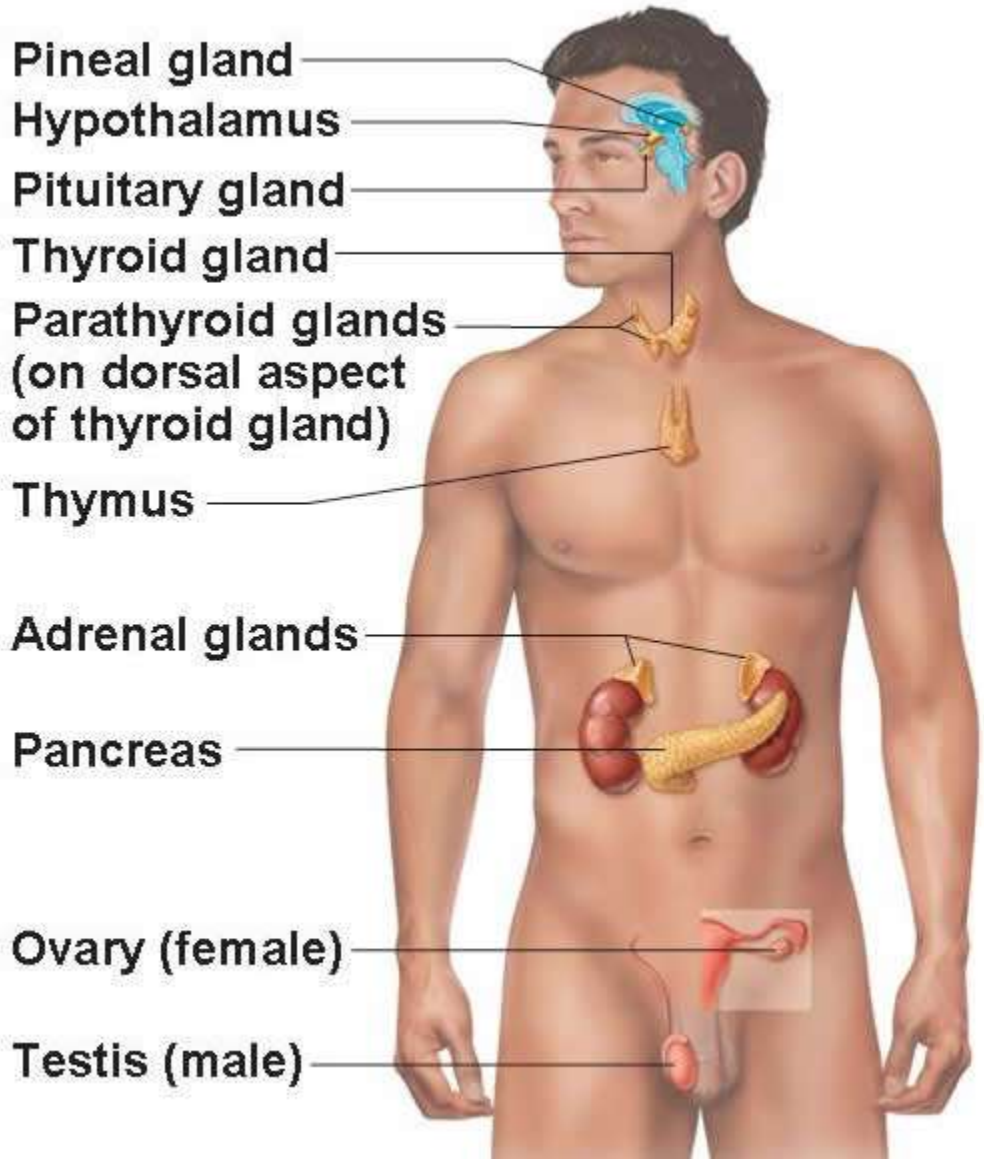
The Endocrine System: An Overview

Endocrine glands are ductless glands that produce and release hormones to the blood through diffusion.

Endocrine glands may be strictly endocrine, such as the pituitary, thyroid, parathyroid, adrenal, pineal and thymus; or they may be organs that have hormone production as one of many functions, such as the pancreas, gonads, hypothalamus, and others.



Hormones

Chemistry of Hormones

Hormones are long-distance chemical signals that are secreted by the cells to the extracellular fluid and regulate the metabolic functions of other cells.

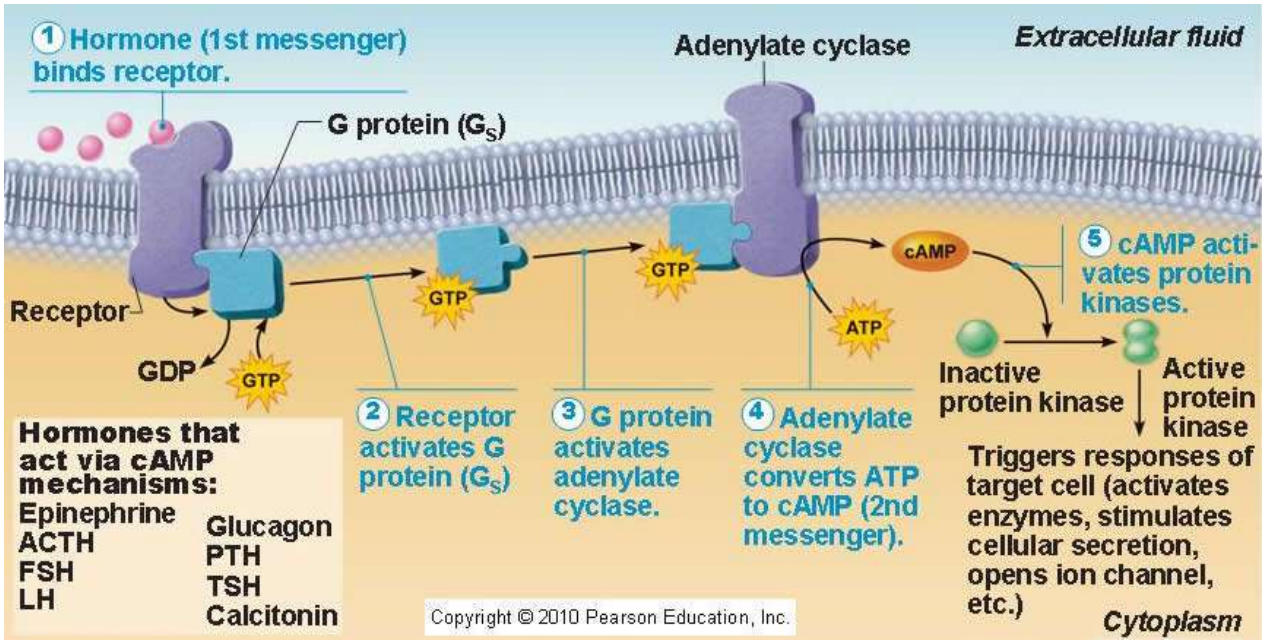
Most hormones are amino acid based, but gonadal and adrenocortical hormones are steroids, derived from cholesterol.

Mechanisms of Hormone Action

Hormones typically produce changes in membrane permeability or potential, stimulate synthesis of proteins or regulatory molecules, activate or deactivate enzymes, induce secretory activity, or stimulate mitosis.

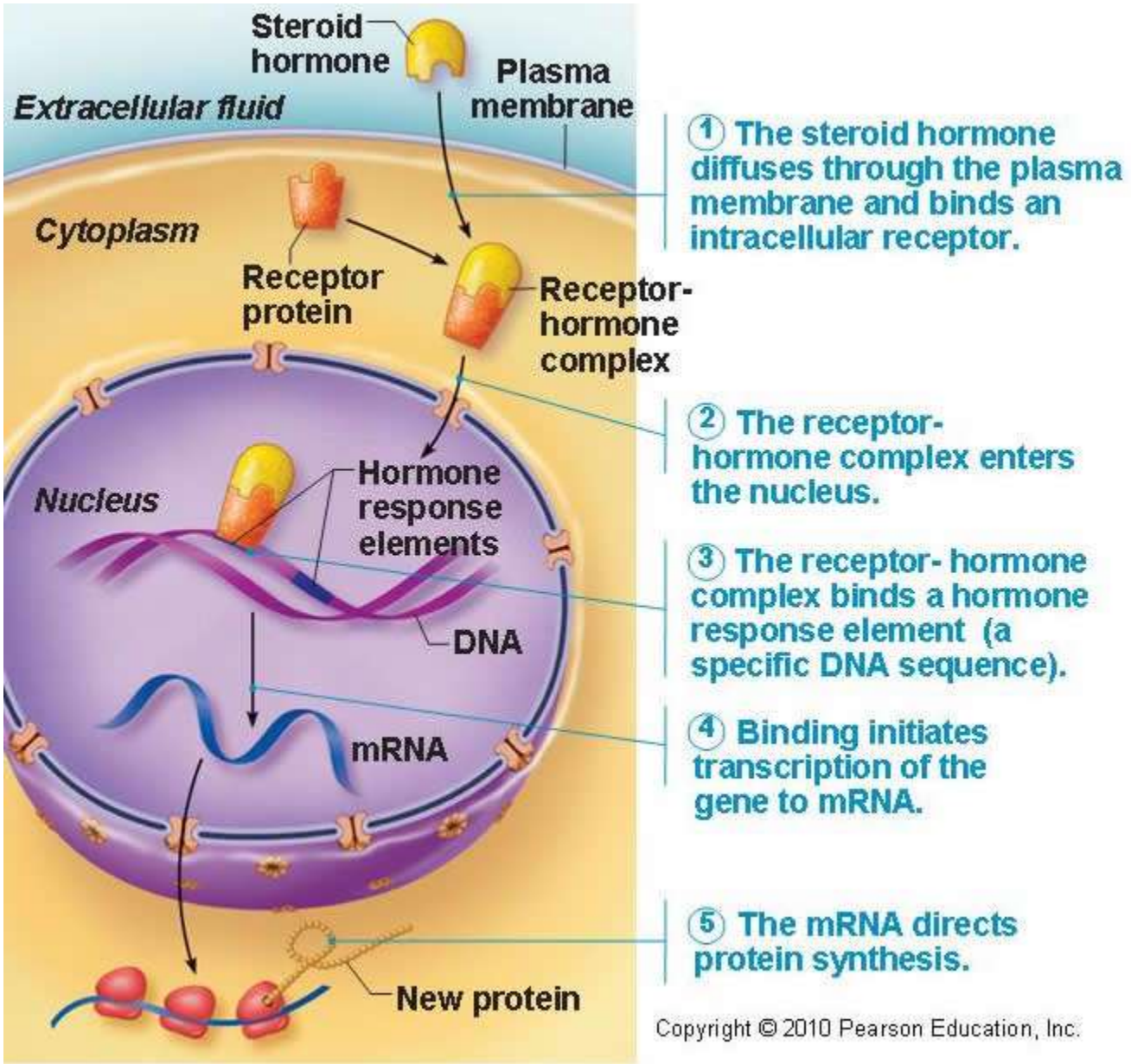
Water-soluble hormones (all amino acid-based hormones except thyroid hormone) exert their effects through an intracellular second messenger that is activated when a hormone binds to a membrane receptor.

Second messenger systems, activated when a hormone binds to a plasma membrane receptor, activate G-proteins within the cell that alter enzyme activity.



Lipid-soluble hormones (steroids and thyroid hormone) diffuse into the cell, where they bind to intracellular receptors, migrate to the nucleus, and activate specific target sequences of DNA.

Direct gene activation occurs when a hormone binds to an intracellular receptor, which activates a specific region of DNA, causing the production of mRNA, and intitiation of protein synthesis.



Target Cell Specificity

Cells must have specific membrane or intracellular receptors to which hormones can bind.

Target cell response depends on three factors: blood levels of the hormone, relative numbers of target cell receptors, and affinity of the receptor for the hormone.

Target cells can change their sensitivity to a hormone by changing the number of receptors.

Half-Life, Onset, and Duration of Hormone Activity

The concentration of a hormone reflects its rate of release, and the rate of inactivation and removal from the body.

The half-life of a hormone is the duration of time a hormone remains in the blood, and is shortest for water-soluble hormones.

Target organ response and duration of response vary widely among hormones.

Interaction of Hormones at Target Cells

Permissiveness occurs when one hormone cannot exert its full effect without another hormone being present (reproductive hormones need thyroxine to properly stimulate development of reproductive organs).

Synergism occurs when more than one hormone produces the same effects in a target cell, and their combined effects are amplified (glucagon + epinephrine together stimulate more glucose release from the liver than when each acts alone).

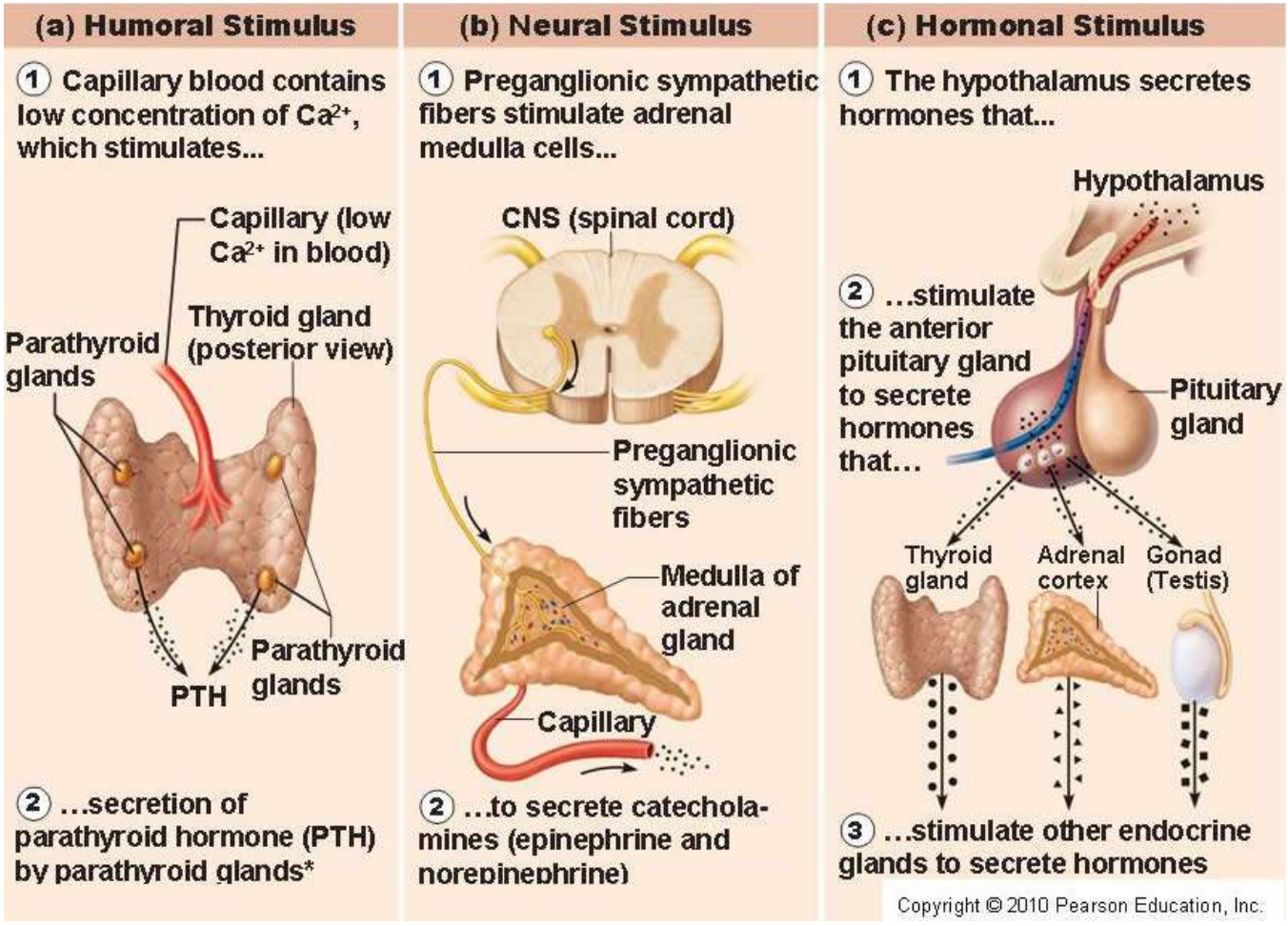
Antagonism occurs when one hormone opposes the action of another hormone (glucagon antagonizes insulin).

Control of Hormone Release

Most hormone synthesis and release is regulated through negative feedback mechanisms.

Endocrine gland stimuli may be humoral, neural, or hormonal.

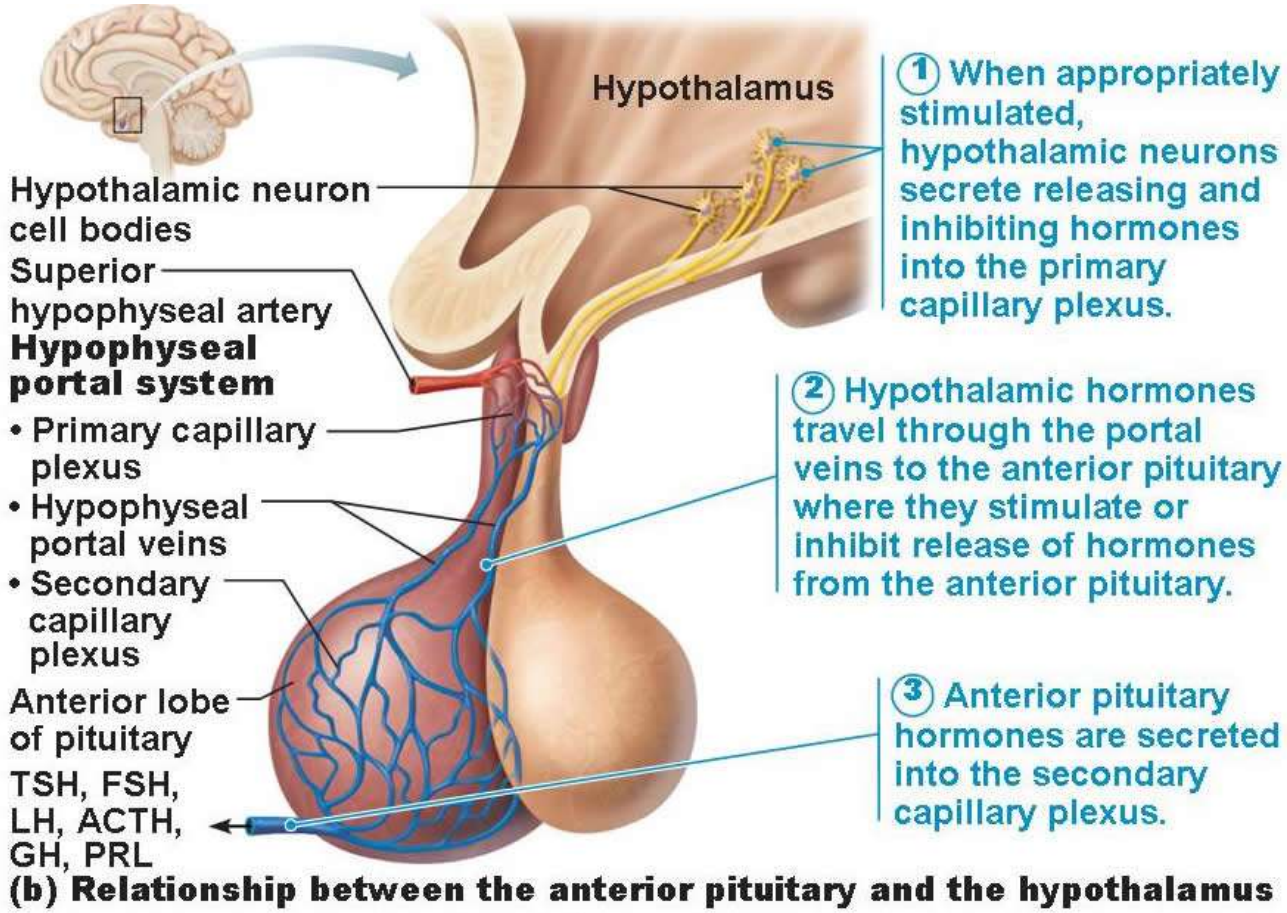
Nervous system modulation allows hormone secretion to be modified by the nervous stimulation in response to changing body needs.



Major Endocrine Organs

The Pituitary Gland (Hypophysis)

The pituitary gland is connected to the hypothalamus via a stalk, the infundibulum, and consists of two lobes: the anterior pituitary, or adenohypophysis, and the posterior pituitary, or neurohypophysis.



(b) Relationship between the anterior pituitary and the hypothalamus

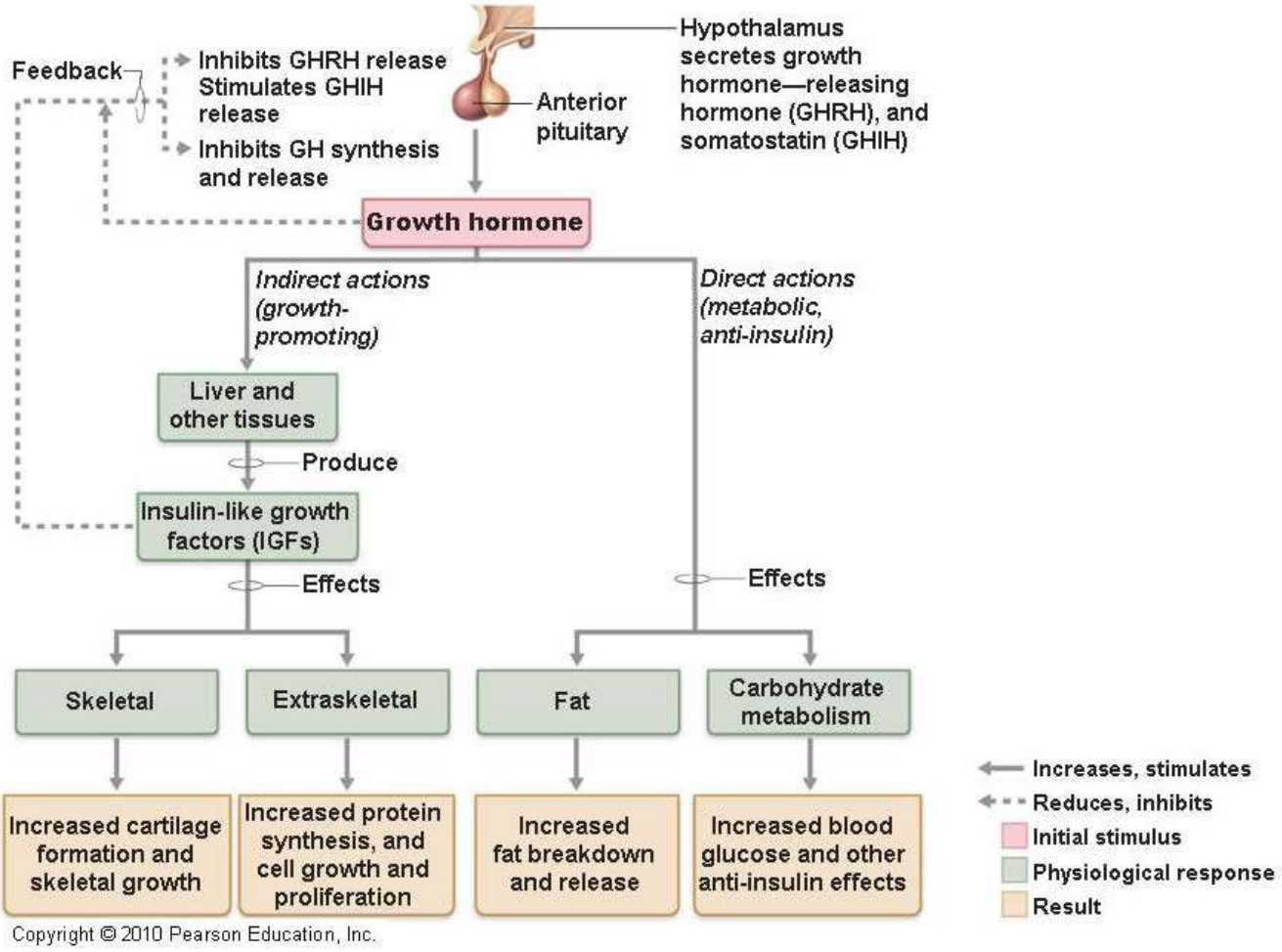
There are six adenohypophyseal hormones and one prohormone.

Growth hormone (GH) stimulates body cells to increase in size and divide.

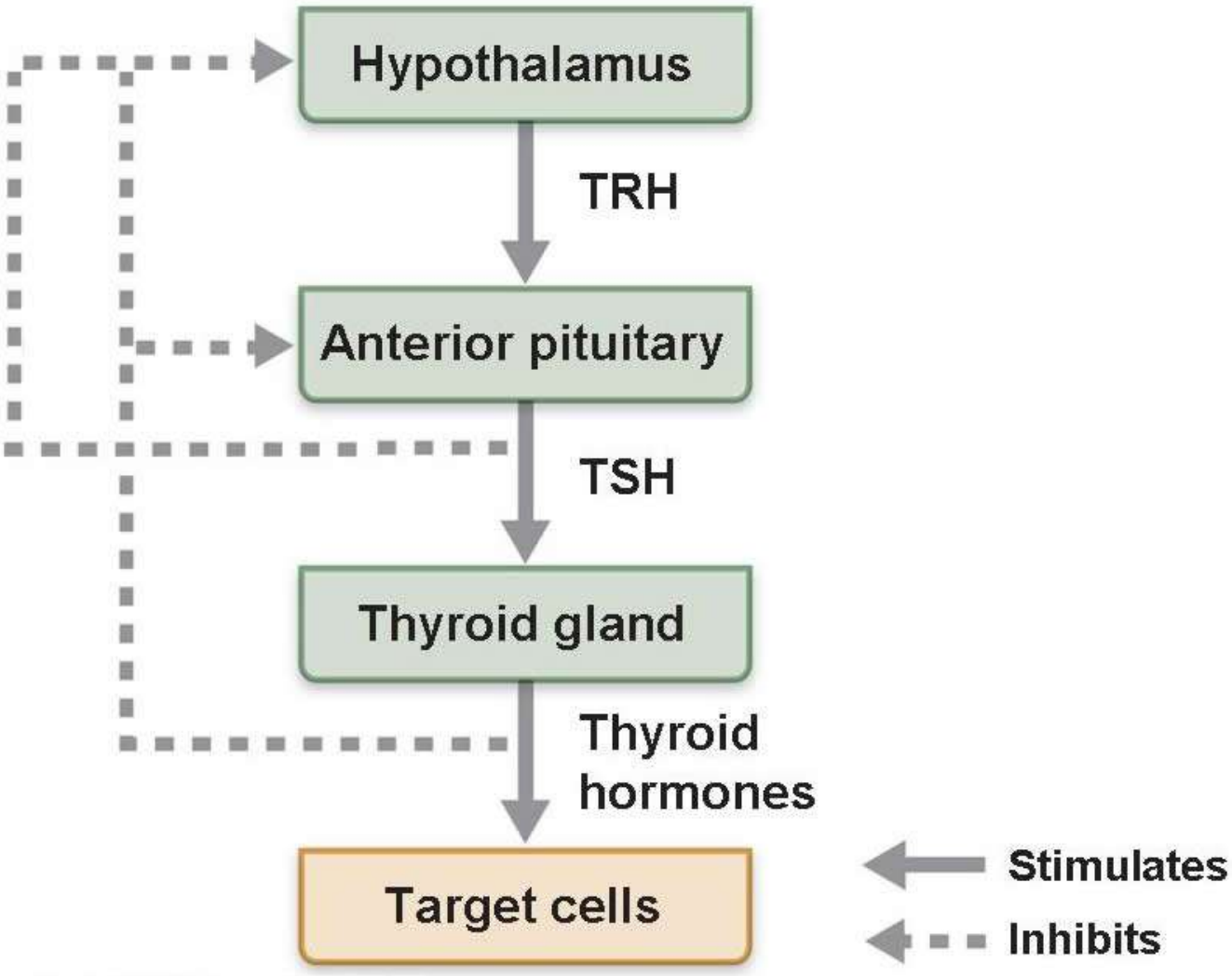
TABLE 16.1 Pituitary Hormones: Summary of Regulation and Effects

HORMONE (CHEMICAL STRUCTURE AND CELL TYPE)	REGULATION OF RELEASE	TARGET ORGAN AND EFFECTS	EFFECTS OF HYPOSECRETION ↓ AND HYPERSECRETION ↑
 **Anterior Pituitary Hormones**			
Growth hormone (GH) (Protein, somatotroph)	**Stimulated** by GHRH* release, which is triggered by low blood levels of GH as well as by a number of secondary triggers including hypoglycemia, increases in blood levels of amino acids, low levels of fatty acids, exercise, other types of stressors, and estrogens **Inhibited** by feedback inhibition exerted by GH and IGFs, and by hyperglycemia, hyperlipidemia, obesity, and emotional deprivation via either increased GHIH* (somatostatin) or decreased GHRH* release	 Liver, muscle, bone, cartilage, and other tissues: anabolic hormone; stimulates somatic growth; mobilizes fats; spares glucose Growth-promoting effects mediated indirectly by IGFs	↓ Pituitary dwarfism in children ↑ Gigantism in children; acromegaly in adults

*Indicates hypothalamic releasing and inhibiting hormones:
GHRH = growth hormone–releasing hormone; GHIH = growth hormone–inhibiting hormone



Thyroid stimulating hormone (TSH) is a tropic hormone that stimulates normal development and secretion of the thyroid gland.



Adrenocorticotropic hormone (ACTH) is a tropic hormone stimulates the adrenal cortex to release corticosteroid hormones. Pro-opiomelanocortin (POMC) is a prohormone that is the source of adrenocorticotropic hormone, melanocyte stimulating hormone (which, at normal levels acts in the CNS) and two opiates.

Follicle-stimulating hormone (FSH) is a tropic hormone that stimulates gamete production.

Leutinizing hormone (LH) is a tropic hormone that promotes ovulation in females and production of gonadal hormones.

Prolactin stimulates milk production in females, and may enhance testosterone in males.

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HORMONE (CHEMICAL STRUCTURE AND CELL TYPE)	REGULATION OF RELEASE	TARGET ORGAN AND EFFECTS	EFFECTS OF HYPOSECRETION ↓ AND HYPERSECRETION ↑
Anterior Pituitary Hormones 			
Thyroid-stimulating hormone (TSH) (Glycoprotein, thyrotroph)	**Stimulated** by TRH* and indirectly by pregnancy and (in infants) cold temperature **Inhibited** by feedback inhibition exerted by thyroid hormones on anterior pituitary and hypothalamus and by GHIH*	 Thyroid gland: stimulates thyroid gland to release thyroid hormones	↓ Cretinism in children; myxedema in adults ↑ Hyperthyroidism; effects similar to those of Graves' disease, in which antibodies mimic TSH
Adrenocorticotropic hormone (ACTH) (Polypeptide of 39 amino acids, corticotroph)	**Stimulated** by CRH;* stimuli that increase CRH release include fever, hypoglycemia, and other stressors **Inhibited** by feedback inhibition exerted by glucocorticoids	 Adrenal cortex: promotes release of glucocorticoids and androgens (mineralocorticoids to a lesser extent)	↓ Rare ↑ Cushing's disease
Follicle-stimulating hormone (FSH) (Glycoprotein, gonadotroph)	**Stimulated** by GnRH* **Inhibited** by feedback inhibition exerted by inhibin, and estrogen in females and testosterone in males	 Ovaries and testes: in females, stimulates ovarian follicle maturation and estrogen production; in males, stimulates sperm production	↓ Failure of sexual maturation ↑ No important effects
Luteinizing hormone (LH) (Glycoprotein, gonadotroph)	**Stimulated** by GnRH* **Inhibited** by feedback inhibition exerted by estrogen and progesterone in females and testosterone in males	 Ovaries and testes: in females, triggers ovulation and stimulates ovarian production of estrogen and progesterone; in males, promotes testosterone production	As for FSH
Prolactin (PRL) (Protein, lactotroph)	**Stimulated** by decreased PIH*; release enhanced by estrogens, birth control pills, breast-feeding, and dopamine-blocking drugs **Inhibited** by PIH* (dopamine)	 Breast secretory tissue: promotes lactation	↓ Poor milk production in nursing women ↑ Inappropriate milk production (galactorrhea); cessation of menses in females; impotence in males

*Indicates hypothalamic releasing and inhibiting hormones: GHRH = growth hormone–releasing hormone; GHIH = growth hormone–inhibiting hormone; TRH = thyrotropin-releasing hormone; CRH = corticotropin-releasing hormone; GnRH = gonadotropin-releasing hormone; PIH = prolactin-inhibiting hormone

Two neurohormones are synthesized by the hypothalamus and secreted by the posterior pituitary.

Oxytocin acts on the smooth muscle of the uterus and breast to cause uterine contractions during childbirth and milk let-down during nursing.

Antidiuretic hormone (ADH) acts on kidney tubules to promote increased water reabsorption.

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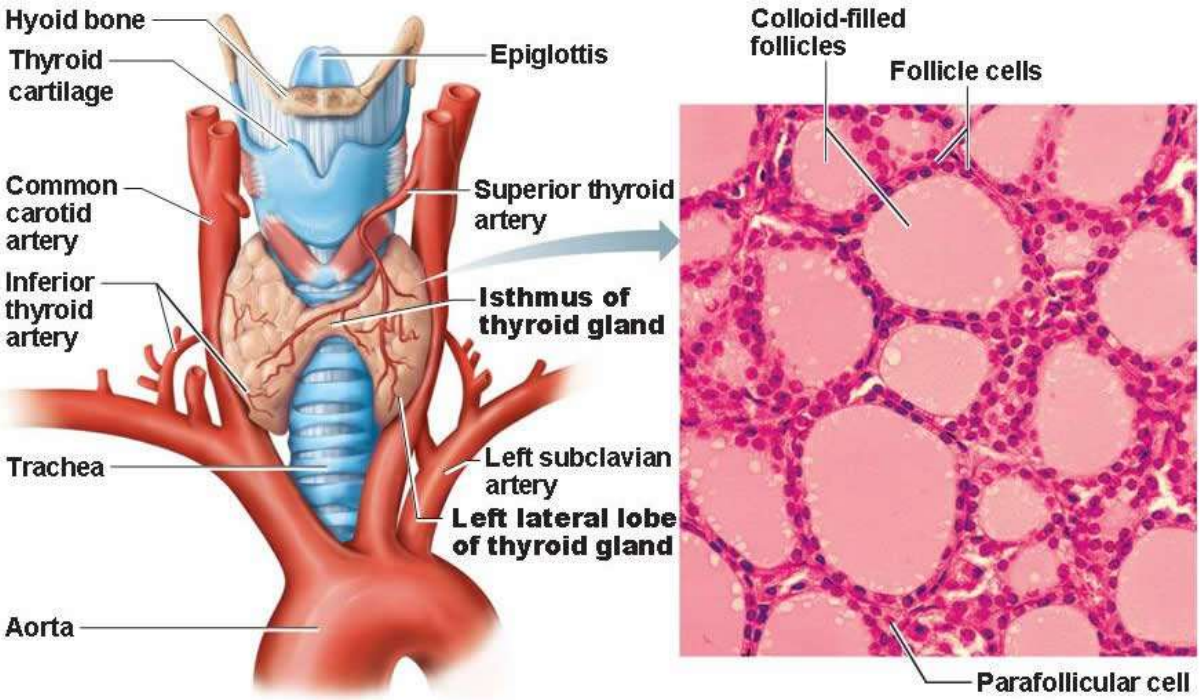
HORMONE (CHEMICAL STRUCTURE AND CELL TYPE)	REGULATION OF RELEASE	TARGET ORGAN AND EFFECTS	EFFECTS OF HYPOSECRETION ↓ AND HYPERSECRETION ↑
Posterior Pituitary Hormones (Made by Hypothalamic Neurons and Stored in Posterior Pituitary)			
			
Oxytocin (Peptide mostly from neurons in paraventricular nucleus of hypothalamus)	**Stimulated** by impulses from hypothalamic neurons in response to cervical/uterine stretching and suckling of infant at breast **Inhibited** by lack of appropriate neural stimuli	 Uterus: stimulates uterine contractions; initiates labor; breast: initiates milk ejection	Unknown
Antidiuretic hormone (ADH) or **vasopressin** (Peptide, mostly from neurons in supraoptic nucleus of hypothalamus)	**Stimulated** by impulses from hypothalamic neurons in response to increased osmolality of blood or decreased blood volume; also stimulated by pain, some drugs, low blood pressure **Inhibited** by adequate hydration of the body and by alcohol	 Kidneys: stimulates kidney tubule cells to reabsorb water	↓ Diabetes insipidus ↑ Syndrome of inappropriate ADH secretion (SIADH)

The Thyroid Gland

The thyroid gland consists of hollow follicles with follicle cells that produce thyroglobulin, and parafollicular cells that produce calcitonin.



(a) Gross anatomy of the thyroid gland, anterior view

(b) Photomicrograph of thyroid gland follicles (125x)

Thyroid hormone consists of two amine hormones: thyroxine (T_4) and triiodothyronine (T_3), that act on all body cells to increase basal metabolic rate and body heat production.

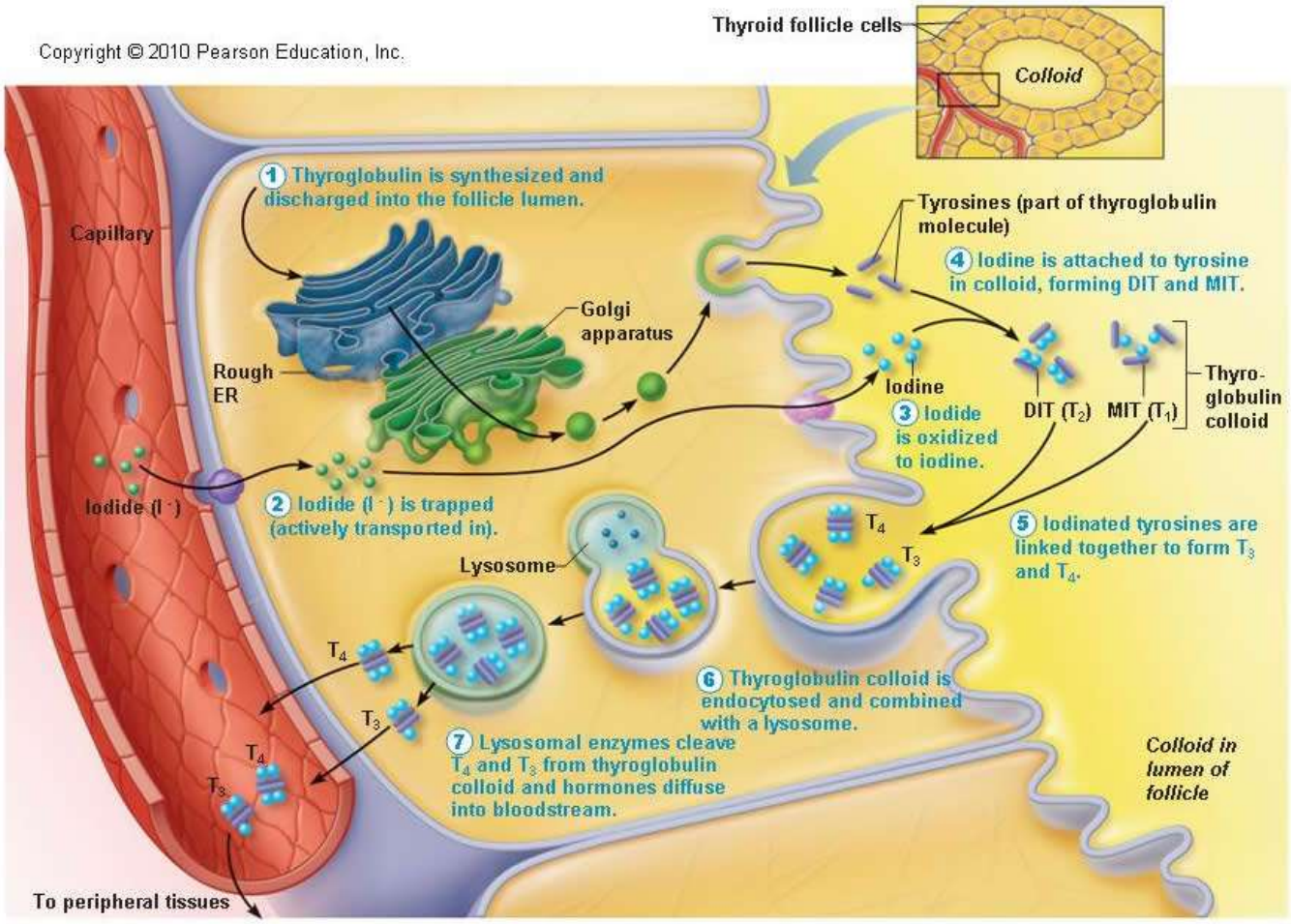


TABLE 16.2 Major Effects of Thyroid Hormone (T_4 and T_3) in the Body

PROCESS OR SYSTEM AFFECTED	NORMAL PHYSIOLOGICAL EFFECTS	EFFECTS OF HYPOSECRETION	EFFECTS OF HYPERSECRETION
Basal metabolic rate (BMR)/ temperature regulation	Promotes normal oxygen use and BMR; calorigenesis; enhances effects of sympathetic nervous system	BMR below normal; decreased body temperature and cold intolerance; decreased appetite; weight gain; reduced sensitivity to catecholamines	BMR above normal; increased body temperature and heat intolerance; increased appetite; weight loss
Carbohydrate/lipid/protein metabolism	Promotes glucose catabolism; mobilizes fats; essential for protein synthesis; enhances liver's synthesis of cholesterol	Decreased glucose metabolism; elevated cholesterol/triglyceride levels in blood; decreased protein synthesis; edema	Enhanced catabolism of glucose, proteins, and fats; weight loss; loss of muscle mass
Nervous system	Promotes normal development of nervous system in fetus and infant; promotes normal adult nervous system function	In infant, slowed/deficient brain development, retardation; in adult, mental dulling, depression, paresthesias, memory impairment, hypoactive reflexes	Irritability, restlessness, insomnia, personality changes, exophthalmos (in Graves' disease)
Cardiovascular system	Promotes normal functioning of the heart	Decreased efficiency of pumping action of the heart; low heart rate and blood pressure	Increased sensitivity to catecholamines leads to rapid heart rate and possible palpitations; high blood pressure; if prolonged, heart failure
Muscular system	Promotes normal muscular development and function	Sluggish muscle action; muscle cramps; myalgia	Muscle atrophy and weakness
Skeletal system	Promotes normal growth and maturation of the skeleton	In child, growth retardation, skeletal stunting and retention of child's body proportions; in adult, joint pain	In child, excessive skeletal growth initially, followed by early epiphyseal closure and short stature; in adult, demineralization of skeleton
Gastrointestinal system	Promotes normal GI motility and tone; increases secretion of digestive juices	Depressed GI motility, tone, and secretory activity; constipation	Excessive GI motility; diarrhea; loss of appetite
Reproductive system	Promotes normal female reproductive ability and lactation	Depressed ovarian function; sterility; depressed lactation	In females, depressed ovarian function; in males, impotence
Integumentary system	Promotes normal hydration and secretory activity of skin	Skin pale, thick, and dry; facial edema; hair coarse and thick	Skin flushed, thin, and moist; hair fine and soft; nails soft and thin

Hypothyroidism may result from inadequate TRH release, inadequate TSH release, dysfunction of the thyroid gland itself, inadequate dietary iodine, or autoimmune destruction (Hashimoto's autoimmune throiditis).

Full blown hypothyroidism in adults is known as myxedema (mucous swelling). If myxedema results from lack of iodine the thyroid gland continues to make thyroglobulin but iodinate it, resulting in an enlarged thyroid, or colloidal/endemic goiter (figure 16a, below).

Treatment typically involves iodine supplementation, thyroid hormone supplementation, and sometimes ablation of the thyroid followed by thyroid hormone replacement. Ablation, which is also the treatment for

Graves' disease, is typically accomplished by administration of radioactive iodine.

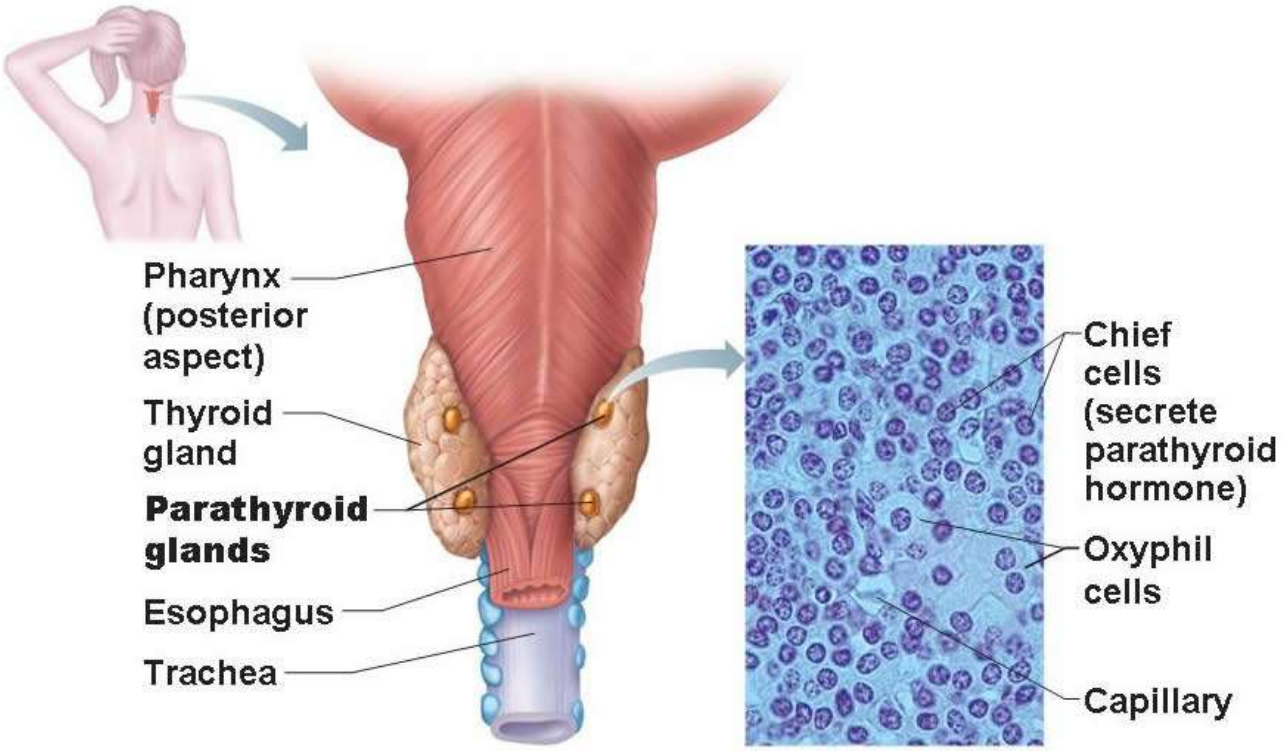
The most common cause of hyperthyroidism is an autoimmune disease (Graves' disease) in which anti-TSH receptor antibodies bind to TSH receptors on the thyroid and stimulate continuous thyroid hormone release. The feedback mechanism is short-circuited because the production and release of thyroid hormone is not dependent on TSH.

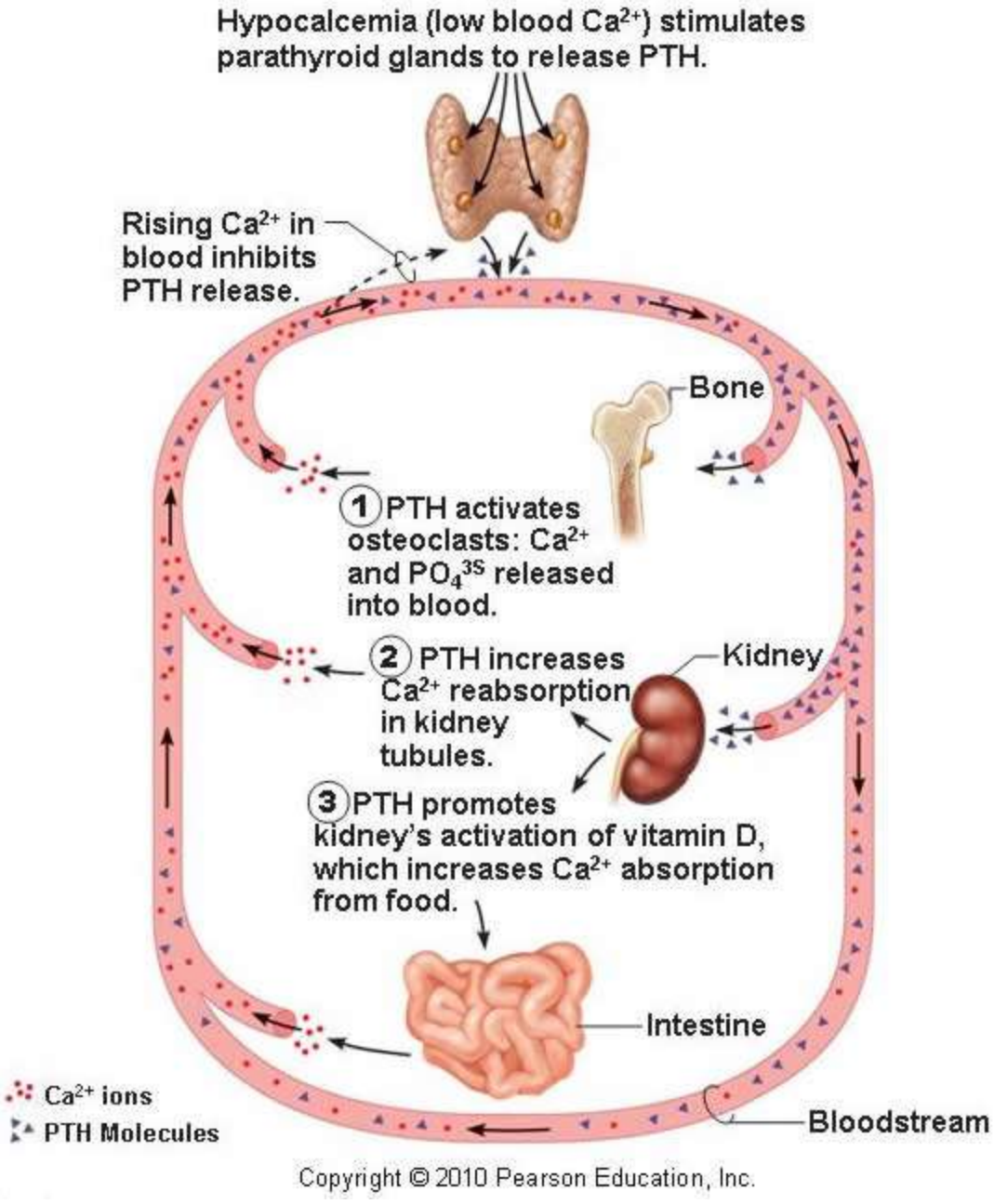
Exopthalmos may occur, indicating edema and fibrosis of tissue behind the eyes (figure 16b, below).

Calcitonin (produced by parafollicular or "C" cells) is a peptide hormone that lowers blood calcium by inhibiting osteoclast activity, and stimulates Ca^{2+} uptake and incorporation into the bone matrix.

The Parathyroid Glands

The parathyroid glands contain chief cells that secrete parathyroid hormone, or parathormone.

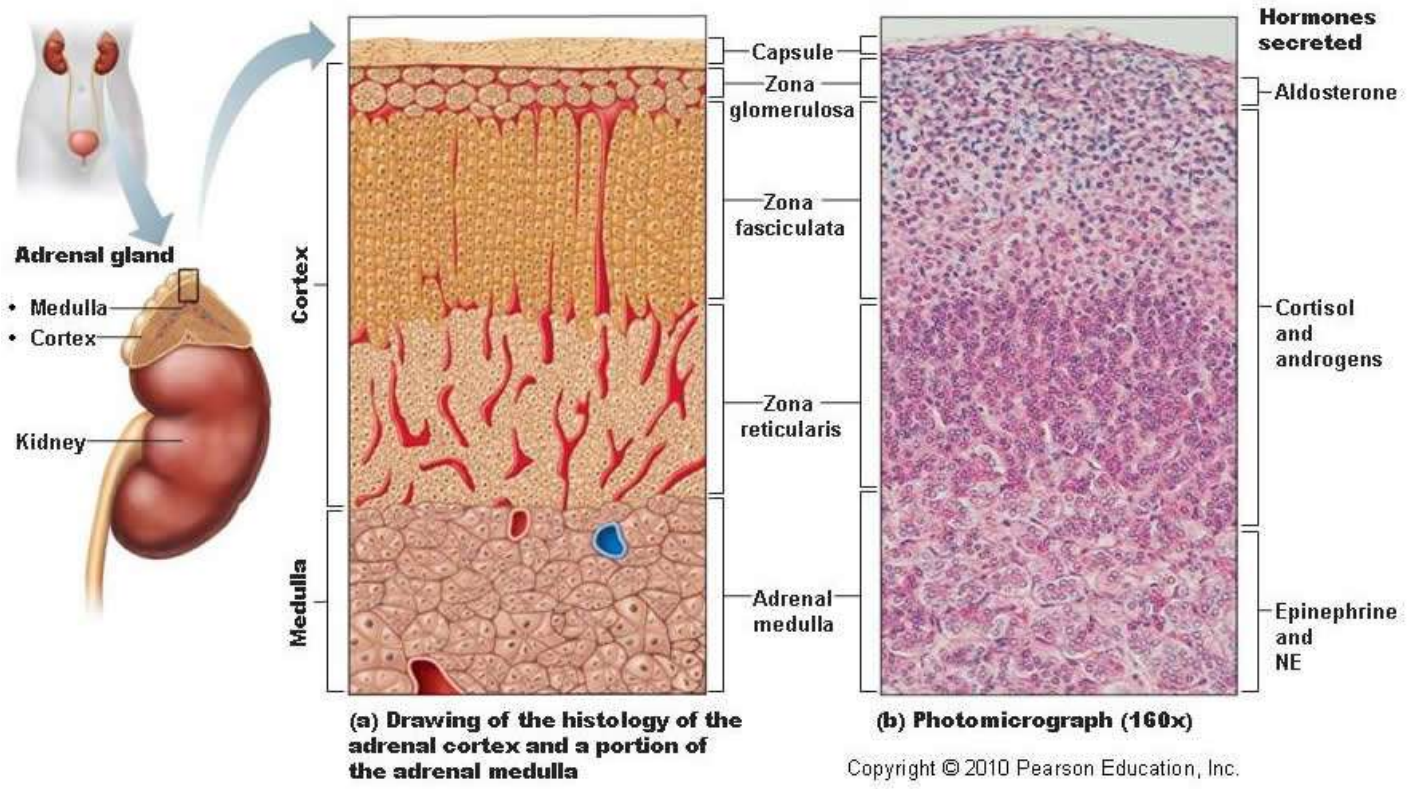




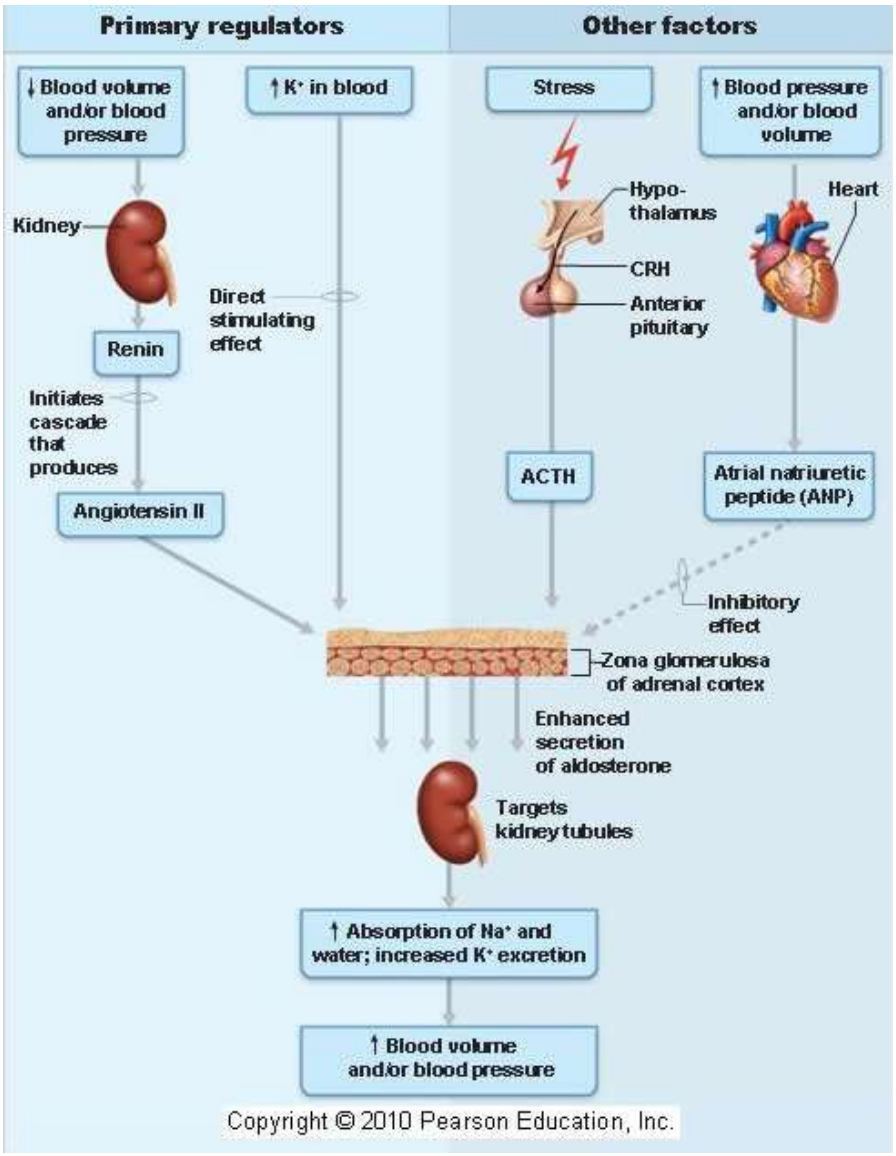
The Adrenal (Suprarenal) Glands

The adrenal glands, or suprarenal glands, consist of two regions: an inner adrenal medulla and an outer adrenal cortex.

The adrenal cortex produces corticosteroids from three distinct regions: the zona glomerulosa, the zona fasciculata, and the zona reticularis.



Glomerulosa: primarily mineralocorticoids, mostly aldosterone, are essential to regulation of electrolyte concentrations of extracellular fluids (Na^+ & K^+).



Aldosterone secretion is regulated by the renin-angiotensin mechanism, fluctuating blood concentrations of sodium and potassium ions, and secretion of ACTH.

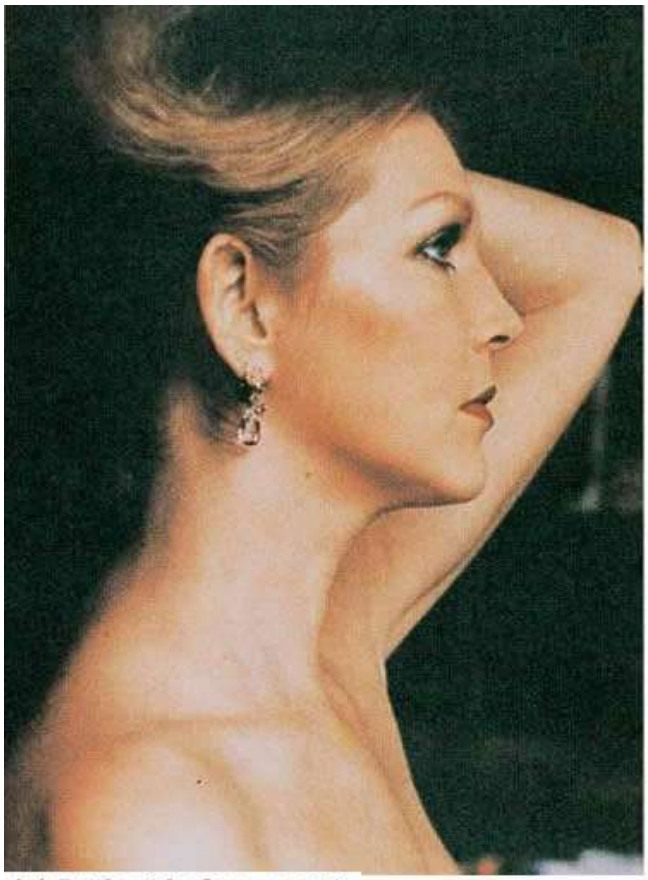
Fasiculata: primarily glucocorticoids are released in response to stress through the action of ACTH.

Reticularis: primarily gonadocorticoids are mostly weak androgens, which are converted to testosterone and estrogens in the tissue cells.

Cushing's syndrome/disease is caused by an excess of glucocorticoids. The disease may be caused by a glucocorticoid producing tumor but in most cases administration of glucocorticoids clinically results in the syndrome. Cushing's syndrome is characterized by elevated blood

glucose, loss of muscle and protein from bone, and hypertension and edema due to salt and water retention. Anti-inflammatory effects can cause increased susceptibility to disease and poor wound healing.

The signs include "moon" face (due to edema), and redistribution of fat to the back of the neck (buffalo hump) and abdomen.

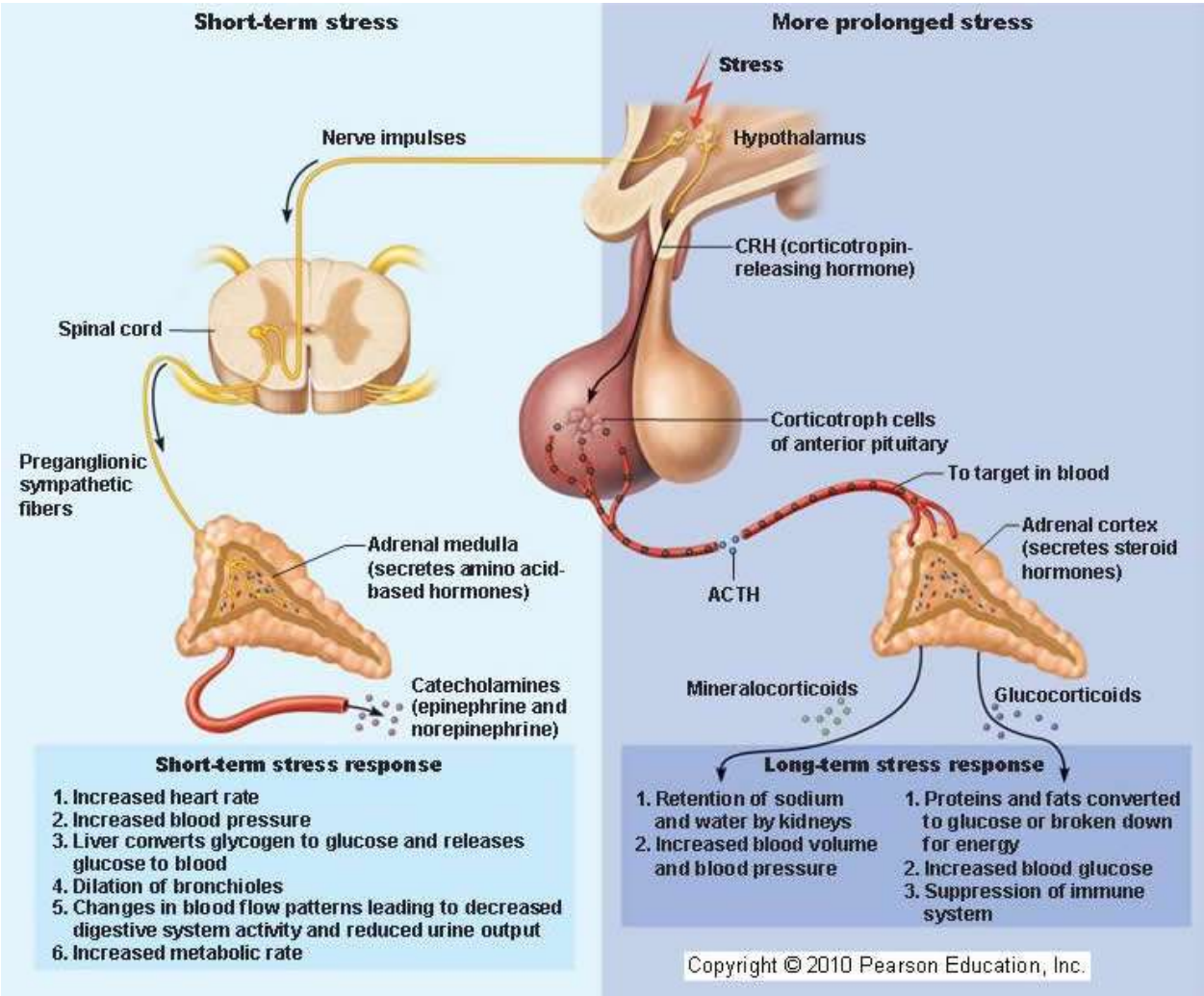


(a) Patient before onset.

(b) Same patient with Cushing's syndrome. The white arrow shows the characteristic "buffalo hump" of fat on the upper back.

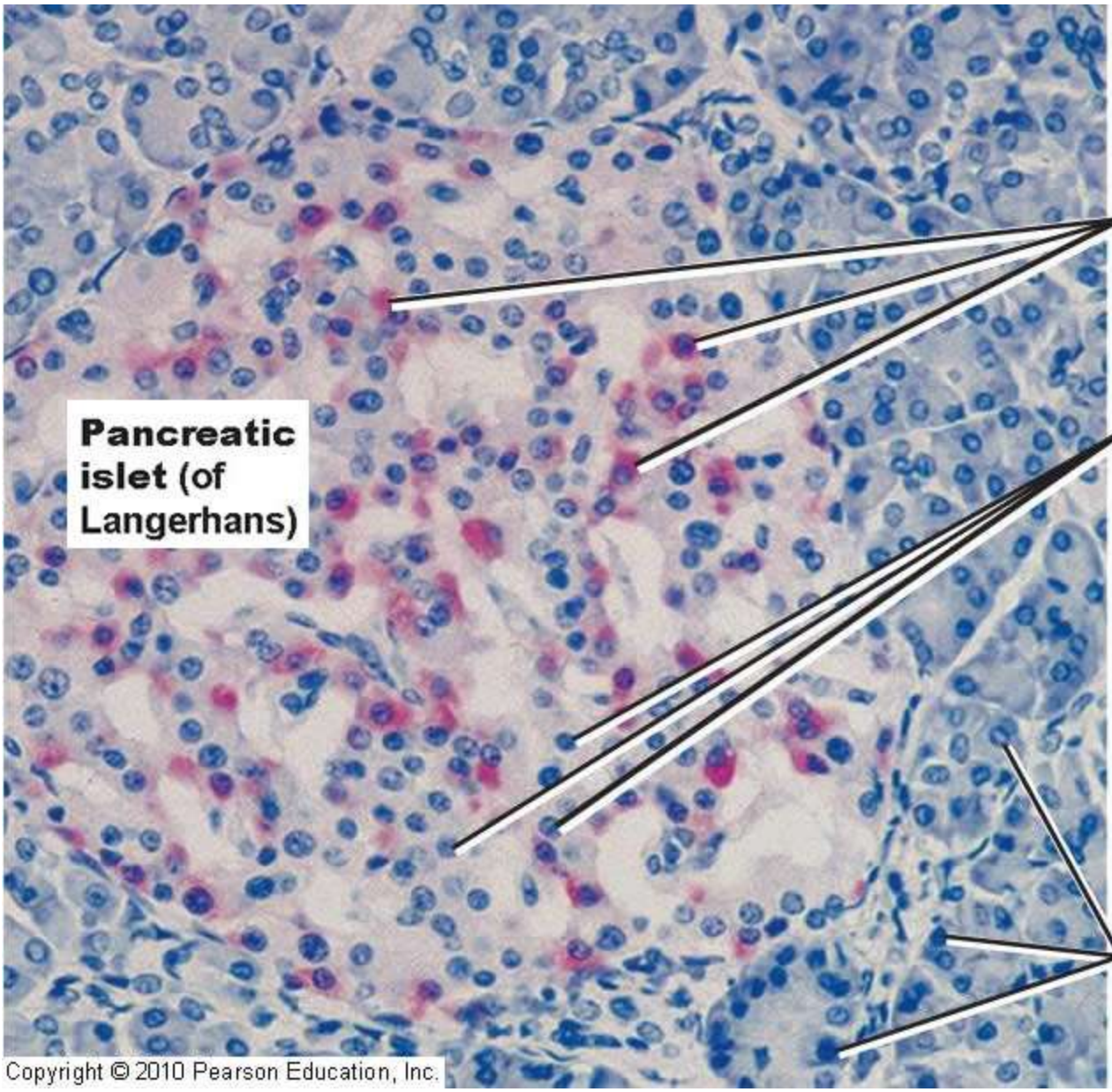
Addison's disease is a disease of cortical insufficiency, resulting in weight loss, low plasma glucose and sodium levels, and an in crease in plasma potassium levels. Common signs are severe dehydration and hypotension. Disruption of the feedback mechanism that controls POMC release may result in over production of MSH and a general bronzing/darkening of the skin.

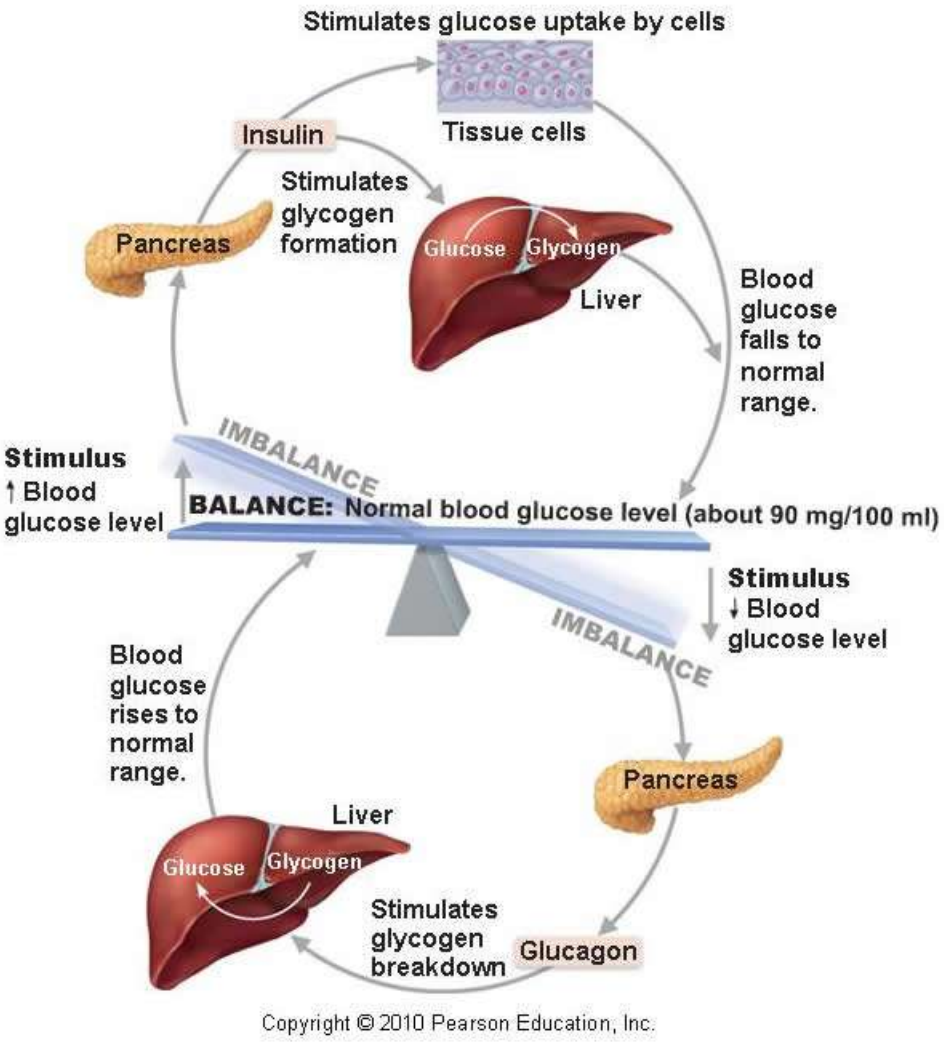
The adrenal medulla contains chromaffin cells that synthesize epinephrine and norepinephrine (stimulus is acetylcholine released by preganglionic sympathetic fibers).



The Pancreas

The pancreas is a mixed gland that contains both endocrine and exocrine gland cells.





Insulin lowers blood suga levels by enhancing membrane transport of glucose into body cells.

Glucagon targets the live where it promotes glycogenolysis, gluconeogenesis, and release of glucose to the blood.

Diabetes mellitus is a disease of insulin insufficiency (type I) or insulin resistance (type II), resulting in elevated blood glucose levels.

Glucose spilling into the urine results in osmotic diuresis, giving rise to dehydration and increased thirst. Inability of cells to utilize glucose leads to hunger, all of which give rise to the three classic signs of diabetes, polyuria, polydipsia, and polyphagia.

To meet energy needs of the body fats are mobilized and proteins broken down to utilize amino acids for fuel, resulting in metabolic acidosis.

TABLE 16.4 Symptoms of Insulin Deficit (Diabetes Mellitus)

ORGANS/TISSUES INVOLVED	ORGAN/TISSUE RESPONSES TO INSULIN DEFICIENCY	*RESULTING CONDITIONS* IN BLOOD	*RESULTING CONDITIONS* IN URINE	SIGNS AND SYMPTOMS
 Liver, Adipose tissue, Muscle	Decreased glucose uptake and utilization	Hyperglycemia	Glycosuria Osmotic diuresis	Polyuria (and dehydration, soft eyeballs) Polydipsia (and fatigue, weight loss) Polyphagia
	Glycogenolysis			
	Protein catabolism and gluconeogenesis			
	Lipolysis and ketogenesis	Lipidemia and ketoacidosis	Ketonuria Loss of Na^+, K^+; electrolyte and acid-base imbalances	Acetone breath Hyperpnea Nausea, vomiting, abdominal pain Cardiac irregularities Central nervous system depression; coma

Long-term complications include decreased circulatory efficiency, peripheral neuropathy, hypertension, and acceleration of atherosclerosis.

Type I diabetes results from destruction of pancreatic beta cells and subsequent loss of insulin production.

Autoimmune destruction of pancreatic beta cells appears to be linked to certain viral infections and correlates with HLA haplotypes (more in the immune system chapter).

Type II diabetes results from insulin resistance and is associated with obesity and genetic factors.

Adipocyte-derived adiponectin is an insulin-sensitizing and antiatherosclerotic hormone, and recent studies have demonstrated that adiponectin level is a good predictor of developing type 2 diabetes and coronary artery disease. Decreasing adiponectin levels are linked to an interaction between genetic factors, such as mutations in the adiponectin gene, and environmental factors, such as high-fat diet.

Other candidates for involvement include PC-1, which inhibits phosphorylation of the insulin receptor, and inhibition or mutations in glucose transporter proteins (glut-4 for example).

The Gonads

The ovaries produce estrogens and progesterone.

The testes produce testosterone.

The Pineal Gland

Secretes melatonin, a hormone derived from serotonin, in a diurnal cycle.

Indirectly receives input from the visual pathways in order to determine the timing of day and night.

The Thymus

The thymus produces thymopoietin, thymic factor, and thymosin, which are essential for the development of T-lymphocytes and the immune response.

Thymopoietin - growth factor for immature T-cells

Thymic factor (thymulin) - T-cell differentiation and enhancement of T and NK cell actions, neuroendocrine activity (positive correlation between thymulin plasma levels and ACTH levels), and seems to have an effect on pro-inflammatory cytokines. Analgesic and anti-inflammatory effects in the CNS.

Thymosin - promotes differentiation of T_0 cells to T_1 and late T_2 differentiation, accelerates proliferation of mature and immature lymphoid cells.

Other Hormone-Producing Structures

The atria of the heart contain specialized cells that secrete atrial natriuretic factor resulting in decreased blood volume, blood pressure, and blood sodium concentration.

The gastrointestinal tract contains enteroendocrine cells throughout the mucosa that secrete hormones to regulate digestive functions.

The placenta secretes estrogens, progesterone, and human chorionic gonadotropin, which act on the uterus to influence pregnancy.

The kidneys produce erythropoietin, which signals the bone marrow to produce red blood cells.

The skin produces cholecalciferol, an inactive form of vitamin D_3.

Adipose tissue produces leptin, which acts on the CNS to produce a feeling of satiety, and resistin, an insulin antagonist.

TABLE 16.5 Selected Examples of Hormones Produced by Organs Other Than the Major Endocrine Organs

SOURCE	HORMONE	CHEMICAL COMPOSITION	TRIGGER	TARGET ORGAN AND EFFECTS
Adipose tissue	Leptin	Peptide	Secretion proportional to fat stores; increased by nutrient uptake	Brain: suppresses appetite; increases energy expenditure
Adipose tissue	Resistin, adiponectin	Peptides	Unknown	Fat, muscle, liver: resistin antagonizes insulin's action and adiponectin enhances it
GI tract mucosa				
• Stomach	Gastrin	Peptide	Secreted in response to food	Stomach: stimulates glands to release hydrochloric acid (HCl)
• Duodenum (of small intestine)	Intestinal gastrin	Peptide	Secreted in response to food, especially fats	Stomach: stimulates HCl secretion and gastrointestinal tract motility
• Duodenum	Secretin	Peptide	Secreted in response to food	Pancreas and liver: stimulates release of bicarbonate-rich juice; Stomach: inhibits secretory activity
• Duodenum	Cholecystokinin (CCK)	Peptide	Secreted in response to food	Pancreas: stimulates release of enzyme-rich juice; Gallbladder: stimulates expulsion of stored bile; Hepatopancreatic sphincter: causes sphincter to relax, allowing bile and pancreatic juice to enter duodenum
• Duodenum (and other gut regions)	Incretins [glucose-dependent insulinotropic peptide (GIP) and glucagon-like peptide 1 (GLP-1)]	Peptide	Secreted in response to glucose in intestinal lumen	Pancreas: enhances insulin release and inhibits glucagon release caused by increased blood glucose
Heart (atria)	Atrial natriuretic peptide	Peptide	Secreted in response to stretching of atria (by rising blood pressure)	Kidney: inhibits sodium ion reabsorption and renin release; adrenal cortex: inhibits secretion of aldosterone; decreases blood pressure
Kidney	Erythropoietin (EPO)	Glycoprotein	Secreted in response to hypoxia	Red bone marrow: stimulates production of red blood cells
	Renin	Peptide	Secreted in response to low blood pressure or plasma volume, or sympathetic stimulation	Acts as an enzyme to initiate renin-angiotensin mechanism of aldosterone release; returns blood pressure to normal
Skeleton	Osteocalcin	Peptide	Unknown	Increases insulin production and insulin sensitivity
Skin (epidermal cells)	Cholecalciferol (provitamin D_3)	Steroid	Activated by the kidneys to active vitamin D_3 (calcitriol) in response to parathyroid hormone	Intestine: stimulates active transport of dietary calcium across intestinal cell membranes
Thymus	Thymulin, thymopoietins, thymosins	Peptides	Unknown	Mostly act locally as paracrines; involved in T lymphocyte development and in immune responses

Developmental Aspects of the Endocrine System

Endocrine glands derived from mesoderm produce steroid hormones; those derived from ectoderm or endoderm produce amines, peptides, or protein hormones.

Environmental pollutants have been demonstrated to have effects on sex hormones, thyroid hormone, and glucocorticoids.

Old age may bring about changes in rate of hormone secretion, breakdown, excretion, and target cell sensitivity.