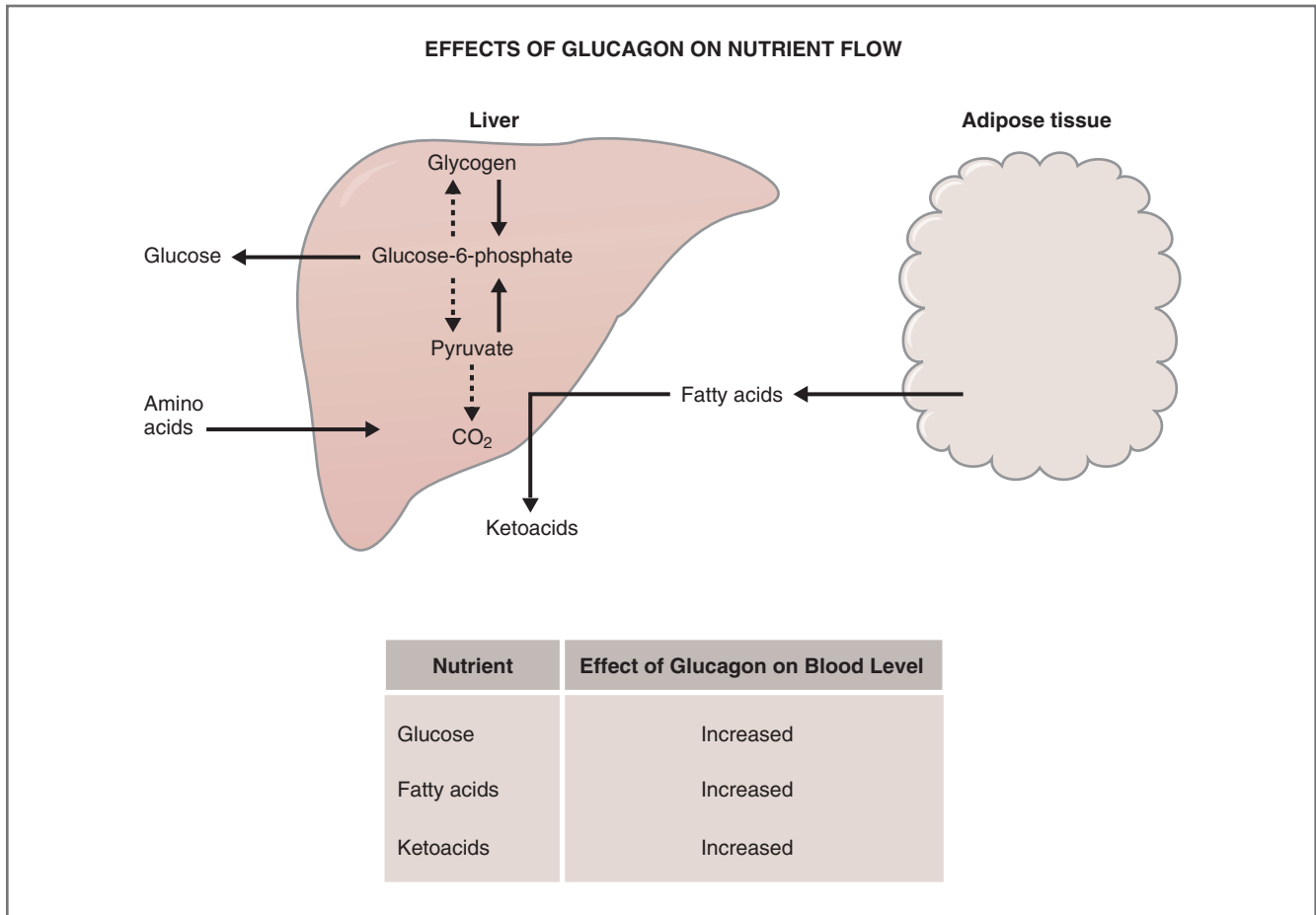


Fig. 9.32 Effects of glucagon on nutrient flow in liver and adipose tissue and resulting effects on blood levels of nutrients. *Solid arrows* indicate that the step is stimulated; *dashed arrows* indicate that the step is inhibited.

TABLE 9.16 Major Actions of Glucagon and Effect on Blood Levels

Action of Glucagon	Effect on Blood Level
Increases glycogenolysis	Increases blood [glucose]
Increases gluconeogenesis	
Increases lipolysis	Increases blood [fatty acid]
Increases ketoacid formation	Increases blood [ketoacid]

the following effects on blood levels, which are summarized in [Table 9.16](#) and described as follows:

- ◆ **Increases blood glucose concentration.** Glucagon increases the blood glucose concentration by the following coordinated actions: (1) Glucagon stimulates glycogenolysis and simultaneously inhibits glycogen formation from glucose, and (2) Glucagon increases gluconeogenesis by decreasing the production of

fructose 2,6-bisphosphate, which decreases phosphofruktokinase activity. Thus substrate is directed *toward* the formation of glucose. Amino acids are utilized for gluconeogenesis, and the resulting amino groups are incorporated into urea.

- ◆ **Increases blood fatty acid and ketoacid concentration.** Glucagon increases lipolysis and inhibits fatty acid synthesis, which also shunts substrates toward gluconeogenesis. The ketoacids β -hydroxybutyric acid and acetoacetic acid are produced from fatty acids.

Somatostatin

Pancreatic somatostatin, a polypeptide with 14 amino acids, is secreted by the δ cells of the islets of Langerhans. (The gastrointestinal counterpart of somatostatin has 28 amino acids and shares many of the physiologic actions of the pancreatic hormone.) Secretion of somatostatin is stimulated by the ingestion of *all* forms of nutrients (i.e., glucose, amino acids, and fatty acids), by several gastrointestinal hormones, by

glucagon, and by β -adrenergic agonists. Secretion of somatostatin is inhibited by insulin via an intraislet paracrine mechanism.

Pancreatic somatostatin **inhibits secretion of insulin and glucagon** via paracrine actions on the α and β cells. Thus somatostatin is secreted by the δ cells in response to a meal, diffuses to the nearby α and β cells, and inhibits secretion of their respective hormones. Apparently, the function of somatostatin is to modulate or limit the responses of insulin and glucagon to ingestion of food.

REGULATION OF CALCIUM AND PHOSPHATE METABOLISM

Forms of Ca^{2+} in Blood

The total Ca^{2+} concentration in blood is normally 10 mg/dL (Fig. 9.33). Of the total Ca^{2+} , 40% is bound to plasma proteins, mainly albumin. The remaining 60%, which is not protein bound, is ultrafilterable. The ultrafilterable component includes a small portion that is complexed to anions (e.g., phosphate, sulfate, citrate) and free, ionized Ca^{2+} . Free, **ionized Ca^{2+}** amounts to 50% of the total (i.e., 5 mg/dL), and it is the *only form of Ca^{2+} that is biologically active*.

Hypocalcemia is a decrease in the plasma Ca^{2+} concentration. The symptoms of hypocalcemia are hyperreflexia, spontaneous twitching, muscle cramps, and tingling and numbness. Specific indicators of hypocalcemia include the **Chvostek sign**, or twitching of the facial muscles elicited by tapping on the facial nerve, and the **Trousseau sign**, which is carpopedal spasm upon inflation of a blood pressure cuff. It may be surprising to learn that hypocalcemia causes twitching and cramping of skeletal muscle (as Ca^{2+} is required for cross-bridge cycling in muscle contraction). However,

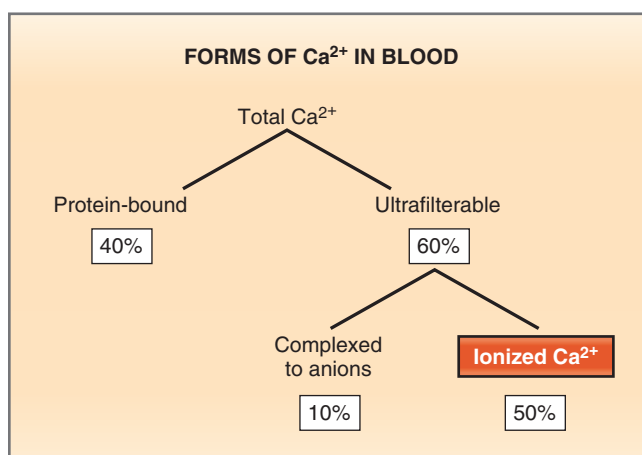


Fig. 9.33 Forms of Ca^{2+} in blood. Percentages give percent of total Ca^{2+} concentration in each form. Only free, ionized Ca^{2+} is physiologically active.

the Ca^{2+} that initiates the cross-bridge cycle in skeletal muscle contraction is *intracellular Ca^{2+}* . This discussion of the effects of hypocalcemia refers to low *extracellular Ca^{2+}* . Decreased extracellular Ca^{2+} causes increased excitability of excitable cells including sensory and motor nerves and muscle. Decreased extracellular Ca^{2+} lowers (makes more negative) the threshold potential; by lowering threshold potential, less inward current is required to depolarize to threshold and to fire action potentials. Thus hypocalcemia produces tingling and numbness (effects on sensory nerves) and spontaneous muscle twitches (effects on motoneurons and the muscle itself).

Hypercalcemia is an increase in the plasma Ca^{2+} concentration. Manifestations of hypercalcemia include constipation, polyuria, polydipsia, and neurologic signs of hyporeflexia, lethargy, coma, and death.

Changes in plasma protein concentration, changes in complexing anion concentration, and acid-base disturbances may alter the forms of Ca^{2+} in plasma. Such changes will be physiologically significant, however, only if they alter the ionized Ca^{2+} concentration because that is the form with biologic activity.

- ◆ **Changes in plasma protein concentration** alter the *total Ca^{2+}* concentration in the same direction as the protein concentration; thus increases in protein concentration are associated with increases in total Ca^{2+} concentration, and decreases in protein concentration are associated with decreases in total Ca^{2+} concentration. Because changes in plasma protein concentration usually are chronic and develop slowly over time, they do not cause a parallel change in *ionized Ca^{2+}* concentration. Regulatory mechanisms such as those involving PTH (see later) sense any transient change in ionized Ca^{2+} concentration and have time to make the appropriate correction.

- ◆ **Changes in anion concentration** alter the ionized Ca^{2+} concentration by changing the fraction of Ca^{2+} complexed with anions. For example, if the plasma phosphate concentration increases, the fraction of Ca^{2+} that is complexed increases, thereby decreasing the ionized Ca^{2+} concentration. If the plasma phosphate concentration decreases, the complexed Ca^{2+} decreases and the ionized Ca^{2+} increases.

- ◆ **Acid-base abnormalities** alter the ionized Ca^{2+} concentration by changing the fraction of Ca^{2+} bound to plasma albumin, as illustrated in Figure 9.34. Albumin has negatively charged sites, which can bind either H^+ ions or Ca^{2+} ions. In **acidemia**, there is an excess of H^+ in blood; thus more H^+ binds to albumin, leaving fewer sites for Ca^{2+} to bind. In acidemia, the free ionized Ca^{2+} concentration increases because less Ca^{2+} is bound to albumin. In **alkalemia**, there is a deficit of H^+ in blood, and less H^+ will be

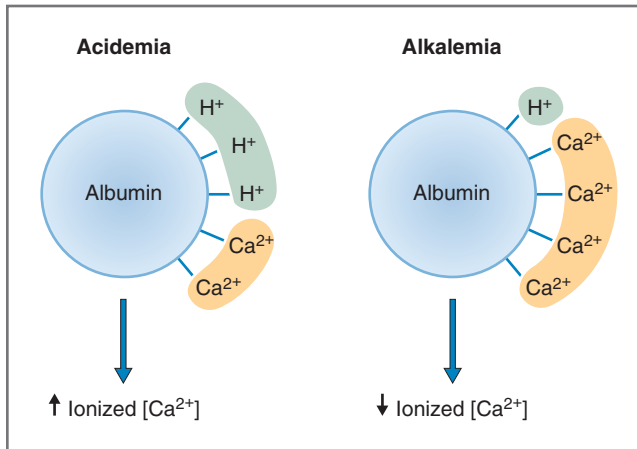


Fig. 9.34 Effects of acid-base disturbances on plasma protein-binding of Ca^{2+} and the ionized Ca^{2+} concentration in blood.

bound to albumin, leaving more sites for Ca^{2+} to bind. Thus in alkalemia (e.g., **acute respiratory alkalosis**) the free, ionized Ca^{2+} concentration decreases, often accompanied by symptoms of hypocalcemia.

Overall Calcium Homeostasis

Ca^{2+} homeostasis involves the coordinated interaction of three organ systems (bone, kidney, and intestine) and three hormones (PTH, calcitonin, and vitamin D). The relationship between the organ systems and the hormones in maintaining Ca^{2+} balance is depicted in **Figure 9.35**.

To illustrate, the “person” shown in **Figure 9.35** is said to be in Ca^{2+} balance. In this person, net excretion of Ca^{2+} by the kidney is equal to net absorption of Ca^{2+} from the gastrointestinal tract.

If the person ingests 1000 mg of elemental Ca^{2+} daily, approximately 350 mg is absorbed from the gastrointestinal tract, a process that is stimulated by the active form of vitamin D, 1,25-dihydroxycholecalciferol. However, about 150 mg/day is secreted into the

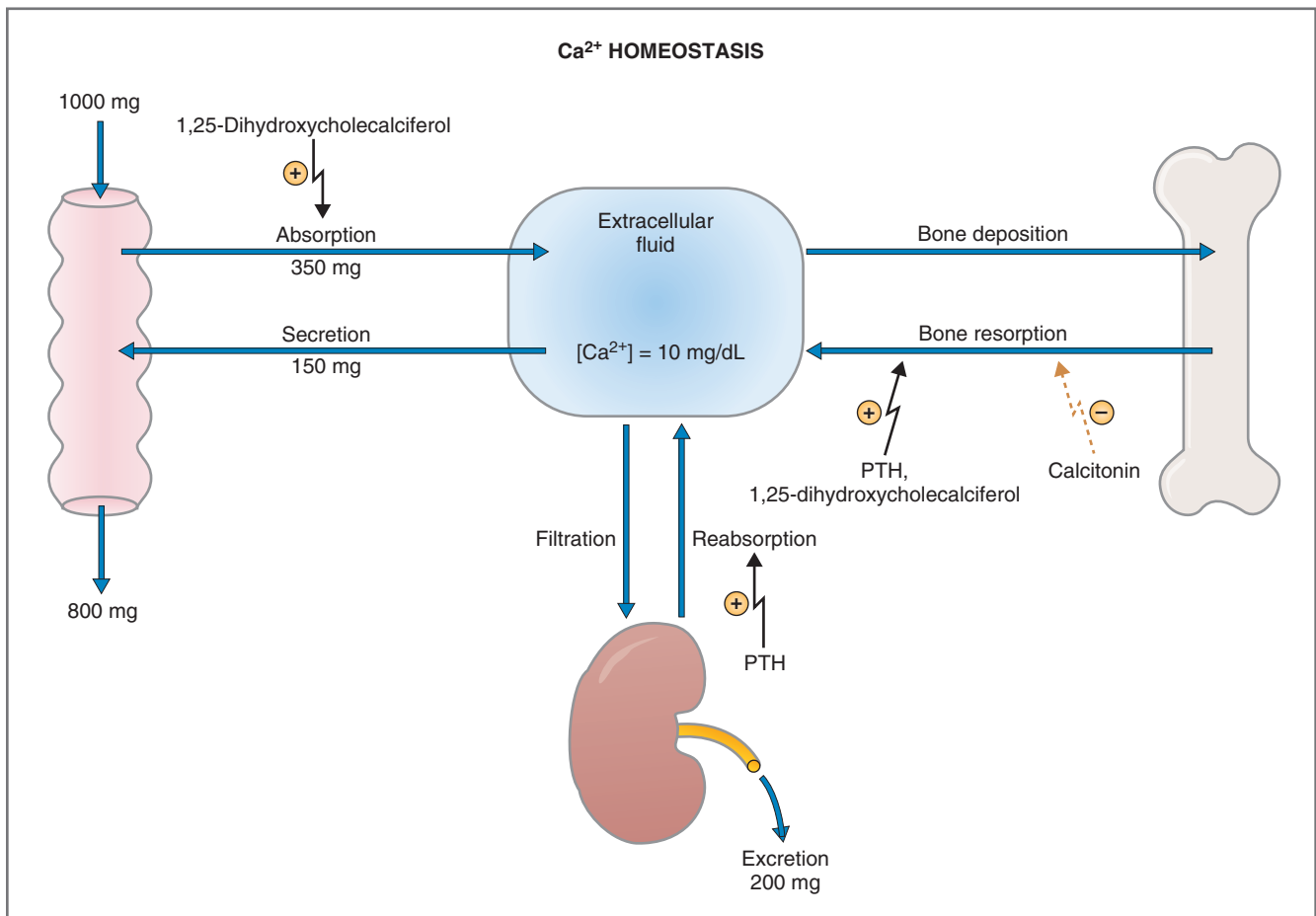


Fig. 9.35 Ca^{2+} homeostasis in an adult eating 1000 mg/day of elemental Ca^{2+} . Hormonal effects on Ca^{2+} absorption from the gastrointestinal tract, bone remodeling, and Ca^{2+} reabsorption in the kidney are shown. *PTH*, Parathyroid hormone.

gastrointestinal tract in salivary, pancreatic, and intestinal fluids. Thus **net absorption of Ca^{2+}** is 200 mg/day (350 mg – 150 mg), and the remaining 800 mg/day (of the 1000 mg ingested) is excreted in feces. The absorbed Ca^{2+} enters the Ca^{2+} pool in ECF.

The person depicted in Figure 9.35 is presumed to have no net gain or loss of Ca^{2+} from bone. Nevertheless, there is continuous **bone remodeling**, in which new bone is formed (deposited) and old bone is resorbed. Bone resorption is stimulated by PTH and 1,25-dihydroxycholecalciferol and is inhibited by calcitonin.

Ultimately, to maintain Ca^{2+} balance, the kidneys must excrete the same amount of Ca^{2+} that is absorbed from the gastrointestinal tract, or, in this case, 200 mg/day. The renal mechanisms (which are discussed in Chapter 6) include filtration of Ca^{2+} , followed by extensive reabsorption.

Parathyroid Hormone

The role of PTH is to regulate the concentration of Ca^{2+} in ECF (i.e., plasma or serum). When the plasma Ca^{2+} concentration decreases, PTH is secreted by the parathyroid glands. In turn, PTH has physiologic actions on bone, kidney, and intestine that are coordinated to increase the plasma Ca^{2+} concentration back to normal.

Structure of Parathyroid Hormone

There are four parathyroid glands in humans, located in the neck under the thyroid gland. The **chief cells** of the parathyroid glands synthesize and secrete PTH, a single-chain polypeptide with 84 amino acids. The molecule's biologic activity resides entirely in the N-terminal 34 amino acids. PTH is synthesized on the ribosomes as **preproPTH**, which has 115 amino acids. A 25-amino acid signal peptide sequence is cleaved while synthesis of the molecule is being completed

on the ribosomes. The 90-amino acid **proPTH** then is transported to the Golgi apparatus, where 6 more amino acids are cleaved, yielding the final 84-amino acid form of the hormone. PTH is packaged in secretory granules for subsequent release.

Regulation of Parathyroid Hormone Secretion

PTH secretion is regulated by the **plasma Ca^{2+} concentration**. As shown in Figure 9.36, when the total Ca^{2+} concentration is in the normal range (i.e., 10 mg/dL) or higher, PTH is secreted at a low (basal) level. However, when the plasma Ca^{2+} concentration decreases to less than 10 mg/dL, PTH secretion is stimulated, reaching maximal rates when the Ca^{2+} concentration is 7.5 mg/dL. The relationship between *total* Ca^{2+} concentration and PTH secretion is shown in Figure 9.36, although it is actually the *ionized* Ca^{2+} concentration that regulates secretion by the parathyroid glands. The response of the parathyroid glands to a decrease in ionized Ca^{2+} concentration is remarkably prompt, occurring within seconds. Furthermore, the faster the ionized Ca^{2+} falls, the greater the PTH secretory response.

It may seem paradoxical that the chief cells would secrete PTH in response to a *decrease* in Ca^{2+} concentration because many endocrine glands secrete their hormones in response to an *increase* in intracellular Ca^{2+} concentration. Actually, this is no paradox because what is sensed by the chief cells is a decrease in *extracellular* Ca^{2+} concentration, not a decrease in *intracellular* Ca^{2+} . The mechanism of PTH secretion is explained as follows: The parathyroid cell membrane contains **Ca^{2+} sensing receptors** that are linked, via a G protein (G_q), to phospholipase C. When the extracellular Ca^{2+} concentration is increased, Ca^{2+} binds to the receptor and activates phospholipase C. Activation of phospholipase C leads to increased levels of $\text{IP}_3/\text{Ca}^{2+}$, which *inhibits* PTH secretion. When extracellular Ca^{2+} is

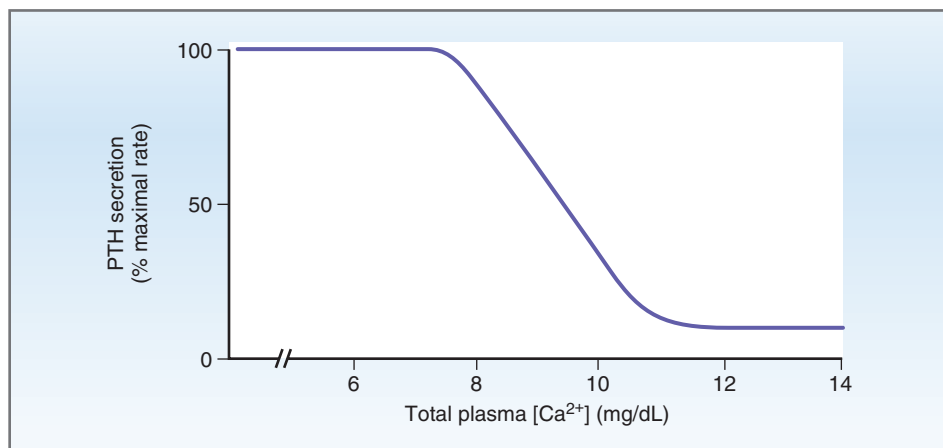


Fig. 9.36 Relationship between plasma Ca^{2+} concentration and parathyroid hormone (PTH) secretion.

decreased, there is decreased Ca^{2+} binding to the receptor, which *stimulates* PTH secretion.

In addition to these acute (rapid) changes in PTH secretion, chronic (long-term) changes in plasma Ca^{2+} concentration alter transcription of the gene for pre-proPTH, synthesis and storage of PTH, and growth of the parathyroid glands. Thus **chronic hypocalcemia** (decreased plasma Ca^{2+} concentration) causes **secondary hyperparathyroidism**, which is characterized by increased synthesis and storage of PTH and hyperplasia of the parathyroid glands. On the other hand, **chronic hypercalcemia** (increased plasma Ca^{2+} concentration) causes decreased synthesis and storage of PTH, increased breakdown of stored PTH, and release of inactive PTH fragments into the circulation.

Magnesium (Mg^{2+}) has parallel, although less important, effects on PTH secretion. Thus like hypocalcemia, hypomagnesemia stimulates PTH secretion and hypermagnesemia inhibits PTH secretion. An exception is the case of severe hypomagnesemia associated with chronic Mg^{2+} depletion (e.g., alcoholism); severe hypomagnesemia *inhibits* PTH synthesis, storage, and secretion by the parathyroid glands.

Complementing the inhibitory effect of increased plasma Ca^{2+} concentration on PTH secretion, 1,25-dihydroxycholecalciferol also inhibits PTH synthesis and secretion directly.

Actions of Parathyroid Hormone

PTH has actions on bone, kidney, and intestine, all of which are coordinated to produce an increase in plasma

Ca^{2+} concentration. The actions on bone and kidney are direct and are mediated by cAMP; the action on intestine is indirect, via activation of vitamin D.

The **mechanism of action** of PTH on bone and kidney is initiated when PTH binds to its receptor on the cell membrane of the target tissue. The receptor for PTH is coupled, via a G_s protein, to **adenylyl cyclase**, as illustrated for one of its actions, inhibition of renal phosphate reabsorption, in [Figure 9.37](#). The circled numbers in the figure correlate with the steps described as follows: The action of PTH on the renal proximal tubule begins at the basolateral membrane, where the hormone binds to its receptor. The receptor is coupled, via a G_s protein, to adenylyl cyclase (Step 1). When activated, adenylyl cyclase catalyzes the conversion of ATP to cAMP (Step 2), which activates a series of protein kinases (Step 3). Activated protein kinases phosphorylate intracellular proteins (Step 4), leading to the final physiologic action at the luminal membrane, inhibition of Na^+ -phosphate cotransport (Step 5). Inhibition of Na^+ -phosphate cotransport results in decreased phosphate reabsorption and phosphaturia (increased phosphate excretion).

The actions of PTH on bone, kidney, and intestine are summarized in [Figure 9.38](#) and are described as follows:

- ◆ **Bone.** PTH has several actions on bone, some direct and some indirect. In bone, **PTH receptors** are located on **osteoblasts** but not on osteoclasts. Initially and transiently, PTH causes an increase in

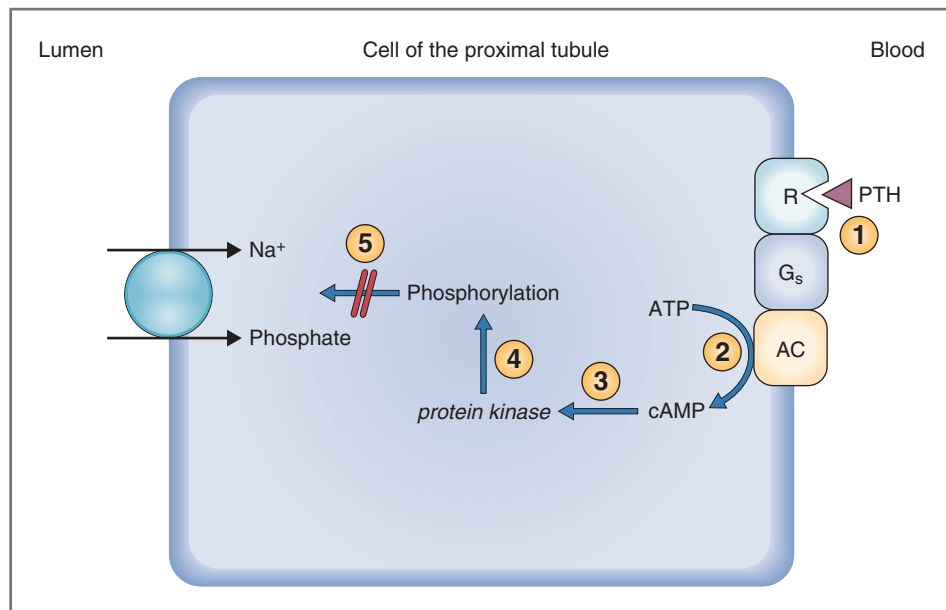


Fig. 9.37 Mechanism of action of PTH on the renal proximal tubule. See the text for an explanation of the circled numbers. AC, Adenylyl cyclase; ATP, adenosine triphosphate; cAMP, cyclic adenosine monophosphate; G_s , stimulatory G protein; PTH, parathyroid hormone; R, receptor for PTH.

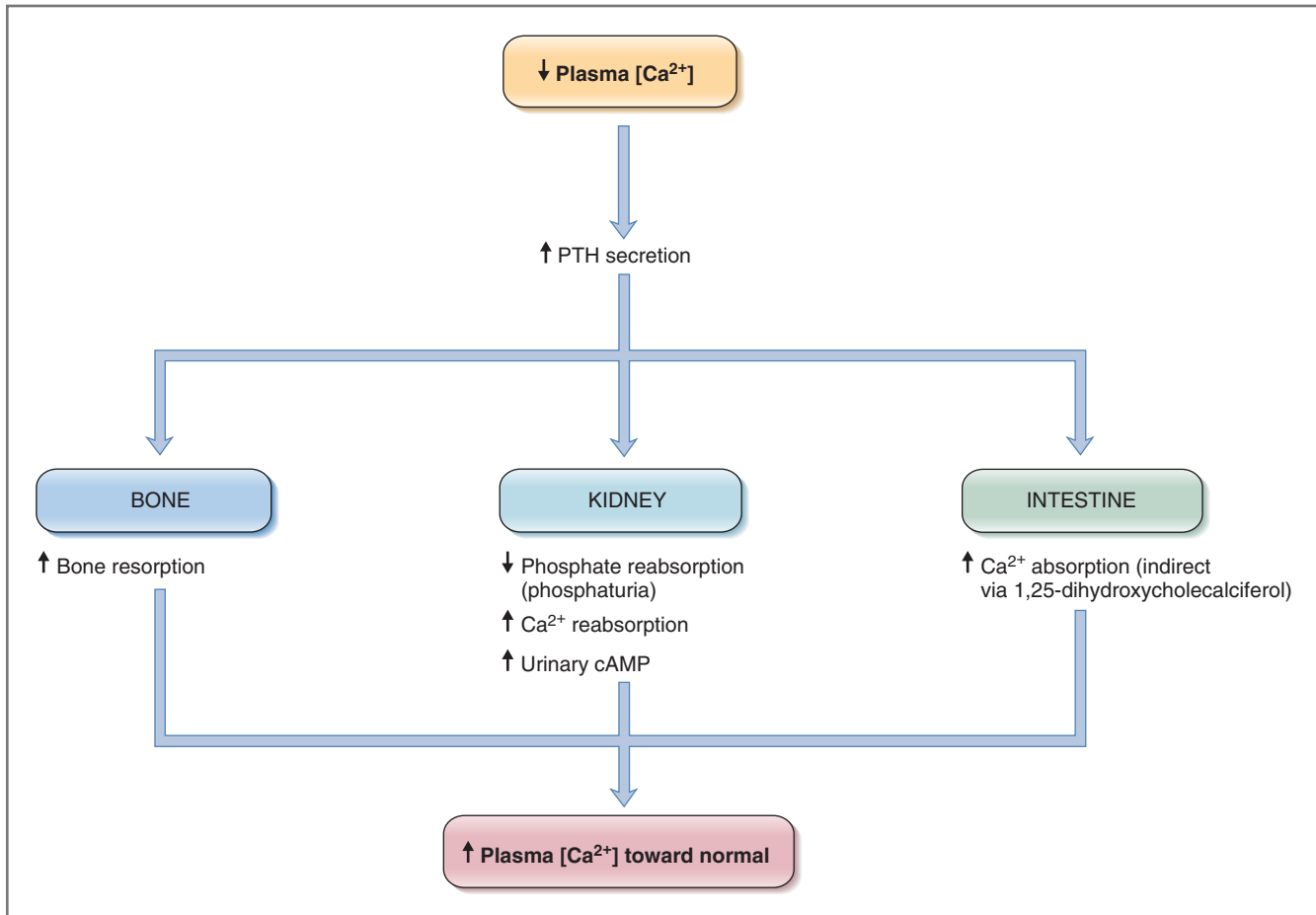


Fig. 9.38 Regulation of PTH secretion and PTH actions on bone, kidney, and intestine. cAMP, Cyclic adenosine monophosphate; PTH, parathyroid hormone.

bone formation by a direct action on osteoblasts. (This brief action is the basis for the usefulness of intermittent synthetic PTH administration in the **treatment of osteoporosis**.) In a second, long-lasting action on osteoclasts, PTH causes an increase in **bone resorption**. This second action on osteoclasts is indirect and mediated by cytokines released from osteoblasts; these cytokines then increase the number and activity of the bone-resorbing osteoclasts. Thus the bone-forming cells, osteoblasts, are required for the bone-resorbing action of PTH on osteoclasts. When PTH levels are chronically elevated, as in hyperparathyroidism, the rate of bone resorption is persistently elevated, which increases the serum Ca^{2+} concentration.

The *overall* effect of PTH on bone is to promote bone resorption, delivering *both* Ca^{2+} and phosphate to ECF. Hydroxyproline that is released from bone matrix is excreted in urine.

Alone, the effects of PTH on bone cannot account for its overall action to increase the plasma-ionized Ca^{2+} concentration. The phosphate released from

bone will complex with Ca^{2+} in ECF and limit the rise in ionized Ca^{2+} concentration. Thus an additional mechanism must coordinate with the PTH effect on bone to cause the plasma ionized Ca^{2+} concentration to increase. (That additional mechanism is the phosphaturic action of PTH.)

- ◆ **Kidney.** PTH has two actions on the kidney. (1) PTH **inhibits phosphate reabsorption** by inhibiting Na^+ -phosphate cotransport in the proximal convoluted tubule. As a result of this action, PTH causes **phosphaturia**, an increased excretion of phosphate in urine. The cAMP generated in cells of the proximal tubule is excreted in urine and is called nephrogenous or **urinary cAMP**. The phosphaturic action of PTH is critical because the phosphate that was resorbed from bone is excreted in the urine; this phosphate would have otherwise complexed Ca^{2+} in ECF. Excreting phosphate in urine “allows” the plasma ionized Ca^{2+} concentration to increase! (2) PTH **stimulates Ca^{2+} reabsorption**. This second renal action of PTH is on the distal convoluted tubule and

complements the increase in plasma Ca^{2+} concentration that resulted from the combination of bone resorption and phosphaturia.

- ◆ **Small intestine.** PTH does not have direct actions on the small intestine, although indirectly it stimulates intestinal Ca^{2+} absorption via activation of vitamin D. PTH stimulates renal 1α -hydroxylase, the enzyme that converts 25-hydroxycholecalciferol to the active form, 1,25-dihydroxycholecalciferol. In turn, 1,25-dihydroxycholecalciferol stimulates intestinal Ca^{2+} absorption.

Pathophysiology of Parathyroid Hormone

The pathophysiology of the PTH system can involve an excess of PTH, a deficiency of PTH, or target tissue resistance to PTH. Disorders associated with PTH are summarized in Table 9.17.

- ◆ **Primary hyperparathyroidism.** Primary hyperparathyroidism is most commonly caused by parathyroid adenomas (tumors), which secrete excessive amounts of PTH (Box 9.3). The consequences of primary hyperparathyroidism are predictable from the known physiologic actions of PTH on bone, kidney, and intestine: increased circulating levels of PTH, hypercalcemia, and hypophosphatemia. **Hypercalcemia** results from increased bone resorption, increased renal Ca^{2+} reabsorption, and increased intestinal Ca^{2+} absorption. **Hypophosphatemia** results from decreased renal phosphate reabsorption and phosphaturia.

Persons with primary hyperparathyroidism excrete excessive amounts of phosphate, cAMP, and Ca^{2+} in their urine. The increased urinary Ca^{2+} (hypercalciuria) can precipitate in the urine as Ca^{2+} -phosphate or Ca^{2+} -oxalate stones. The presence of hypercalciuria may seem surprising because the direct effect of PTH on the renal tubule is to *increase* Ca^{2+} reabsorption, thus decreasing Ca^{2+} excretion. The presence of hypercalciuria is explained, however, because the high plasma Ca^{2+} concentration in primary hyperparathyroidism results in a high filtered load of Ca^{2+} , which overwhelms the reabsorptive capacity of the nephron—the Ca^{2+} that is not reabsorbed is spilled into the urine. Persons with primary hyperparathyroidism are said to have “**stones, bones, and groans**”—stones from hypercalciuria, bones from increased bone resorption, and groans from constipation. Treatment of primary hyperparathyroidism usually is parathyroidectomy (surgical removal of the parathyroid glands).

- ◆ **Secondary hyperparathyroidism.** The causes of secondary hyperparathyroidism are different from the causes of primary hyperparathyroidism. In primary hyperparathyroidism, the disorder is *in* the parathyroid gland, which is secreting excessive PTH. In secondary hyperparathyroidism, the parathyroid glands are normal but are stimulated to secrete excessive PTH *secondary* to **hypocalcemia**, which can be caused by vitamin D deficiency or chronic renal failure. In secondary hyperparathyroidism, circulating levels of PTH are elevated and blood levels of Ca^{2+} are low or normal but never high.

BOX 9.3 Clinical Physiology: Primary Hyperparathyroidism

DESCRIPTION OF CASE. A 52-year-old woman reports that she suffers from symptoms of generalized weakness, easy fatigability, loss of appetite, and occasional vomiting. Also, she reports that her urine output is higher than normal and that she is unusually thirsty. Laboratory tests show hypercalcemia (increased serum $[\text{Ca}^{2+}]$), hypophosphatemia (decreased serum phosphate concentration), and phosphaturia (increased urinary phosphate excretion). Suspecting that the woman may have a disorder of the parathyroid glands, her physician orders a PTH level, which is found to be significantly elevated.

The woman undergoes surgery, and a single parathyroid adenoma is located and removed. The woman's blood and urine values return to normal. She regains her strength and reports feeling well.

EXPLANATION OF CASE. The woman has primary hyperparathyroidism caused by a single parathyroid adenoma, a benign lesion. The tumor secretes large amounts of PTH chemically identical to the hormone

secreted by the normal parathyroid glands. This excess PTH acts directly on bone and kidney and indirectly on the intestine to cause hypercalcemia and hypophosphatemia. Her hypercalcemia results from the effects of PTH to increase bone resorption, renal Ca^{2+} reabsorption, and intestinal Ca^{2+} absorption via activation of vitamin D to 1,25-dihydroxycholecalciferol. Her hypophosphatemia is caused by the effect of PTH to decrease renal phosphate reabsorption and produce phosphaturia.

Most of the woman's symptoms including hyporeflexia, weakness, loss of appetite, and vomiting are caused by hypercalcemia. Her polyuria and polydipsia result from deposition of Ca^{2+} in the inner medulla of the kidney, where ADH acts on the collecting ducts. High Ca^{2+} in the inner medulla inhibits the action of ADH on the collecting ducts, causing a form of nephrogenic diabetes insipidus.

TREATMENT. Surgery was curative for this patient.

TABLE 9.17 Pathophysiology of Parathyroid Hormone

Disorder	PTH	1,25-Dihydroxy-cholecalciferol	Bone	Urine	Serum [Calcium]	Serum [Phosphate]
Primary Hyperparathyroidism	↑ ^a	↑ (PTH effect on 1 α -hydroxylase)	↑ Resorption	↑ Urine phosphate (phosphaturia) ↑ Urine Ca ²⁺ (due to high-filtered load) ↑ Urine cAMP	↑	↓
Surgical Hypoparathyroidism	↓ ^a	↓ (PTH effect on 1 α -hydroxylase)	↓ Resorption	↓ Urine phosphate ↓ Urine cAMP	↓	↑
Pseudohypoparathyroidism	↑	↓	↓ Resorption (defective G _s) ^a	↓ Urine phosphate ↓ Urine cAMP (defective G _s) ^a	↓	↑
Humoral Hypercalcemia of Malignancy (↑ PTH-rp)^a	↓	↑	↑ Resorption	↑ Urine phosphate (phosphaturia) ↑ Urine Ca ²⁺ (due to high-filtered load) ↑ Urine cAMP	↑	↓
Chronic Renal Failure	↑ (secondary)	↓ ^a	Osteomalacia (due to ↓ 1,25-dihydroxycholecalciferol) ↑ Resorption (due to ↑ PTH)	↓ Urine phosphate (due to ↓ GFR) ^a	↓ (due to ↓ 1,25-dihydroxycholecalciferol)	↑ (due to ↓ urine phosphate)

^aPrimary events or disturbances. cAMP, Cyclic adenosine monophosphate; PTH, parathyroid hormone.

- ◆ **Hypoparathyroidism.** Hypoparathyroidism is a relatively common, inadvertent consequence of thyroid surgery (for treatment of thyroid cancer or Graves disease) or parathyroid surgery (for treatment of hyperparathyroidism). Autoimmune and congenital hypoparathyroidism are less common. The characteristics of hypoparathyroidism are predictable: low-circulating levels of PTH, hypocalcemia, and hyperphosphatemia. **Hypocalcemia** results from decreased bone resorption, decreased renal Ca^{2+} reabsorption, and decreased intestinal Ca^{2+} absorption. **Hyperphosphatemia** results from increased phosphate reabsorption. This disorder usually is treated with the combination of an oral Ca^{2+} supplement and the active form of vitamin D, 1,25-dihydroxycholecalciferol.
- ◆ **Pseudohypoparathyroidism.** Patients with pseudohypoparathyroidism type Ia were described in the early 1940s by the endocrinologist Fuller Albright as follows: They had hypocalcemia, hyperphosphatemia, and a characteristic phenotype consisting of short stature, short neck, obesity, subcutaneous calcification, and shortened fourth metatarsals and metacarpals. Thereafter, this phenotype was called **Albright hereditary osteodystrophy**.
As in hypoparathyroidism, patients with pseudohypoparathyroidism have hypocalcemia and hyperphosphatemia. However, in pseudohypoparathyroidism, circulating levels of PTH are increased rather than decreased, and administration of exogenous PTH produces no phosphaturic response and no increase in urinary cAMP. It is now known that pseudohypoparathyroidism is an inherited autosomal dominant disorder in which the **G_s protein** for PTH in kidney and bone is defective. When PTH binds to its receptor in these tissues, it does not activate adenyl cyclase or produce its usual physiologic actions. As a result, hypocalcemia and hyperphosphatemia develop.
- ◆ **Humoral hypercalcemia of malignancy.** Some malignant tumors (e.g., lung, breast) secrete PTH-related peptide (**PTH-rp**), which is structurally homologous with the PTH secreted by the parathyroid glands. PTH-rp is not only structurally similar but has all the physiologic actions of PTH including increased bone resorption, inhibition of renal phosphate reabsorption, and increased renal Ca^{2+} reabsorption. Together, the effects of PTH-rp on bone and kidney cause hypercalcemia and hypophosphatemia, a blood profile similar to that seen in primary hyperparathyroidism. However, in humoral hypercalcemia of malignancy, circulating levels of PTH are low, not high (as would occur in primary hyperparathyroidism); PTH secretion by the parathyroid glands, which are normal, is suppressed

by the hypercalcemia. Humoral hypercalcemia of malignancy is treated with **furosemide**, which inhibits renal Ca^{2+} reabsorption and increases Ca^{2+} excretion, and inhibitors of bone resorption such as **etidronate** (Box 9.4).

- ◆ **Familial hypocalciuric hypercalcemia (FHH).** This autosomal dominant disorder is characterized by decreased urinary Ca^{2+} excretion and increased serum Ca^{2+} concentration. It is caused by inactivating mutations of the **Ca^{2+} sensing receptors** in the parathyroid glands (that regulate PTH secretion) and parallel Ca^{2+} receptors in the thick, ascending limb of the kidney (that mediate Ca^{2+} reabsorption). When the renal receptors are defective, a high serum Ca^{2+} concentration is incorrectly sensed as “normal” and Ca^{2+} reabsorption is increased (leading to decreased urinary Ca^{2+} [hypocalciuria] and increased serum Ca^{2+} concentration). Because the Ca^{2+} receptors in the parathyroid glands are also defective, they incorrectly sense the increased serum Ca^{2+} as normal and PTH secretion is not inhibited as it would be in normal persons.

Calcitonin

Calcitonin is a straight-chain peptide with 32 amino acids. It is synthesized and secreted by the **parafollicular** or C (“C” for calcitonin) cells of the thyroid gland. The calcitonin gene directs the synthesis of preprocalcitonin and a signal peptide is cleaved to yield procalcitonin; other peptide sequences are then removed, and the final hormone, calcitonin, is stored in secretory granules for subsequent release.

The major stimulus for calcitonin secretion is increased plasma Ca^{2+} concentration (contrast this with the stimulus for PTH secretion, decreased plasma Ca^{2+} concentration). The major action of calcitonin is to inhibit osteoclastic bone resorption, which decreases the plasma Ca^{2+} concentration.

In contrast to PTH, calcitonin *does not* participate in the minute-to-minute regulation of the plasma Ca^{2+} concentration in humans. In fact, a physiologic role for calcitonin in humans is uncertain because neither thyroidectomy (with decreased calcitonin levels) nor thyroid tumors (with increased calcitonin levels) cause a derangement of Ca^{2+} metabolism, as would be expected if calcitonin had important regulatory functions.

Vitamin D

Vitamin D, in conjunction with PTH, is the second major regulatory hormone for Ca^{2+} and phosphate metabolism. The roles of PTH and vitamin D can be distinguished as follows: The role of *PTH* is to maintain the plasma Ca^{2+} concentration, and its actions are

BOX 9.4 Clinical Physiology: Humoral Hypercalcemia of Malignancy

DESCRIPTION OF CASE. A 72-year-old man was diagnosed with lung cancer 2 years ago. Despite surgery, radiation, and chemotherapy, his cancer returned. The man decided he did not want further treatment and would rather spend his remaining time at home with family. In the past week, the man has become lethargic and is producing large volumes of urine (polyuria). He is also incredibly thirsty and drinks water almost constantly. His physician admits him to the hospital, where he is found to have significantly increased serum Ca^{2+} concentration and decreased serum phosphate concentration. His serum albumin is normal and his serum PTH is decreased below normal. Serum alkaline phosphatase is very elevated. During a brief water-deprivation test, the man's serum osmolarity is elevated at 310 mOsm/L and his urine osmolarity is 90 mOsm/L; administration of an ADH analogue (dDAVP) by nasal spray does not change his serum or urine osmolarity.

EXPLANATION OF CASE. The man has humoral hypercalcemia of malignancy, in which his malignant lung cancer secretes parathyroid hormone-related peptide (PTH-rp). PTH-rp is chemically homologous with, and has the biologic actions of, PTH secreted by the parathyroid glands. The high levels of PTH-rp cause increased bone resorption (evidenced by the elevated alkaline phosphatase and increased serum Ca^{2+} concentration); decreased renal phosphate reabsorption and phosphaturia (evidenced by the decreased serum phosphate concentration); and increased renal Ca^{2+}

reabsorption (contributing to the increased serum Ca^{2+} concentration). The man's normal serum albumin confirms that the increased total serum Ca^{2+} is *not* caused by increased protein-bound Ca^{2+} but rather to increased free ionized serum Ca^{2+} . The decreased serum PTH level is a result of negative feedback inhibition of the high-serum Ca^{2+} on PTH secretion by the parathyroid gland.

The combination of an elevated serum osmolarity and very dilute urine suggests that the man has developed diabetes insipidus, either central or nephrogenic. Administration of dDAVP proves that it is nephrogenic diabetes insipidus, in which even exogenous ADH does not cause his urine to become concentrated. Hypercalcemia is associated with deposition of Ca^{2+} in the inner medulla, which inhibits the ADH-dependent adenyl cyclase and prevents the action of ADH to increase water permeability of the collecting ducts.

TREATMENT. In the hospital, the man is given saline and furosemide (a loop diuretic) to decrease his serum Ca^{2+} concentration. Furosemide inhibits the $\text{Na}^+\text{-K}^+\text{-2Cl}^-$ cotransporter in the thick ascending limb of the kidney. When this cotransporter is inhibited, the normal lumen positive potential in the thick ascending limb is abolished, thereby inhibiting Ca^{2+} reabsorption and increasing Ca^{2+} excretion. He is sent home with a prescription for pamidronate, an inhibitor of bone resorption that will help keep his serum Ca^{2+} in the normal range.

coordinated to increase the ionized Ca^{2+} concentration toward normal. The role of *vitamin D* is to promote mineralization of new bone, and its actions are coordinated to increase *both* Ca^{2+} and phosphate concentrations in plasma so that these elements can be deposited in new bone mineral.

Synthesis of Vitamin D

Vitamin D (**cholecalciferol**) is provided in the diet and is produced in the skin from cholesterol. Vitamin D has formal “hormone” status because cholecalciferol itself is inactive and must be successively hydroxylated to an active metabolite. Hydroxylation of cholecalciferol is regulated by negative feedback mechanisms. The pathways for vitamin D metabolism are shown in [Figure 9.39](#).

There are two sources of cholecalciferol in the body: It is either ingested in the diet or synthesized in the skin from 7-dehydrocholesterol in the presence of ultraviolet light. As noted, cholecalciferol itself is physiologically inactive. It is hydroxylated in the liver to form **25-hydroxycholecalciferol**, which also is inactive. This hydroxylation step occurs in the endoplasmic

reticulum and requires NADPH, O_2 , and Mg^{2+} , but not cytochrome P-450. 25-Hydroxycholecalciferol is bound to an α -globulin in plasma and is the principal circulating form of vitamin D.

In the **kidney**, 25-hydroxycholecalciferol undergoes one of two routes of hydroxylation: It can be hydroxylated at the C1 position to produce **1,25-dihydroxycholecalciferol**, which is the physiologically *active* form, or it can be hydroxylated at C24 to produce **24,25-dihydroxycholecalciferol**, which is *inactive*. C1 hydroxylation is catalyzed by the enzyme **1 α -hydroxylase**, which is regulated by several factors including the plasma Ca^{2+} concentration and PTH. C1 hydroxylation occurs in the renal mitochondria and requires NADPH, O_2 , Mg^{2+} , and cytochrome **P-450**.

Regulation of Vitamin D Synthesis

Whether the renal cells produce 1,25-dihydroxycholecalciferol (the active metabolite) or 24,25-dihydroxycholecalciferol (the inactive metabolite) depends on the “status” of Ca^{2+} in the body. When Ca^{2+} is sufficient, with an adequate dietary intake of Ca^{2+} and normal or increased plasma Ca^{2+}

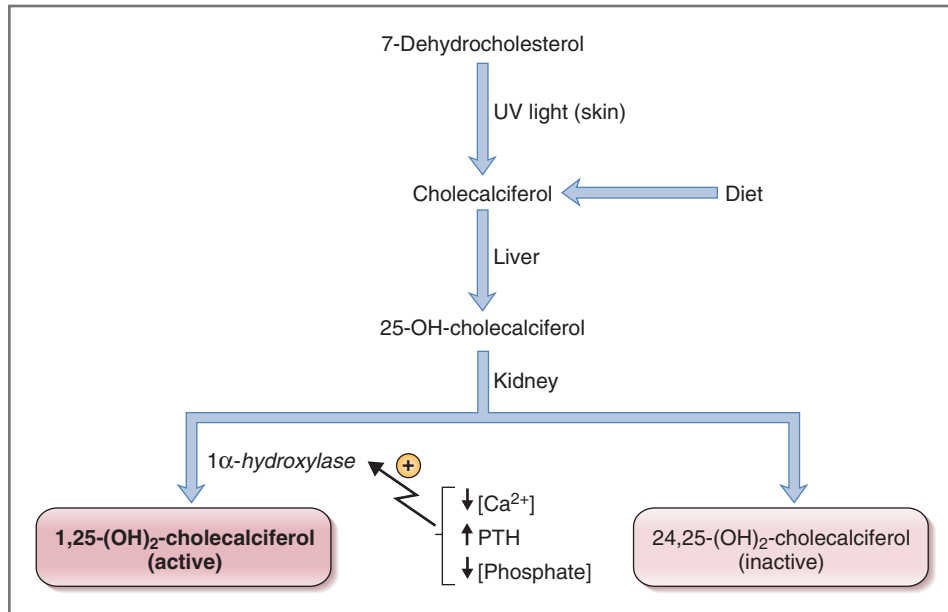


Fig. 9.39 Steps involved in the synthesis of 1,25-dihydroxycholecalciferol. PTH, Parathyroid hormone; UV, ultraviolet.

concentration, the inactive metabolite is preferentially synthesized because there is no need for more Ca^{2+} . When Ca^{2+} is insufficient, with a low dietary intake of Ca^{2+} and decreased plasma Ca^{2+} concentration, the active metabolite is preferentially synthesized to ensure that additional Ca^{2+} will be absorbed from the gastrointestinal tract.

The production of the active metabolite, 1,25-dihydroxycholecalciferol, is regulated by changing the activity of the **1 α -hydroxylase enzyme** (see Fig. 9.39). 1 α -Hydroxylase activity is increased by each of the following three factors: decreased plasma Ca^{2+} concentration, increased circulating levels of PTH, and decreased plasma phosphate concentration.

Actions of Vitamin D

The overall role of vitamin D (1,25-dihydroxycholecalciferol) is to increase the plasma concentrations of *both* Ca^{2+} and phosphate and to increase the $\text{Ca}^{2+} \times$ phosphate product to promote mineralization of new bone. To increase plasma Ca^{2+} and phosphate concentrations, vitamin D has coordinated actions on intestine, kidney, and bone. Because 1,25-dihydroxycholecalciferol is a steroid hormone, its mechanism of action involves stimulation of gene transcription and synthesis of new proteins, which have the following physiologic actions:

- ◆ **Intestine.** The major actions of 1,25-dihydroxycholecalciferol are on the intestine. There, 1,25-dihydroxycholecalciferol increases both Ca^{2+} and phosphate absorption, although far more is

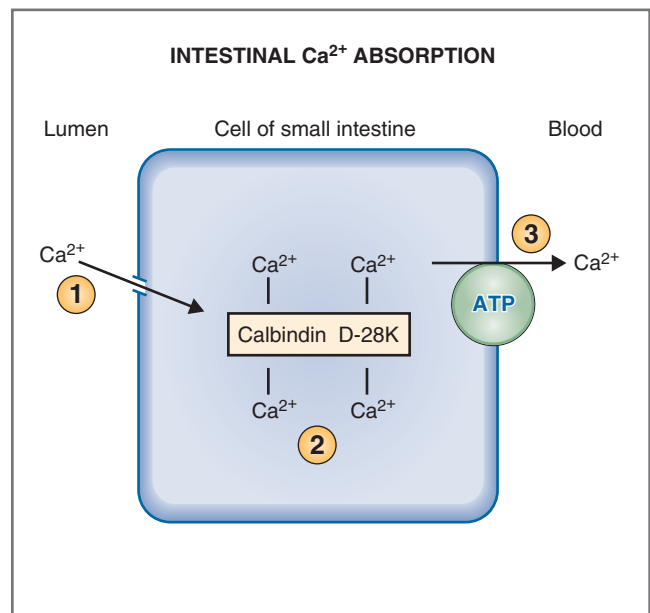


Fig. 9.40 Role of calbindin D-28K in intestinal Ca^{2+} absorption. 1,25-Dihydroxycholecalciferol induces the synthesis of calbindin D-28K. See the text for an explanation of the circled numbers. ATP, Adenosine triphosphate.

known about its effect on Ca^{2+} absorption. In the intestine, 1,25-dihydroxycholecalciferol induces the synthesis of a vitamin D-dependent Ca^{2+} -binding protein called **calbindin D-28K**, a cytosolic protein that can bind four Ca^{2+} ions.

The mechanism of Ca^{2+} absorption in intestinal epithelial cells is illustrated in Figure 9.40. Ca^{2+}

diffuses from the lumen into the cell, down its electrochemical gradient (Step 1). It is bound inside the cell to calbindin D-28K (Step 2) and subsequently is pumped across the basolateral membrane by a Ca^{2+} ATPase (Step 3). The exact role of calbindin D-28K in promoting absorption in intestinal epithelial cells is uncertain. It may act as a shuttle, moving Ca^{2+} across the cell from lumen to blood, or it may act as a Ca^{2+} buffer to keep intracellular free Ca^{2+} low, thus maintaining the concentration gradient for Ca^{2+} diffusion across the luminal membrane.

- ◆ **Kidney.** The actions of 1,25-dihydroxycholecalciferol on the kidney are parallel to its actions on the intestine—it stimulates both Ca^{2+} and phosphate reabsorption. In the kidney, the actions of 1,25-dihydroxycholecalciferol are clearly distinguishable from those of PTH. PTH stimulates Ca^{2+} reabsorption and inhibits phosphate reabsorption, and 1,25-dihydroxycholecalciferol stimulates the reabsorption of *both* ions.
- ◆ **Bone.** In bone, 1,25-dihydroxycholecalciferol acts synergistically with PTH to stimulate osteoclast activity and bone resorption. This action may seem paradoxical because the overall action of 1,25-dihydroxycholecalciferol is to promote bone mineralization. However, mineralized “old” bone is resorbed to provide more Ca^{2+} and phosphate to ECF so that “new” bone can be mineralized (bone remodeling).

Pathophysiology of Vitamin D

In children, vitamin D deficiency causes **rickets**, a condition in which insufficient amounts of Ca^{2+} and phosphate are available to mineralize the growing bones. Rickets is characterized by growth failure and skeletal deformities. This condition is rare in areas of the world where vitamin D is supplemented and when there is adequate exposure to sunlight. In adults, vitamin D deficiency results in **osteomalacia**, in which new bone fails to mineralize, resulting in bending and softening of the weight-bearing bones.

Vitamin D resistance occurs when the kidney is unable to produce the active metabolite, 1,25-dihydroxycholecalciferol. This condition is called “resistant” because no matter how much vitamin D is supplemented in the diet, it will be inactive because the C1 hydroxylation step in the kidney is absent or is inhibited. Vitamin D resistance can be caused by the congenital absence of 1α -hydroxylase or, more commonly, by **chronic renal failure**. Chronic renal failure is associated with a constellation of bone abnormalities including osteomalacia, a consequence of the inability of the diseased renal tissue to produce 1,25-dihydroxycholecalciferol, the active form of vitamin D.

SUMMARY

- The endocrine glands synthesize and secrete hormones, which circulate to their target tissues. Chemically, hormones may be classified as peptides, steroids, or amines. Hormone levels are measured by radioimmunoassay.
- Peptide hormones are synthesized by transcription of genes to mRNAs and translation of mRNAs to preprohormones. Signal peptides and other peptide sequences are cleaved from preprohormones to form the peptide hormones, which are packaged in secretory granules. Steroid hormones are synthesized from cholesterol in the adrenal cortex, testes, ovaries, and placenta. Amine hormones are derivatives of tyrosine.
- Hormone synthesis and secretion are regulated by negative and positive feedback mechanisms. Negative feedback is self-limiting; positive feedback is self-augmenting. Hormone receptors are also regulated by increasing (up-regulation) or decreasing (down-regulation) their number or activity.
- Mechanisms of hormone action (and their second messengers) include adenylyl cyclase (cAMP), phospholipase C ($\text{IP}_3/\text{Ca}^{2+}$), steroid hormone mechanism, and the tyrosine kinase mechanism.
- The connection between the hypothalamus and the posterior lobe of the pituitary is neuronal. The cell bodies are in the hypothalamus, and the hormones are secreted from nerve terminals in the posterior lobe of the pituitary. The hypothalamus is connected to the anterior lobe of the pituitary by hypothalamic-hypophysial portal blood vessels.
- Hormones of the anterior lobe are TSH, FSH, LH, ACTH, growth hormone, and prolactin. Hormones of the posterior lobe are ADH and oxytocin.
- Growth hormone is required for growth to normal stature and has actions on carbohydrate metabolism, protein synthesis, organ growth, and bone growth. Many of the actions of growth hormone are mediated by somatomedins. In children, a deficiency of growth hormone causes growth retardation. Excess growth hormone causes acromegaly.
- Prolactin is responsible for breast development and lactogenesis. Prolactin secretion is under tonic inhibition, mediated by dopamine from the hypothalamus. Excess prolactin secretion (e.g., prolactinoma) causes galactorrhea, which can be treated with dopamine agonists (e.g., bromocriptine).
- ADH is responsible for osmoregulation by increasing water reabsorption in the principal cells of the

kidney. ADH secretion is stimulated by increases in serum osmolarity and by decreases in ECF volume. Deficiency of ADH causes diabetes insipidus; excess ADH causes SIADH.

- Oxytocin secretion is stimulated by suckling and is responsible for milk ejection from the lactating breast.
- Thyroid hormones are synthesized by thyroid follicular cells. Tyrosines of TG are iodinated, yielding MIT and DIT. Coupling of MIT and DIT produces T_3 and T_4 . T_4 is activated to T_3 in target tissues. The actions of thyroid hormones include increased Na^+K^+ ATPase, increased oxygen consumption and BMR, and increased cardiac output. Hyperthyroidism is commonly caused by thyroid-stimulating immunoglobulins (Graves disease) and exhibits weight loss, increased BMR, excess heat production, rapid heart rate, and nervousness. Hypothyroidism exhibits weight gain, decreased BMR, cold intolerance, slowed movements, and lethargy.
- Adrenocortical steroid hormones are glucocorticoids, mineralocorticoids, and adrenal androgens, all of which are synthesized from cholesterol. Glucocorticoids stimulate gluconeogenesis and have antiinflammatory and immunosuppressive actions. Mineralocorticoids stimulate Na^+ reabsorption and K^+ and H^+ secretion by the kidney. Addison disease is primary adrenocortical insufficiency. Cushing syndrome is overproduction of glucocorticoids. Conn syndrome is overproduction of mineralocorticoids.
- The islets of Langerhans have three cell types: α , which secrete glucagon; β , which secrete insulin; and δ , which secrete somatostatin. Insulin is the hormone of “abundance” and promotes storage of glucose as glycogen, storage of fatty acids in adipose, and storage of amino acids as protein. Deficiency of insulin is type I diabetes mellitus; insulin resistance of target tissues is type II diabetes mellitus. Glucagon is the hormone of “starvation” and promotes utilization of stored nutrients.
- Ca^{2+} homeostasis is controlled by the interplay of bone, kidney, and intestine and the actions of the hormones PTH, calcitonin, and vitamin D. The function of PTH is to increase serum ionized Ca^{2+} concentration by increasing bone resorption, increasing intestinal Ca^{2+} absorption, increasing renal Ca^{2+} reabsorption, and decreasing renal phosphate reabsorption. Hyperparathyroidism is associated with hypercalcemia and hypophosphatemia. Hypoparathyroidism is associated with hypocalcemia and hyperphosphatemia. Vitamin D is converted to its active form, 1,25-dihydroxycholecalciferol, in the

kidney. The function of vitamin D is to promote bone mineralization by increasing the Ca^{2+} and phosphate concentrations in ECF. Its actions are to increase intestinal and renal Ca^{2+} and phosphate absorption and to increase bone resorption. Deficiency of vitamin D causes rickets in children and osteomalacia in adults.

Challenge Yourself

Each numbered question begins with an endocrine disorder or a disturbance to an endocrine system. The disorder or disturbance is followed by a list of parameters (e.g., blood level of various substances). For each parameter, predict whether it is increased, decreased, or unchanged.

1 Addison Disease

Cortisol
ACTH
Blood glucose

2 Nephrogenic Diabetes Insipidus

ADH
Urine osmolarity

3 Conn Syndrome

Serum K^+
Blood pressure
Renin

4 Cushing Disease

ACTH
Cortisol
Blood glucose

5 Surgical Hypoparathyroidism

Serum Ca^{2+}
Serum phosphate
Urinary cAMP

6 Car Accident That Severs the Hypothalamic-Pituitary Stalk

Prolactin
ADH
Serum osmolarity
PTH

7 Autoimmune Destruction of the Thyroid

T_4
TSH
Basal metabolic rate
 T_3 resin uptake

8 **21 β -Hydroxylase Deficiency**

ACTH

Cortisol

Deoxycorticosterone (DOC)

Aldosterone

Dehydroepiandrosterone (DHEA)

Urinary 17-ketosteroids

9 **Administration of Synthetic Glucocorticoid (Dexamethasone) to a Normal Person**

ACTH

Cortisol

10 **Lung Cancer Producing Parathyroid Hormone-Related Peptide (PTH-rp)**

Serum Ca²⁺

PTH

11 **17 α -Hydroxylase Deficiency**

Blood pressure

Blood glucose

DHEA

Aldosterone