- **Mechanisms of physiological regulation.**
- **Humoral regulation of physiological functions.**
- **Interrelations of nervous and humoral regulation**

Snegir AG

Neural and humoral regulation of body functions

Neural regulation	Humoral regulation
Local action	Diffuse action
Information transfer through nerve fibers	Information transfer through fluids (blood)
Fast (120 m/s)	Slow (0,5 m/s)
Short time period	Long time period (half-life)
Depends of nerve fibers and synapses properties	Depends of blood flow and transport proteins

Coordination of Body Functions by Chemical Messengers

1. **Neurotransmitters** are released by axon terminals of neurons into the synaptic junctions and act locally to control nerve cell functions.
2. **Neuromodulator** - a chemical agent that is released by a neurosecretory cell and acts on other neurons in a local region of the central nervous system by modulating their response to neurotransmitters.
3. **Endocrine hormones** are released by glands or specialized cells into the circulating blood and influence the function of cells at another location in the body.

4. **Neuroendocrine hormones** are secreted **by neurons** into the circulating blood and influence the function of cells at another location in the body.

5. **Tissue hormones** are hormones synthesized by cells **other than those in the endocrine** system (prostaglandins).

6. **Cytokines** are peptides secreted by cells into the extracellular fluid and can function as autocrines, paracrines, or endocrine hormones. Examples of cytokines include the interleukins and other lymphokines that are secreted by helper cells and act on other **cells of the immune system**.

7. **Metabolites** (CO_2, NO)

The action of humoral factors

- **Endocrine** hormones are released by glands or specialized cells into the circulating blood and influence the function of cells at another location in the body.
- **Neuroendocrine** hormones are secreted by neurons into the circulating blood and influence the function of cells at another location in the body.
- **Paracrines** are secreted by cells into the extracellular fluid and affect neighboring cells of a different type.
- **Autocrines** are secreted by cells into the extracellular fluid and affect the function of the same cells that produced them by binding to cell surface receptors

Other hormones affect only specific target tissues, because only these tissues have receptors for the hormone

- The locations for the different types of hormone receptors are generally the following:

1. In or on the surface of the cell membrane. The membrane receptors are specific mostly for the protein, peptide, and catecholamine hormones.

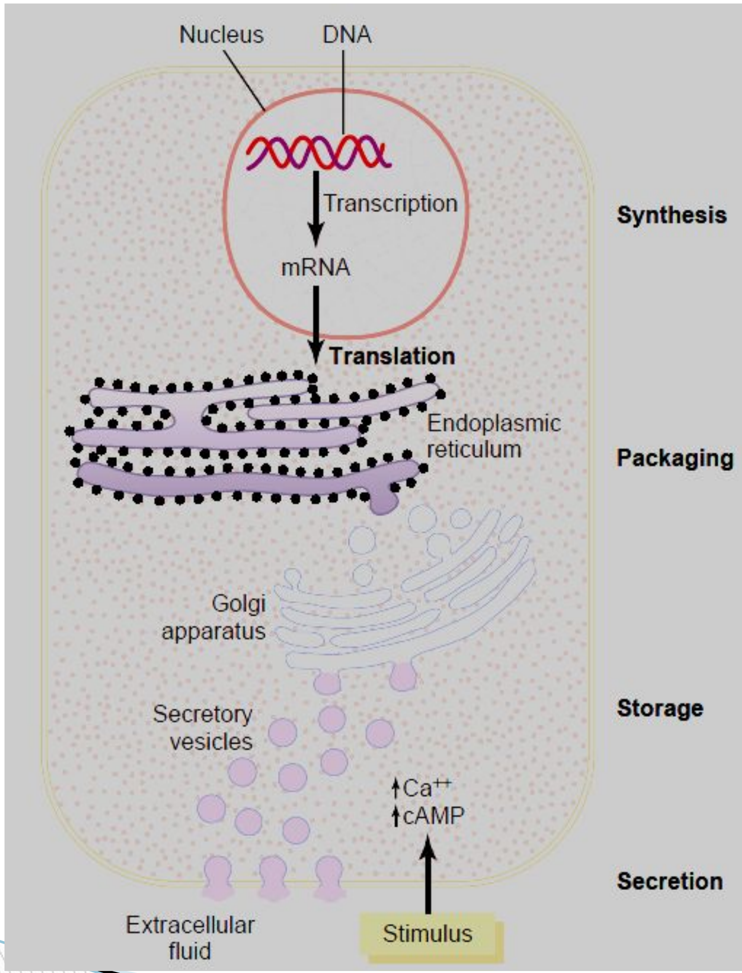
2. In the cell cytoplasm. The primary receptors for the different steroid hormones are found mainly in the cytoplasm.

3. In the cell nucleus. The receptors for the thyroid hormones are found in the nucleus and are believed to be located in direct association with one or more of the chromosomes.

There are three general classes of hormones:

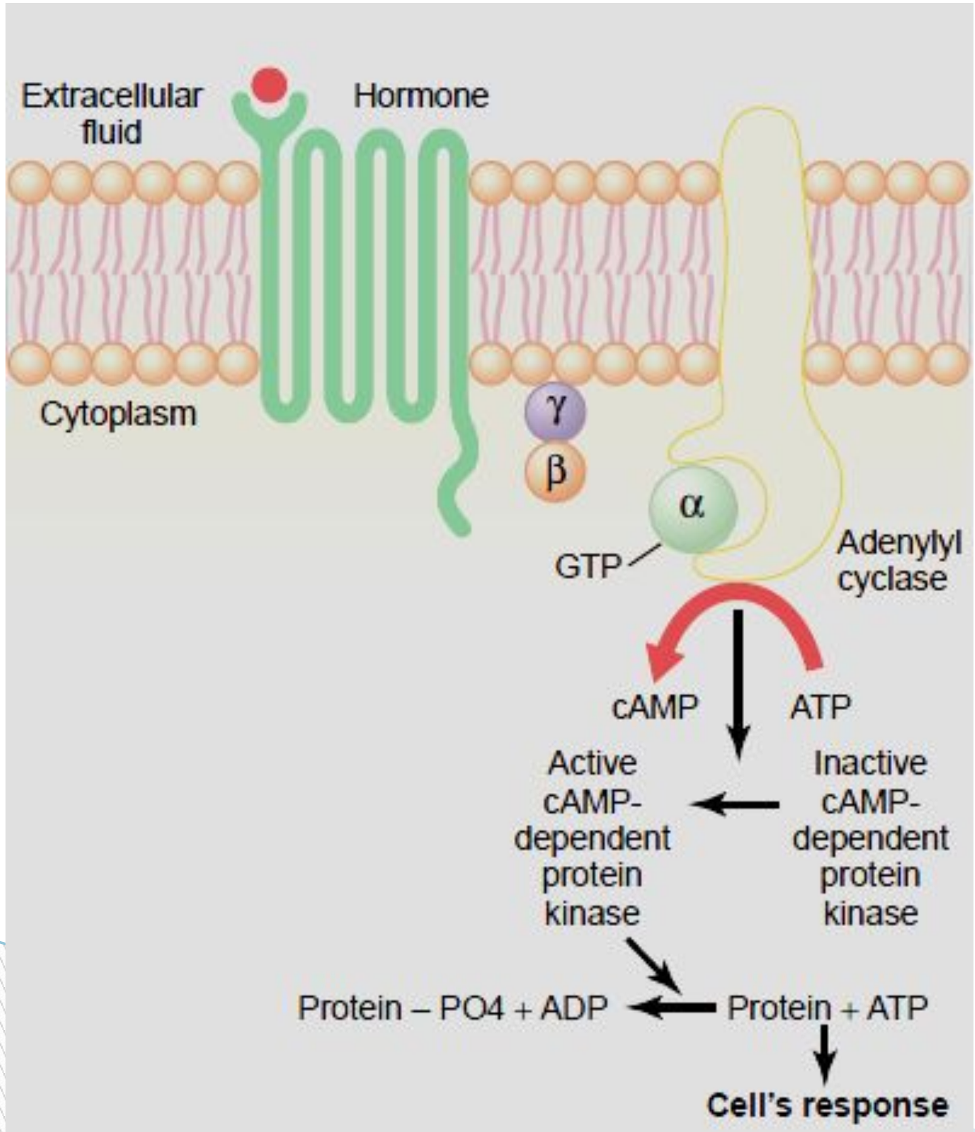
1. **Proteins and polypeptides**, including hormones secreted by the anterior and posterior pituitary gland, the pancreas (insulin and glucagon), the parathyroid gland (parathyroid hormone), and many others.
2. **Steroids** secreted by the adrenal cortex (cortisol and aldosterone), the ovaries (estrogen and progesterone), the testes (testosterone), and the placenta (estrogen and progesterone).
3. **Derivatives of the amino acid** tyrosine, secreted by the thyroid (thyroxine and triiodothyronine) and the adrenal medullae (epinephrine and norepinephrine).

Polypeptide and Protein Hormones



- Most of the hormones in the body are **polypeptides and proteins**.
- The peptide hormones are **water soluble**, allowing them to enter the circulatory system easily, where they are carried to their target tissues.
- The stimulus for hormone secretion often involves changes in **intracellular calcium** or changes in **cyclic adenosine monophosphate (cAMP)** in the cell

Adenylyl Cyclase–cAMP Second Messenger System



- Cyclic adenosine monophosphate (cAMP) mechanism by which many hormones exert their control of cell function.

- ADP, adenosine diphosphate;
- ATP, adenosine triphosphate

- Many hormones activate receptors (**Protein-Linked Hormone Receptors**) that indirectly regulate the activity of target proteins (e.g., enzymes or ion channels) by coupling with groups of cell membrane proteins called heterotrimeric GTP-binding proteins (**G proteins**).
- When the **ligand (hormone)** binds to the **extracellular part of the receptor**, a conformational change occurs in the receptor that **activates the G proteins** and induces intracellular signals that either

(1) open or close cell membrane ion channels or

(2) change the activity of an enzyme in the cytoplasm of the cell.

The second messengers

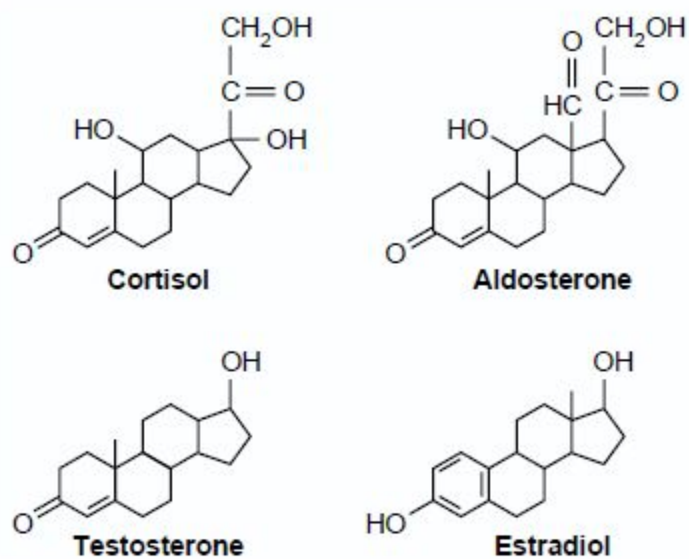
- **cAMP** is not the only second messenger used by the different hormones.
- Two other especially important ones are

(1) **calcium** ions and associated **calmodulin** and

(2) **products of membrane phospholipid breakdown (**inositol triphosphate (IP3) and diacylglycerol (DAG)**)**

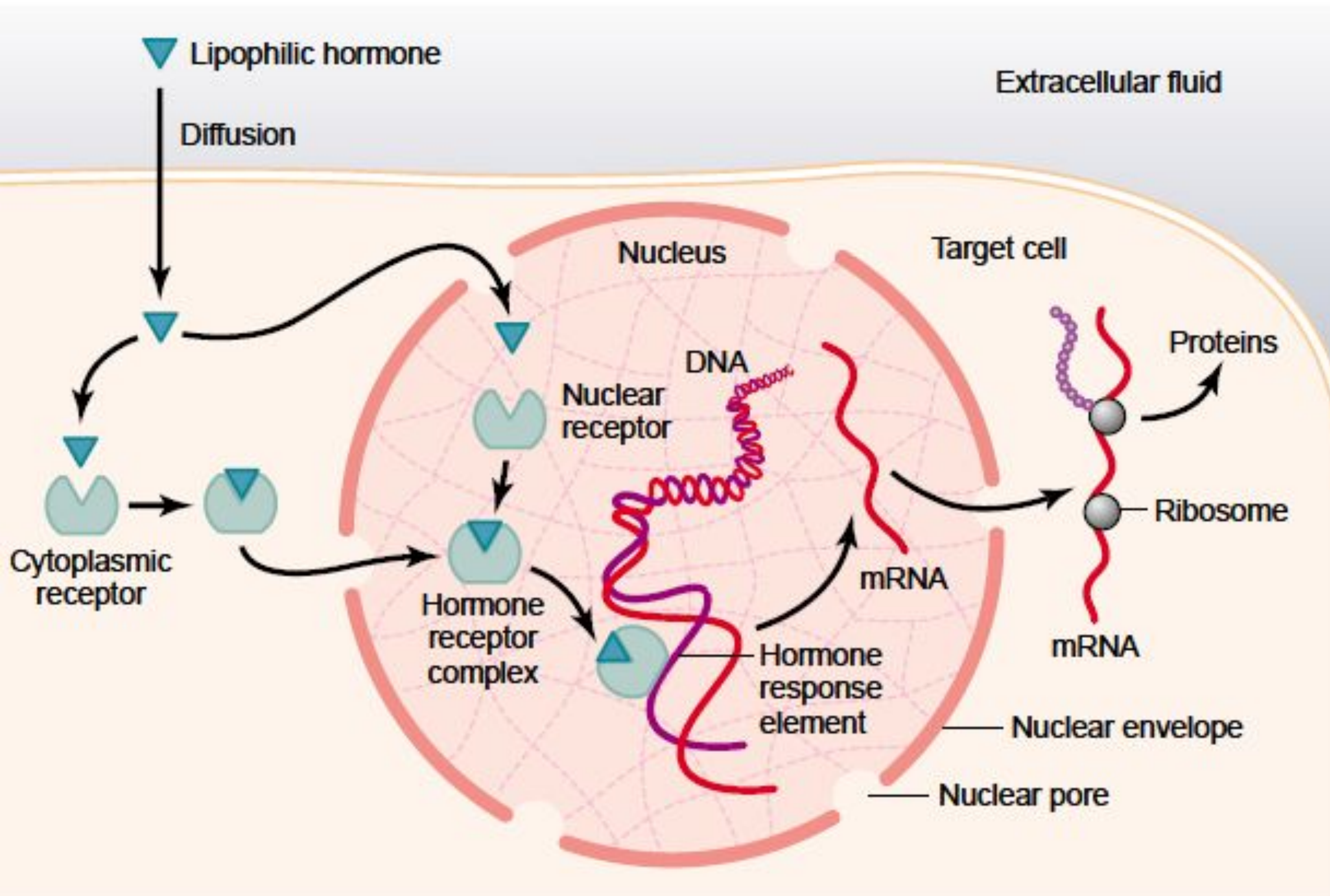
- **Enzyme-linked receptors** have their hormone-binding site on the **outside** of the cell membrane and their catalytic or enzyme-binding site on the **inside**.
- When the hormone binds to the extracellular part of the receptor, an enzyme immediately inside the cell membrane is activated (or occasionally inactivated).
- Although many enzyme-linked receptors have intrinsic enzyme activity, others rely on enzymes that are closely associated with the receptor to produce changes in cell function.

Steroid Hormones



- The chemical structure of steroid hormones is similar to that of cholesterol.
- Because the steroids are highly lipid soluble, once they are synthesized, they simply diffuse across the cell membrane and enter the interstitial fluid and then the blood

Mechanisms of interaction of lipophilic hormones, such as steroids, with intracellular receptors in target cells



After the hormone binds to the receptor in the cytoplasm or in the nucleus, the hormone-receptor complex binds to the hormone response element (promoter) on the DNA.

This either activates or inhibits gene **transcription, formation of messenger RNA** (mRNA), and **protein synthesis**

- 1. The steroid hormone diffuses **across the cell** membrane and enters the cytoplasm of the cell, where it binds with a specific **receptor protein**.
- 2. The combined receptor protein–hormone then diffuses into or is transported **into the nucleus**.
- 3. The combination binds at specific points on the DNA strands in the chromosomes, which **activatesthe transcription process** of specific genes to form mRNA.
- 4. The mRNA diffuses into the cytoplasm, where it promotes the translation process at the ribosomesto form **new proteins**

Amine Hormones

- Amine hormones are derived from tyrosine (the thyroid and the adrenal medullary hormones).
- Contrary to common belief, thyroid hormones can not traverse cell membranes in a passive manner like other lipophilic substances.
- The receptors for the thyroid hormones are found in the nucleus and are believed to be located in direct association with one or more of the chromosomes

The main regulatory functions of the endocrine system include:

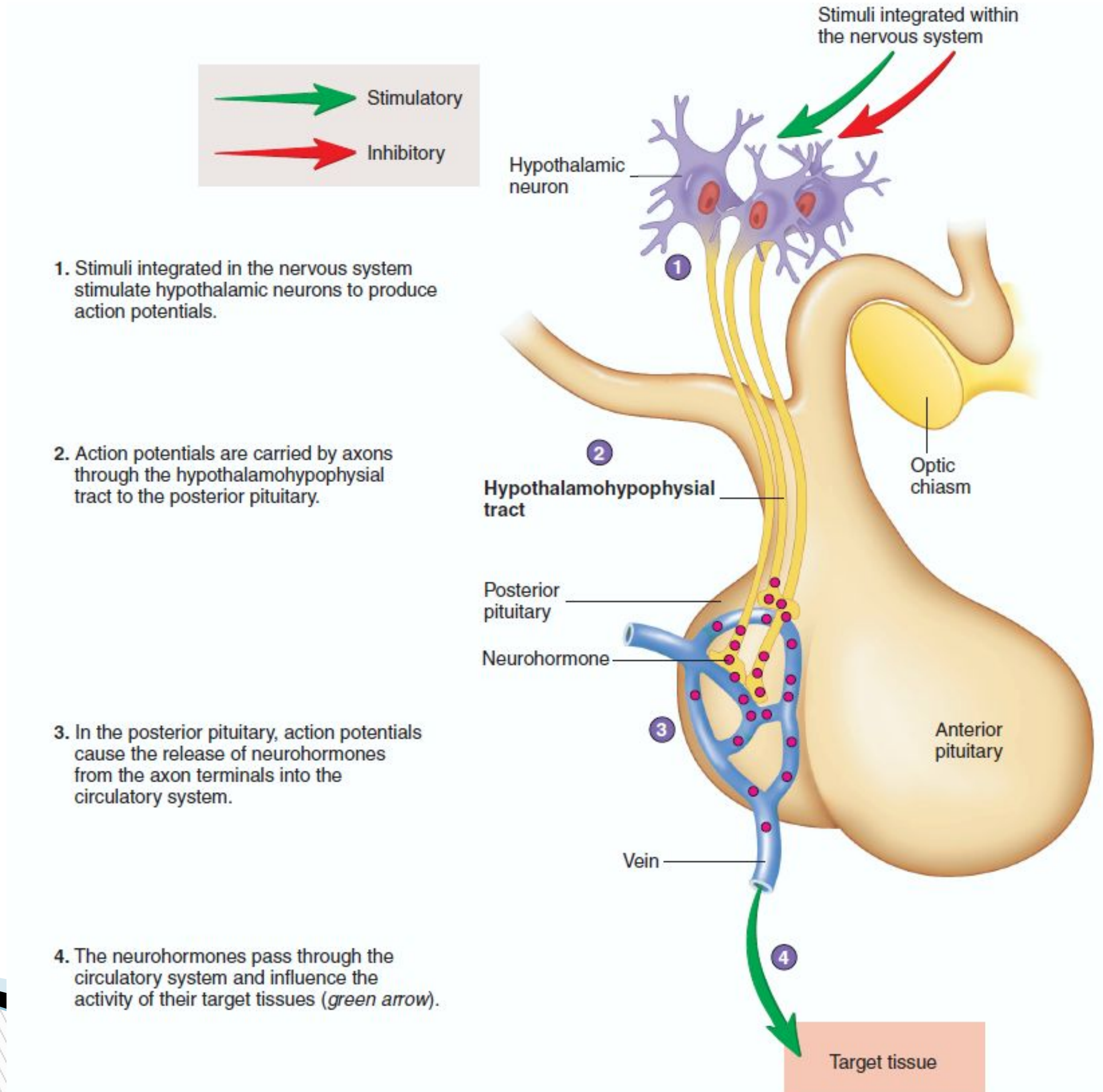
- 1. Metabolism and tissue maturation. The endocrine system regulates the rate of metabolism and influences the maturation of tissues such as those of the nervous system.
- 2. Ion regulation. The endocrine system helps regulate blood pH as well as Na^+, K^+, and Ca^{2+} concentrations in the blood.
- 3. Water balance. The endocrine system regulates water balance by controlling the solute concentration of the blood.
- 4. Immune system regulation. The endocrine system helps control the production of immune cells.

- 5. Heart rate and blood pressure regulation. The endocrine system helps regulate the heart rate and blood pressure and helps prepare the body for physical activity.
- 6. Control of blood glucose and other nutrients. The endocrine system regulates blood glucose levels and other nutrient levels in the blood.
- 7. Control of reproductive functions. The endocrine system controls the development and functions of the reproductive systems in males and females.
- 8. Uterine contractions and milk release. The endocrine system regulates uterine contractions during delivery and stimulates milk release from the breasts in lactating females.

Pituitary Gland and Hypothalamus

- The **pituitary gland, or hypophysis**, secretes nine major hormones that regulate numerous body functions and the secretory activity of several other endocrine glands.
- The **hypothalamus** of the brain and the pituitary gland are major sites where the nervous and endocrine systems interact. The hypothalamus regulates the secretory activity of the pituitary gland.
- Indeed, the posterior pituitary is an extension of the hypothalamus. Hormones, sensory information that enters the central nervous system, and emotions, in turn, influence the activity of the hypothalamus.

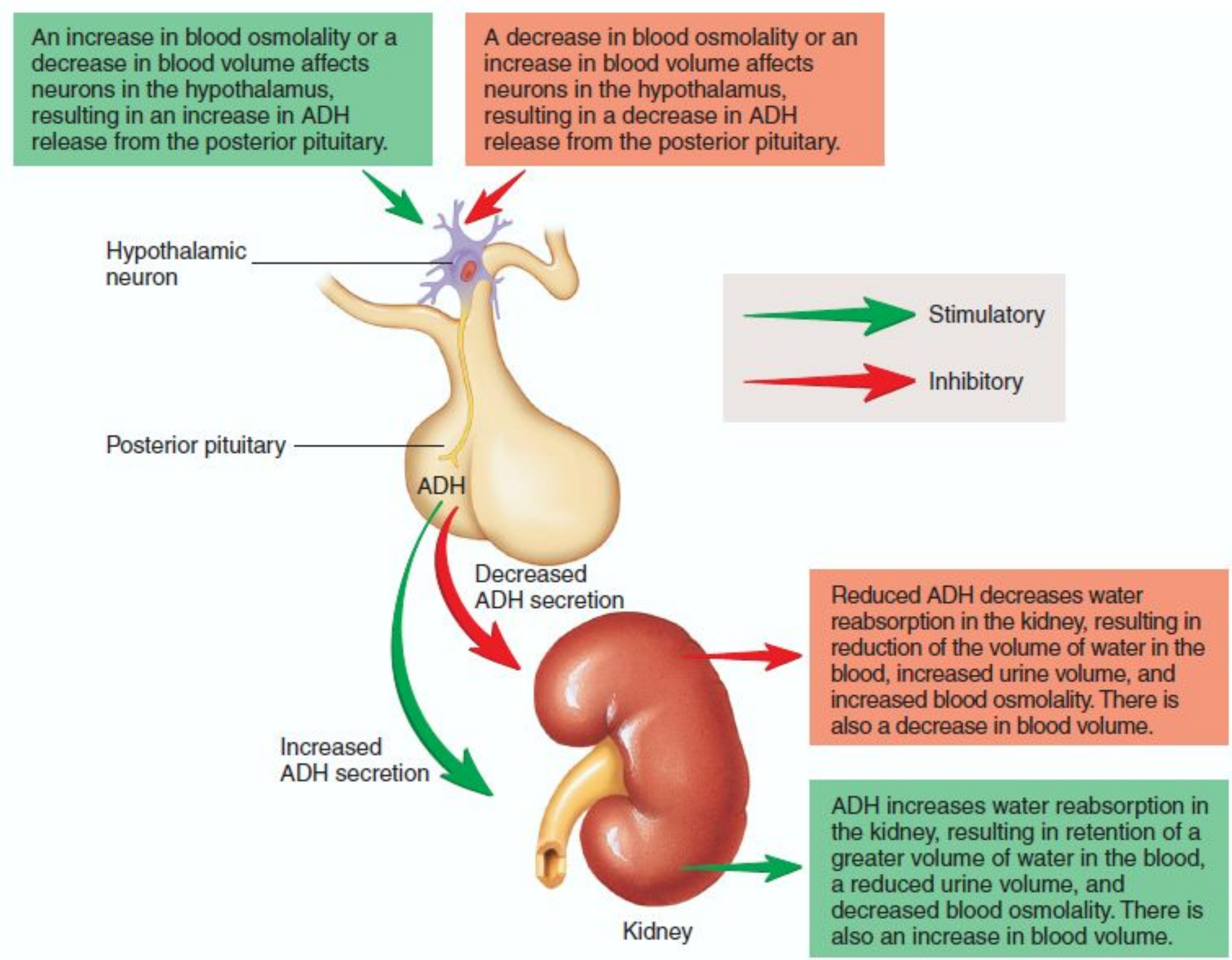
Relationship Among the Hypothalamus, Posterior Pituitary, and Target Tissues



Posterior Pituitary Hormones

- **Antidiuretic Hormone** is so named because it prevents the output of large amounts of urine (diuresis). ADH is sometimes called vasopressin) because it constricts blood vessels and raises blood pressure when large amounts are released.
- ADH is synthesized by neuron cell bodies in the supraoptic nuclei of the hypothalamus and transported within the axons of the hypothalamohypophysial tract to the posterior pituitary, where it is stored in axon terminals.
- ADH is released from these axon terminals into the blood and carried to its primary target tissue, the kidneys, where it promotes the retention of water and reduces urine volume

Control of Antidiuretic Hormone (ADH) Secretion



- When blood osmolality increases, the frequency of action potentials in the osmoreceptors increases, resulting in a greater frequency of action potentials in the neurosecretory cells. As a consequence, ADH secretion increases.
- Alternatively, an increase in blood osmolality can directly stimulate the ADH neurosecretory cells.
- Because ADH stimulates the kidneys to retain water, it functions to reduce blood osmolality and resists any further increase in the osmolality of body fluids.
- As the osmolality of the blood decreases, the action potential frequency in the osmoreceptors and the neurosecretory cells decreases.

Diabetes Insipidus

- A lack of ADH secretion is one cause of diabetes insipidus and leads to the production of a large amount of dilute urine, which can approach 20 L/day.
- The loss of many liters of water in the form of urine causes an increase in the osmolality of the body fluids, and a decrease in extracellular fluid volume, but negative-feedback mechanisms fail to stimulate ADH release.

Posterior Pituitary Hormones

- **Oxytocin** is synthesized by neuron cell bodies in the paraventricular nuclei of the hypothalamus and then is transported through axons to the posterior pituitary, where it is stored in the axon terminals.
- Oxytocin stimulates smooth muscle cells of the uterus. This hormone plays an important role in the expulsion of the fetus from the uterus during delivery by stimulating uterine smooth muscle contraction.
- Oxytocin is also responsible for milk ejection in lactating females by promoting contraction of smooth musclelike cells surrounding the alveoli of the mammary glands.

- Action potentials are carried by sensory neurons from the uterus and from the nipples to the spinal cord.
- Action potentials are then carried up the
- spinal cord to the hypothalamus, where they increase action potentials in the oxytocin-secreting neurons.
- Action potentials in the oxytocin-secreting neurons pass along the axons in the hypothalamohypophysial tract to the posterior pituitary, where they cause the axon terminals to release oxytocin.

Relationship of the Pituitary to the Brain

- Portal vessels are blood vessels that begin and end in a capillary network.
- Neurohormones, produced and secreted by neurons of the hypothalamus, enter the primary capillary network and are carried to the secondary capillary network.
- There the neurohormones leave the blood and act on cells of the anterior pituitary.
- They act either as releasing hormones, increasing the secretion of anterior pituitary hormones, or as inhibiting hormones, decreasing the secretion of anterior pituitary hormones.

Relationship Among the Hypothalamus, Anterior Pituitary, and Target Tissues

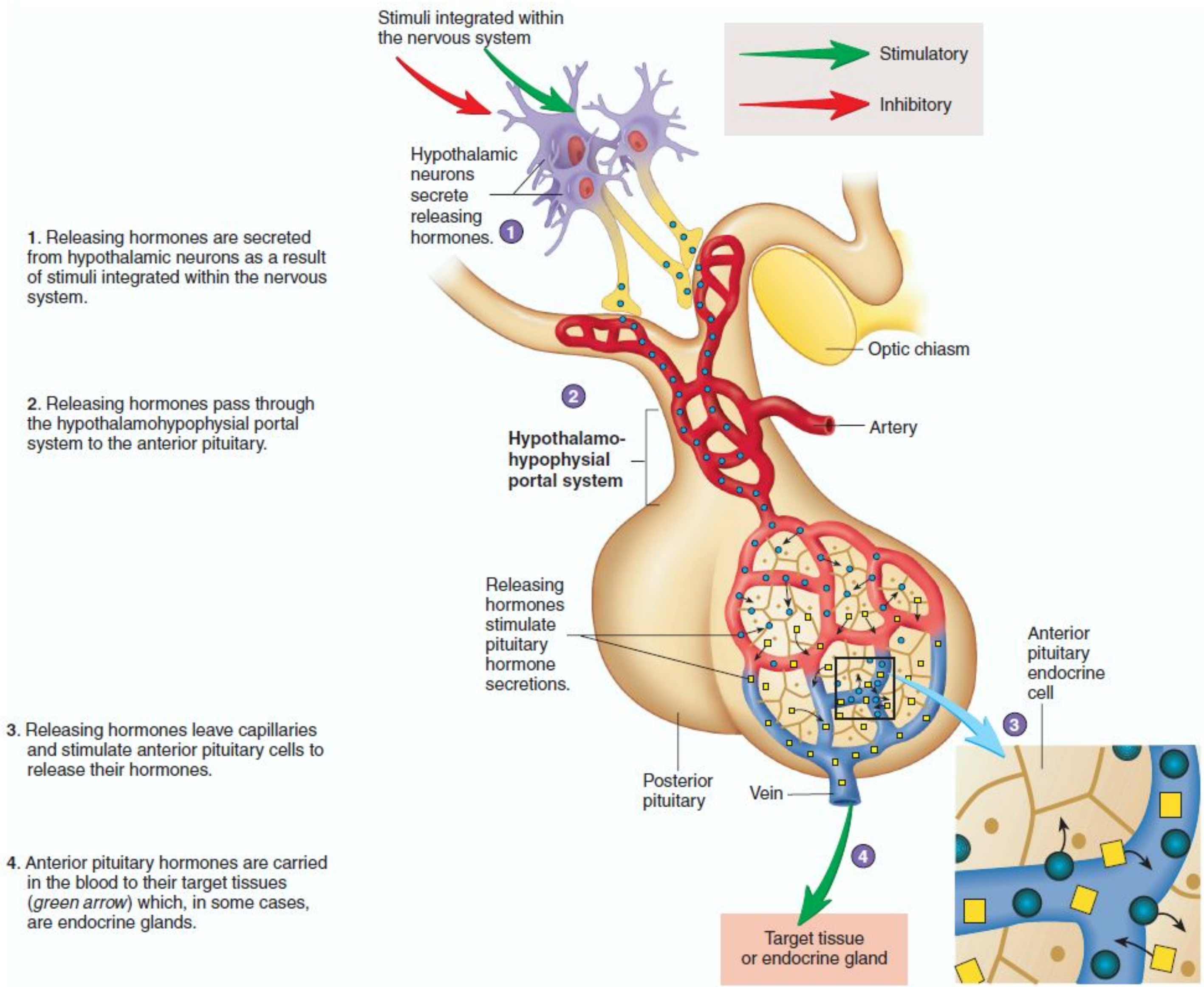


Table 18.1 Hormones of the Hypothalamus

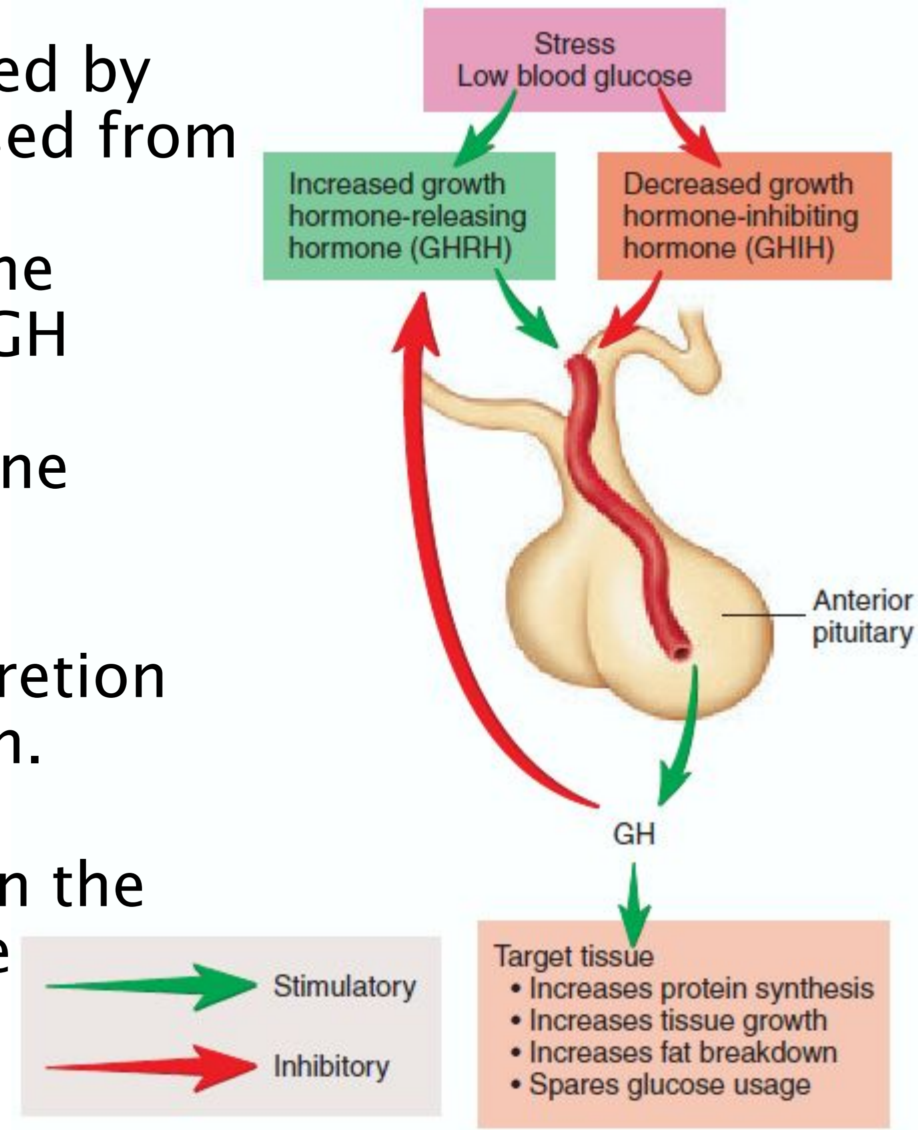
Hormones	Structure	Target Tissue	Response
Growth hormone-releasing hormone (GHRH)	Small peptide	Anterior pituitary cells that secrete growth hormone	Increased growth hormone secretion
Growth hormone-inhibiting hormone (GHIH), or somatostatin	Small peptide	Anterior pituitary cells that secrete growth hormone	Decreased growth hormone secretion
Thyroid-releasing hormone (TRH)	Small peptide	Anterior pituitary cells that secrete thyroid-stimulating hormone	Increased thyroid-stimulating hormone secretion
Corticotropin-releasing hormone (CRH	Peptide	Anterior pituitary cells that secrete adrenocorticotropic hormone	Increased adrenocorticotropic hormone secretion
Gonadotropin-releasing hormone (GnRH)	Small peptide	Anterior pituitary cells that secrete luteinizing hormone and follicle-stimulating hormone	Increased secretion of luteinizing hormone and follicle-stimulating hormone
Prolactin-inhibiting hormone (PIH)	Unknown (possibly dopamine)	Anterior pituitary cells that secrete prolactin	Decreased prolactin secretion
Prolactin-releasing hormone (PRH)	Unknown	Anterior pituitary cells that secrete prolactin	Increased prolactin secretion

Table 18.2 Hormones of the Pituitary Gland

Hormones	Structure	Target Tissue	Response
Posterior Pituitary (Neurohypophysis)			
Antidiuretic hormone (ADH)	Small peptide	Kidney	Increased water reabsorption (less water is lost in the form of urine)
Oxytocin	Small peptide	Uterus; mammary glands	Increased uterine contractions; increased milk expulsion from mammary glands; unclear function in males
Anterior Pituitary (Adenohypophysis)			
Growth hormone (GH), or somatotropin	Protein	Most tissues	Increased growth in tissues; increased amino acid uptake and protein synthesis; increased breakdown of lipids and release of fatty acids from cells; increased glycogen synthesis and increased blood glucose levels; increased somatomedin production
Thyroid-stimulating hormone (TSH)	Glycoprotein	Thyroid gland	Increased thyroid hormone secretion
Adrenocorticotropic hormone (ACTH)	Peptide	Adrenal cortex	Increased glucocorticoid hormone secretion
Lipotropins	Peptides	Fat tissues	Increased fat breakdown
β endorphins	Peptides	Brain, but not all target tissues are known	Analgesia in the brain; inhibition of gonadotropin-releasing hormone secretion
Melanocyte-stimulating hormone (MSH)	Peptide	Melanocytes in the skin	Increased melanin production in melanocytes to make the skin darker in color
Luteinizing hormone (LH)	Glycoprotein	Ovaries in females; testes in males	Ovulation and progesterone production in ovaries; testosterone synthesis and support for sperm cell production in testes
Follicle-stimulating hormone (FSH)	Glycoprotein	Follicles in ovaries in females; seminiferous tubes in males	Follicle maturation and estrogen secretion in ovaries; sperm cell production in testes
Prolactin	Protein	Ovaries and mammary glands in females	Milk production in lactating women; increased response of follicle to LH and FSH; unclear function in males

Control of Growth Hormone (GH) Secretion

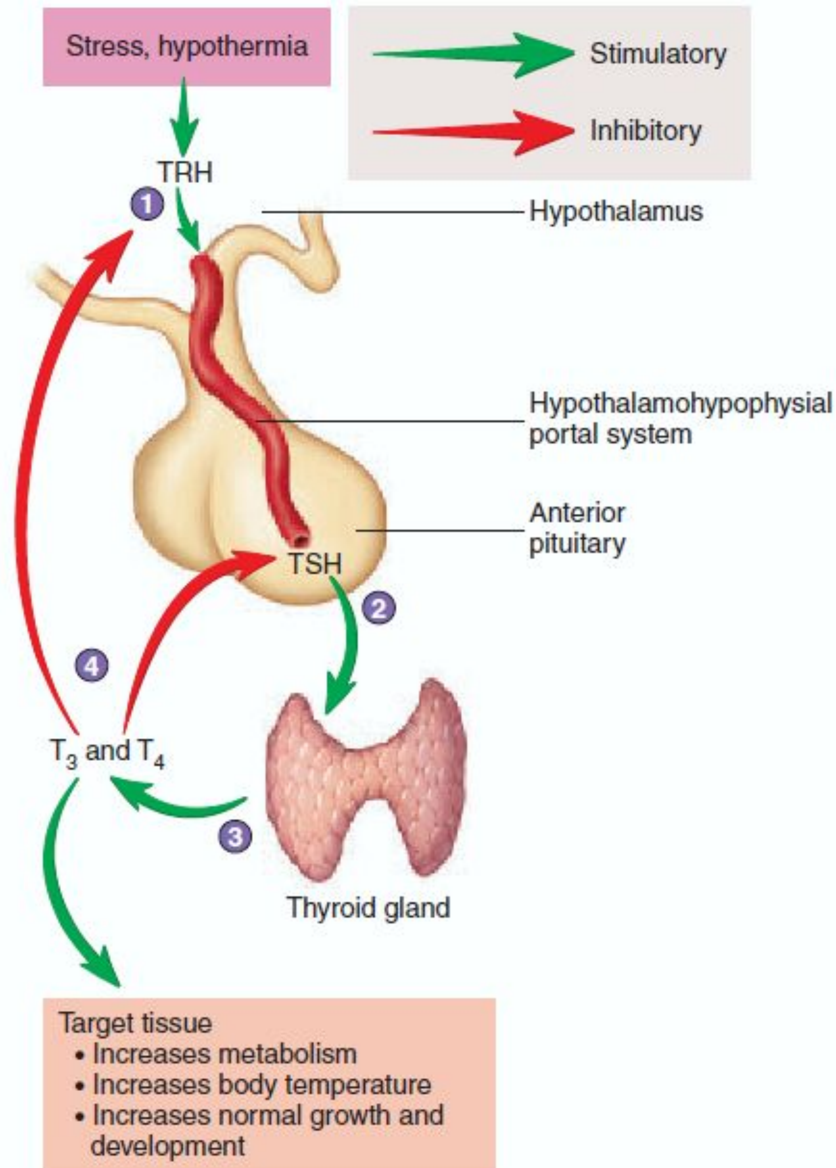
- Secretion of GH is controlled by two neurohormones released from the hypothalamus: growth hormone-releasing hormone (GHRH), which stimulates GH secretion, and growth hormone-inhibiting hormone (GHIH), which inhibits GH secretion.
- Stress increases GHRH secretion and inhibits GHIH secretion.
- High levels of GH have a negative-feedback effect on the production of GHRH by the hypothalamus.



- Chronic hyposecretion of GH in infants and children leads to **dwarfism**, or short stature due to delayed bone growth.
- Chronic hypersecretion of GH leads to **giantism** or **acromegaly**, depending on whether the hypersecretion occurs before or after complete ossification of the epiphysial plates in the skeletal system.
- Chronic hypersecretion of GH before the epiphysial plates have ossified causes exaggerated and prolonged growth in long bones, resulting in giantism. Some individuals thus affected have grown to be 8 feet tall or more.

Regulation of Thyroid Hormone (T3 and T4) Secretion

1. Thyroid-releasing hormone (TRH) is released from neurons within the hypothalamus into the blood. It passes through the hypothalamohypophysial portal system to the anterior pituitary.
2. TRH causes cells of the anterior pituitary to secrete thyroid-stimulating hormone (TSH).
3. TSH passes through the general circulation to the thyroid gland, where it causes both increased synthesis and secretion of thyroid hormones (T_3 and T_4).
4. T_3 and T_4 have an inhibitory effect on the secretion of TRH from the hypothalamus and TSH from the anterior pituitary.



Goiter

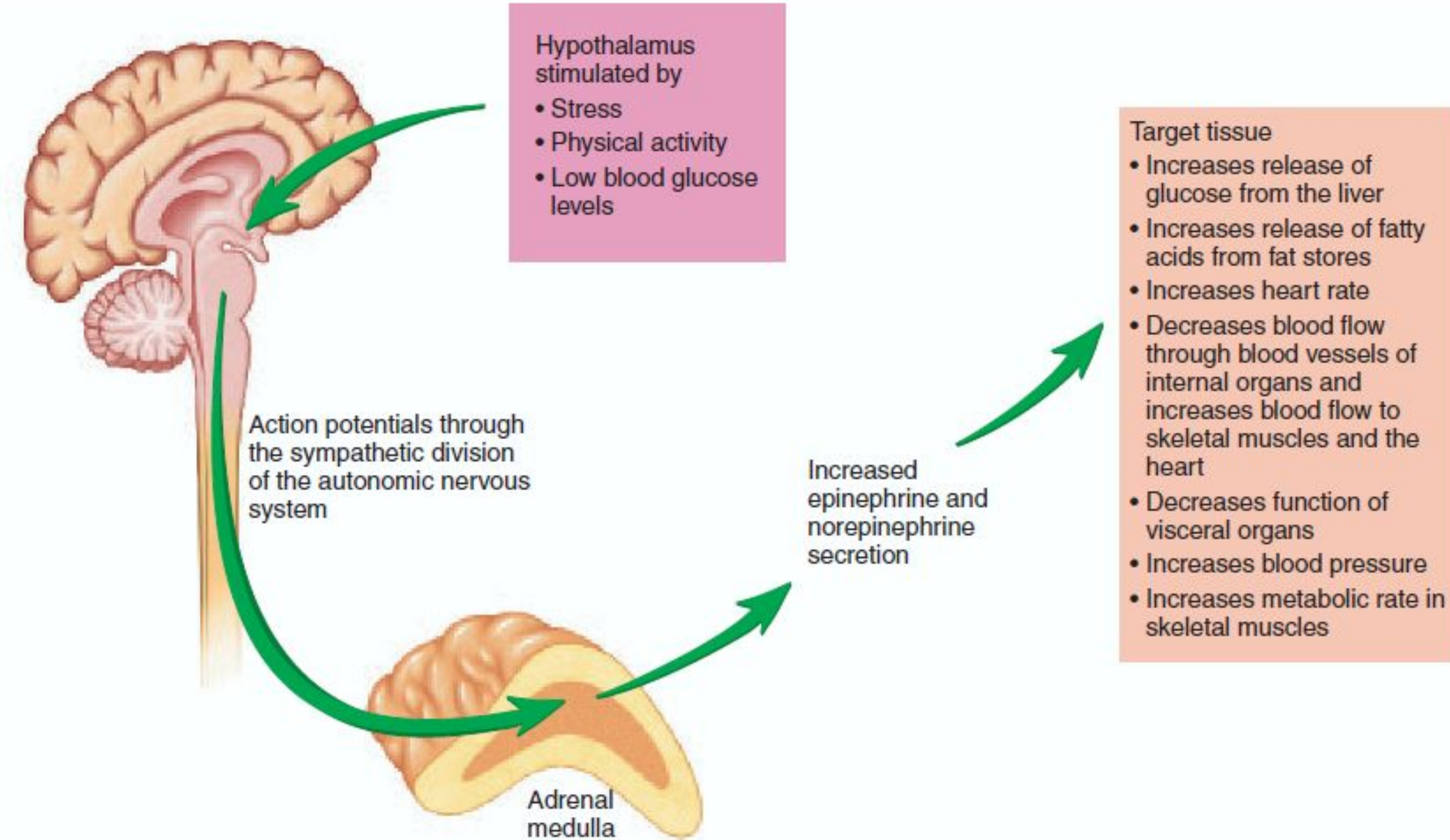
- An abnormal enlargement of the thyroid gland is called a goiter. Goiters can result from conditions that cause hypothyroidism as well as conditions that cause hyperthyroidism.
- An iodine deficiency goiter results when dietary iodine intake is very low and there is too little iodine to synthesize T3 and T4. As a result, blood levels of T3 and T4 decrease and the person may exhibit symptoms of hypothyroidism.
- The reduced negative feedback of T3 and T4 on the anterior pituitary and hypothalamus result in elevated TSH secretion. TSH causes hypertrophy and hyperplasia of the thyroid gland and increased thyroglobulin synthesis even though there is not enough iodine to synthesize T3 and T4. Consequently, the thyroid gland enlarges.
- Toxic goiter secretes excess T3 and T4, and it can result from elevated TSH secretion or elevated TSH-like immune globulin molecules (Graves' Disease).

Hormones of the Adrenal Gland

Table 18.7 Hormones of the Adrenal Gland

Hormones	Structure	Target Tissue	Response
Adrenal Medulla			
Epinephrine primarily; norepinephrine	Amino acid derivatives	Heart, blood vessels, liver, fat cells	Increased cardiac output; increased blood flow to skeletal muscles and increased blood flow to the heart (see chapter 20); increased release of glucose and fatty acids into blood; in general, preparation for physical activity
Adrenal Cortex			
Cortisol	Steroid	Most tissues	Increased protein and fat breakdown; increased glucose production; inhibition of immune response
Aldosterone	Steroid	Kidney	Increased Na^+ reabsorption and K^+ and H^+ excretion
Sex steroids (primarily androgens)	Steroids	Many tissues	Minor importance in males; in females, development of some secondary sexual characteristics, such as axillary and pubic hair

Regulation of Adrenal Medullary Secretions



Hormones of the Adrenal Cortex

- The adrenal cortex secretes three hormone types: **mineralocorticoids**, **glucocorticoids**, and **androgens.**
- All are similar in structure in that they are steroids, highly specialized lipids that are derived from cholesterol.
- Because they are lipidsoluble, they are not stored in the adrenal gland cells but diffuse from the cells as they are synthesized.
- Adrenal cortical hormones are transported in the blood in combination with specific plasma proteins; they are metabolized in the liver and excreted in the bile and urine.

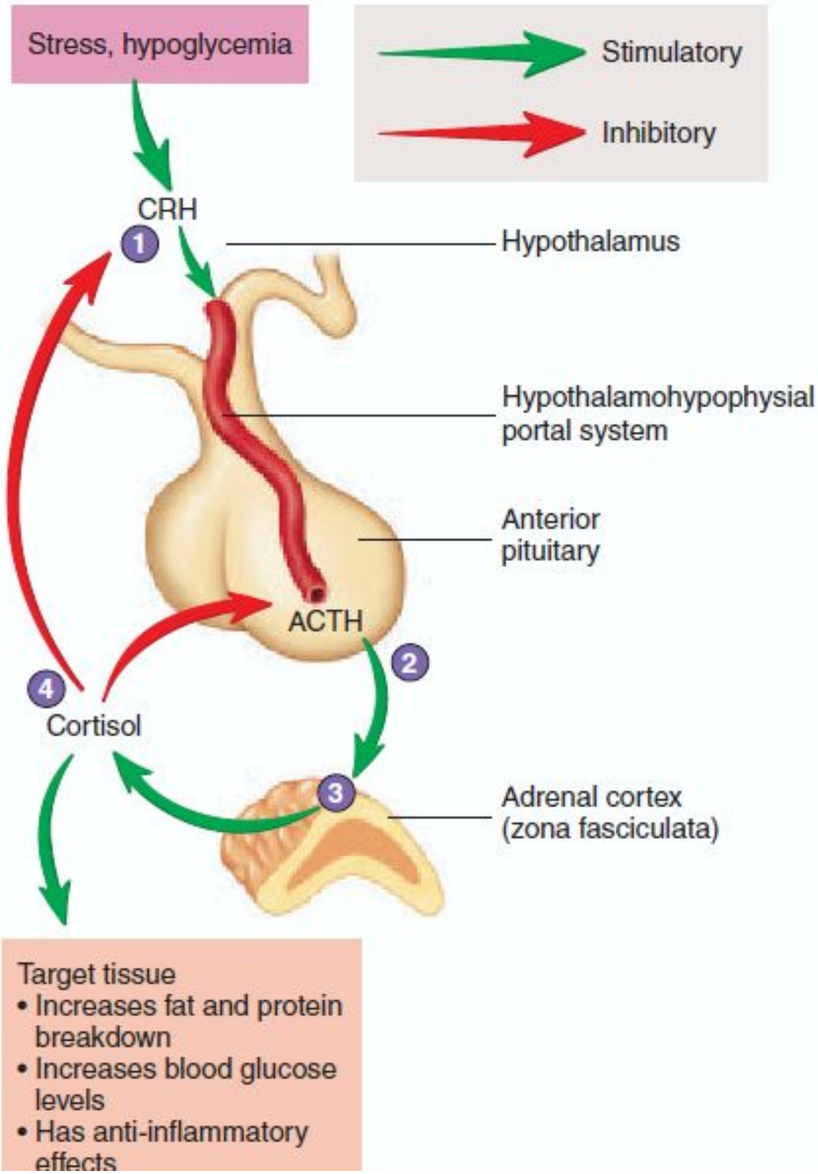
Target Tissues and Their Responses to Glucocorticoid Hormones

Table 18.8 Target Tissues and Their Responses to Glucocorticoid Hormones

Target Tissues	Responses
Peripheral tissues, such as skeletal muscle, liver, and adipose tissue	Inhibits glucose use; stimulates formation of glucose from amino acids and, to some degree, from fats (gluconeogenesis) in the liver, which results in elevated blood glucose levels; stimulates glycogen synthesis in cells; mobilizes fats by increasing lipolysis, which results in the release of fatty acids into the blood and an increased rate of fatty acid metabolism; increases protein breakdown and decreases protein synthesis
Immune tissues	Anti-inflammatory—depresses antibody production, white blood cell production, and the release of inflammatory components in response to injury
Target cells for epinephrine	Receptor molecules for epinephrine and norepinephrine decrease without adequate amounts of glucocorticoid hormone

Regulation of Cortisol Secretion

1. Cortiocotropin-releasing hormone (CRH) is released from hypothalamic neurons in response to stress or hypoglycemia and passes, by way of the hypothalamohypophysial portal system, to the anterior pituitary.
2. In the anterior pituitary CRH binds to and stimulates cells that secrete adrenocorticotropic hormone (ACTH).
3. ACTH binds to membrane-bound receptors on cells of the adrenal cortex and stimulates the secretion of glucocorticoids, primarily cortisol.
4. Cortisol inhibits CRH and ACTH secretion.



Mineralocorticoids

- The major secretory products of the zona glomerulosa are the mineralocorticoids.
- **Aldosterone** is produced in the greatest amounts, although other closely related mineralocorticoids are also secreted.
- Aldosterone increases the rate of sodium reabsorption by the kidneys, thereby increasing blood levels of sodium. Sodium reabsorption can result in increased water reabsorption by the kidneys and an increase in blood volume providing ADH is also secreted.

- Aldosterone increases K excretion into the urine by the kidneys, thereby decreasing blood levels of K. It also increases the rate of H excretion into the urine.
- When aldosterone is secreted in high concentrations, it can result in reduced blood levels of K and alkalosis (elevated pH of body fluids).

Symptoms of Hyposecretion and Hypersecretion of Adrenal Cortex Hormones

Table 18.9 Symptoms of Hyposecretion and Hypersecretion of Adrenal Cortex Hormones

Hyposecretion	Hypersecretion
Aldosterone	
Hyponatremia (low blood levels of sodium)	Slight hypernatremia (high blood levels of sodium)
Hyperkalemia (high blood levels of potassium)	Hypokalemia (low blood levels of potassium)
Acidosis	Alkalosis
Low blood pressure	High blood pressure
Tremors and tetany of skeletal muscles	Weakness of skeletal muscles
Polyuria	Acidic urine
Cortisol	
Hypoglycemia (low blood glucose levels)	Hyperglycemia (high blood glucose levels; adrenal diabetes)—leads to diabetes mellitus
Depressed immune system	Depressed immune system
Protein and fats from diet are unused, resulting in weight loss	Destruction of tissue proteins, causing muscle atrophy and weakness, osteoporosis, weak capillaries (easy bruising), thin skin, and impaired wound healing; mobilization and redistribution of fats, causing depletion of fat from limbs and deposition in face (moon face), neck (buffalo hump), and abdomen
Loss of appetite, nausea, and vomiting	Emotional effects, including euphoria and depression
Increased skin pigmentation (caused by elevated ACTH)	
Androgens	
In women reduction of pubic and axillary hair	In women hirsuitism (excessive facial and body hair), acne, increased sex drive, regression of breast tissue, and loss of regular menses

Adrenal Androgens

- Some adrenal steroids, including **androstenedione** are weak androgens.
- They are secreted by the zona reticularis and converted by peripheral tissues to the more potent androgen, testosterone.
- Adrenal androgens stimulate pubic and axillary hair growth and sexual drive in females. Their effects in males are negligible in comparison to testosterone secreted by the testes.