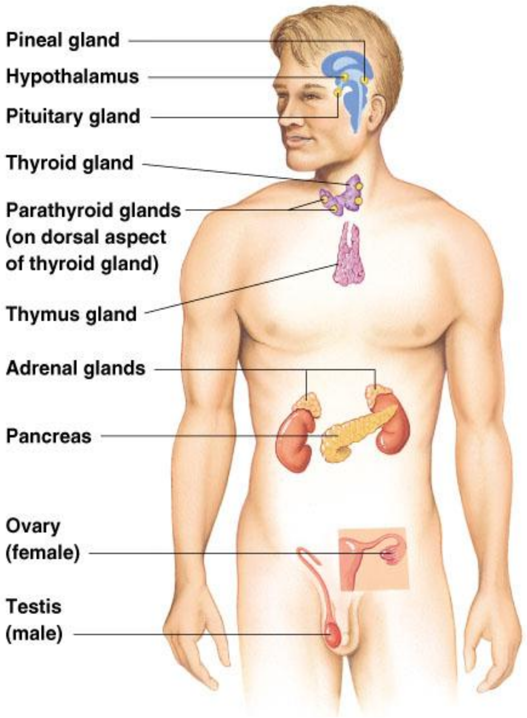
Lecture No . 1

The Endocrine system



Introduction to Endocrinology

Coordination of Body Functions by Chemical Messengers :

The multiple activities of the cells, tissues, and organs of the body are coordinated by the interplay of several types of chemical messenger systems:

1. ***Neurotransmitters*** are released by axon terminals of neurons into the synaptic junctions and act locally to control nerve cell functions.
2. ***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.
3. ***Neuroendocrine hormones*** are secreted by neurons into the circulating blood and influence the function of cells at another location in the body.
4. ***Paracrines*** are secreted by cells into the extracellular fluid and affect neighboring cells of a different type.
5. ***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.

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 . Cytokine hormones (e.g., *leptin*) produced by adipocytes are sometimes called *adipokines*.

Later we will discuss mainly the endocrine and neuroendocrine hormone systems, keeping in mind that many of the body's chemical messenger systems interact with one another to maintain homeostasis. For example, the adrenal medullae and the pituitary gland secrete their hormones primarily in response to neural stimuli. The neuroendocrine cells, located in the hypothalamus, have axons that terminate in the posterior pituitary gland and median eminence and secrete several neurohormones, including *antidiuretic hormone (ADH)*, *oxytocin*, and *hypophysiotropic hormones,* which control the secretion of anterior pituitary hormones.

The *endocrine hormones* are carried by the circulatory system to cells throughout the body, including the nervous system in some cases, where they bind with receptors and initiate many reactions. Some endocrine hormones affect many different types of cells of the body; for example, *growth hormone* (from the anterior pituitary gland) causes growth in most parts of the body, and *thyroxine* (from the thyroid gland) increases the rate of many chemical reactions in almost all the body's cells. Other hormones affect only specific *target tissues*, because only these tissues have receptors for the hormone. For example, *adrenocorticotropic hormone (ACTH)* from the anterior pituitary gland specifically stimulates the adrenal cortex, causing it to secrete adrenocortical hormones, and the *ovarian hormones* have specific effects on the female sex organs as well as on the secondary sexual characteristics of the female body.

The multiple hormone systems play a key role in regulating almost all body functions, including metabolism, growth and development, water and electrolyte balance, reproduction, and behavior. For instance, without growth hormone, a person would be a dwarf. Without thyroxine and triiodothyronine from the thyroid gland, almost all the chemical reactions of the body would become sluggish, and the person would become sluggish as well.Without insulin from the pancreas, the body's cells could use little of the food carbohydrates for energy. And without the sex hormones, sexual development and sexual functions would be absent.

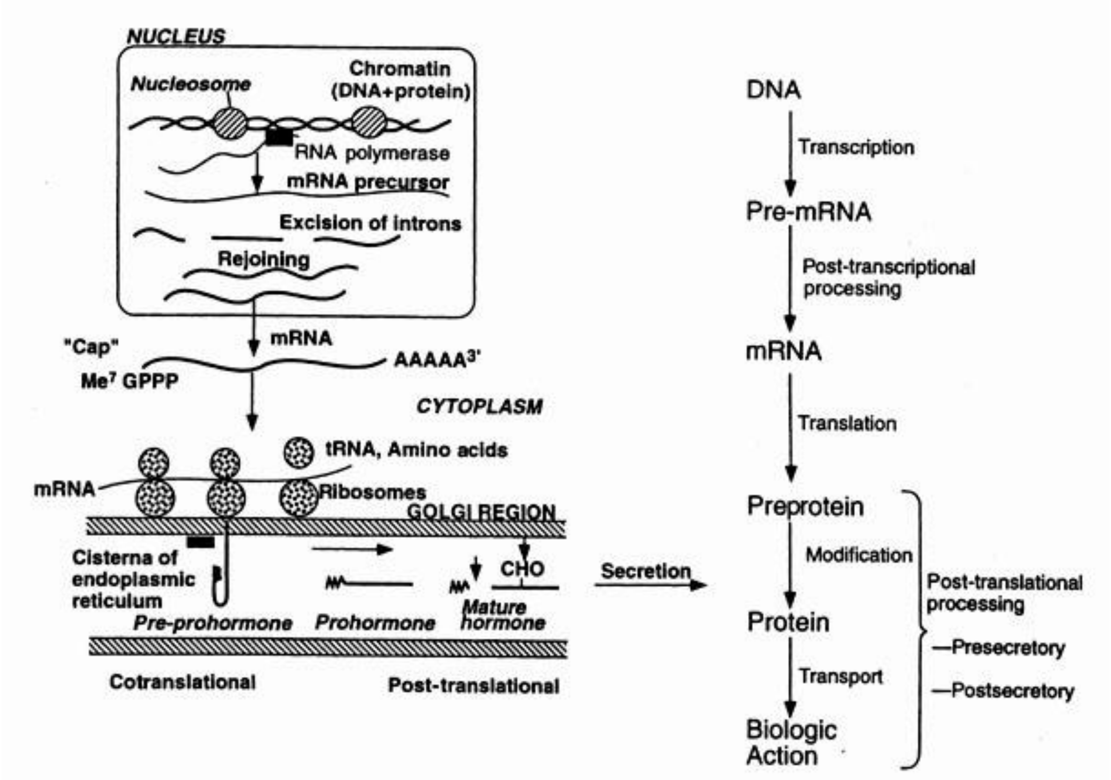
Chemical Structure and Synthesis of Hormones

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). There are no known polysaccharides or nucleic acid hormones.

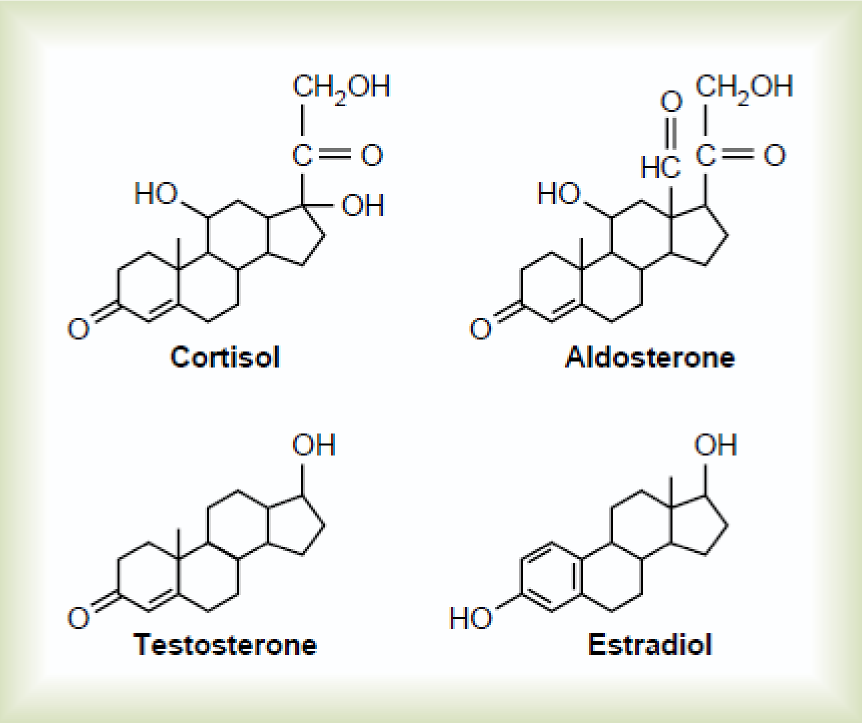
***Polypeptide and Protein Hormones Are Stored in Secretory Vesicles Until Needed*.**

Most of the hormones in the body are polypeptides and proteins. These hormones range in size from small peptides with as few as 3 amino acids (thyrotropin-releasing hormone) to proteins with almost 200 amino acids (growth hormone and prolactin). In general, polypeptides with 100 or more amino acids are called proteins, and those with fewer than 100 amino acids are referred to as peptides. Protein and peptide hormones are synthesized on the rough end of the endoplasmic reticulum of the different endocrine cells, in the same fashion as most other proteins. They are usually synthesized first as larger proteins that are not biologically active (*preprohormones*) and are cleaved to form smaller *prohormones* in the endoplasmic reticulum. These are then transferred to the Golgi apparatus for packaging into secretory vesicles. In this process, enzymes in the vesicles cleave the prohormones to produce smaller, biologically active hormones and inactive fragments. The vesicles are stored within the cytoplasm, and many are bound to the cell membrane until their secretion is needed. Secretion of the hormones (as well as the inactive fragments) occurs when the secretory vesicles fuse with the cell membrane and the granular contents are extruded into the interstitial fluid or directly into the blood stream by *exocytosis*. In many cases, the stimulus for exocytosis is an increase in cytosolic calcium concentration caused by depolarization of the plasma membrane. In other instances, stimulation of an endocrine cell surface receptor causes increased cyclic adenosine monophosphate (cAMP) and subsequently activation of protein kinases that initiate secretion of the hormone. The peptide hormones are water soluble, allowing them to enter the circulatory system easily, where they are carried to their target tissues.

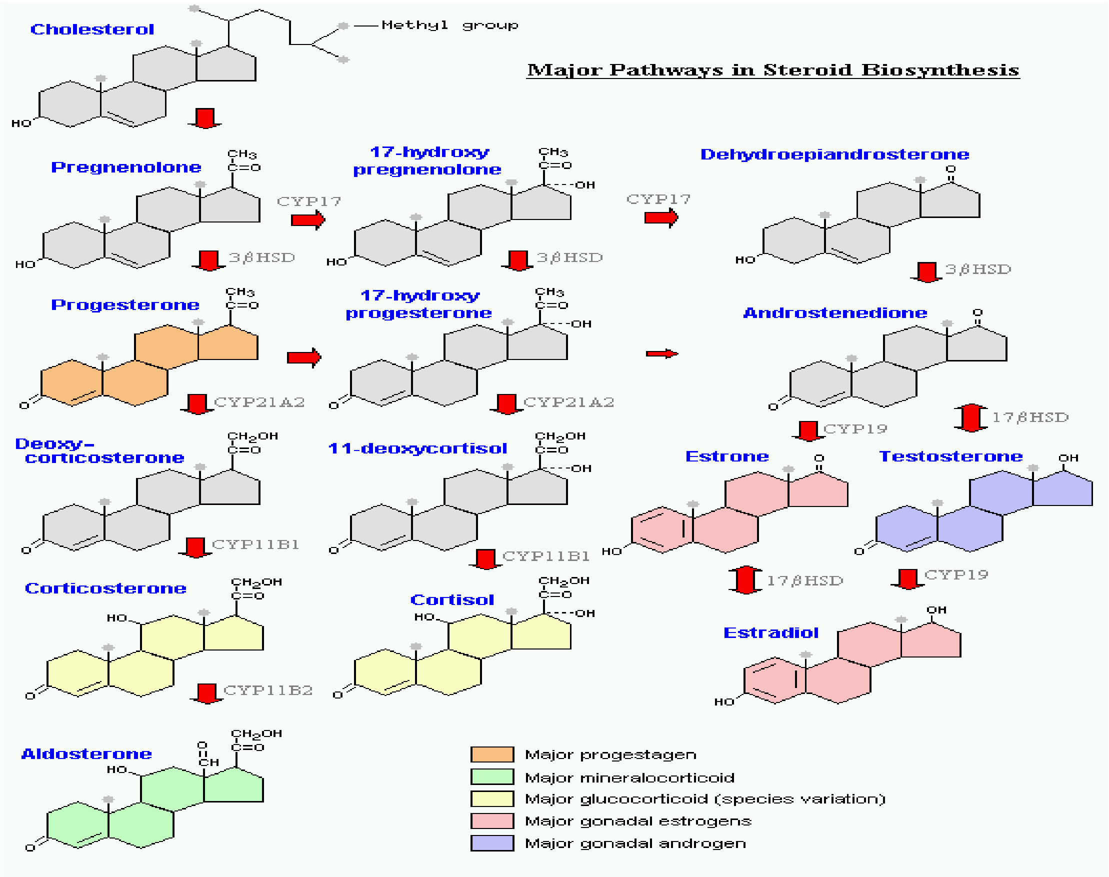


***Steroid Hormones Are Usually Synthesized from Cholesterol and Are Not Stored*.**

The chemical structure of steroid hormones is similar to that of cholesterol, and in most instances they are synthesized from cholesterol itself. They are lipid soluble and consist of three cyclohexyl rings and one cyclopentyl ring combined into a single structure. Although there is usually very little hormone storage in steroid-producing endocrine cells, large stores of cholesterol esters in cytoplasm vacuoles can be rapidly mobilized for steroid synthesis after a stimulus. Much of the cholesterol in steroid-producing cells comes from the plasma, but there is also de novo synthesis of cholesterol in steroid-producing cells. 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.

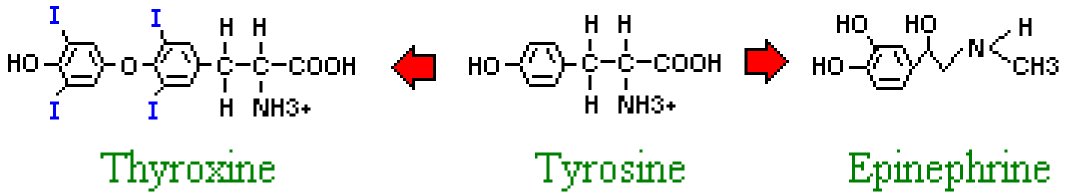


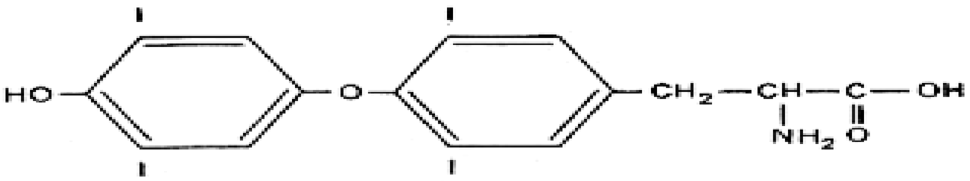
Chemical structures of several steroid hormones.



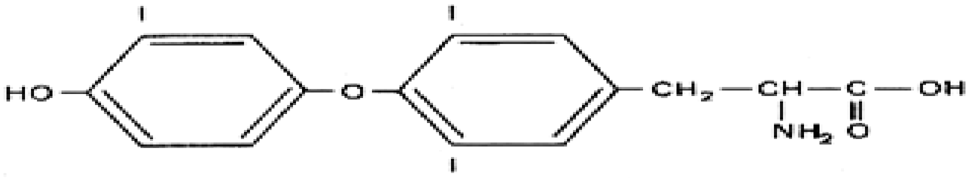
Amine Hormones Are Derived from Tyrosine.

The two groups of hormones derived from tyrosine, the thyroid and the adrenal medullary hormones, are formed by the actions of enzymes in the cytoplasmic compartments of the glandular cells. The thyroid hormones are synthesized and stored in the thyroid gland and incorporated into macromolecules of the protein *thyroglobulin*, which is stored in large follicles within the thyroid gland. Hormone secretion occurs when the amines are split from thyroglobulin, and the free hormones are then released into the blood stream. After entering the blood, most of the thyroid hormones combine with plasma proteins, especially *thyroxine-binding globulin*, which slowly releases the hormones to the target tissues. Epinephrine and norepinephrine are formed in the adrenal medulla, which normally secretes about four times more epinephrine than norepinephrine. Catecholamines are taken up into preformed vesicles and stored until secreted. Similar to the protein hormones stored in secretory granules, catecholamines are also released from adrenal medullary cells by exocytosis. Once the catecholamines enter the circulation, they can exist in the plasma in free form or in conjugation with other substances.





3, 5, 3', 5' – Tetraiodothyronine (thyroxine, T_4)



3, 5, 3'–Triiodothyronine (T_3)

Gland/Tissue	Hormones	Major Functions	Chemical structure
Hypothalamus	Thyrotropin-releasing hormone (TRH)	Stimulates secretion of TSH and prolactin	Peptide
	Corticotropin-releasing hormone (CRH)	Causes release of ACTH	Peptide
	Growth hormone–releasing hormone (GHRH)	Causes release of growth hormone	Peptide
	Growth hormone inhibitory hormone (GHIH) (somatostatin)	Inhibits release of growth hormone	Peptide
	Gonadotropin-releasing hormone (GnRH)	Causes release of LH and FSH	
	Dopamine or prolactin-inhibiting factor (PIF)	Inhibits release of prolactin	Amine
Anterior pituitary	Growth hormone	Stimulates protein synthesis and overall growth of most cells and tissues	Peptide
	Thyroid-stimulating hormone (TSH)	Stimulates synthesis and secretion of thyroid hormones (thyroxine and triiodothyronine)	Peptide
	Adrenocorticotropic hormone (ACTH)	Stimulates synthesis and secretion of adrenocortical hormones (cortisol, androgens, and aldosterone)	Peptide
	Prolactin	Promotes development of the female breasts and secretion of milk	Peptide
	Follicle-stimulating hormone (FSH)	Causes growth of follicles in the ovaries and sperm maturation in Sertoli cells of testes	Peptide
	Luteinizing hormone (LH)	Stimulates testosterone synthesis in Leydig cells of testes; stimulates ovulation, formation of corpus luteum, and estrogen and progesterone synthesis in ovaries	Peptide
Posterior pituitary	Antidiuretic hormone (ADH) (also called vasopressin)	Increases water reabsorption by the kidneys and causes vasoconstriction and increased blood Pressure	Peptide
	Oxytocin	Stimulates milk ejection from breasts	Peptide

		and uterine contractions	
Thyroid	Thyroxine (T4) and triiodothyronine (T3)	Increases the rates of chemical reactions in most cells, thus increasing body metabolic rate	Amine
	Calcitonin	Promotes deposition of calcium in the bones and decreases extracellular fluid calcium ion concentration	Peptide
Adrenal cortex	Cortisol	Has multiple metabolic functions for controlling metabolism of proteins, carbohydrates, and fats; also has anti-inflammatory effects	Steroid
	Aldosterone	Increases renal sodium reabsorption, potassium secretion, and hydrogen ion secretion	Steroid
Adrenal medulla	Norepinephrine, epinephrine	Same effects as sympathetic stimulation	Amine
Pancreas	Insulin (b cells)	Promotes glucose entry in many cells, and in this way controls carbohydrate metabolism	Peptide
	Glucagon (a cells)	Increases synthesis and release of glucose from the liver into the body fluids	Peptide
Parathyroid	Parathyroid hormone (PTH)	Controls serum calcium ion concentration by increasing calcium absorption by the gut and kidneys and releasing calcium from bones	Peptide
Testes	Testosterone	Promotes development of male reproductive system and male secondary sexual characteristics	Steroid
Ovaries	Estrogens	Promotes growth and development of female reproductive system, female breasts, and female	Steroid

		secondary sexual characteristics	
	Progesterone	Stimulates secretion of “uterine milk” by the uterine endometrial glands and promotes development of secretory apparatus of breasts	Steroid
Placenta	Human chorionic gonadotropin (HCG)	Promotes growth of corpus luteum and secretion of estrogens and progesterone by corpus luteum	Peptide
	Human somatomammotropin	Probably helps promote development of some fetal tissues as well as the mother’s breasts	Peptide
	Estrogens	See actions of estrogens from ovaries	Steroid
	Progesterone	See actions of progesterone from ovaries	Steroid
Kidney	Renin	Catalyzes conversion of angiotensinogen to angiotensin I (acts as an enzyme)	Peptide
	1,25-Dihydroxycholecalciferol	Increases intestinal absorption of calcium and bone mineralization	Steroid
	Erythropoietin	Increases erythrocyte production	Peptide
Heart	Atrial natriuretic peptide (ANP)	Increases sodium excretion by kidneys, reduces blood pressure	Peptide
Stomach	Gastrin	Stimulates HCl secretion by parietal cells	Peptide
Small intestine	Secretin	Stimulates pancreatic acinar cells to release bicarbonate and water	Peptide
	Cholecystokinin (CCK)	Stimulates gallbladder contraction and release of pancreatic enzymes	Peptide
Adipocytes	Leptin	Inhibits appetite, stimulates thermogenesis	Peptide

Hormone Secretion, Transport, and Clearance from the Blood

Onset of Hormone Secretion After a Stimulus, and Duration of Action of Different Hormones.

Some hormones, such as norepinephrine and epinephrine, are secreted within seconds after the gland is stimulated, and they may develop full action within another few seconds to minutes; the actions of other hormones, such as thyroxine or growth hormone, may require months for full effect .Thus, each of the different hormones has its own characteristic onset and duration of action - each tailored to perform its specific control function.

Concentrations of Hormones in the Circulating Blood, and Hormonal Secretion Rates.

The concentrations of hormones required to control most metabolic and endocrine functions are incredibly small. Their concentrations in the blood range from as little as 1 picogram (which is one millionth of one millionth of a gram) in each milliliter of blood up to at most a few micrograms (a few millionths of a gram) per milliliter of blood. Similarly, the rates of secretion of the various hormones are extremely small, usually measured in micrograms or milligrams per day. We shall see later that highly specialized mechanisms are available in the target tissues that allow even these minute quantities of hormones to exert powerful control over the physiological systems.

Feedback Control of Hormone Secretion

Negative Feedback Prevents Overactivity of Hormone Systems.

Although the plasma concentrations of many hormones fluctuate in response to various stimuli that occur throughout the day, all hormones studied thus far appear to be closely controlled. In most instances, this control is exerted through *negative feedback mechanisms* that ensure a proper level of hormone activity at the target tissue. After a stimulus causes release of the hormone, conditions or products resulting from the action of the hormone tend to suppress its further release. In other words, the hormone (or one of its products) has a negative feedback effect to prevent oversecretion of the hormone or overactivity at the target tissue. The controlled variable is often not the secretory rate of the hormone itself but the degree of activity of the target tissue. Therefore, only when the target tissue activity rises to an appropriate level will feedback signals to the endocrine gland become powerful enough to slow further secretion of the hormone. Feedback regulation of hormones can occur at all levels, including gene transcription and translation steps involved in the synthesis of hormones and steps involved in processing hormones or releasing stored hormones.

***Surges of Hormones Can Occur with Positive Feedback*.**

In a few instances, *positive feedback* occurs when the biological action of the hormone causes additional secretion of the hormone. One example of this is the surge of *luteinizing hormone (LH)* that occurs as a result of the stimulatory effect of estrogen on the anterior pituitary before ovulation. The secreted LH then acts on the ovaries to stimulate additional secretion of estrogen, which in turn causes more secretion of LH. Eventually, LH reaches an appropriate concentration, and typical negative feedback control of hormone secretion is then exerted.

Cyclical Variations Occur in Hormone Release.

Superimposed on the negative and positive feedback control of hormone secretion are periodic variations in hormone release that are influenced by seasonal changes, various stages of development and aging, the diurnal (daily) cycle, and sleep. For example, the secretion of growth hormone is markedly increased during the early period of sleep but is reduced during the later stages of sleep. In many cases, these cyclical variations in hormone secretion are due to changes in activity of neural pathways involved in controlling hormone release.

Transport of Hormones in the Blood

Water-soluble hormones (peptides and catecholamines) are dissolved in the plasma and transported from their sites of synthesis to target tissues, where they diffuse out of the capillaries, into the interstitial fluid, and ultimately to target cells. *Steroid and thyroid hormones,* in contrast, circulate in the blood mainly bound to plasma proteins. Usually less than 10 per cent of steroid or thyroid hormones in the plasma exist free in solution. For example, more than 99 per cent of the thyroxine in the blood is bound to plasma proteins. However, protein-bound hormones cannot easily diffuse across the capillaries and gain access to their target cells and are therefore biologically inactive until they dissociate from plasma proteins. The relatively large amounts of hormones bound to proteins serve as reservoirs, replenishing the concentration of free hormones when they are bound to target receptors or lost from the circulation. Binding of hormones to plasma proteins greatly slows their clearance from the plasma.

“Clearance” of Hormones from the Blood

Two factors can increase or decrease the concentration of a hormone in the blood. One of these is the rate of hormone secretion into the blood. The second is the rate of removal of the hormone from the blood, which is called the *metabolic clearance rate.* This is usually expressed in terms of the number of milliliters of plasma cleared of the hormone per minute. To calculate this clearance rate, one measures (1) the rate of disappearance of the hormone from the plasma per minute and (2) the concentration of the hormone in each milliliter of plasma. Then, the metabolic clearance rate is calculated by the following formula:

Metabolic clearance rate = Rate of disappearance
of hormone from the plasma/Concentration of
hormone in each milliliter of plasma

The usual procedure for making this measurement is the following: A purified solution of the hormone to be measured is tagged with a radioactive substance. Then the radioactive hormone is infused at a constant rate into the blood stream until the radioactive concentration in the plasma becomes steady. At this time, the rate of disappearance of the radioactive hormone from the plasma equals the rate at which it is infused, which gives one the rate of disappearance. At the same time, the plasma concentration of the radioactive hormone is measured using a standard radioactive counting procedure. Then, using the formula just cited, the metabolic clearance rate is calculated.

Hormones are “cleared” from the plasma in several ways, including (1) metabolic destruction by the tissues, (2) binding with the tissues, (3) excretion by the liver into the bile, and (4) excretion by the kidneys into the urine. For certain hormones, a decreased metabolic clearance rate may cause an excessively high concentration of the hormone in the circulating body fluids. For instance, this occurs for several of the steroid hormones when the liver is diseased, because these hormones are conjugated mainly in the liver and then “cleared” into the bile. Hormones are sometimes degraded at their target cells by enzymatic processes that cause endocytosis of the cell membrane hormone-receptor complex; the hormone is then metabolized in the cell, and the receptors are usually recycled back to the cell membrane. Most of the peptide hormones and catecholamines are water soluble and circulate freely in the blood. They are usually degraded by enzymes in the blood and tissues and rapidly excreted by the kidneys and liver, thus remaining in the blood for only a short time. For example, the half-life of angiotensin II circulating in the blood is less than a minute. Hormones that are bound to plasma proteins are cleared from the blood at much slower rates and may remain in the circulation for several hours or even days. The half-life of adrenal steroids in the circulation, for example, ranges between 20 and 100 minutes, whereas the half-life of the protein-bound thyroid hormones may be as long as 1 to 6 days.