

ENDOCRINE SYSTEM

The nervous and endocrine systems act together to coordinate functions of all body systems. Recall that the nervous system acts through nerve impulses (action potentials) conducted along axons of neurons. **At synapses, nerve impulses trigger the release\ of mediator (messenger) molecules called *neurotransmitters***

The endocrine system also controls body activities by releasing mediators, called *hormones*, but the means of control of the two systems are very different

A **hormone** (*hormon* _ to excite or get moving) is a mediator molecule that is released in one part of the body but regulates the activity of cells in other parts of the body.

Most hormones enter interstitial fluid and then the bloodstream. The circulating blood delivers hormones to cells throughout the body.

Both neurotransmitters and hormones exert their effects by binding to receptors on or in their “target” cells.

Several mediators act as both neurotransmitters and hormones.

One familiar example is norepinephrine, which is released as a neurotransmitter by sympathetic postganglionic neurons and as a hormone by chromaffin cells of the adrenal medullae.

The body contains two kinds of glands: exocrine glands and endocrine glands.

Exocrine glands (*exo-* _ outside) **secrete their products into ducts** that carry the secretions into body cavities, into the lumen of an organ, or to the outer surface of the body. Exocrine glands include sudoriferous (sweat), sebaceous (oil), mucous, and digestive glands.

Endocrine glands (*endo-* _ within) **secrete their products (hormones) into the interstitial fluid** surrounding the secretory cells rather than into ducts. From the interstitial fluid, hormones

diffuse into blood capillaries and blood carries them to target cells throughout the body. Because most hormones are required in very small amounts, circulating levels typically are low.

The endocrine glands include the pituitary, thyroid, parathyroid, adrenal, and pineal glands.

In addition, several organs and tissues are not exclusively classified as endocrine glands but contain cells that secrete hormones.

These include the hypothalamus, thymus, pancreas, ovaries, testes, kidneys, stomach, liver, small intestine, skin, heart, adipose tissue, and placenta.

Taken together, all endocrine glands and hormone-secreting cells constitute the **endocrine system**. The Science of the structure and function of the endocrine glands

Functions of Hormones

1. Help regulate:

- Chemical composition and volume of internal environment (interstitial fluid)
- Metabolism and energy balance
- Contraction of smooth and cardiac muscle fibers
- Glandular secretions
- Some immune system activities

2. Control growth and development.

3. Regulate operation of reproductive systems.

4. Help establish circadian rhythms.

The Role of Hormone Receptors

Although a given hormone travels throughout the body in the blood, it affects only specific target cells. Hormones, like neurotransmitters, influence their target cells by chemically binding to specific protein **receptors**. Only the target cells for a given hormone have receptors that bind and recognize that hormone. For example, thyroid-stimulating hormone (TSH) binds to receptors on cells of the thyroid gland, but it does not bind to cells of the ovaries because ovarian cells do not have TSH receptors.

Receptors, like other cellular proteins, are constantly being synthesized and broken down. Generally, a target cell has 2000 to 100,000 receptors for a particular hormone. If a hormone is

present in excess, the number of target-cell receptors may decrease—an effect called **down-regulation**.

For example, when certain cells of the testes are exposed to a high concentration of luteinizing hormone (LH), the number of LH receptors decreases.

Down-regulation makes a target cell *less sensitive* to a hormone. In contrast, when a hormone is deficient, the number of receptors may increase. This phenomenon, known as **upregulation**, makes a target cell *more sensitive* to a hormone.

Circulating and Local Hormones

Most endocrine hormones are **circulating hormones**—they pass from the secretory cells that make them into interstitial fluid and then into the blood.

Other hormones, termed **local hormones**, act locally on neighboring cells or on the same cell that secreted them without first entering the bloodstream.

Local hormones that act on neighboring cells are called **paracrines** (*para-* _ beside or near), and those that act on the same cell that secreted them are called **autocrines** (*auto-* _ self).

One example of a local hormone is interleukin 2 (IL-2), which is released by helper T cells (a type of white blood cell) during immune responses.

IL-2 helps activate other nearby immune cells, a paracrine effect. But it also acts as an autocrine by stimulating the same cell that released it to proliferate.

This action generates more helper T cells that can secrete even more IL-2 and thus strengthen the immune Response.

Another example of a local hormone is the gas nitric oxide (NO), which is released by endothelial cells lining blood vessels. NO causes relaxation of nearby smooth muscle fibers in blood vessels, which in turn causes vasodilation (increase in blood vessel diameter). The effects of such vasodilation range from a lowering of blood pressure to erection of the penis in males. The drug *Viagra* (sildenafil) enhances the effects stimulated by nitric oxide in the penis.

Chemical Classes of Hormones

Chemically, hormones can be divided into two broad classes: those that are soluble in lipids, and those that are soluble in water. This chemical classification is also useful functionally because the two classes exert their effects differently.

Lipid-soluble Hormones

The lipid-soluble hormones include steroid hormones, thyroid hormones, and nitric oxide.

1. **Steroid hormones** are derived from cholesterol. Each steroid hormone is unique due to the presence of different chemical groups attached at various sites on the four rings at the core of its structure. These small differences allow for a large diversity of functions.
2. Two **thyroid hormones** (T3 and T4) are synthesized by attaching iodine to the amino acid tyrosine. The benzene ring of tyrosine plus the attached iodines make T3 and T4 very lipid soluble.
3. The gas **nitric oxide (NO)** is both a hormone and a neurotransmitter. Its synthesis is catalyzed by the enzyme nitric oxide synthase.

Water-soluble Hormones

The water-soluble hormones include amine hormones, peptide and protein hormones, and eicosanoid hormones.

1. **Amine hormones** are synthesized by decarboxylating (removing a molecule of CO₂) and otherwise modifying certain amino acids. They are called amines because they retain an amino group (NH₃⁺). The catecholamines—epinephrine, norepinephrine, and dopamine—are synthesized by modifying the amino acid tyrosine. Histamine is synthesized from the amino acid histidine by mast cells and platelets. Serotonin and melatonin is derived from tryptophan.
2. **Peptide hormones** and **protein hormones** are amino acid polymers. The smaller peptide hormones consist of chains of 3 to 49 amino acids; the larger protein hormones include 50 to 200 amino acids. Examples of peptide hormones are antidiuretic hormone and oxytocin; protein hormones include human growth hormone and insulin.

Several of the protein hormones, such as thyroid-stimulating hormone, have attached carbohydrate groups and thus are **glycoprotein hormones**.

3. The eicosanoid hormones (1^{-} -KO $^{-}$ -sa-noid; *eicos-* _ twenty forms; *-oid* _ resembling) are derived from arachidonic acid, a 20-carbon fatty acid. The two major types of eicosanoids are **prostaglandins** and **leukotrienes**. The eicosanoids are important local hormones, and they may act as circulating hormones as well. The classes of lipid-soluble and watersoluble hormones and provides an overview of the major hormones and their sites of secretion.

Local hormones usually are inactivated quickly; circulating hormones may linger in the blood and exert their effects for a few minutes or occasionally for a few hours. In time, circulating hormones are inactivated by the liver and excreted by the kidneys. In cases of kidney or liver failure, excessive levels of hormones may build up in the blood.

Hormone Transport in the Blood

Most water-soluble hormone molecules circulate in the watery blood plasma in a “free” form (not attached to other molecules), but most lipid-soluble hormone molecules are bound to **transport proteins**. The transport proteins, which are synthesized by cells in the liver, have three functions:

1. They make lipid-soluble hormones temporarily water soluble, thus increasing their solubility in blood.
2. They retard passage of small hormone molecules through the filtering mechanism in the kidneys, thus slowing the rate of hormone loss in the urine.
3. They provide a ready reserve of hormone, already present in the bloodstream.

Action of Lipid-soluble Hormones

As you just learned, lipid-soluble hormones, including steroid hormones and thyroid hormones, bind to receptors within target cells. Their mechanism of action is as follows (Figure 18.3):

- A free lipid-soluble hormone molecule diffuses from the blood, through interstitial fluid, and through the lipid bilayer of the plasma membrane into a cell.

- If the cell is a target cell, the hormone binds to and activates receptors located within the cytosol or nucleus. The activated receptor–hormone complex then alters gene expression: It turns specific genes of the nuclear DNA on or off.
- As the DNA is transcribed, new messenger RNA (mRNA) forms, leaves the nucleus, and enters the cytosol. There, it directs synthesis of a new protein, often an enzyme, on the ribosomes.
- The new proteins alter the cell's activity and cause the responses typical of that hormone.

Action of Water-soluble Hormones

Because amine, peptide, protein, and eicosanoid hormones are not lipid-soluble, they cannot diffuse through the lipid bilayer of the plasma membrane and bind to receptors inside target cells. Instead, water-soluble hormones bind to receptors that protrude from the target cell surface. The receptors are integral transmembrane proteins in the plasma membrane. When a water-soluble hormone binds to its receptor at the outer surface of the plasma membrane; it acts as the **first messenger**. The first messenger (the hormone) then causes production of a **second messenger** inside the cell, where specific hormone-stimulated responses take place.

One common second messenger is **cyclic AMP (cAMP)**. Neurotransmitters, neuropeptides, and several sensory transduction mechanisms also act via second-messenger systems.

The action of a typical water-soluble hormone occurs as follows

- A water-soluble hormone (the first messenger) diffuses from the blood through interstitial fluid and then binds to its receptor at the exterior surface of a target cell's plasma membrane. The hormone–receptor complex activates a membrane protein called a **G protein**. The activated G protein in turn activates **adenylate cyclase**.
- Adenylate cyclase converts ATP into cyclic AMP (cAMP). Because the enzyme's active site is on the inner surface of the plasma membrane, this reaction occurs in the cytosol of the cell.
- Cyclic AMP (the second messenger) activates one or more protein kinases, which may be free in the cytosol or bound to the plasma membrane. A **protein kinase** is an enzyme that phosphorylates (adds a phosphate group to) other cellular proteins (such as enzymes). The donor of the phosphate group is ATP, which is converted to ADP.
- Activated protein kinases phosphorylate one or more cellular proteins. Phosphorylation activates some of these proteins and inactivates others, rather like turning a switch on or off.

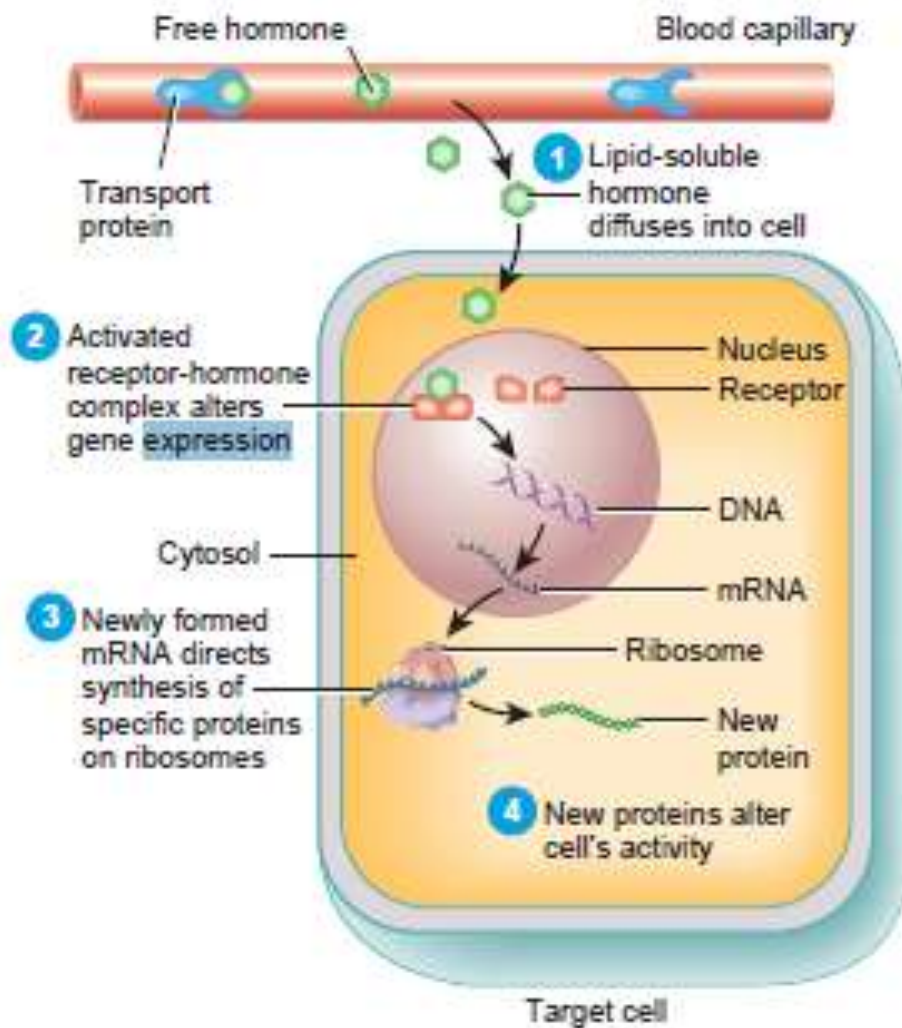
- Phosphorylated proteins in turn cause reactions that produce Biological responses. Different protein kinases exist within different target cells and within different organelles of the same target cell. Thus, one protein kinase might trigger glycogen synthesis, a second might cause the breakdown of triglyceride, a third may promote protein synthesis, and so forth.

As noted in step-

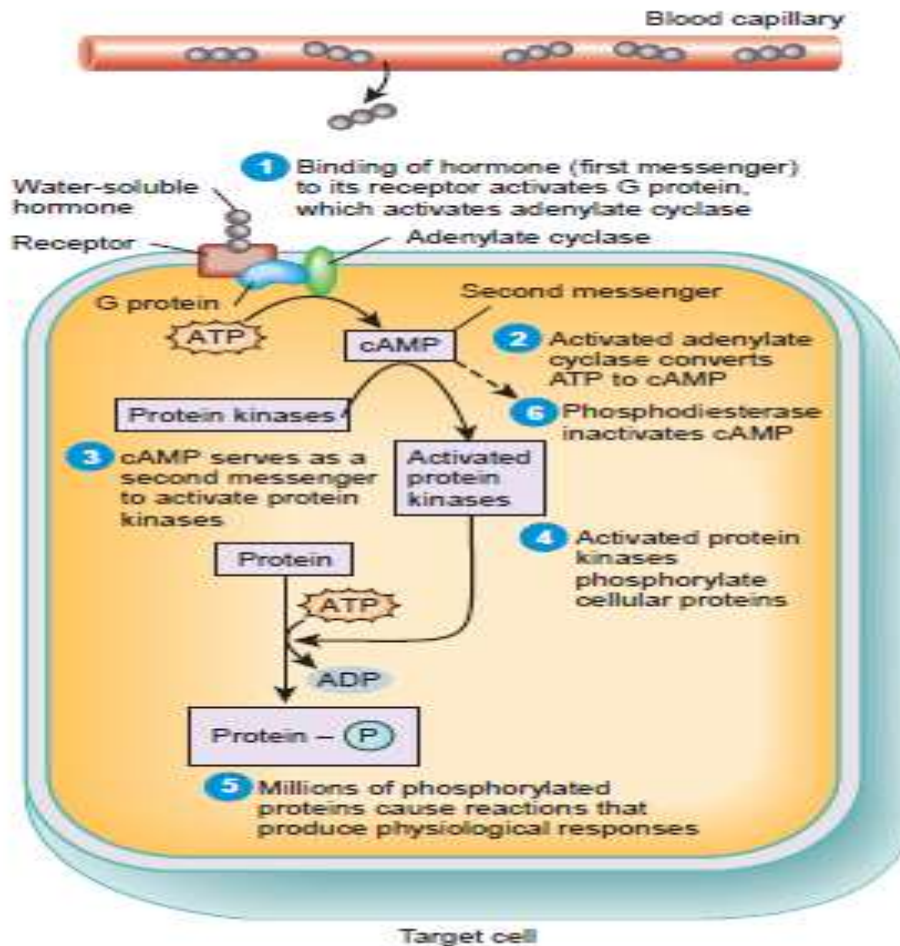
- , phosphorylation by a protein kinase can also inhibit certain proteins. For example, some of the kinases unleashed when epinephrine binds to liver cells inactivate an enzyme needed for glycogen synthesis.
- After a brief period, an enzyme called **phosphodiesterase** inactivates cAMP. Thus, the cell's response is turned off unless new hormone molecules continue to bind to their receptors in the plasma membrane.

Figure 18.3 Mechanism of action of the lipid-soluble steroid hormones and thyroid hormones.

6 Lipid-soluble hormones bind to receptors inside target cells.



⑥ Water-soluble hormones bind to receptors embedded in the plasma membranes of target cells.



CONTROL OF HORMONE SECRETION

. The release of most hormones occurs in short bursts, with little or no secretion between bursts. When stimulated, an endocrine gland will release its hormone in more frequent bursts, increasing the concentration of the hormone in the blood. In the absence of stimulation, the blood level of the hormone decreases. Regulation of secretion normally prevents overproduction or underproduction of any given hormone.\

Hormone secretion is regulated by (1) signals from the nervous system, (2) chemical changes in the blood, and (3) other hormones.

For example, nerve impulses to the adrenal medullae regulate the release of epinephrine; blood Ca^{2+} level regulates the secretion of parathyroid hormone; and a hormone from the anterior

pituitary (adrenocorticotrophic hormone) stimulates the release of cortisol by the adrenal cortex. Most hormonal regulatory systems work via negative feedback but a few operate via positive feedback. For example, during childbirth, the hormone oxytocin stimulates contractions of the uterus, and uterine contractions in turn stimulate more oxytocin release, a positive feedback effect.

THYROID GLAND

The butterfly-shaped **thyroid gland** is located just inferior to the larynx (voice box). It is composed of right and left **lateral lobes**, one on either side of the trachea, that are connected by an **isthmus** (IS-mus _ a narrow passage) anterior to the trachea.

A small, pyramidal-shaped lobe sometimes extends upward from the isthmus. The normal mass of the thyroid is about 30 g (1 oz). It is highly vascularized and receives 80–120 mL of blood per minute.

Microscopic spherical sacs called **thyroid follicles** make up most of the thyroid gland. The wall of each follicle consists primarily of cells called **follicular cells**, most of which extend to the lumen (internal space) of the follicle.

A **basement membrane** surrounds each follicle. When the follicular cells are inactive, their shape is low cuboidal to squamous, but under the influence of TSH they become active in secretion and range from cuboidal to low columnar in shape.

The follicular cells produce two hormones: **thyroxine** (thi⁻-ROK-se⁻n), which is also called **tetraiodothyronine** (tet-ra-i⁻-o⁻-do⁻-THI⁻-ro⁻-ne⁻n) or **T4** because it contains four atoms of iodine, and **triiodothyronine** (tri⁻-i⁻-o⁻-do⁻-THI⁻-ro⁻-ne⁻n) or **T3**, which contains three atoms of iodine. T3 and T4 together are also known as **thyroid hormones**.

A few cells called **parafollicular cells** or **C cells** lie between follicles. They produce the hormone **calcitonin** (kal-si-TO⁻-nin), which helps regulate calcium homeostasis.

Actions of Thyroid Hormones:

Increase basal metabolic rate

Regulate development and growth of nervous tissue and bones

Enhance some actions of catecholamines

Stimulate lipolysis

Stimulate protein synthesis

Increase body temperature (calorigenic effect)

Stimulate synthesis of Na^+/K^+ ATPase

Increase the use of glucose and fatty acids for ATP production

Control of Thyroid Hormone Secretion

Thyrotropin-releasing hormone (TRH) from the hypothalamus and thyroid-stimulating hormone (TSH) from the anterior pituitary stimulate synthesis and release of thyroid hormones,\

- Low blood levels of T3 and T4 or low metabolic rate stimulate the hypothalamus to secrete TRH.
- TRH enters the hypophyseal portal veins and flows to the anterior pituitary, where it stimulates thyrotrophs to secrete TSH.
- TSH stimulates virtually all aspects of thyroid follicular cell activity, synthesis and secretion and in and growth of the follicular cells.
- The thyroid follicular cells release T3 and T4 into the blood until the metabolic rate returns to normal.
- An elevated level of T3 inhibits release of TRH and TSH (negative feedback inhibition).

The hormone produced by the **parafollicular cells** of the thyroid gland) is **calcitonin (CT)** (kalsi-TO⁻-nin).

CT can decrease the level of calcium in the blood by inhibiting the action of osteoclasts, the cells that break down bone extracellular matrix. The secretion of CT is controlled by a negative feedback system

PARATHYROID GLANDS

Partially embedded in the posterior surface of the lateral lobes of the thyroid gland are several small, round masses of tissue called the **parathyroid glands** (*para-* – beside). Each has a mass of about 40 mg (0.04 g). Usually, one superior and one inferior parathyroid gland are attached to each lateral thyroid lobe for a total of four.

Microscopically, the parathyroid glands contain two kinds of epithelial cells. The more numerous cells, called **chief (principal) cells**, produce **parathyroid hormone (PTH)**, also called **parathormone**. The function of the other kind of cell, called an *oxyphil cell*, is not known.

Parathyroid Hormone

Parathyroid hormone is the major regulator of the levels of calcium (Ca^{2+}), magnesium (Mg^{2+}), and phosphate (HPO_4^{2-}) ions in the blood. The specific action of PTH is to increase the number and activity of osteoclasts. The result is elevated bone *resorption*, which releases ionic calcium (Ca^{2+}) and phosphates (HPO_4^{2-}) into the blood. PTH also acts on the kidneys. First, it slows the rate at which Ca^{2+} and Mg^{2+} are lost from blood into the urine. Second, it increases loss of HPO_4^{2-} from blood into the urine. Because more HPO_4^{2-} is lost in the urine than is gained from the bones, PTH decreases blood HPO_4^{2-} level and increases blood Ca^{2+} and Mg^{2+} levels. A third effect of PTH on the kidneys is to promote formation of the hormone **calcitriol**, the active form of vitamin D. Calcitriol, also known as *1, 25-dihydroxy vitamin D₃*, increases the rate of Ca^{2+} , HPO_4^{2-} , and Mg^{2+} *absorption* from the gastrointestinal tract into the blood. The blood calcium level directly controls the secretion of both calcitonin and parathyroid hormone via negative feedback loops that do not involve the pituitary gland

PANCREAS

The cells which make up the pancreatic islets (islets of Langerhans) are found in clusters irregularly distributed

throughout the substance of the pancreas.

Unlike the exocrine pancreas, which produces pancreatic juice, there are no ducts leading from the clusters of islet cells. Pancreatic hormones are secreted directly into the bloodstream and circulate throughout the body. There are three main types of cells in the pancreatic islets:

- (alpha) cells that secrete *glucagon*

(beta) cells that secrete *insulin*

m (delta) cells that secrete *somatostatin* (GHRIH)

The normal blood glucose level is between 2.5 and 5.3 mmol/litre (45 to 95 mg/100 ml). Blood glucose levels are controlled mainly by the opposing actions of insulin and glucagon:

- glucagon increases blood glucose levels insulin reduces blood glucose levels.

1. Alpha or A cells constitute about 17% of pancreatic islet cells and secrete **glucagon** (GLOO-ka-gon).

2. Beta or B cells constitute about 70% of pancreatic islet cells and secrete **insulin** (IN-soo-lin).

3. Delta or D cells constitute about 7% of pancreatic islet cells and secrete **somatostatin** (identical to the growth hormone– inhibiting hormone secreted by the hypothalamus).

4. F cells constitute the remainder of pancreatic islet cells and secrete **pancreatic polypeptide**.

Insulin

The main function of insulin is to lower blood levels of absorbed nutrients when they rise above normal.

When these nutrients, especially glucose, are in excess of immediate needs insulin promotes storage by:

- acting on cell membranes and stimulating uptake and use of glucose by muscle and connective tissue cells
- increasing conversion of glucose to glycogen (glycogenesis), especially in the liver and skeletal muscles
- accelerating uptake of amino acids by cells, and the synthesis of protein
- promoting synthesis of fatty acids and storage of fat in adipose tissue (lipogenesis)
- decreasing glycogenolysis
- preventing the breakdown of protein and fat, and *gluconeogenesis* (formation of new sugar from, e.g. protein).

Insulin is a polypeptide consisting of about 50 amino acids. Amounts are expressed in international units (IU).

Glucagon

The effects of glucagon increase blood glucose levels by stimulating, e.g.:

- conversion of glycogen to glucose in the liver and skeletal muscles (glycogenolysis)
- gluconeogenesis.

Secretion of glucagon is stimulated by a low blood glucose level and exercise and decreased by somatostatin and insulin.

Somatostatin (GHRH)

The effect of this hormone, also produced by the hypothalamus, is to inhibit the secretion of both insulin and glucagon.

PINEAL GLAND

- The **pineal gland** (PI⁻N-e⁻ -al _ pinecone shape) is a small endocrine gland attached to the roof of the third ventricle of the brain at the midline .
- Part of the epithalamus, it is positioned between the two superior colliculi, has a mass of 0.1–0.2 g, and is covered by a capsule formed by the pia mater.
- The gland consists of masses of neuroglia and secretory cells called **pinealocytes**
- The pineal gland secretes **melatonin**, an amine hormone derived from serotonin. Melatonin appears to contribute to the setting of the body's biological clock, which is controlled by the suprachiasmatic nucleus of the hypothalamus. As more melatonin is liberated during darkness than in light, this hormone is thought to promote sleepiness.
- dUring sleep, plasma levels of melatonin increase tenfold and then decline to a low level again before awakening.
- Small doses of melatonin given orally can induce sleep and reset daily rhythms, which might benefit workers whose shifts alternate between daylight and nighttime hours.