LEC. 1+2 PHYSIOLOGY

2nd year students

BY DR. AHMED HAMED ATAIMISH

Hormones and Endocrine Glands.

Introduction

Two major regulatory systems make important contributions to homeostasis: the **nervous system** and the **endocrine system**. In order to maintain relatively constant conditions in the internal environment of the body, each of these systems influences the activity of all the other organ systems. The nervous system coordinates fast, precise responses, such as muscle contraction. Electrical impulses generated by this system are very rapid and of short duration (milliseconds). The endocrine system regulates metabolic activity within the cells of organs and tissues. In contrast to the nervous system, endocrine system coordinates activities that require longer duration (hours, days) rather than speed. Examples of such activities include growth; long-term regulation of blood pressure; and coordination of menstrual cycles in females.

What is a Gland?

Gland is an organized collection of secretory epithelial cells. Most glands are formed during development by proliferation of epithelial cells so that they project into the underlying connective tissue. Some glands retain their continuity with the surface via a duct and are known as **EXOCRINE GLANDS** (as in sweat gland). Other glands lose this direct continuity with the surface when their ducts degenerate during development, these glands are known as **ENDOCRINE** glands.

You may be puzzled to see some organs—the heart, for instance—that clearly have other functions yet are listed as part of the endocrine system represented by releasing atrial natriuretic peptide (ANP), a hormone that

maintain Na excretion by the kidney and maintain blood pressure. The explanation is that, in addition to the cells that carry out other functions, the organ also contains cells that secrete hormone. That the hypothalamus, a part of the brain, is considered part of the endocrine system. This is because the chemical messengers released by certain axon terminals in both the hypothalamus and its extension, the posterior pituitary, do not function as neurotransmitters affecting adjacent cells but, rather, enter the blood as hormones. The blood then carries these hormones to their sites of action.

The endocrine system carries out its effects through the production of *hormones*. Classic **endocrine glands** are scattered throughout the body and secrete **hormones** into the circulatory system, usually via ductless secretion into the interstitial fluid. **Target organs** express receptors that bind the specific hormone to initiate a cellular response. *Hormones* are chemical messengers that exert a regulatory effect on the cells of the body. Secreted from *endocrine glands*, which are ductless structures, hormones are released directly into the blood. They are then transported by the circulation to the tissues upon which they exert their effects. Because they travel in the blood, the serum concentrations of hormones are very low (10^{-11} to $10^{-9}M$); therefore, these molecules must be very potent.

Generally, a single hormone does not affect all of the body's cells. The tissues that respond to a hormone are referred to as the *target tissues*. The cells of these tissues possess specific receptors to which the hormone binds. This receptor binding then elicits a series of events that influences cellular activities.

Biochemical classification of hormones

Hormones are classified into three biochemical categories:

- Steroids
- Proteins/peptides
- Amines

Steroid hormones are produced by the adrenal cortex, testes, ovaries, and placenta. Synthesized from cholesterol, these hormones are lipid soluble; therefore, they cross cell membranes readily and bind to receptors found intracellularly. However, because their lipid solubility renders them insoluble in blood, these hormones are transported in the blood bound to proteins.

Furthermore, steroid hormones are not typically preformed and stored for future use within the endocrine gland. Because they are lipid soluble, they could diffuse out of the cells and physiological regulation of their release would not be possible. Finally, steroid hormones are absorbed easily by the gastrointestinal tract and therefore may be administered orally.

Protein/peptide hormones are derived from amino acids. These hormones are preformed and stored for future use in membrane-bound secretory granules.

When needed, they are released by exocytose. Protein/peptide hormones are water soluble, circulate in the blood predominantly in an unbound form, and thus tend to have short half-lives. Because these hormones are unable to cross the cell membranes of their target tissues, they bind to receptors on the membrane surface. Protein/peptide hormones cannot be administered orally because they would be digested in the gastrointestinal tract. Instead, they are usually administered by injection (e.g., insulin). Because small peptides are able to cross through mucus membranes, they

may be given sublingually or intranasal. For example, Miacalcin, the synthetic form of the hormone calcitonin {which is counteracts parathyroid hormone (PTH)} is prepared in the form of a nasal spray.

Amine hormones include the thyroid hormones and the catecholamine. The thyroid hormones tend to be biologically similar to the steroid hormones.

They are mainly insoluble in the blood and are transported predominantly (>99%) bound to proteins. As such, these hormones have longer half-lives (triiodothyronine, T3, = 24 h; thyroxine, T4, = 7 days). Furthermore, thyroid hormones cross cell membranes to bind with intracellular receptors and may be administered orally {e.g., (levothyroxine)}. In contrast to steroid hormones, however, thyroid hormones have the unique property of being stored extracellularly in the thyroid gland as part of the thyroglobulin molecule.

The catecholamine's are biologically similar to protein/peptide hormones. These hormones are soluble in the blood and are transported in an unbound form. Therefore, the catecholamine's have a relatively short half-life. Because these hormones do not cross cell membranes, they bind to receptors on the membrane surface. Finally, the catecholamines are stored intracellularly in secretory granules for future use.

Transport of hormones

Steroid and thyroid hormones are transported in the blood bound to plasma proteins. The serum concentrations of free hormone (*H*), plasma protein (*P*), and bound hormone (*HP*) are in equilibrium:

$[H]^* [P] = [HP]$

When the concentration of the free form of a hormone decreases, then more of this hormone will be released from the binding proteins. The free

hormone is the biologically active form. It binds to the target tissue to cause its actions and is involved with the negative feedback control of its secretion. The binding of hormones to plasma proteins has several beneficial effects, including:

• Facilitation of transport

• Prolonged half-life

• Hormone reservoir

Steroid and thyroid hormones are minimally soluble in the blood. Binding to plasma proteins renders them water soluble and facilitates their transport. Protein binding also prolongs the circulating half-life of these hormones.

Because they are lipid soluble, they cross cell membranes easily. As the blood flows through the kidney, these hormones would enter cells or be filtered and lost to the urine if they were not held in the blood by the impermeable plasma proteins. Finally, the protein-bound form of the hormone serves as a "reservoir" of hormone that minimizes the changes in free hormone concentration when hormone secretion from its endocrine gland changes abruptly.

Functional classification of hormones

Hormones are classified into two functional categories:

• Trophic hormones

• Non-trophic hormones

A *trophic hormone* acts on another endocrine gland to stimulate secretion of its hormone. For example, thyrotropin, or thyroid-stimulating hormone (TSH), stimulates the secretion of thyroid hormones. Adrenocorticotropin, or adrenocorticotropic hormone (ACTH), stimulates the adrenal cortex to secret the hormone cortisol. Both trophic hormones are produced by the pituitary gland; in fact, many trophic hormones are

secreted by the pituitary. The pituitary gland is sometimes referred to as the "master gland" because its hormones regulate the activity of other endocrine glands.

A *non-trophic hormone* acts on non-endocrine target tissues. For example, parathormone {**Parathyroid hormone** (PTH)} released from the parathyroid glands acts on bone tissue to stimulate the release of calcium into the blood. Aldosterone released from the cortical region of the adrenal glands acts on the kidney to stimulate the reabsorption of sodium into the blood.

Hormone interactions

Multiple hormones may affect a single target tissue simultaneously. Therefore, the response of the target tissue depends not only on the effects of each hormone individually, but also on the nature of the interaction of the hormones at the tissue. The three types of hormone interactions include:

- Synergism
- Permissiveness
- Antagonism

When two hormones interact at the target tissue such that the combination of their effects is more than additive, *Synergism* occurs. In other words, their combined effect is greater than the sum of their separate effects. For example, epinephrine, cortisol, and glucagon are three hormones that each increase the level of blood glucose. The magnitude of their individual effects on glucose levels tends to be low to moderate. However, the simultaneous activity of all three hormones results in an increase in blood glucose that is several times greater than the sum of their individual effects.

In *permissiveness*, one hormone enhances the responsiveness of the target tissue to a second hormone; in other words, the first hormone increases the activity of the second. For example, the normal maturation of the reproductive system requires reproductive hormones from the hypothalamus, pituitary, and gonads as well as the presence of thyroid hormone. Although thyroid hormone by itself has no effect on the reproductive system, if it is absent the development of this system is delayed. Therefore, thyroid hormone is considered to have a permissive effect on the reproductive hormones, facilitating their actions causing sexual maturation.

When the actions of one hormone oppose the effects of another, the result is *antagonism*. For example, insulin decreases blood glucose and promotes the formation of fat. Glucagon, on the other hand, increases blood glucose and promotes the degradation of fat. Therefore, the effects of insulin and glucagon are antagonistic.

Hormone Receptors and Their Activation

The first step of a hormone's action is to bind to specific *receptors* at the target cell. Cells that lack receptors for the hormones do not respond. Receptors for some hormones are located on the target cell membrane, whereas other hormone receptors are located in the cytoplasm or the nucleus. When the hormone combines with its receptor, this usually initiates a cascade of reactions in the cell, with each stage becoming more powerfully activated so that even small concentrations of the hormone can have a large effect.

Hormonal receptors are large proteins, and each cell that is to be stimulated usually has some 2000 to 100,000 receptors. Also, each receptor is usually highly specific for a single hormone; this determines

the type of hormone that will act on a particular tissue. The target tissues that are affected by a hormone are those that contain its specific receptors.

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.

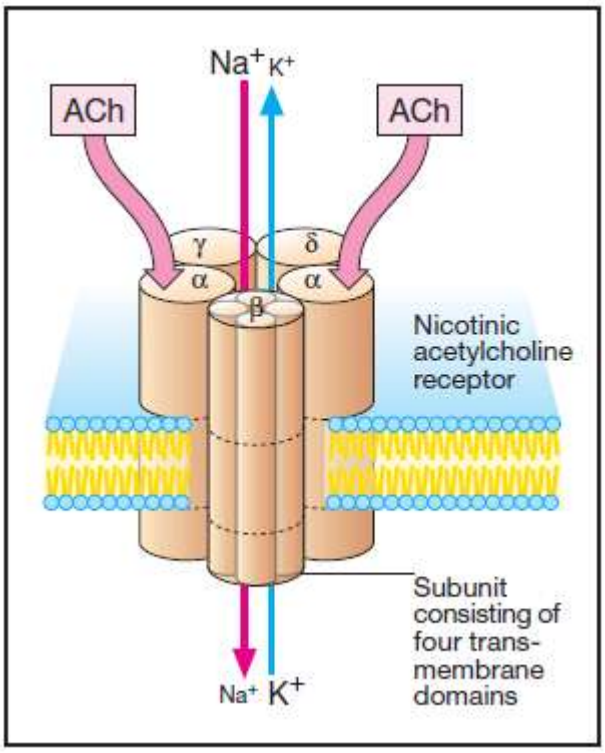
Intracellular Signaling After Hormone Receptor Activation

Almost without exception, a hormone affects its target tissues by first forming a hormone-receptor complex. This alters the function of the receptor itself, and the activated receptor initiates the hormonal effects. To explain this, let us give a few examples of the different types of interactions.

Ion Channel-Linked Receptors

Virtually all the neurotransmitter substances, such as acetylcholine and norepinephrine, combine with receptors in the postsynaptic membrane. This almost always causes a change in the structure of the receptor, usually opening or closing a channel for one or more ions. Some of these *ion channel-linked receptors* open (or close) channels for sodium ions,

others for potassium ions, others for calcium ions, and so forth. The altered movement of these ions through the channels causes the subsequent effects on the postsynaptic cells. Although a few hormones may exert some of their actions through activation of ion channel receptors, most hormones that open or close ions channels do this indirectly by coupling with G protein-linked or enzyme-linked receptors.



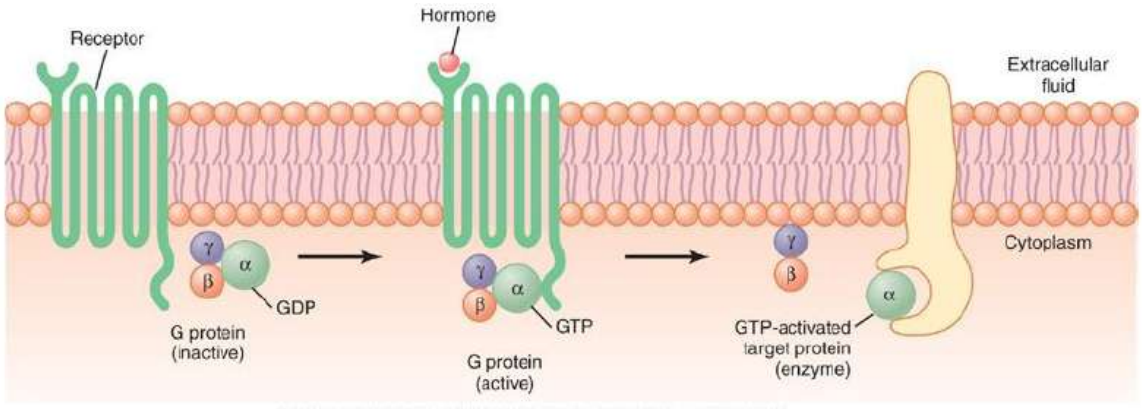
G Protein-Linked Hormone Receptors

Many hormones activate 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).*

Some parts of the receptor that protrude into the cell cytoplasm (especially the cytoplasmic tail of the receptor) are coupled to G proteins that include three (i.e., trimeric) parts the: α, β, and γ subunits. 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 trimeric G proteins are named for their ability to bind *guanosine nucleotides.* In their inactive state, the α, β, and γ subunits of G proteins form a complex that binds *guanosine diphosphate* (GDP) on the α subunit. When the receptor is activated, it undergoes a conformational change that causes the GDP-bound trimeric G protein to associate with the cytoplasmic part of the receptor and to exchange GDP for *guanosine triphosphate* (GTP). Displacement of GDP by GTP causes the α subunit to dissociate from the trimeric complex and to associate with other intracellular signaling proteins; these proteins, in turn, alter the activity of ion channels or intracellular enzymes such as *adenylyl cyclase* or *phospholipase C*, which alters cell function.



Some hormones are coupled to *inhibitory G proteins* (denoted Gi proteins), whereas others are coupled to *stimulatory G proteins* (denoted

Gs proteins). Thus, depending on the coupling of a hormone receptor to an inhibitory or stimulatory G protein, a hormone can either increase or decrease the activity of intracellular enzymes. This complex system of cell membrane G proteins provides a vast array of potential cell responses to different hormones in the various target tissues of the body.

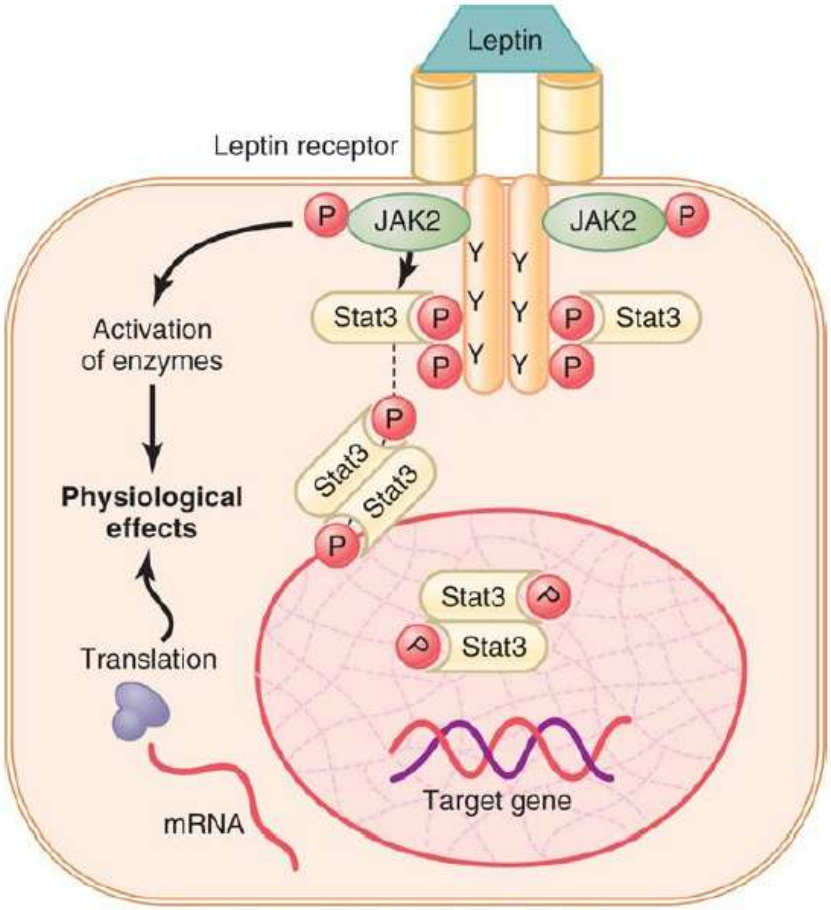
Enzyme-Linked Hormone Receptors

Some receptors, when activated, function directly as enzymes or are closely associated with enzymes that they activate. These *enzyme-linked receptors* are proteins that pass through the membrane only once, in contrast to the seven transmembrane G protein-coupled receptors. 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.

One example of an enzyme-linked receptor is the *leptin receptor*. Leptin is a hormone secreted by fat cells and has many physiological effects, but it is especially important in regulating appetite and energy balance. The leptin receptor is a member of a large family of *cytokine receptors* that do not themselves contain enzymatic activity but signal through associated enzymes. In the case of the leptin receptor, one of the signaling pathways occurs through a *tyrosine kinase* of the *janus kinase* (JAK) family, *JAK2*. The leptin receptor exists as a dimer (i.e., in two parts), and binding of leptin to the extracellular part of the receptor alters its conformation, enabling phosphorylation and activation of the intracellular associated

JAK2 molecules. The activated JAK2 molecules then phosphorylate other tyrosine residues within the leptin receptor-JAK2 complex to mediate intracellular signaling. The intracellular signals include phosphorylation of *signal transducer and activator of transcription* (STAT) proteins, which activates transcription by leptin target genes to initiate protein synthesis.

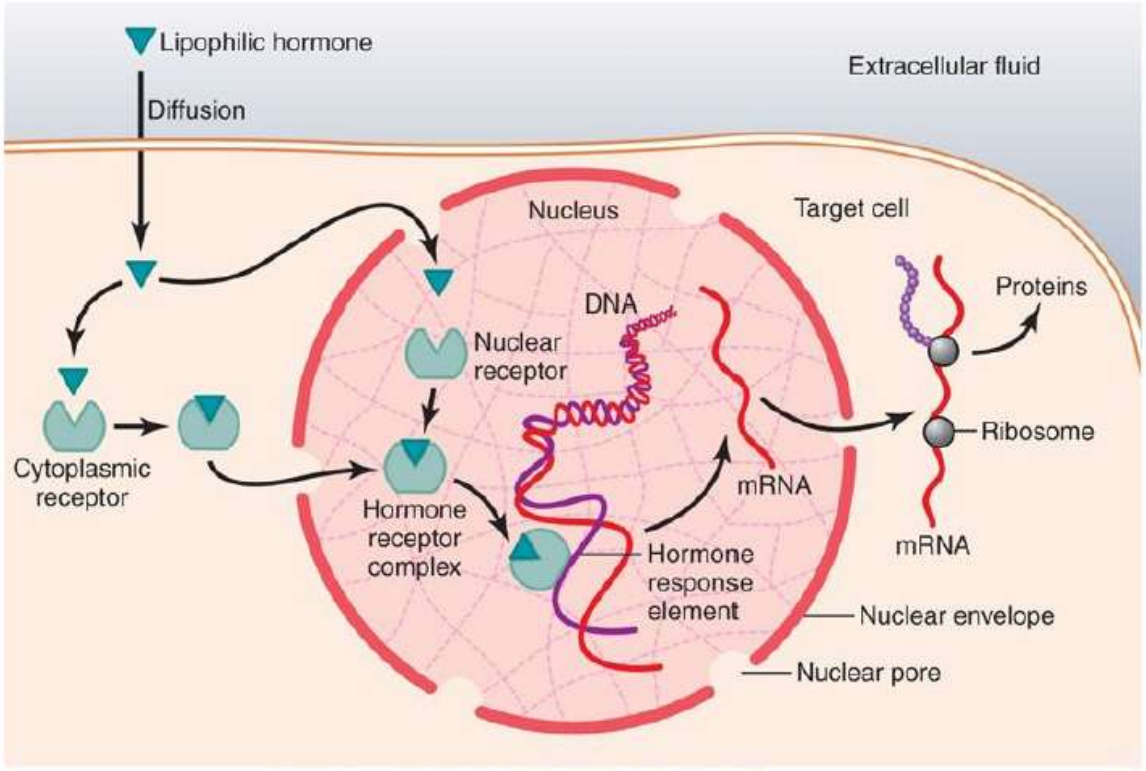
Phosphorylation of JAK2 also leads to activation of other intracellular enzyme pathways such as *mitogen-activated protein kinases* (MAPK) and *phosphatidylinositol 3-kinase* (PI3K). Some of the effects of leptin occur rapidly as a result of activation of these intracellular enzymes, whereas other actions occur more slowly and require synthesis of new proteins.



Intracellular Hormone Receptors and Activation of Genes

Several hormones, including adrenal and gonadal steroid hormones, thyroid hormones, retinoid hormones, and vitamin D, bind with protein receptors inside the cell rather than in the cell membrane.

Because these hormones are lipid soluble, they readily cross the cell membrane and interact with receptors in the cytoplasm or nucleus. The activated hormone-receptor complex then binds with a specific regulatory (promoter) sequence of the DNA called the *hormone response element*, and in this manner either activates or represses transcription of specific genes and formation of messenger RNA (mRNA). Therefore, minutes, hours, or even days after the hormone has entered the cell, newly formed proteins appear in the cell and become the controllers of new or altered cellular functions.



Many different tissues have identical intracellular hormone receptors, but the genes that the receptors regulate are different in the various tissues. An intracellular receptor can activate a gene response only if the appropriate combination of gene regulatory proteins is present, and many of these regulatory proteins are tissue specific. Thus, the responses of different tissues to a hormone are determined not only by the specificity of the receptors but also by the expression of genes that the receptor regulates.

Second Messenger Mechanisms for Mediating Intracellular Hormonal Functions

We noted earlier that one of the means by which hormones exert intracellular actions is to stimulate formation of the second messenger cAMP inside the cell membrane. The cAMP then causes subsequent intracellular effects of the hormone. Thus, the only direct effect that the

hormone has on the cell is to activate a single type of membrane receptor, the second messenger does the rest.

Adenylyl Cyclase-cAMP Second Messenger System

Table 1 shows a few of the many hormones that use the adenylyl cyclase cAMP mechanism to stimulate their target tissues. Binding of the hormones with the receptor allows coupling of the receptor to a *G protein.*

If the G protein stimulates the adenylyl cyclase-cAMP system, it is called a *G*s *protein,* denoting a stimulatory G protein. Stimulation of adenylyl cyclase, a membrane-bound enzyme, by the Gs protein then catalyzes the conversion of a small amount of cytoplasmic *adenosine triphosphate* (ATP) into Camp inside the cell. This then activates *cAMP-dependent protein kinase,* which phosphorylates specific proteins in the cell, triggering biochemical reactions that ultimately lead to the cell's response to the hormone.

Once cAMP is formed inside the cell, it usually activates a *cascade of enzymes.* That is, first one enzyme is activated, which activates a second enzyme, which activates a third, and so forth. The importance of this mechanism is that only a few molecules of activated adenylyl cyclase immediately inside the cell membrane can cause many more molecules of the next enzyme to be activated, which can cause still more molecules of the third enzyme to be activated, and so forth. In this way, even the slightest amount of hormone acting on the cell surface can initiate a powerful cascading activating force for the entire cell.

If binding of the hormone to its receptors is coupled to an inhibitory G protein (denoted *G*i protein), adenylyl cyclase will be inhibited, reducing the formation of cAMP and ultimately leading to an inhibitory action in

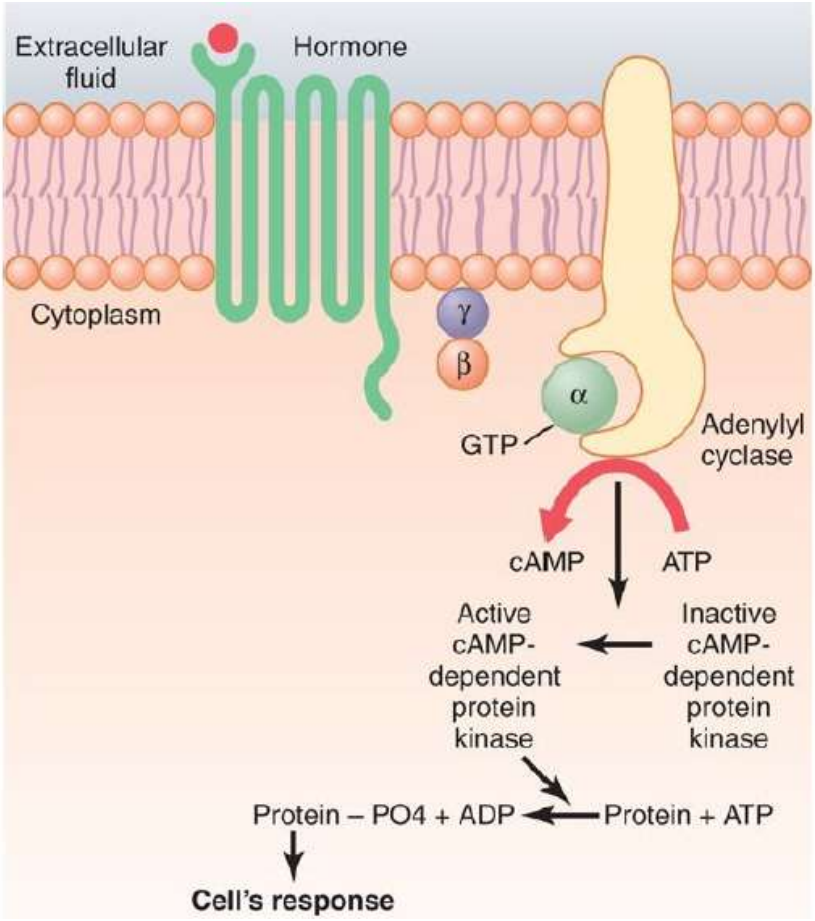
the cell. Thus, depending on the coupling of the hormone receptor to an inhibitory or a stimulatory G protein, a hormone can either increase or decrease the concentration of cAMP and phosphorylation of key proteins inside the cell.

The specific action that occurs in response to increases or decreases of cAMP in each type of target cell depends on the nature of the intracellular machinery-some cells have one set of enzymes, and other cells have other enzymes. Therefore, different functions are elicited in different target cells, such as initiating synthesis of specific intracellular chemicals, causing muscle contraction or relaxation, initiating secretion by the cells, and altering cell permeability.

Thus, a thyroid cell stimulated by cAMP forms the metabolic hormones thyroxine and triiodothyronine, whereas the same cAMP in an adrenocortical cell causes secretion of the adrenocortical steroid hormones. In epithelial cells of the renal tubules, cAMP increases their permeability to water.

Table 1. Hormones That Use the Adenylyl Cyclase-cAMP Second Messenger System

Adrenocorticotropic hormone (ACTH)
Angiotensin II (epithelial cells)
Calcitonin
Catecholamines (β receptors)
Corticotropin-releasing hormone (CRH)
Follicle-stimulating hormone (FSH)
Glucagon
Human chorionic gonadotropin (HCG)
Luteinizing hormone (LH)
Parathyroid hormone (PTH)
Secretin
Somatostatin
Thyroid-stimulating hormone (TSH)
Vasopressin (V_2 receptor, epithelial cells)



Cell Membrane Phospholipid Second Messenger System

Some hormones activate transmembrane receptors that activate the enzyme *phospholipase C* attached to the inside projections of the receptors (Table 2). This enzyme catalyzes the breakdown of some phospholipids in the cell membrane, especially *phosphatidylinositol biphosphate* (PIP2), into two different second messenger products: *inositol triphosphate* (IP3) and *diacylglycerol* (DAG). The IP3 mobilizes calcium ions from mitochondria and the endoplasmic reticulum, and the calcium ions then have their own second messenger effects, such as smooth muscle contraction and changes in cell secretion.

DAG, the other lipid second messenger, activates the enzyme *protein kinase C* (PKC), which then phosphorylates a large number of proteins, leading to the cell's response. In addition to these effects, the lipid portion of DAG is *arachidonic acid*, which is the precursor for the *prostaglandins* and other local hormones that cause multiple effects in tissues throughout the body.

Table2. Hormones That Use the Phospholipase C Second Messenger System

Angiotensin II (vascular smooth muscle)
Catecholamines (α receptors)
Gonadotropin-releasing hormone (GnRH)
Growth hormone-releasing hormone (GHRH)
Oxytocin
Thyrotropin releasing hormone (TRH)
Vasopressin (V1 receptor, vascular smooth muscle)

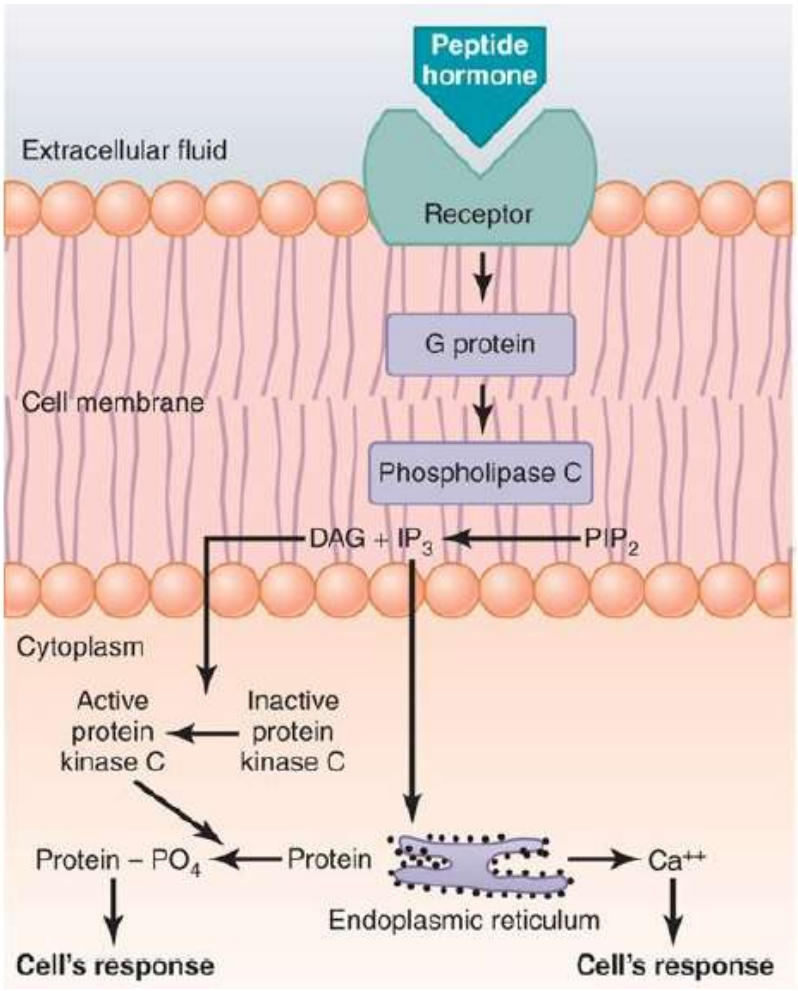


Figure 5:

Calcium-Calmodulin Second Messenger System

Another second messenger system operates in response to the entry of calcium into the cells. Calcium entry may be initiated by (1) changes in membrane potential that open calcium channels or (2) a hormone interacting with membrane receptors that open calcium channels.

On entering a cell, calcium ions bind with the protein *calmodulin*. This protein has four calcium sites, and when three or four of these sites have bound with calcium, the calmodulin changes its shape and initiates multiple effects inside the cell, including activation or inhibition of protein kinases. Activation of calmodulin-dependent protein kinases

causes, via phosphorylation, activation or inhibition of proteins involved in the cell's response to the hormone. For example, one specific function of calmodulin is to activate *myosin light chain kinase,* which acts directly on the myosin of smooth muscle to cause smooth muscle contraction.

The normal calcium ion concentration in most cells of the body is 10^{-8} to 10^{-7}mol/L, which is not enough to activate the calmodulin system. But when the calcium ion concentration rises to 10^{-6} to 10^{-5}mol/L, enough binding occurs to cause all the intracellular actions of calmodulin. This is almost exactly the same amount of calcium ion change that is required in skeletal muscle to activate troponin C, which causes skeletal muscle contraction. It is interesting that troponin C is similar to calmodulin in both function and protein structure.

Negative Feedback Prevents Over-activity 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 over secretion of the hormone or over-activity at the target tissue.

The controlled variable is sometimes 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.

In general, the endocrine system uses a network of feedback responses to maintain a steady state. Steady state can be explained using blood osmolality as an example.

Blood osmolality in humans must be maintained within a physiological range of 275–299 mOsm, and to maintain homeostasis this variable should not exceed that range. To ensure that osmolality does not change in the context of an open system, processes are in place that will add or remove water from the system to ensure a constant osmolality. The osmolality of blood will increase with dehydration and decrease with over hydration.

If blood osmolality increases outside the ideal range (by 10 mOsm or more), osmo receptors are activated. These signal release of the peptide hormone, vasopressin, into the circulation (from the pituitary). Vasopressin acts on the renal collecting duct, and increases the permeability of the plasma membrane to water via the insertion of a protein called an aquaporin.

Water is then moved from the urine into the circulation via transcellular transport. The reabsorption of water from the urine to the blood resets the osmolality of the blood to within the physiological range. The decrease in blood osmolality then exerts a negative feedback on the cells of the hypothalamus and the pituitary and vasopressin release is inhibited, meaning that water reabsorption from the urine is reduced.

Lec.3

Hypothalamus and Pituitary Gland

2nd Year Students

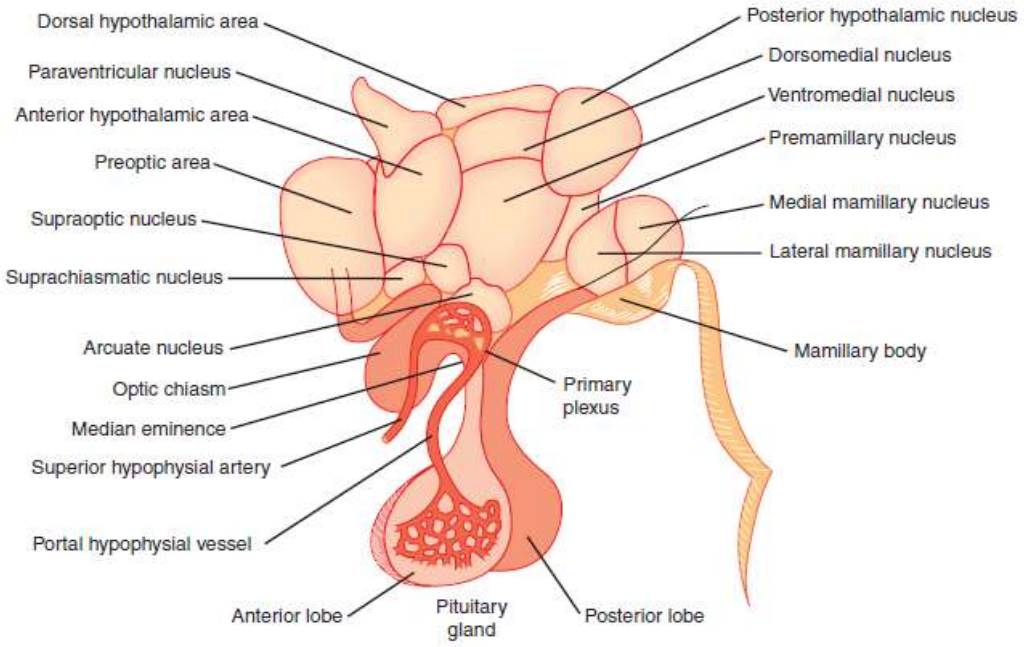
AHMED HAMED ATAIMISH

INTRODUCTION

Many of the complex autonomic mechanisms that maintain the chemical constancy and temperature of the internal environment are integrated in the hypothalamus. The hypothalamus also functions with the limbic system as a unit that regulates emotional and behavior.

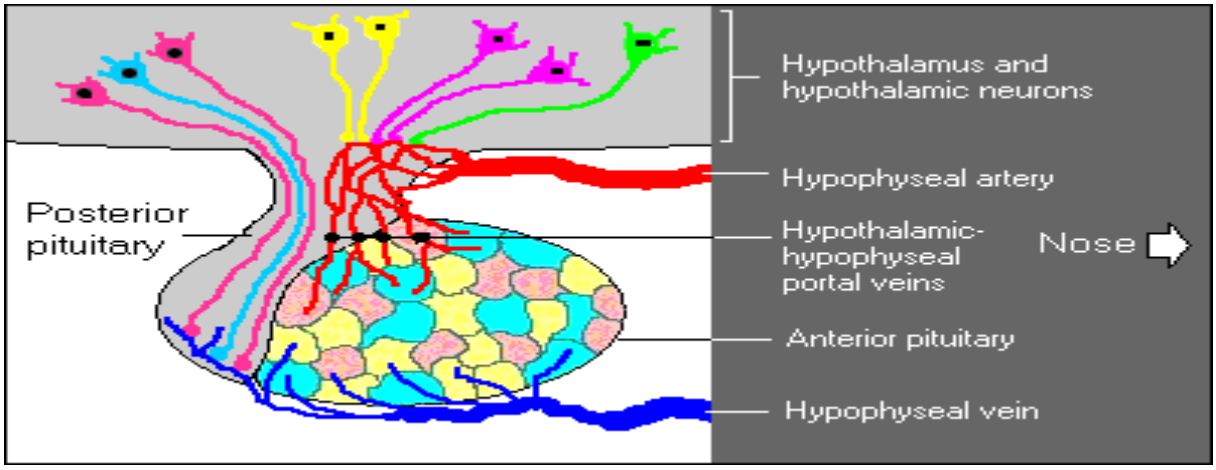
HYPOTHALAMUS: ANATOMIC CONSIDERATIONS:

The hypothalamus is the portion of the anterior end of the diencephalon that lies below the hypothalamic sulcus and in front of the interpeduncular nuclei. It is divided into a variety of nuclei and nuclear areas.



RELATION TO THE PITUITARY GLAND

There are neural connections between the hypothalamus and the posterior lobe of the pituitary gland and vascular connections between the hypothalamus and the anterior lobe.



The bodies of the cells that secrete the *posterior* pituitary hormones are not located in the pituitary gland itself but are large neurons, called *magnocellular neurons,* located in the *supraoptic* and *paraventricular nuclei* of the hypothalamus.

The **portal hypophyseal vessels which is a system of blood vessels in the brain that** form a direct vascular link between the hypothalamus and the anterior pituitary.

The anterior pituitary is a highly vascular gland with extensive capillary sinuses among the glandular cells. Almost all the blood that enters these sinuses passes first through another capillary bed in the lower hypothalamus. The blood then flows through small *hypothalamic-hypophyseal portal blood vessels* into the anterior pituitary sinuses.

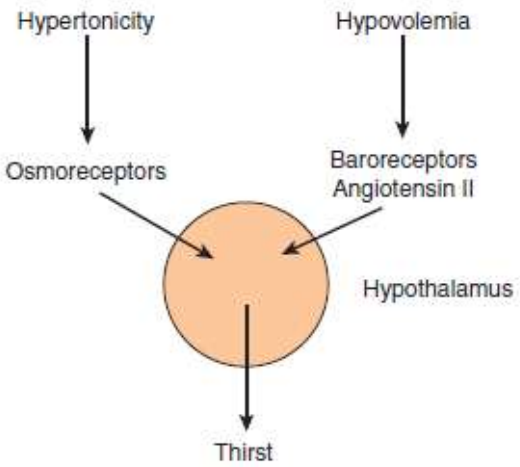
Secretion from the posterior pituitary is controlled by nerve signals that originate in the hypothalamus and terminate in the posterior pituitary. In contrast, secretion by the anterior pituitary is controlled by hormones called *hypothalamic releasing* and *hypothalamic inhibitory hormones* (or *factors*) secreted within the hypothalamus and then conducted to the anterior pituitary through minute blood vessels called *hypothalamic-hypophyseal portal vessels.* In the anterior pituitary, these releasing and inhibitory hormones act on the glandular cells to control their secretion.

The hypothalamus receives signals from many sources in the nervous system. Thus, when a person is exposed to pain, a portion of the pain signal is transmitted into the hypothalamus. Likewise, when a person experiences some powerful depressing or exciting thought, a portion of the signal is transmitted into the hypothalamus.

Even the concentrations of nutrients, electrolytes, water, and various hormones in the blood excite or inhibit various portions of the hypothalamus.

THIRST

Another appetitive mechanism under hypothalamic control is thirst. Drinking is regulated by plasma osmolality and extracellular fluid (ECF) volume in much the same fashion as vasopressin secretion. Water intake is increased by increased effective osmotic pressure of the plasma, by decreases in ECF volume, and by psychologic and other factors. Osmolality acts via **osmoreceptors,** {receptors that sense the osmolality of the body fluids}. These osmoreceptors are located in the anterior hypothalamus.



Decreases in ECF volume also stimulate thirst by a pathway independent of that mediating thirst in response to increased plasma osmolality. Thus,

hemorrhage causes increased drinking even if there is no change in the osmolality of the plasma. The effect of ECF volume depletion on thirst is mediated in part via the renin–angiotensin system. Renin secretion is increased by hypovolemia and results in an increase in circulating angiotensin II. The angiotensin II acts on the **subfornical organ,** a specialized receptor area in the diencephalon, to stimulate the neural areas concerned with thirst.

CONTROL OF POSTERIOR PITUITARY SECRETION

VASOPRESSIN & OXYTOCIN

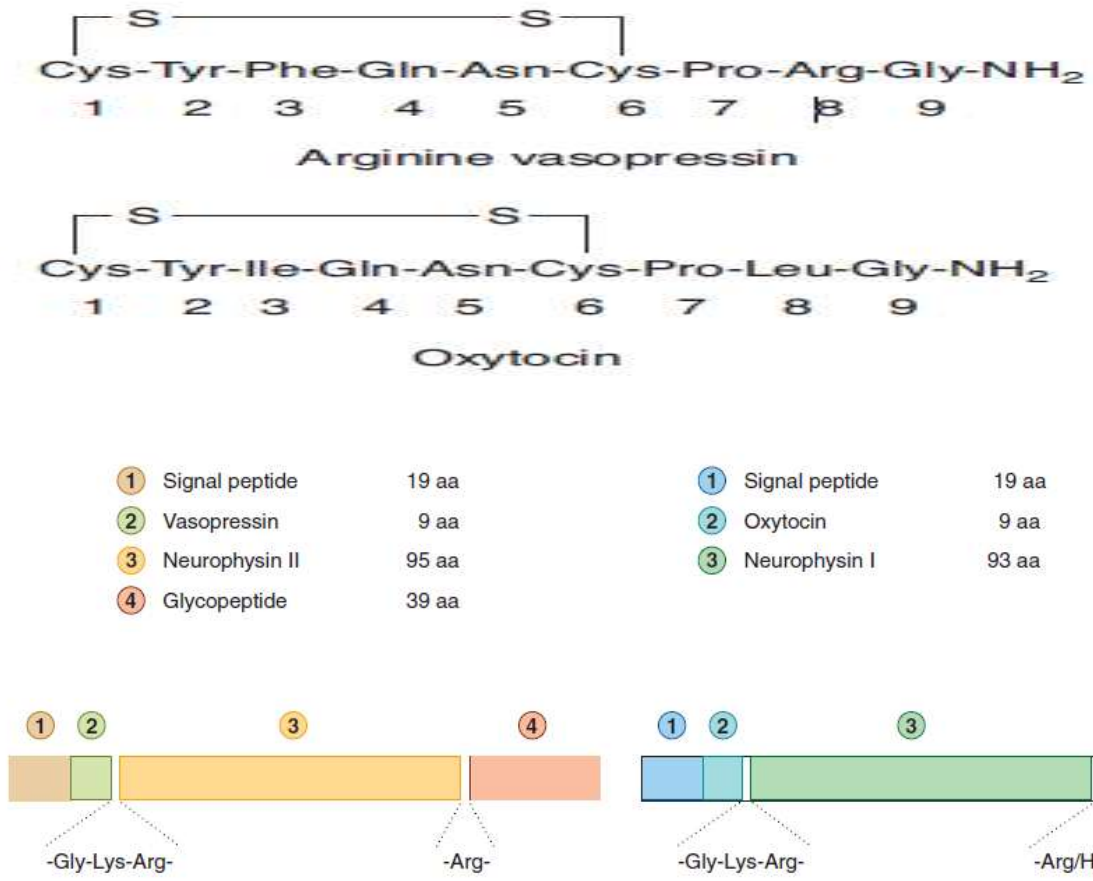
The hormones of the posterior pituitary gland are synthesized in the cell bodies of the magnocellular neurons in the supraoptic and paraventricular nuclei and transported down the axons of these neurons to their endings in the posterior lobe, where they are secreted in response to electrical activity in the endings.

Oxytocin and vasopressin are typical **neural hormones,** that is, hormones secreted into the circulation by nerve cells.

Like other peptide hormones, the posterior lobe hormones are synthesized as part of larger precursor molecules. Vasopressin and oxytocin each have a characteristic **neurophysin** associated with them in the granules in the neurons that secrete them— neurophysin I in the case of oxytocin and neurophysin II in the case of vasopressin. The neurophysins were originally thought to be binding polypeptides, but it now appears that they are simply parts of the precursor molecules.

The precursor for AVP, **prepropressophysin,** contains a 19-amino-acid residue leader sequence followed by AVP, neurophysin II, and a

glycopeptide. **Prepro-oxyphysin,** the precursor for oxytocin, is a similar but smaller molecule that lacks the glycopeptide.



Vasopressin Receptors & Effects:

There are at least three kinds of vasopressin receptors: V_{1A}, V_{1B} , and V_2 . All are G protein-coupled. The V_{1A} and V_{1B} receptors act through phosphatidylinositol hydrolysis to increase intracellular Ca^{2+} concentrations. The V_2 receptors act through Gs to increase cAMP levels.

Because one of its principal physiologic effects is the retention of water by the kidney, vasopressin is often called the **antidiuretic hormone (ADH).** It increases the permeability of the collecting ducts of the kidney

so that water enters the hypertonic interstitium of the renal pyramids. The urine becomes concentrated and its volume decreases.

In the absence of vasopressin, the urine is hypotonic to plasma, urine volume is increased, and there is a net water loss. Consequently, the osmolality of the body fluid rises.

Effects of Oxytocin

In humans, oxytocin acts primarily on the breasts and uterus. Oxytocin causes contraction of the **myoepithelial cells** that line the ducts of the breast. This squeezes the milk out of the alveoli of the lactating breast into the large ducts (sinuses) and then out of the nipple **(milk ejection).**

Milk ejection is normally initiated by a neuroendocrine reflex. The receptors involved are touch receptors, which are plentiful in the breast—especially around the nipple. Impulses generated in these receptors are relayed from the somatic touch pathways to the supraoptic and paraventricular nuclei.

The suckling of an infant at the breast stimulates the touch receptors, the nuclei are stimulated, oxytocin is released, and the milk is expressed into the sinuses, ready to flow into the mouth of the waiting infant. In lactating women, genital stimulation and emotional stimuli also produce oxytocin secretion, sometimes causing milk to spurt from the breasts.

Other Actions of Oxytocin

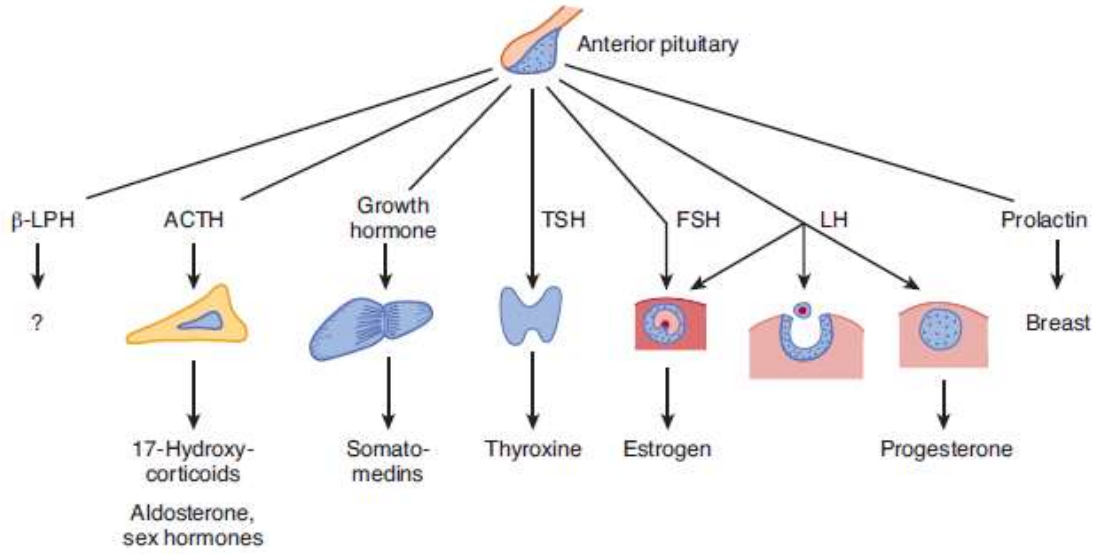
Oxytocin causes contraction of the smooth muscle of the uterus. The sensitivity of the uterine musculature to oxytocin is enhanced by estrogen and inhibited by progesterone. The inhibitory effect of progesterone is due to a direct action of the steroid on uterine oxytocin receptors. In late pregnancy, the uterus becomes very sensitive to oxytocin coincident with

a marked increase in the number of oxytocin receptors and oxytocin receptor mRNA.

CONTROL OF ANTERIOR PITUITARY SECRETION

ANTERIOR PITUITARY HORMONES

The anterior pituitary secretes six hormones: **adrenocorticotropic hormone (corticotropin, ACTH) , thyroid- stimulating hormone (thyrotropin, TSH) , growth hormone , follicle stimulating hormone (FSH) , luteinizing hormone (LH) ,** and **prolactin (PRL) .** An additional polypeptide, β-lipotropin (β-LPH), is secreted with ACTH, but its physiologic role is unknown. The actions of the anterior pituitary hormones aresummarized inthe **Figure**.



In women, FSH and LH act in sequence on the ovary to produce growth of the ovarian follicle, ovulation, and formation and maintenance of the corpus luteum. Prolactin stimulates lactation. In men, FSH and LH control the functions of the testes.

NATURE OF HYPOTHALAMIC CONTROL

Anterior pituitary secretion is controlled by chemical agents carried in the portal hypophyseal vessels from the hypothalamus to the pituitary. These substances used to be called releasing and inhibiting factors, but now they are commonly called **hypophysiotropic hormones.**

HYPOPHYSIOTROPIC HORMONES

There are six established hypothalamic releasing and inhibiting hormones:

1- **corticotropin-releasing hormone(CRH) ;**
2- **thyrotropin-releasing hormone (TRH) ;**
3- **growthhormone-releasing hormone (GRH) ;**
4- **growth hormone inhibitinghormone (GIH ,** now generally called **somatostatin);**
5- **luteinizing hormone-releasing hormone (LHRH ,** now generally known as **gonadotropin-releasing hormone(GnRH)) ;**
6- and **prolactin-inhibiting hormone (PIH) .** In addition, hypothalamic extracts contain prolactin-releasing activity, and a **prolactin-releasing hormone (PRH)** has been postulated to exist very high because they are not diluted in the blood of the entire systemic circulation..

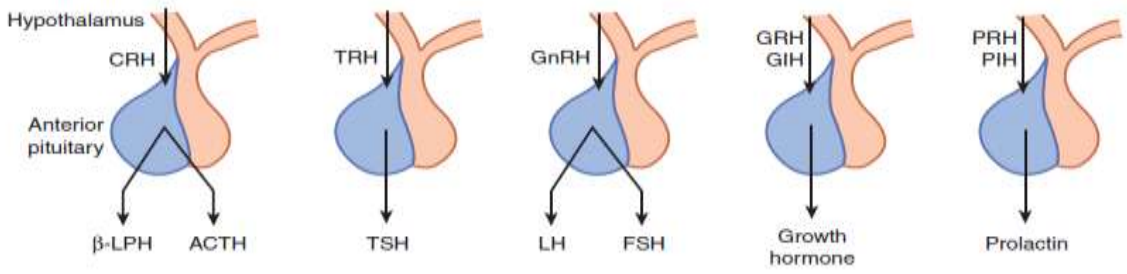
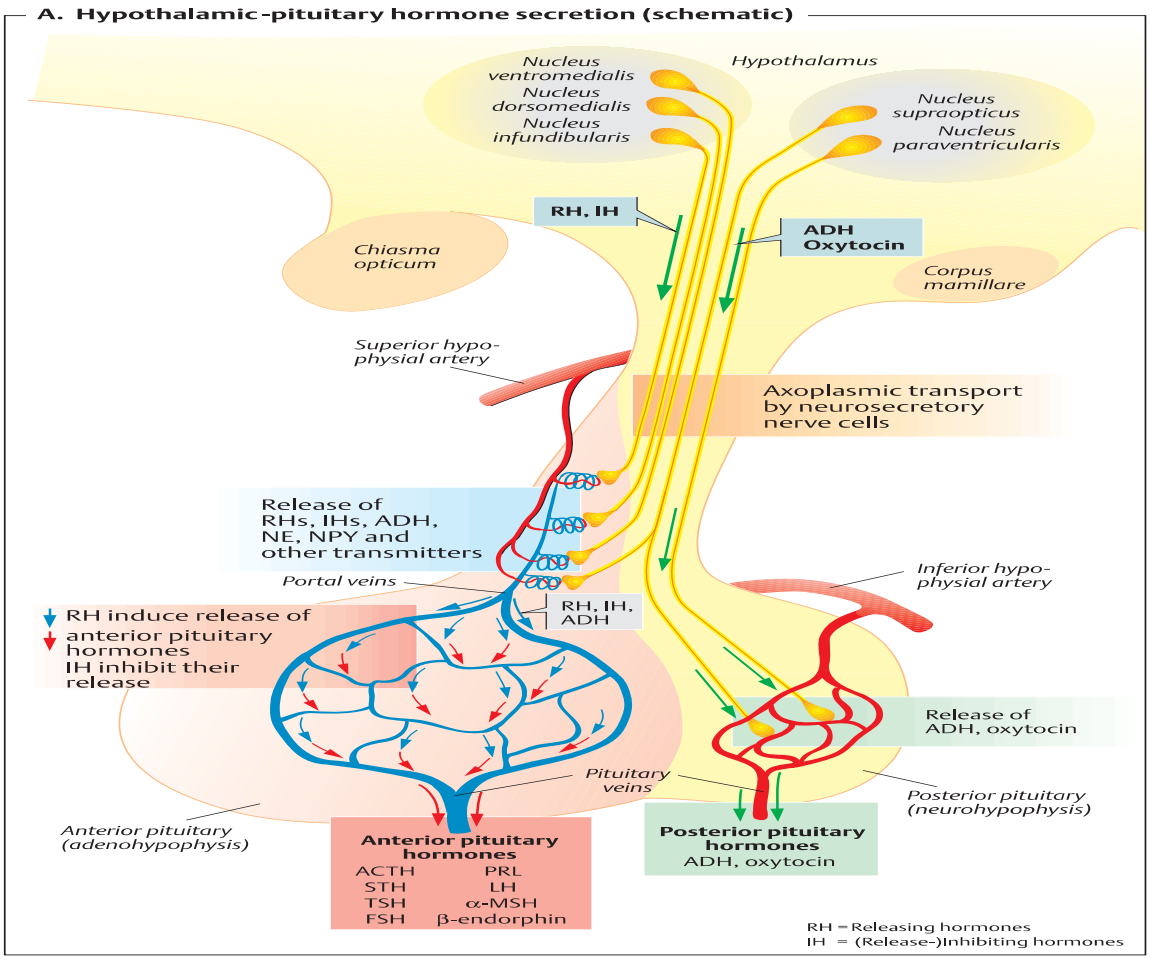


FIGURE 5: ***Effects of hypophysiotropic hormones on the secretion of anterior pituitary hormones.***

Pituitary Gland and Growth Hormone

INTRODUCTION

The pituitary gland, or hypophysis, lies in a pocket of the sphenoid bone at the base of the brain. The anterior pituitary secretes thyroid-stimulating hormone (TSH, thyrotropin), adrenocorticotropic hormone (ACTH), luteinizing hormone (LH), follicle- stimulating hormone (FSH), prolactin, and growth hormone (Figure 1), and receives almost all of its blood supply from the portal hypophysial vessels. The posterior pituitary in mammals consists predominantly of nerves that have their cell bodies in the hypothalamus, and stores oxytocin and vasopressin in the termini of these neurons, to be released into the bloodstream.



CELL TYPES IN THE ANTERIOR PITUITARY

Five types of secretory cells have been identified in the anterior pituitary by immunocytochemistry and electron microscopy. The cell types are the **somatotropes**, which secrete growth hormone; the **lactotropes** (also called mammotropes), which secrete prolactin; the **corticotropes,** which secrete ACTH; the **thyrotropes**, which secrete TSH; and the **gonadotropes**, which secrete FSH and LH. Some cells may contain two or more hormones. It is also notable that the three pituitary glycoprotein hormones, FSH, LH, and TSH, while being made up of two subunits, all share a common α subunit that is the product of a single gene and has the same amino acid composition in each hormone, although their carbohydrate residues vary. The α subunit must be combined with a β subunit characteristic of each hormone for maximal physiologic activity. The β subunits, which are produced by separate genes and differ in structure, confer hormonal specificity.

Cell Type	Hormones Secreted	Percentage of Total Secretory Cells
Somatotrope	Growth hormone	50
Lactotrope	Prolactin	10–30
Corticotrope	ACTH	10
Thyrotrope	TSH	5
Gonadotrope	FSH, LH	20

TABLE 1: Hormone-secreting cells of the human anterior pituitary gland.

Physiological Functions of Growth Hormone

Growth hormone, in contrast to other hormones, does not function through a target gland but exerts its effects directly on all or almost all tissues of the body.

Growth Hormone Promotes Growth of Many Body Tissues

Growth hormone, also called somatotropic hormone or somatotropin, is a small protein molecule that contains 191 amino acids in a single chain and has a molecular weight of 22,005. It causes growth of almost all tissues of the body that are capable of growing. It promotes increased sizes of the cells and increased mitosis, with development of greater numbers of cells and specific differentiation of certain types of cells such as bone growth cells and early muscle cells.

A side from its general effect in causing growth, growth hormone has multiple specific metabolic effects, including

(1) Increased rate of protein synthesis in most cells of the body;

(2) Increased mobilization of fatty acids from adipose tissue, increased free fatty acids in the blood, and increased use of fatty acids for energy;

(3) Decreased rate of glucose utilization throughout the body.

Thus, in effect, growth hormone enhances body protein, uses up fat stores, and conserves carbohydrates.

Growth Hormone Promotes Protein Deposition in Tissues

- Enhancement of Amino Acid Transport through the Cell Membranes

- Enhancement of RNA Translation to Cause Protein Synthesis by the Ribosomes

- Increased Nuclear Transcription of DNA to Form RNA

- Decreased Catabolism of Protein and Amino Acids

Growth Hormone Enhances Fat Utilization for Energy

Growth hormone has a specific effect in causing the release of fatty acids from adipose tissue and, therefore, increasing the concentration of fatty acids in the body fluids. In addition, in tissues throughout the body, growth hormone enhances the conversion of fatty acids to acetyl coenzyme A (acetyl-CoA) and its subsequent utilization for energy. Growth hormone's ability to promote fat utilization, together with its protein anabolic effect, causes an increase in lean body mass. However, mobilization of fat by growth hormone requires several hours to occur, whereas enhancement of protein synthesis can begin in minutes under the influence of growth hormone.

Growth Hormone Decreases Carbohydrate Utilization

Growth hormone causes multiple effects that influence carbohydrate metabolism, including (1) decreased glucose uptake in tissues such as skeletal muscle and fat, (2) increased glucose production by the liver, and (3) increased insulin secretion. Each of these changes results from growth hormone-induced "insulin resistance," which attenuates insulin's actions to stimulate the uptake and utilization of glucose in skeletal muscle and adipose tissue and to inhibit gluconeogenesis (glucose production) by the liver; this leads to increased blood glucose concentration and a compensatory increase in insulin secretion. For these reasons, growth hormone's effects are called diabetogenic, and excess secretion of growth hormone can produce metabolic disturbances similar to those found in patients with type II (non-insulin-dependent) diabetes, who are also resistant to the metabolic effects of insulin.

Growth Hormone Stimulates Cartilage and Bone Growth

Although growth hormone stimulates increased deposition of protein and increased growth in almost all tissues of the body, its most obvious effect is to increase growth of the skeletal frame. This results from multiple effects of growth hormone on bone, including (1) increased deposition of protein by the chondrocytic and osteogenic cells that cause bone growth, (2) increased rate of reproduction of these cells, and (3) a specific effect of converting chondrocytes into osteogenic cells, thus causing deposition of new bone.

Growth Hormone Exerts Much of Its Effect through Intermediate Substances Called "Somatomedins" (Also Called "Insulin-Like Growth Factors")

In brief, it has been found that growth hormone causes the liver (and, to a much less extent, other tissues) to form several small proteins called somatomedins that have the potent effect of increasing all aspects of bone growth. Many of the somatomedin effects on growth are similar to the effects of insulin on growth. Therefore, the somatomedins are also called insulin-like growth factors (IGFs).

At least four somatomedins have been isolated, but by far the most important of these is somatomedin C (also called insulin-like growth factor-1, or IGF-I). The molecular weight of somatomedin C is about 7500, and its concentration in the plasma closely follows the rate of growth hormone secretion.

The pygmies of Africa have a congenital inability to synthesize significant amounts of somatomedin C. Therefore, even though their plasma concentration of growth hormone is either normal or high, they

have diminished amounts of somatomedin C in the plasma; this apparently accounts for the small stature of these people. Some other dwarfs also have this problem.

Short Duration of Action of Growth Hormone but Prolonged Action of Somatomedin C

Growth hormone attaches only weakly to the plasma proteins in the blood. Therefore, it is released from the blood into the tissues rapidly, having a half-time in the blood of less than **20 minutes**. By contrast, somatomedin C attaches strongly to a carrier protein in the blood that, like somatomedin C, is produced in response to growth hormone. As a result, somatomedin C is released only slowly from the blood to the tissues, with a half-time of about **20 hours**.

Regulation of Growth Hormone Secretion

For many years it was believed that growth hormone was secreted primarily during the period of growth but then disappeared from the blood at adolescence. This has proved to be untrue. After adolescence, secretion decreases slowly with aging, finally falling to about 25 percent of the adolescent level in very old age.

Growth hormone is secreted in a **pulsatile pattern**, increasing and decreasing. The precise mechanisms that control secretion of growth hormone are not fully understood, but several factors related to a person's state of nutrition or stress are known to stimulate secretion: (1) starvation, especially with severe protein deficiency; (2) hypoglycemia or low concentration of fatty acids in the blood; (3) exercise; (4) excitement; (5) trauma; and (6) ghrelin, a hormone secreted by the stomach before meals. Growth hormone also characteristically increases during the first 2 hours of deep sleep.

Table 2. Factors That Stimulate or Inhibit Secretion of Growth Hormone

Stimulate Growth Hormone Secretion	Inhibit Growth Hormone Secretion
Decreased blood glucose Decreased blood free fatty acids Increased blood amino acids (arginine) Starvation or fasting, protein deficiency Trauma, stress, excitement Exercise Testosterone, estrogen Deep sleep (stages II and IV) Growth hormone-releasing hormone Ghrelin	Increased blood glucose Increased blood free fatty acids Aging Obesity Growth hormone inhibitory hormone (somatostatin) Growth hormone (exogenous) Somatomedins (insulin-like growth factors)

The normal concentration of growth hormone in the plasma of *an adult is between* **1.6 and 3 ng/ml**; in a *child or adolescent*, it is about **6 ng/ml**. These values often increase to as high as **50 ng/ml** after depletion of the body stores of proteins or carbohydrates during *prolonged starvation*.

Under acute conditions, hypoglycemia is a far more potent stimulator of growth hormone secretion than is an acute decrease in protein intake.

Figure 2 demonstrates the effect of protein deficiency on plasma growth hormone and then the effect of adding protein to the diet.

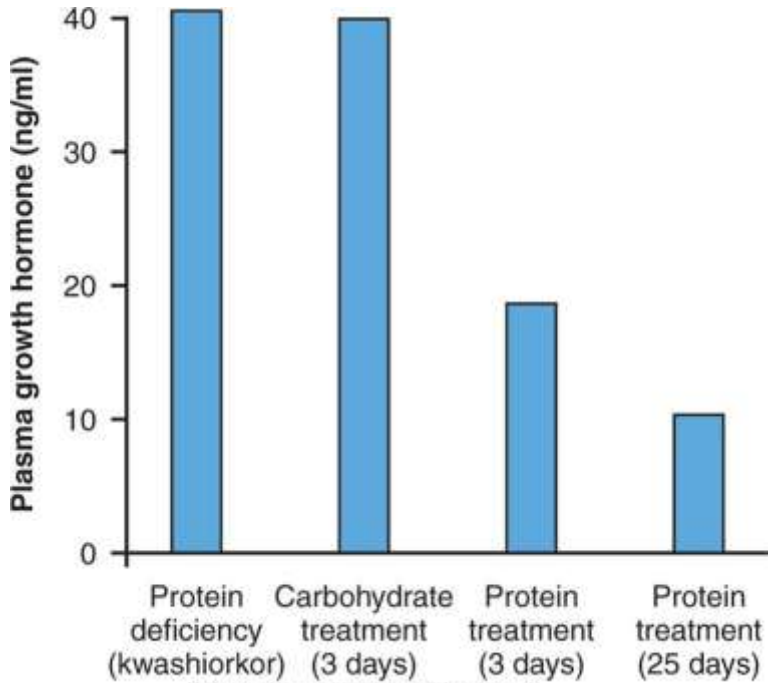


Figure 2: Effect of extreme protein deficiency on the plasma concentration of growth hormone in the disease kwashiorkor. Also shown is the failure of carbohydrate treatment but the effectiveness of protein treatment in lowering growth hormone concentration.

Role of the Hypothalamus, Growth Hormone-Releasing Hormone, and Somatostatin in the Control of Growth Hormone Secretion

It is known that growth hormone secretion is controlled by two factors secreted in the hypothalamus and then transported to the anterior pituitary gland through the hypothalamic-hypophysial portal vessels. They are growth hormone-releasing hormone and growth hormone inhibitory hormone (also called somatostatin). Both of these are polypeptides; GHRH is composed of 44 amino acids, and somatostatin is composed of 14 amino acids.

The part of the hypothalamus that causes secretion of GHRH is the ventromedial nucleus; this is the same area of the hypothalamus that is sensitive to blood glucose concentration, causing satiety in

hyperglycemic states and hunger in hypoglycemic states. The secretion of somatostatin is controlled by other nearby areas of the hypothalamus.

Most of the control of growth hormone secretion is probably mediated through GHRH rather than through the inhibitory hormone somatostatin. GHRH stimulates growth hormone secretion by attaching to specific cell membrane receptors on the outer surfaces of the growth hormone cells in the pituitary gland. The receptors activate the adenylyl cyclase system inside the cell membrane, increasing the intracellular level of cyclic adenosine monophosphate (cAMP). This has both short-term and long-term effects. The short-term effect is to increase calcium ion transport into the cell; within minutes, this causes fusion of the growth hormone secretory vesicles with the cell membrane and release of the hormone into the blood. The long-term effect is to increase transcription in the nucleus by the genes to stimulate the synthesis of new growth hormone.

When growth hormone is administered directly into the blood of an animal over a period of hours, the rate of endogenous growth hormone secretion decreases. This demonstrates that growth hormone secretion is subject to typical negative feedback control, as is true for essentially all hormones. The nature of this feedback mechanism and whether it is mediated mainly through inhibition of GHRH or enhancement of somatostatin, which inhibits growth hormone secretion, are uncertain.

Thyroid Gland

2nd year students

LEC. 5

AHMED HAMED ATAIMISH

Thyroid Metabolic Hormones

The thyroid gland, located immediately below the larynx on each side of and anterior to the trachea, is one of the largest of the endocrine glands, normally weighing 15 to 20 grams in adults. The thyroid secretes two major hormones, thyroxine and triiodothyronine, commonly called T_4 and T_3, respectively. Both of these hormones profoundly increase the metabolic rate of the body. Thyroid secretion is controlled primarily by thyroid-stimulating hormone (TSH) secreted by the anterior pituitary gland. The thyroid gland also secretes calcitonin, an important hormone for calcium metabolism

Synthesis and Secretion of the Thyroid Metabolic Hormones

About **93 %** of the metabolically active hormones secreted by the thyroid gland is thyroxine, and **7 %** triiodothyronine. However, almost all the thyroxine is eventually converted to triiodothyronine in the tissues, so both are functionally important. The functions of these two hormones are qualitatively the same, but they differ in rapidity and intensity of action. Triiodothyronine is about **four times** as potent as thyroxine, but it is **present in the blood in much smaller quantities and persists for a much shorter time than doe's thyroxine**.

Physiologic Anatomy of the Thyroid Gland

The thyroid gland is composed of large numbers of closed follicles filled with a secretary substance called colloid and lined with cuboidal epithelial cells that secrete into the interior of the follicles. The major constituent of colloid is the large glycoprotein thyroglobulin, which contains the thyroid hormones. Once the secretion has entered the follicles, it must be absorbed back through the follicular epithelium into the blood before it can function in the body.

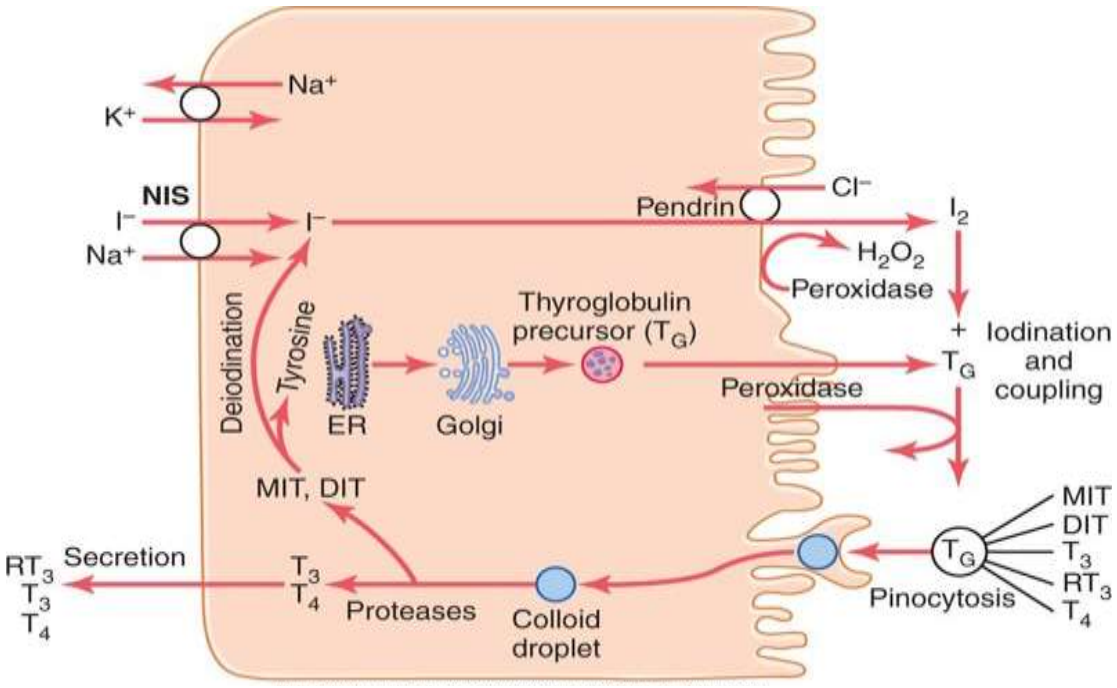
To form normal quantities of thyroxine, about 50 milligrams of ingested iodine in the form of iodides are required each year, or about 1 mg/week.

Iodides ingested orally are absorbed from the gastrointestinal tract into the blood in about the same manner as chlorides. Normally, most of the iodides are rapidly excreted by the kidney, but only after about one fifth are selectively removed from the circulating blood by the cells of the thyroid gland and used for synthesis of the thyroid hormones.

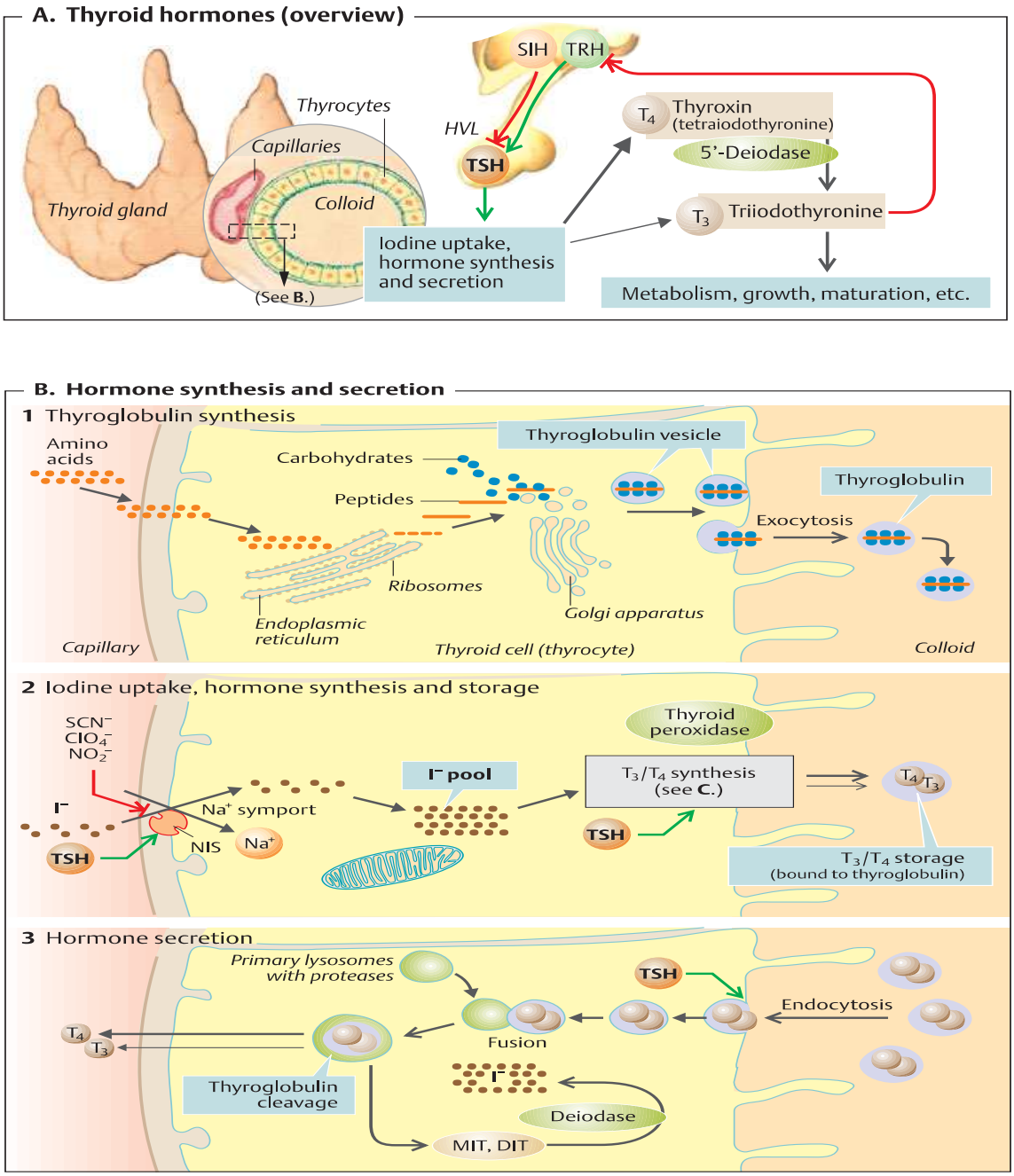
The first stage in the formation of thyroid hormones is transport of iodides from the blood into the thyroid glandular cells and follicles. The basal membrane of the thyroid cell has the specific ability to pump the iodide actively to the interior of the cell. This is achieved by the action of a sodium-iodide symporter (NIS), which co-transports one iodide ion along with two sodium ions across the plasma membrane into the cell. The energy for transporting iodide against a concentration gradient comes from the sodium-potassium ATPase pump, which pumps sodium out of the cell, thereby establishing a low intracellular sodium concentration and a gradient for facilitated diffusion of sodium into the cell.

This process of concentrating the iodide in the cell is called iodide trapping. In a normal gland, the iodide pump concentrates the iodide to about 30 times its concentration in the blood. When the thyroid gland becomes maximally active, this concentration ratio can rise to as high as 250 times. The rate of iodide trapping by the thyroid is influenced by several factors, the most important being the concentration of TSH; TSH stimulates and diminishes the activity of the iodide pump in thyroid cells.

Iodide is transported out of the thyroid cells across the apical membrane into the follicle by a chloride- iodide ion counter-transporter molecule called pendrin. The thyroid epithelial cells also secrete into the follicle thyroglobulin that contains tyrosine amino acids to which the iodide ions will bind.

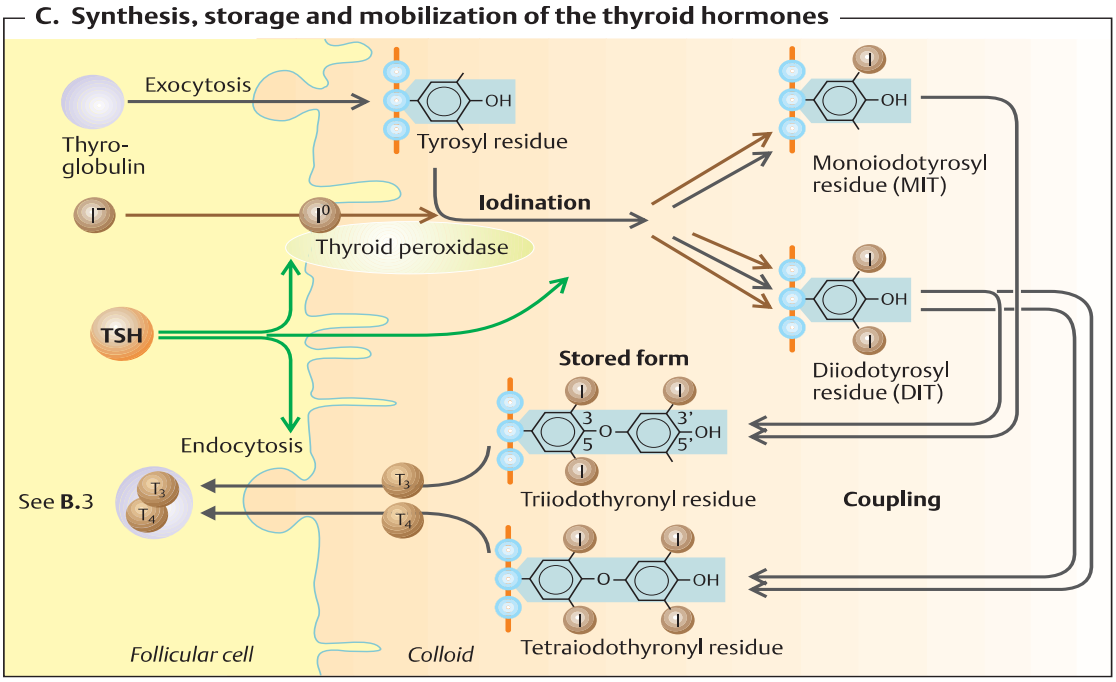


Thyroid cellular mechanisms for iodine transport, thyroxine and triiodothyronine formation, and thyroxine and triiodothyronine release into the blood. DIT, diiodotyrosine; MIT, monoiodotyrosine; NIS, sodium-iodide symporter; RT_3, reverse triiodothyronine; T_3, triiodothyronine; T_4, thyroxine; T_G, thyroglobulin.



Thyroid hormone synthesis and secretion

The first essential step in the formation of the thyroid hormones is conversion of the iodide ions to an oxidized form of iodine, either nascent iodine (I^0) or that is then capable of combining directly with the amino acid tyrosine. This oxidation of iodine is promoted by the enzyme peroxidase and its accompanying hydrogen peroxide, which provide a potent system capable of oxidizing iodides.



Iodination of Tyrosine and Formation of the Thyroid Hormones-"Organification" of Thyroglobulin

The binding of iodine with the thyroglobulin molecule is called organification of the thyroglobulin. Oxidized iodine even in the molecular form will bind directly but slowly with the amino acid tyrosine. Tyrosine is first iodized to monoiodotyrosine and then to diiodotyrosine. Then, during the next few minutes, hours, and even days, more and more of the iodotyrosine residues become coupled with one another.

The major hormonal product of the coupling reaction is the molecule thyroxine (T_4), which is formed when two molecules of diiodotyrosine are joined together; the thyroxine then remains part of the thyroglobulin molecule or one molecule of monoiodotyrosine couples with one

molecule of diiodotyrosine to form triiodothyronine (T_3), which represents about one fifteenth of the final hormones.

Thyroglobulin itself is not released into the circulating blood in measurable amounts; instead, thyroxine and triiodothyronine must first be cleaved from the thyroglobulin molecule, and then these free hormones are released.

Transport of Thyroxin and Triiodothyronine to Tissues

On entering the blood, more than 99 percent of the thyroxine and triiodothyronine combines immediately with several of the plasma proteins, all of which are synthesized by the liver. They combine mainly with thyroxine-binding globulin and much less so with thyroxine-binding prealbumin and albumin.

Because of high affinity of the plasma-binding proteins for the thyroid hormones, these substances-in particular, thyroxine-are released to the tissue cells slowly. Half the thyroxine in the blood is released to the tissue cells about every 6 days, whereas half the triiodothyronine-because of its lower affinity-is released to the cells in about 1 day.

On entering the tissue cells, both thyroxine and triiodothyronine again bind with intracellular proteins, the thyroxine binding more strongly than the triiodothyronine. Therefore, they are again stored, but this time in the target cells themselves, and they are used slowly over a period of days or weeks.

Thyroid Hormones Increase Gene Transcription in the Cell Nucleus

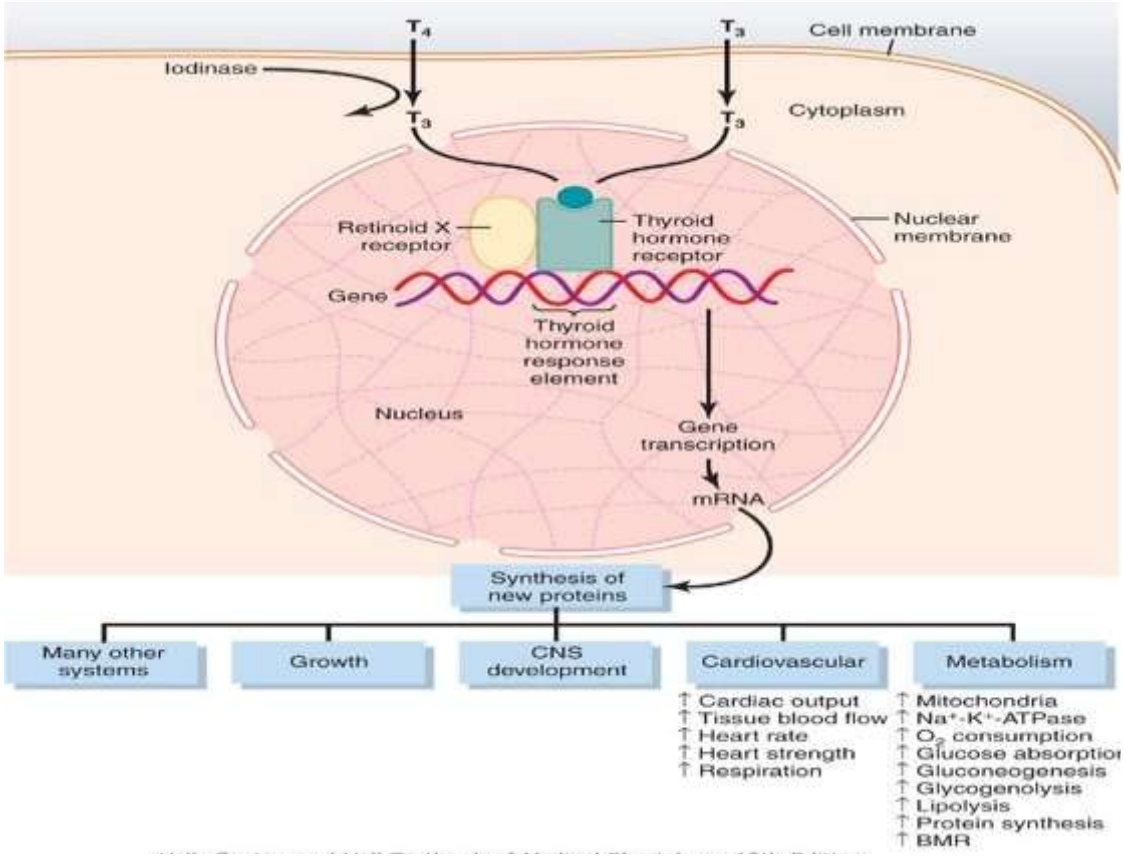
The thyroid hormones *thyroxine* and *triiodothyronine* cause increased transcription by specific genes in the nucleus. To accomplish this, these hormones first bind directly with receptor proteins in the nucleus; these receptors are *activated transcription factors* located within the chromosomal complex, and they control the function of the gene promoters.

Two important features of thyroid hormone function in the nucleus are the following:

1. They activate the genetic mechanisms for the formation of many types of intracellular proteins probably 100 or more. Many of these are enzymes that promote enhanced intracellular metabolic activity in virtually all cells of the body.

2. Once bound to the intranuclear receptors, the thyroid hormones can continue to express their control functions for days or even weeks.

The general effect of thyroid hormone is to activate nuclear transcription of large numbers of genes. Therefore, in virtually all cells of the body, great numbers of protein enzymes, structural proteins, transport proteins, and other substances are synthesized. The net result is generalized increase in functional activity throughout the body.



Before acting on the genes to increase genetic transcription, one iodide is removed from almost all the thyroxine, thus forming triiodothyronine. Intracellular thyroid hormone receptors have a high affinity for triiodothyronine. Consequently, more than 90 percent of the thyroid hormone molecules that bind with the receptors is triiodothyronine.

Thyroid hormones also appear to have nongenomic cellular effects that are independent of their effects on gene transcription. For example, some effects of thyroid hormones occur within minutes, too rapidly to be explained by changes in protein synthesis, and are not affected by inhibitors of gene transcription and translation. Such actions have been described in several tissues, including the heart and pituitary, as well as adipose tissue. The site of nongenomic thyroid hormone action appears to be the plasma membrane, cytoplasm, and perhaps some cell organelles such as mitochondria. Nongenomic actions of thyroid hormone include

the regulation of ion channels and oxidative phosphorylation and appear to involve the activation of intracellular secondary messengers such as cyclic AMP or protein kinase signaling cascades.

Thyroid Hormones Increase Cellular Metabolic Activity

The thyroid hormones increase the metabolic activities of almost all the tissues of the body. The basal metabolic rate can increase to 60 to 100 percent above normal when large quantities of the hormones are secreted.

When thyroxine or triiodothyronine is given to an animal, the mitochondria in most cells of the animal's body increase in size and number. Furthermore, the total membrane surface area of the mitochondria increases almost directly in proportion to the increased metabolic rate of the whole animal. Therefore, one of the principal functions of thyroxine might be simply to increase the number and activity of mitochondria, which in turn increases the rate of formation of adenosine triphosphate (ATP) to energize cellular function.

Effect of Thyroid Hormone on Growth

Thyroid hormone has both general and specific effects on growth. In humans, the effect of thyroid hormone on growth is manifest mainly in growing children. In those who are hypothyroid, the rate of growth is greatly retarded. In those who are hyperthyroid, excessive skeletal growth often occurs, causing the child to become considerably taller at an earlier age.

An important effect of thyroid hormone is to promote growth and development of the brain during fetal life and for the first few years of postnatal life. If the fetus does not secrete sufficient quantities of thyroid

hormone, growth and maturation of the brain both before birth and afterward are greatly retarded and the brain remains smaller than normal. Without specific thyroid therapy within days or weeks after birth, the child without a thyroid gland will remain mentally deficient throughout life.

Target Tissue	Effect	Mechanism
Heart	Chronotropic and Inotropic	Increased number of β-adrenergic receptors Enhanced responses to circulating catecholamines Increased proportion of α-myosin heavy chain (with higher ATPase activity)
Adipose tissue	Catabolic	Stimulated lipolysis
Muscle	Catabolic	Increased protein breakdown
Bone	Developmental	Promote normal growth and skeletal development
Nervous system	Developmental	Promote normal brain development
Gut	Metabolic	Increased rate of carbohydrate absorption
Lipoprotein	Metabolic	Formation of LDL receptors
Other	Calorigenic	Stimulated oxygen consumption by metabolically active tissues (exceptions: testes, uterus, lymph nodes, spleen, anterior pituitary) Increased metabolic rate

Physiologic effects of thyroid hormones.

Effect of Thyroid Hormones on the Cardiovascular System

Increased metabolism in the tissues causes more rapid utilization of oxygen than normal and release of greater than normal quantities of metabolic end products from the tissues. These effects cause vasodilation in most body tissues, thus increasing blood flow. The rate of blood flow in the skin especially increases because of the increased need for heat elimination from the body. As a consequence of the increased blood flow, cardiac output also increases; sometimes rising to 60 percent or more above normal when excessive thyroid hormone is present and falling to only 50 percent of normal in severe hypothyroidism.

Regulation of Thyroid Hormone Secretion

Thyroid function is regulated primarily by variations in the circulating level of pituitary TSH. TSH secretion is increased by the hypothalamic hormone TRH and inhibited in a negative feedback fashion by circulating free T_4 and T_3.

TSH, also known as thyrotropin, is an anterior pituitary hormone, a glycoprotein with a molecular weight of about 28,000. TSH specific effects on the thyroid gland are as follows:

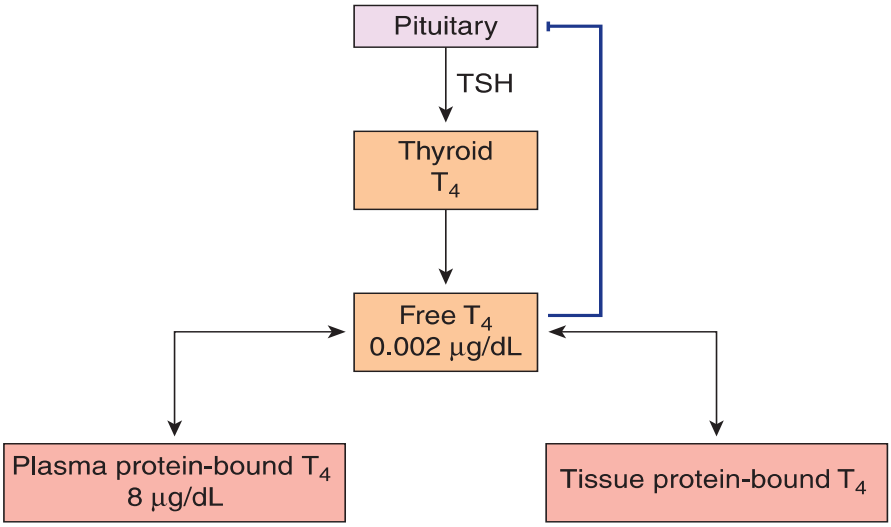
1. Increased proteolysis of the thyroglobulin that has already been stored in the follicles, with resultant release of the thyroid hormones into the circulating blood and diminishment of the follicular substance itself.

2. Increased activity of the iodide pump, which increases the rate of "iodide trapping" in the glandular cells, sometimes increasing the ratio of intracellular to extracellular iodide concentration in the glandular substance to as much as eight times normal.

3. Increased iodination of tyrosine to form the thyroid hormones.

4. Increased size and increased secretory activity of the thyroid cells.

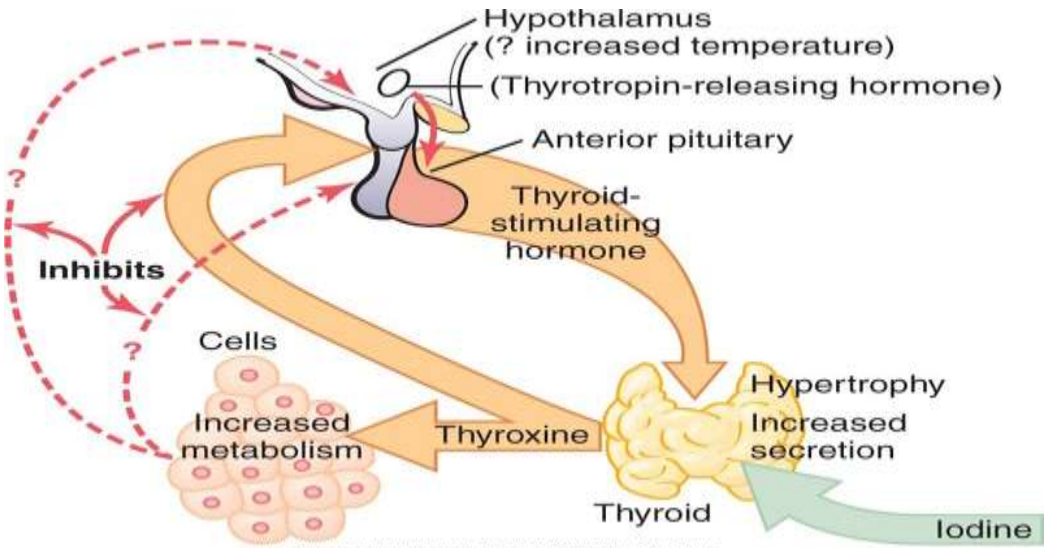
5. Increased number of thyroid cells plus a change from cuboidal to columnar cells and much in folding of the thyroid epithelium into the follicles.



Regulation of thyroid hormone synthesis.

Feedback Effect of Thyroid Hormone to Decrease Anterior Pituitary Secretion of TSH

Increased thyroid hormone in the body fluids decreases secretion of TSH by the anterior pituitary. When the rate of thyroid hormone secretion rises to about 1.75 times normal, the rate of TSH secretion falls essentially to zero. Almost all this feedback depressant effect occurs even when the anterior pituitary has been separated from the hypothalamus.



Diseases of the Thyroid

Hyperthyroidism

Thyroid overactivity
Graves disease
Solitary toxic adenoma
Toxic multinodular goiter
Early stages of Hashimoto thyroiditis[a]
TSH-secreting pituitary tumor
Mutations causing constitutive activation of TSH receptor
Other rare causes
Extrathyroidal
Administration of T_3 or T_4 (factitious or iatrogenic hyperthyroidism)
Ectopic thyroid tissue

Graves' disease, the most common form of hyperthyroidism, is an autoimmune disease in which antibodies called thyroid-stimulating immunoglobulins (TSIs) form against the TSH receptor in the thyroid gland. These antibodies bind with the same membrane receptors that bind TSH and induce continual activation of the cAMP system of the cells, with resultant development of hyperthyroidism.

Thyroid Adenoma: Hyperthyroidism occasionally results from a localized adenoma (a tumor) that develops in the thyroid tissue and secretes large quantities of thyroid hormone. This is different from the more usual type of hyperthyroidism in that it is usually not associated with evidence of any autoimmune disease.

The symptoms of hyperthyroidism are obvious from the preceding discussion of the physiology of the thyroid hormones: (1) a high state of excitability, (2) intolerance to heat, (3) increased sweating, (4) mild to extreme weight loss (sometimes as much as 100 pounds), (5) varying degrees of diarrhea, (6) muscle weakness, (7) nervousness or other psychic disorders, (8) extreme fatigue but inability to sleep, and (9) tremor of the hands.

Most people with hyperthyroidism develop some degree of protrusion of the eyeballs. This condition is called **exophthalmos**. A major degree of exophthalmos occurs in about one third of hyperthyroid patients, and the condition sometimes becomes so severe that the eyeball protrusion stretches the optic nerve enough to damage vision.

Hypothyroidism

The effects of hypothyroidism, in general, are opposite to those of hyperthyroidism. Hypothyroidism, like hyperthyroidism, is often initiated by autoimmunity against the thyroid gland (Hashimoto disease), but immunity that destroys the gland rather than stimulates it.

Several other types of hypothyroidism also occur, often associated with development of enlarged thyroid glands, called thyroid goiter,

The term "goiter" means a greatly enlarged thyroid gland. As pointed out

in the discussion of iodine metabolism, about 50 milligrams of iodine are required each year for the formation of adequate quantities of thyroid hormone. In certain areas of the world, notably in the Swiss Alps, the Andes, and the Great Lakes region of the United States, insufficient iodine is present in the soil for the foodstuffs to contain even this minute quantity. Therefore, in the days before iodized table salt, many people who lived in these areas developed extremely large thyroid glands, called endemic goiters.

The mechanism for development of large endemic goiters is the following: Lack of iodine prevents production of both thyroxine and triiodothyronine. As a result, no hormone is available to inhibit production of TSH by the anterior pituitary; this causes the pituitary to secrete excessively large quantities of TSH. The TSH then stimulates the thyroid cells to secrete tremendous amounts of thyroglobulin colloid into the follicles, and the gland grows larger and larger. But because of lack of iodine, thyroxine and triiodothyronine production does not occur in the thyroglobulin molecule and therefore does not cause the normal suppression of TSH production by the anterior pituitary. The follicles become tremendous in size, and the thyroid gland may increase to 10 to 20 times' normal size.

Adrenal Gland

2nd year students

LEC. 6 + 7

AHMED HAMED ATAIMISH

Adrenocortical Hormones

The two adrenal glands, each of which weighs about 4 grams, lie at the superior poles of the two kidneys. As shown in Figure, each gland is composed of two distinct parts, the adrenal medulla and the adrenal cortex. The adrenal medulla, the central **20 percent** of the gland, is functionally related to the sympathetic nervous system; it secretes the hormones epinephrine and norepinephrine in response to sympathetic stimulation. In turn, these hormones cause almost the same effects as direct stimulation of the sympathetic nerves in all parts of the body.

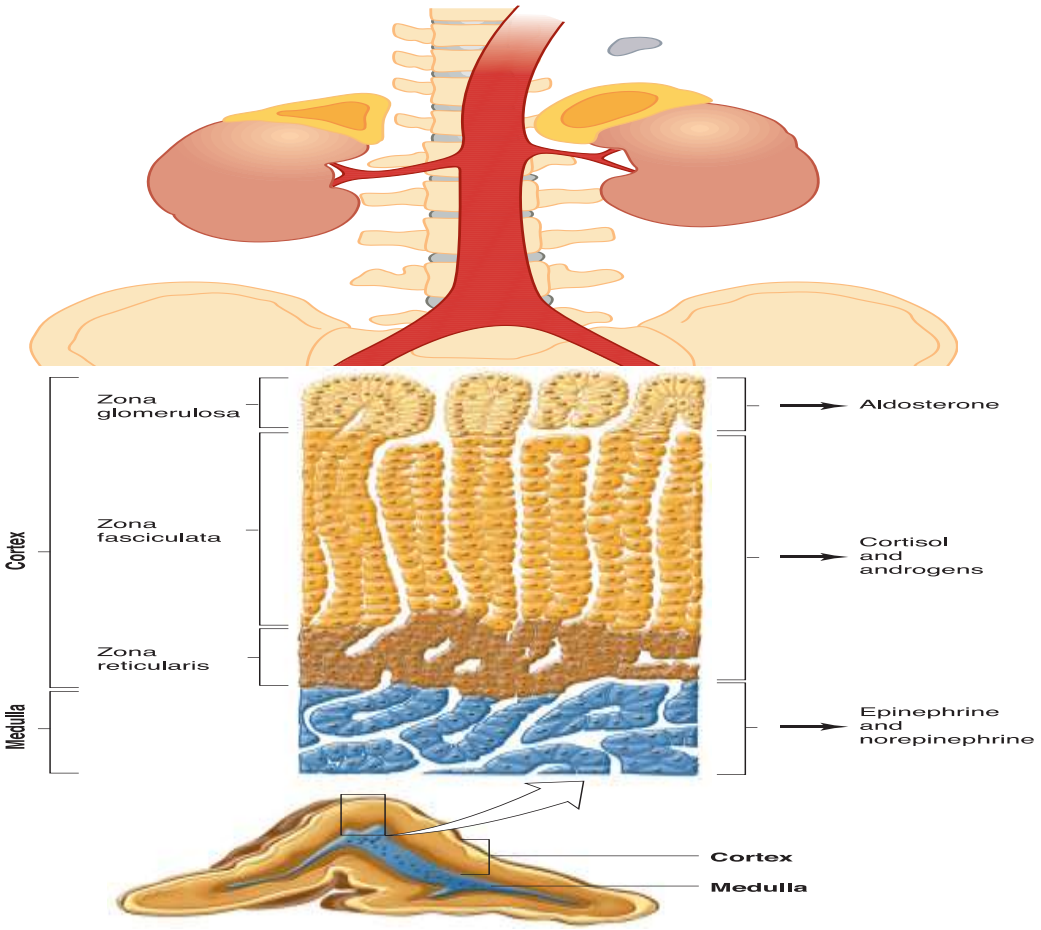


***FIGURE Human** adrenal glands. 2B section through an adrenal gland showing both the medulla and the zones of the cortex, as well as the hormones they secrete.*

The adrenal cortex secretes an entirely different group of hormones, called corticosteroids. These hormones are all synthesized from the steroid cholesterol, and they all have similar chemical formulas. However, slight differences in their molecular structures give them several different but very important functions.

Corticosteroids: Mineralocorticoids, Glucocorticoids, and Androgens

Two major types of adrenocortical hormones, the mineralocorticoids and the glucocorticoids, are secreted by the adrenal cortex. In addition to these, small amounts of sex hormones are secreted, especially androgenic hormones.

The mineralocorticoids have gained this name because they especially affect the electrolytes (the "minerals") of the extracellular fluids, especially sodium and potassium. The glucocorticoids have gained their name because they exhibit important effects that increase blood glucose concentration. They have additional effects on both protein and fat metabolism that are equally as important to body function as their effects on carbohydrate metabolism.

More than 30 steroids have been isolated from the adrenal cortex, but two are of exceptional importance to the normal endocrine function of the human body: aldosterone, which is the principal mineralocorticoid, and cortisol, which is the principal glucocorticoid.

Synthesis and Secretion of Adrenocortical Hormones

The Adrenal Cortex Has Three Distinct Layers

1. The zonaglomerulosa, a thin layer of cells that lies just underneath the capsule, constitutes about **15 percent** of the adrenal cortex. These cells are the only ones in the adrenal gland capable of secreting significant amounts of aldosterone because they contain the enzyme aldosterone synthase, which is necessary for synthesis of aldosterone. The secretion of these cells is controlled mainly by the extracellular fluid concentrations of angiotensin II and potassium, both of which stimulate aldosterone secretion.
2. The zonafasciculata, the middle and widest layer, constitutes about **75 percent** of the adrenal cortex and secretes the glucocorticoids cortisol and corticosterone, as well as small amounts of adrenal androgens and estrogens. The secretion of these cells is controlled in large part by the hypothalamic-pituitary axis via adrenocorticotropic hormone (ACTH).

3. The zonareticularis, the deep layer of the cortex, secretes the adrenal androgens dehydroepiandrosterone (DHEA) and androstenedione, as well as small amounts of estrogens and some glucocorticoids. ACTH also regulates secretion of these cells.

   Aldosterone and cortisol secretion are regulated by independent mechanisms. Factors such as angiotensin II that specifically increase the output of aldosterone and cause hypertrophy of the zonaglomerulosa, have no effect on the other two zones. Similarly,

factors such as ACTH that increase secretion of cortisol and adrenal androgens and cause hypertrophy of the zonafasciculata and zonareticularis have little effect on the zonaglomerulosa.

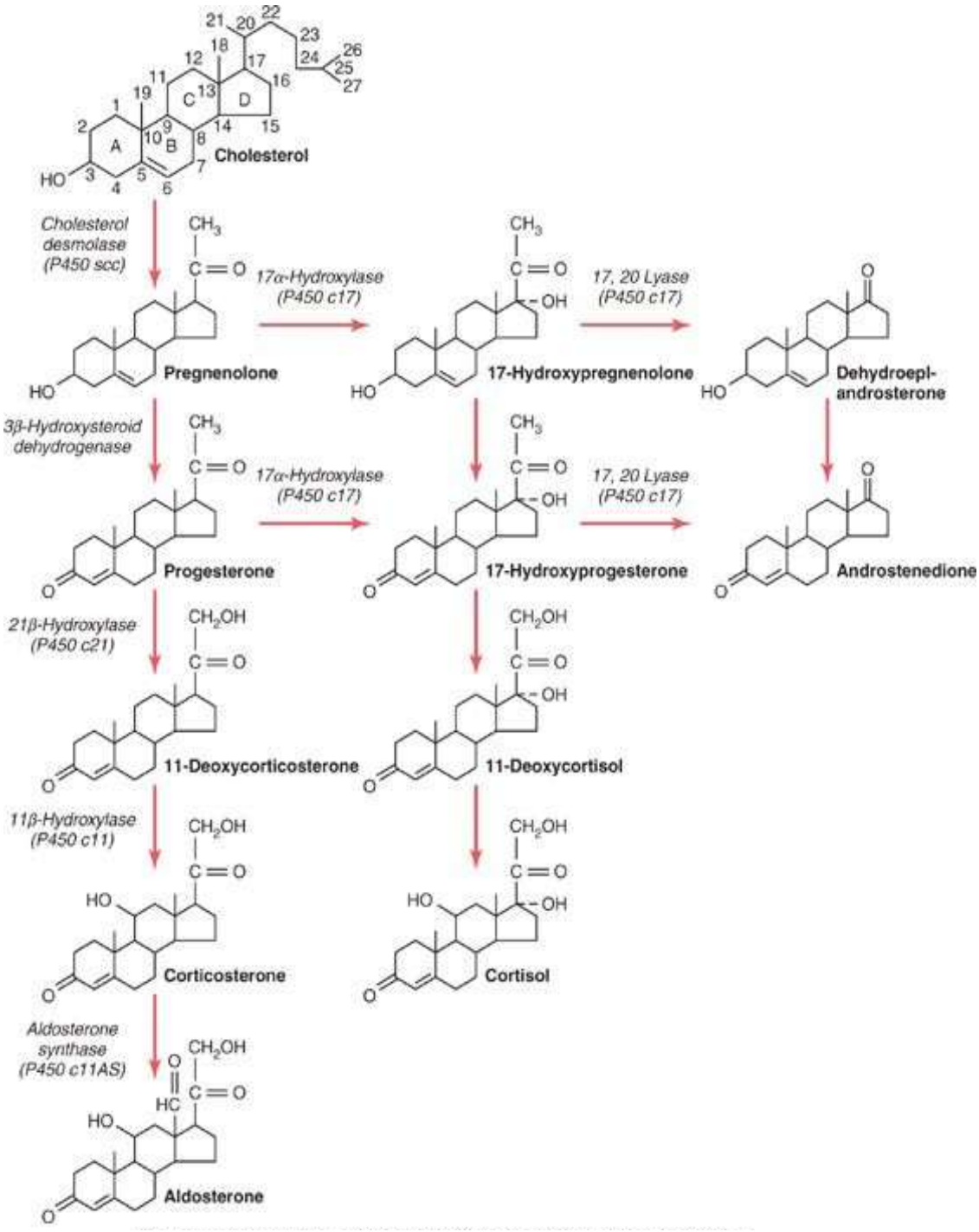


Figure 3 Pathways for synthesis of steroid hormones by the adrenal cortex.

Adrenocortical Hormones and Plasma Proteins

Approximately 90 to 95 percent of the cortisol in the plasma binds to plasma proteins, especially a globulin called cortisol-binding globulin or ***transcortin*** and, to a lesser extent, to albumin. This high degree of binding to plasma proteins slows the elimination of cortisol from the plasma; therefore, cortisol has a relatively long half-life of **60 to 90 minutes**. Only about 60 percent of circulating aldosterone combines with the plasma proteins, so about 40 percent is in the free form; as a result, aldosterone has a relatively short half-life of about **20 minutes**. These hormones are transported throughout the extracellular fluid compartment in both the combined and free forms.

Binding of adrenal steroids to the plasma proteins may serve as a reservoir to lessen rapid fluctuations in free hormone concentrations.

Functions of the Mineralocorticoids-Aldosterone

Total loss of adrenocortical secretion usually causes death within 3 days to 2 weeks unless the person receives extensive salt therapy or injection of mineralocorticoids.

Without mineralocorticoids, potassium ion concentration of the extracellular fluid rises markedly, sodium and chloride are rapidly lost from the body, and the total extracellular fluid volume and blood volume become greatly reduced.

Aldosterone exerts nearly 90 percent of the mineralocorticoid activity of the adrenocortical secretions, but cortisol, the major glucocorticoid

secreted by the adrenal cortex, also provides a significant amount of mineralocorticoid activity. Aldosterone's mineralocorticoid activity is about **3000 times** greater than that of cortisol, but the plasma concentration of cortisol is nearly **2000 times** that of aldosterone.

Cortisol can also bind to mineralocorticoid receptors with high affinity. However, the renal epithelial cells also contain the enzyme 11β-hydroxysteroid dehydrogenase type 2, which converts cortisol to cortisone. Because cortisone does not avidly bind mineralocorticoid receptors, cortisol does not normally exert significant mineralocorticoid effects. However, in patients with genetic deficiency of 11β-hydroxysteroid dehydrogenase type 2 activity, cortisol may have substantial mineralocorticoid effects.

Aldosterone increases reabsorption of sodium and simultaneously increases secretion of potassium by the renal tubular epithelial cells, especially in the principal cells of the collecting tubules and, to a lesser extent, in the distal tubules and collecting ducts. Therefore, aldosterone causes sodium to be conserved in the extracellular fluid while increasing potassium excretion in the urine.

Although aldosterone has a potent effect in decreasing the rate of sodium ion excretion by the kidneys, the concentration of sodium in the extracellular fluid often rises only a few milliequivalents. The reason for this is that when sodium is reabsorbed by the tubules, there is simultaneous osmotic absorption of almost equivalent amounts of water. Also, small increases in extracellular fluid sodium concentration stimulate thirst and increased water intake, if water is available. Therefore, the extracellular fluid volume increases almost as much as the retained sodium, but without much change in sodium concentration.

Even though aldosterone is one of the body's most powerful sodium-retaining hormones, only transient sodium retention occurs when excess amounts are secreted. An aldosterone-mediated increase in extracellular fluid volume lasting more than 1 to 2 days also leads to an increase in arterial pressure. The rise in arterial pressure then increases kidney excretion of both salt and water, **called pressure natriuresis and pressure diuresis, respectively**. Thus, after the extracellular fluid volume increases 5 to 15 percent above normal, arterial pressure also increases 15 to 25 mm Hg, and this elevated blood pressure returns the renal output of salt and water to normal despite the excess aldosterone. This return to normal of salt and water excretion by the kidneys as a result of pressure natriuresis and diuresis is called **aldosterone escape**.

Conversely, when aldosterone secretion becomes zero, large amounts of salt are lost in the urine, not only diminishing the amount of sodium chloride in the extracellular fluid but also decreasing the extracellular fluid volume. The result is severe extracellular fluid dehydration and low blood volume, leading to circulatory shock. Without therapy, this usually causes death within a few days after the adrenal glands suddenly stop secreting aldosterone.

Cellular Mechanism of Aldosterone Action

The cellular sequence of events that leads to increased sodium reabsorption seems to be the following.

First, because of its lipid solubility in the cellular membranes, aldosterone diffuses readily to the interior of the tubular epithelial cells.

Second, in the cytoplasm of the tubular cells, aldosterone combines with a highly specific cytoplasmic mineralocorticoid receptor (MR) protein, a

protein that has a stereomolecular configuration that allows only aldosterone or similar compounds to combine with it. Although renal tubular epithelial cell MR receptors also have a high affinity for cortisol, the enzyme 11β-hydroxysteroid dehydrogenase type 2 normally converts most of the cortisol to cortisone, which does not readily bind to MR receptors, as discussed previously.

Third, the aldosterone-receptor complex or a product of this complex diffuses into the nucleus, where it may undergo further alterations, finally inducing one or more specific portions of the DNA to form one or more types of messenger RNA related to the process of sodium and potassium transport.

Fourth, the messenger RNA diffuses back into the cytoplasm, where, operating in conjunction with the ribosomes, it causes protein formation. The proteins formed are a mixture of (1) one or more enzymes and (2) membrane transport proteins that, all acting together, are required for sodium, potassium, and hydrogen transport through the cell membrane. One of the enzymes especially increased is sodium-potassium adenosine triphosphates, which serves as the principal part of the pump for sodium and potassium exchange at the basolateral membranes of the renal tubular cells. Additional proteins, perhaps equally important, are epithelial sodium channel (ENaC) proteins inserted into the luminal membrane of the same tubular cells that allow rapid diffusion of sodium ions from the tubular lumen into the cell; then the sodium is pumped the rest of the way by the sodium-potassium pump located in the basolateral membranes of the cell.

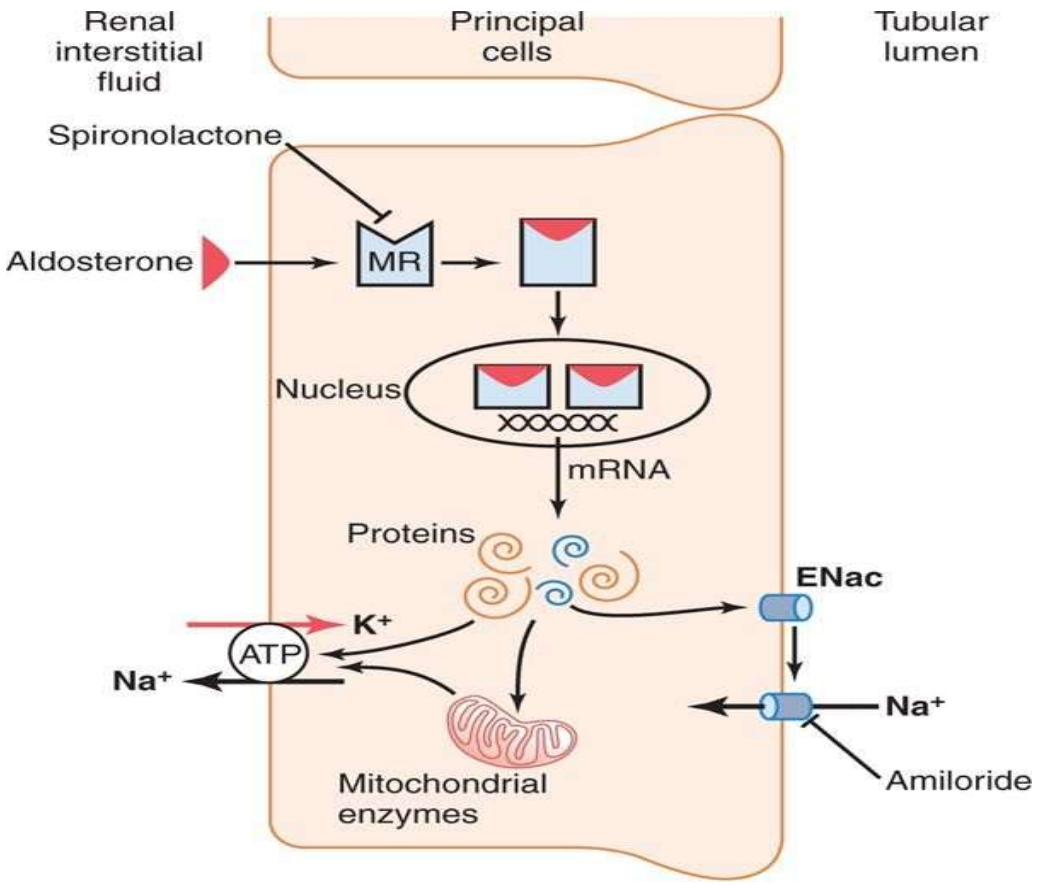


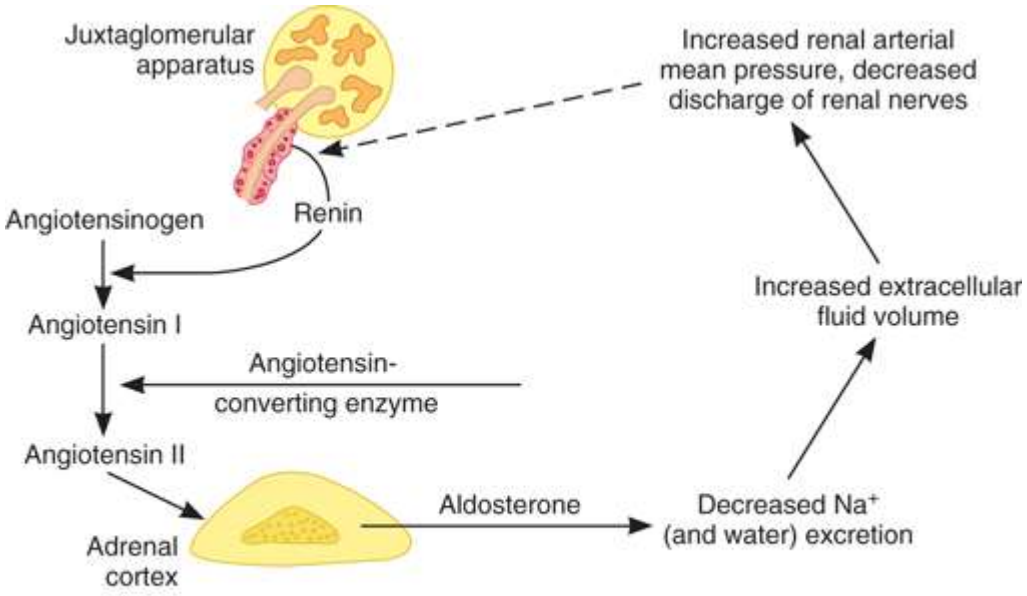
Figure: Aldosterone-responsive epithelial cell signaling pathways. ENaC, epithelial sodium channel proteins; MR, mineralocorticoid receptor. Activation of the MR by aldosterone can be antagonized with spironolactone. Amiloride is a drug that can be used to block ENaC.

Regulation of Aldosterone Secretion

Effects of Angiotensin II & Renin

Renin is secreted from the juxtaglomerular cells that surround the renal afferent arterioles as they enter the glomeruli. Aldosterone secretion is regulated via the renin–angiotensin system in a feedback fashion. A drop in ECF volume or intra-arterial vascular volume leads to a reflex increase in renal nerve discharge and decreases renal arterial pressure. Both changes increase renin secretion, and the angiotensin II formed by the action of the renin increases the rate of secretion of aldosterone. The

aldosterone causes Na^+ and, secondarily, water retention, expanding ECF volume and shutting off the stimulus that initiated increased renin secretion.



Four factors are known to play essential roles in the regulation of aldosterone. In the probable order of their importance, they are as follows:

1. Increased potassium ion concentration in the extracellular fluid greatly increases aldosterone secretion.
2. Increased angiotensin II concentration in the extracellular fluid also greatly increases aldosterone secretion.
3. Increased sodium ion concentration in the extracellular fluid very slightly decreases aldosterone secretion.
4. ACTH from the anterior pituitary gland is necessary for aldosterone secretion but has little effect in controlling the rate of secretion in most physiological conditions.

`Of these factors, potassium ion concentration and the renin-

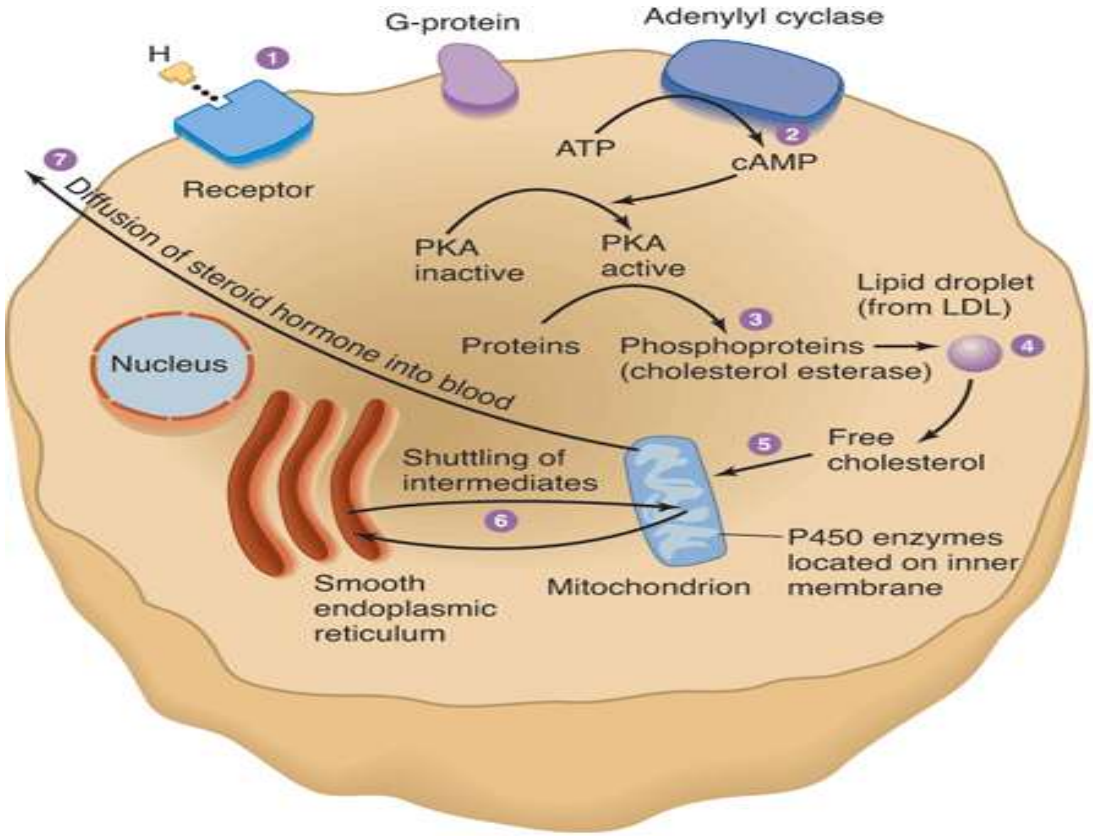
angiotensin system are by far the most potent in regulating aldosterone secretion. A small percentage increase in potassium concentration can cause a several fold increase in aldosterone secretion. Likewise, activation of the renin-angiotensin system, usually in response to diminished blood flow to the kidneys or to sodium loss, can increase in aldosterone secretion several fold.

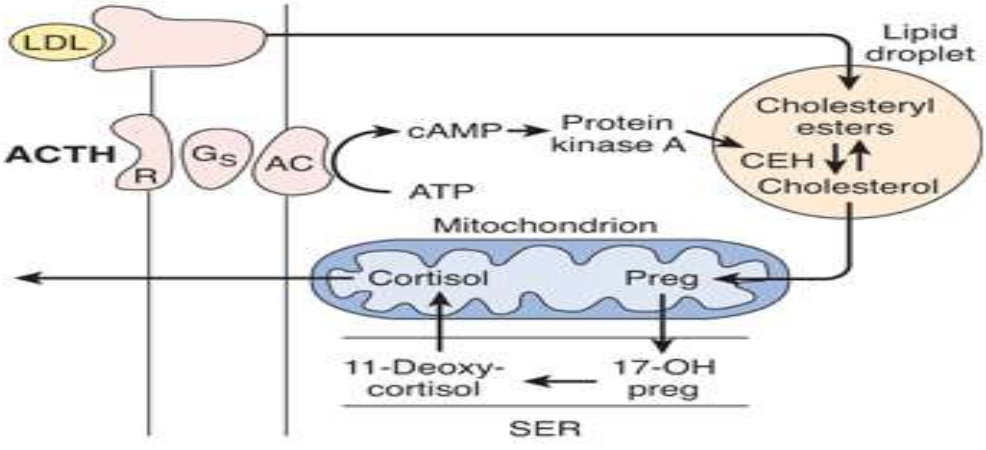
By contrast, the effects of sodium ion concentration and of ACTH in controlling aldosterone secretion are usually minor. Nevertheless, a 10 to 20 percent decrease in extracellular fluid sodium ion concentration, which occurs on rare occasions, can perhaps increase aldosterone secretion by about 50 percent. In the case of ACTH, if there is even a small amount of ACTH secreted by the anterior pituitary gland, it is usually enough to permit the adrenal glands to secrete whatever amount of aldosterone is required, but total absence of ACTH can significantly reduce aldosterone secretion.

Steroid Biosynthesis

The precursor of all steroids is cholesterol. Some of the cholesterol is synthesized from acetate, but most of it is taken up from LDL in the circulation. LDL receptors are especially abundant in adrenocortical cells. The cholesterol is esterified and stored in lipid droplets. **Cholesterol ester hydrolase** catalyzes the formation of free cholesterol in the lipid droplets. The cholesterol is transported to mitochondria and in the mitochondria, it is converted to pregnenolone in a reaction catalyzed by an enzyme known as **cholesterol desmolase** or **side-chain cleavage enzyme.**

The cells of the adrenal cortex contain large amounts of smooth endoplasmic reticulum, which is involved in the steroid-forming process. Other steps in steroid biosynthesis occur in the mitochondria.





When ACTH binds to its receptor (R), adenylyl cyclase (AC) is activated via Gs. The resulting increase in cAMP activates protein kinase A, and the kinase phosphorylates cholesteryl ester hydrolase (CEH), increasing its activity. Consequently, more free cholesterol is formed and converted to pregnenolone.

Physiologic Effects of Glucocorticoids

Mechanism of Action

The multiple effects of glucocorticoids are triggered by binding to glucocorticoid receptors, and the steroid–receptor complexes act as transcription factors that promote the transcription of certain segments of DNA. This, in turn, leads via the appropriate mRNAs to synthesis of enzymes that alter cell function. In addition, it seems likely that glucocorticoids have nongenomic actions.

Effects on Intermediary Metabolism

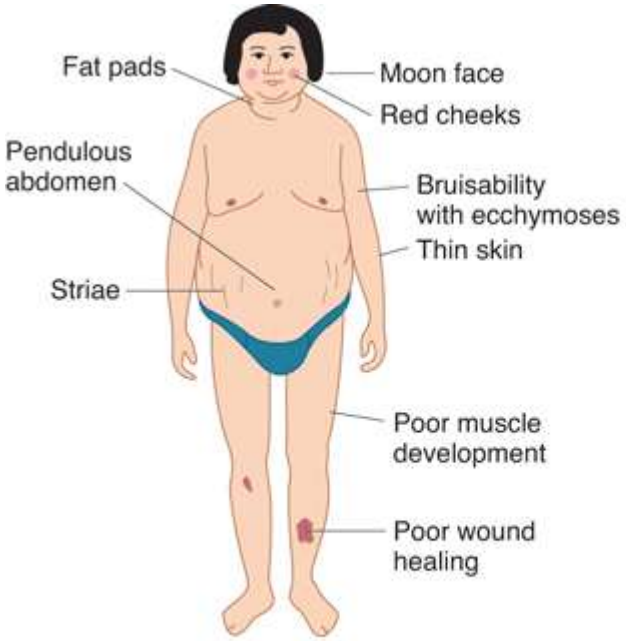
Include: increased protein catabolism and increased hepatic glycogenesis and gluconeogenesis. Glucose 6-phosphatase activity is increased, and the plasma glucose level rises. Glucocorticoids exert an anti-insulin action in peripheral tissues and make diabetes worse. However, the brain and the heart are spared, so the increase in plasma glucose provides extra glucose to these vital organs. In diabetics, glucocorticoids raise plasma lipid levels and increase ketone body formation, but in normal individuals, the increase in insulin secretion

provoked by the rise in plasma glucose obscures these actions. In adrenal insufficiency, the plasma glucose level is normal as long as an adequate caloric intake is maintained, but fasting causes hypoglycemia that can be fatal.

Pharmacologic & Pathologic Effects of Glucocorticoids

Cushing Syndrome

The clinical picture produced by prolonged increases in plasma glucocorticoids was described by Harvey Cushing and is called **Cushing syndrome**. It may be **ACTH-independent** or **ACTH-dependent.** The causes of ACTH-independent Cushing syndrome include glucocorticoid-secreting adrenal tumors, adrenal hyperplasia, and prolonged administration of exogenous glucocorticoids for diseases such as rheumatoid arthritis. Rare but interesting ACTH-independent cases have been reported in which adrenocortical cells abnormally express receptors for gastric inhibitory polypeptide (GIP), vasopressin, -adrenergic agonists, IL-1, or gonadotropin-releasing hormone (GnRH), causing these peptides to increase glucocorticoid secretion. The causes of ACTH-dependent Cushing syndrome include ACTH-secreting tumors of the anterior pituitary gland and tumors of other organs, usually the lungs that secrete ACTH (ectopic ACTH syndrome) or corticotrophin releasing hormone (CRH).



Patients with Cushing syndrome are protein-depleted as a result of excess protein catabolism. The skin and subcutaneous tissues are therefore thin and the muscles are poorly developed. Wounds heal poorly, and minor injuries cause bruises. The hair is thin and scraggly. Many patients with the disease have some increase in facial hair and acne, but this is caused by the increased secretion of adrenal androgens and often accompanies the increase in glucocorticoid secretion.

Body fat is redistributed in a characteristic way. The extremities are thin, but fat collects in the abdominal wall, face, and upper back, where it produces a "buffalo hump." As the thin skin of the abdomen is stretched by the increased subcutaneous fat depots, the subdermal tissues rupture to form prominent reddish purple **striae.** These scars are seen normally whenever a rapid stretching of skin occurs, but in normal individuals the striae are usually inconspicuous and lack the intense purplish color.

Many of the amino acids liberated from catabolized proteins are converted into glucose in the liver and the resultant hyperglycemia and decreased peripheral utilization of glucose by decreasing the translocation of glucose transporters (especially GLUT4) to the cell membrane may be sufficient to precipitate insulin-resistant diabetes mellitus, especially in patients genetically predisposed to diabetes. Cortisol also plays an important, but indirect, role in liver and muscle glycogenolysis, the breaking down of glycogen to glucose-1-phosphate and glucose in which cortisol facilitates the activation of glycogen phosphorylase, which is necessary for epinephrine to have an effect on glycogenolysis Hyperlipemia and ketosis are associated with the diabetes, but acidosis is usually not severe.

About 85% of patients with Cushing syndrome are hypertensive. The hypertension may be due to increased deoxycorticosterone secretion, increased angiotensinogen secretion, or a direct glucocorticoid effect on blood vessels.

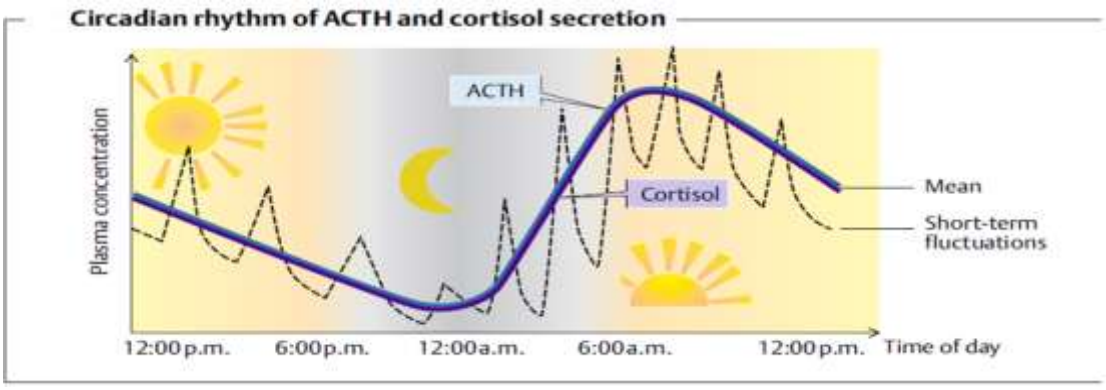
Glucocorticoid excess leads to bone dissolution by decreasing bone formation (decrease osteoblastic activity) and increasing bone resorption (increase osteoclastic activity), decrease calcium absorption from gut and increase PTH secreation. This leads to **osteoporosis.**

Anti-Inflammatory & Anti-Allergic Effects of Glucocorticoids

Glucocorticoids inhibit the inflammatory response to tissue injury. The glucocorticoids also suppress manifestations of allergic disease that are due to the release of histamine from tissues. Both of these effects require high levels of circulating glucocorticoids.

Circadian Rhythm

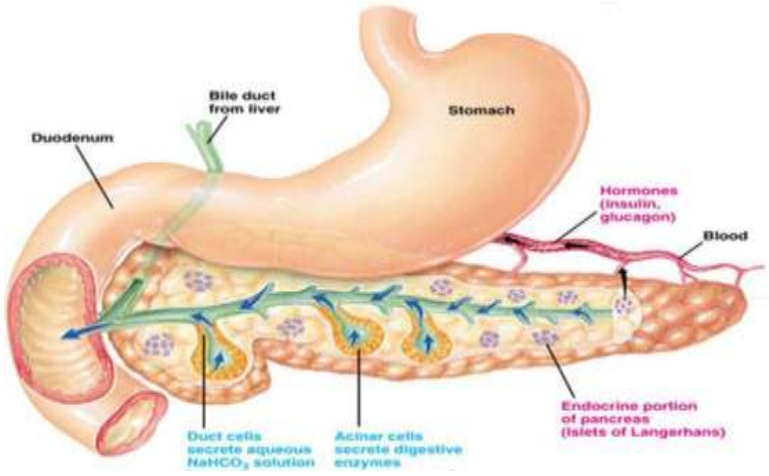
ACTH is secreted in irregular bursts throughout the day and plasma cortisol tends to rise and fall in response to these bursts. In humans, the bursts are most frequent in the early morning, and about 75% of the daily production of cortisol occurs between 4:00 AM and 10:00 AM . The bursts are least frequent in the evening. If the "day" is lengthened experimentally to more than 24 h, that is, if the individual is isolated and the day's activities are spread over more than 24 h, the adrenal cycle also lengthens, but the increase in ACTH secretion still occurs during the period of sleep. The biologic clock responsible for the diurnal ACTH rhythm is located in the suprachiasmatic nuclei of the hypothalamus



Pancreas

The pancreas is an exocrine and an endocrine gland. The exocrine tissue produces a bicarbonate solution and digestive enzymes. These substances are transported to the small intestine where they play a role in the chemical digestion of food.

The pancreas and surrounded by exocrine cells are small clusters of endocrine cells referred to as the *islets of Langerhans*. These islets make up only 2 to 3% of the mass of the pancreas; whereas the exocrine portion of the pancreas makes up 80%, and ducts and blood vessels make up the remainder. However, their blood supply has been modified so that they receive 5 to 10 times more blood than the exocrine pancreas. Furthermore, this blood carrying the pancreatic hormones is then transported through the hepatic portal vein and delivered directly to the liver where the hormones, in a relatively high concentration, carry out many of their metabolic effects.

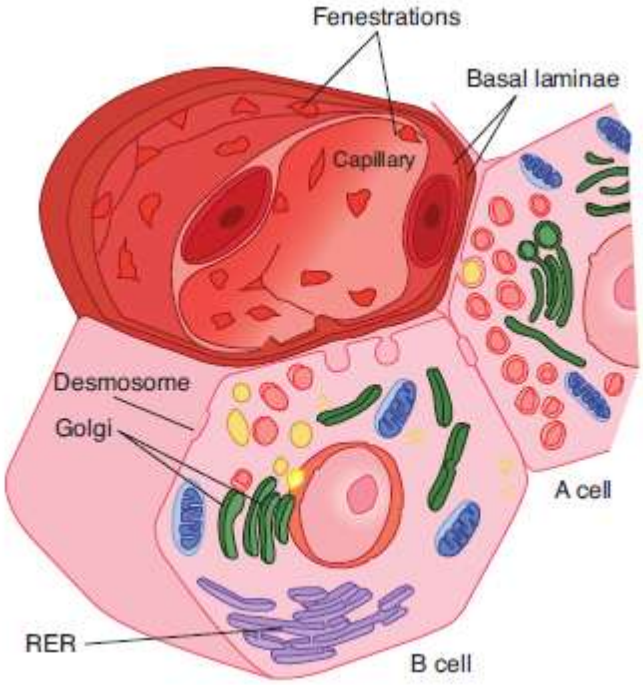


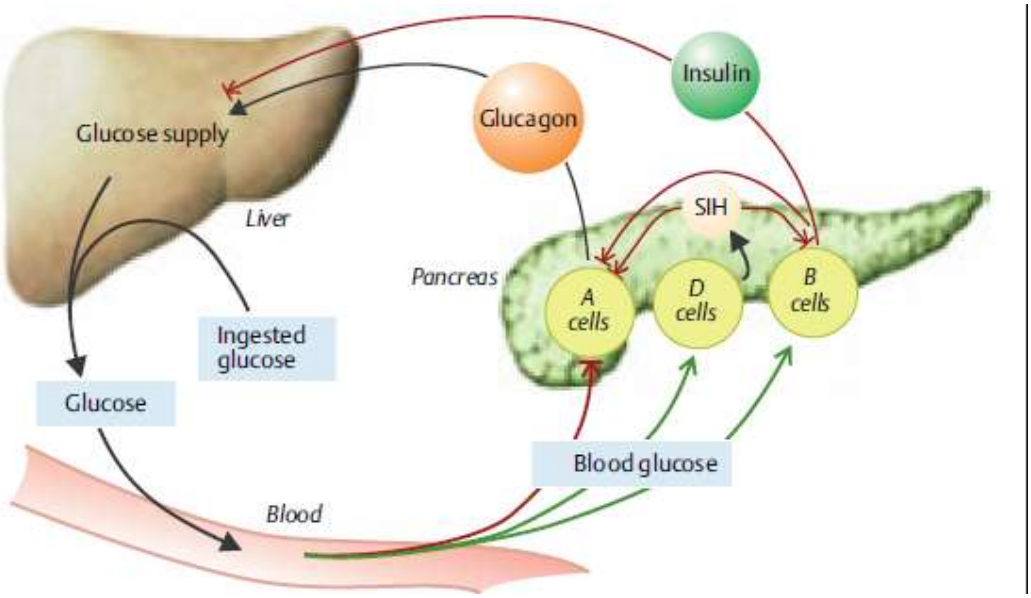
(The pancreas produces 1,000-1,500 mL of digestive juices per day. These juices consist primarily of water, NaCl (salt), and NaHCO3 (sodium bicarbonate). The purpose of the sodium bicarbonate is to neutralize the high acidity of the chyme (food plus stomach acid) raising it to an alkaline pH of 7.1-8.2. This both stops the action of gastric pepsins and stomach acid and prepares chyme for the process of nutrient absorption, which takes place in the small intestine.)

At least four polypeptides with regulatory activity are secreted by the islets of Langerhans in the pancreas. Two of these are hormones **insulin** and **glucagon,** and have important functions in the regulation of the intermediary metabolism of carbohydrates, proteins, and fats. The third polypeptide, **somatostatin,** plays a role in the regulation of islet cell secretion, and the fourth, **pancreatic polypeptide,** is probably concerned primarily with the regulation of HCO_3 secretion to the intestine. Glucagon, somatostatin, and possibly pancreatic polypeptide are also secreted by cells in the mucosa of the gastrointestinal tract.

Islets of Langerhans

Play a primary role in carbohydrate metabolism. Four cell types have been identified so far: A, B, D, and F cell. 20% of all islet cells are type A (α) cells that produce **glucagon**, 60-75% are B (β) cells that synthesize **insulin**, and 10% are D (δ) cells that secrete somatostatin (**SIH**). These hormones mutually influence the synthesis and secretion of each other. Islet cells in the pancreas head synthesize *pancreatic polypeptide* (F cells), the physiological function is probably concerned primarily with the regulation of HCO3 secretion to the intestine, whereas the exocrine portion of the pancreas makes up 80%, and ducts and blood vessels make up the remainder.





High concentrations of these hormones reach the liver by way of the portal venous circulation.

Function.

Pancreatic hormones

(1) Ensure that ingested food is stored as glycogen and fat (insulin);

(2) Mobilize energy reserves in response to food deprivation, physical activity or stress (glucagon and the non-pancreatic hormone epinephrine);

(3) Maintain the plasma glucose concentration as constant as possible; and

(4) Promote growth.

Insulin.

Insulin is a peptide hormone produced by B-cells of the islets of Langerhans. It is an important anabolic hormone secreted at times when the concentration of nutrient molecules in the blood is high, such as periods following a meal. Its overall effects include allowing the body to use carbohydrates as an energy source and to store nutrient molecules. Specifically, insulin exerts its important actions on the following tissues:

Liver

• Increase in glucose (uptake of glucose)

• Increase in lipogenesis (formation of triglycerides, the storage form of lipids)

Adipose tissue

• Increase in glucose uptake

• Increase in free fatty acid uptake

• Increase in lipogenesis

Muscle

• Increase in glucose uptake

• Increase in glycogenesis

• Increase in amino acid uptake

• Increase in protein synthesis

Insulin is the only hormone that lowers blood glucose (epinephrine, growth hormone, cortisol, and glucagon increase blood glucose). It does so by stimulating the uptake of glucose from the blood into the liver, adipose tissue, and muscle. This glucose is first used as an energy source

and then stored in the form of glycogen in the liver and in muscle. Excess glucose is stored as fat in adipose tissue.

Insulin is a polypeptide containing two chains of amino acids (A and B chains) linked by disulfide bridges. Minor differences occur in the amino acid composition of the molecule from species to species. The differences are generally not sufficient to affect the biologic activity of a particular insulin.

Insulin is synthesized as part of a larger preprohormone. **Preproinsulin** has a 110-amino-acid signal peptide removed as it enters the endoplasmic reticulum. The remainder of the molecule is then folded, and the disulfide bonds are formed to make **proinsulin.** The peptide segment connecting the A and B chains, the **connecting peptide (C peptide),** facilitates the folding and then is detached in the granules before secretion.

METABOLISM:

The half-life of insulin in the circulation in humans is about 5 min. Insulin binds to insulin receptors, and some is internalized. It is destroyed by proteases in the endosomes formed by the endocytotic process.

Secretion.

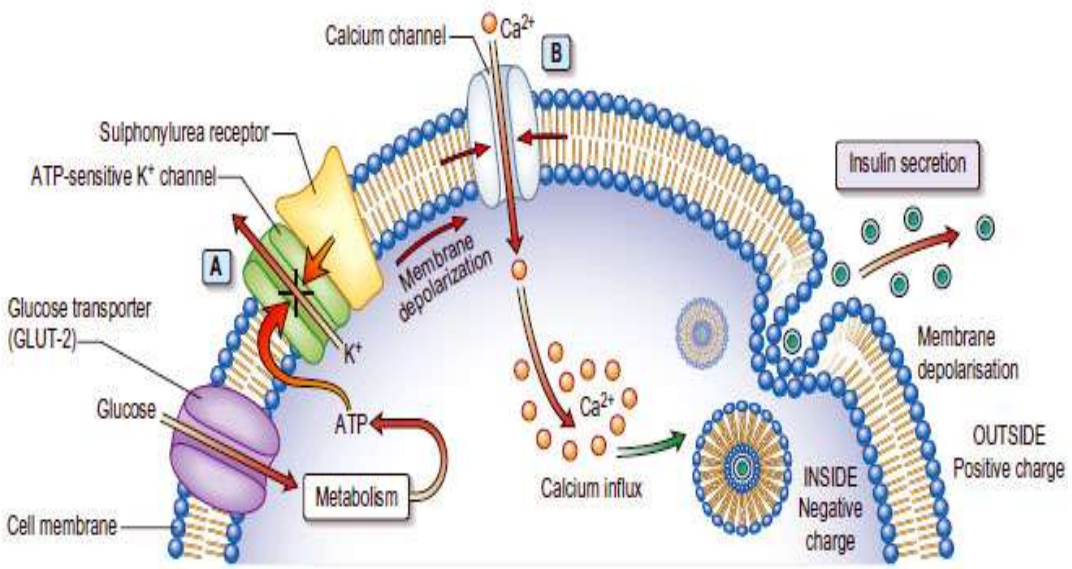
Insulin is secreted in pulsatile bursts, mainly in response to *increases in the blood levels of glucose*, as follows:

plasma glucose↑ → glucose in B cells↑ → glucose oxidation↑ → cytosolic ATP↑ → closure of ATP-gated K+ channels → depolarization→ opening of voltage-gated Ca2+ channels → cytosolic Ca2+↑.

The rising Ca2+ in B cells leads to

(a) *exocytosis* of insulin and

(b) re-opening of K+ channels (deactivated by feedback control).



Stimulation.

Insulin secretion is stimulated mainly during food digestion via acetylcholine (vagus nerve), gastrin, secretin, GIP (**Gastric inhibitory polypeptide**) and GLP-1 (glucagon-like peptide = enteroglucagon), a peptide that dissociates from intestinal proglucagon. Certain amino acids (especially arginine and leucine), free fatty acids, many pituitary hormones and some steroid hormones also increase insulin secretion.

Inhibition.

Epinephrine and norepinephrine (α*2- adrenoceptors*), *SIH* and the neuropeptide *galanin* inhibit insulin secretion.

When *hypoglycemia* occurs due, e.g., to fasting or prolonged physical exercise, the low blood glucose concentration is sensed by central chemosensors for glucose, leading to reflex activation of the sympathetic nervous system.

Action of insulin.

Insulin has *anabolic* and *lipogenic* effects, and promotes the *storage of glucose*, especially in the liver, where it activates enzymes that *promote glycolysis* and *glycogenesis* and *suppresses* those involved in

gluconeogenesis. Insulin also *increases the number of GLUT-4* uniporters in skeletal myocytes. All these actions serve to **lower the plasma glucose concentration** (which increases after food ingestion). About two-thirds of the glucose absorbed by the intestines after a meal (postprandial) is temporarily stored and kept ready for mobilization (via glucagon) during the interdigestive phase. This provides a relatively constant supply of glucose for the glucose-dependent CNS and vital organs in absence of food ingestion. Insulin increases the *storage of amino acids* (AA) in the form of proteins, especially in the skeletal muscles (*anabolism*). In addition, it promotes growth, *inhibits extrahepatic lipolysis* and affects *K+ distribution*.

Glucose

Is the *central energy carrier* of the human metabolism. The brain and red blood cells are fully glucose-dependent. The **plasma glucose concentration** (blood sugar level) is determined by the level of glucose *production* and *consumption*.

The following terms are important for proper understanding of carbohydrate metabolism:

1. **Glycolysis**

Generally refers to the anaerobic conversion of glucose to lactate. This occurs in the red blood cells, renal medulla, and skeletal muscles. Aerobic oxidation of glucose occurs in the CNS, heart, skeletal muscle and in most other organs and produce pyruvate.

2. Glycogenesis,

The synthesis of glycogen from glucose (in liver and muscle), facilitates the storage of glucose and helps to maintain a constant plasma glucose concentration. Glycogen stored in a muscle can only be used by that muscle.

3. Glycogenolysis

Is the breakdown of glycogen to glucose, i.e., the opposite of glycogenesis.

4. Gluconeogenesis

Is the production of glucose (in liver and renal cortex) from non-sugar molecules such as amino acids (e.g., glutamine), lactate (produced by anaerobic glycolysis in muscles and red cells), and glycerol (from lipolysis).

5. Lipolysis

Is the breakdown of triacylglycerols into glycerol and free fatty acids.

6. Lipogenesis

Is the synthesis of triacylglycerols (for storage in fat depots).

GLUCOSE TRANSPORTERS

Glucose enters cells by **facilitated diffusion** or, in the intestine and kidneys, by secondary active transport with Na+. In muscle, adipose, and some other tissues, insulin stimulates glucose entry into cells by increasing the number of glucose transporters in the cell membranes. In the tissues in which insulin increases the number of glucose transporters in the cell membranes, the rate of phosphorylation of the glucose, once it has entered the cells, is regulated by other hormones. Growth hormone and cortisol both inhibit phosphorylation in certain tissues. Transport is normally so rapid that it is not a rate-limiting step in glucose metabolism. However, it is rate-limiting in the B cells. Insulin also increases the entry of glucose into liver cells, but it does not exert this effect by increasing the number of GLUT 4 transporters in the cell membranes. Instead, it induces glucokinase, and this increases the phosphorylation of glucose, so that the intracellular free glucose concentration stays low, facilitating the entry of glucose into the cell. Insulin-sensitive tissues also contain a population of GLUT 4 vesicles that move into the cell membrane in

response to exercise, a process that occurs independent of the action of insulin. This is why exercise lowers blood sugar.

Hypoglycemia develops when the insulin concentration is too high. Glucose levels of _2 mmol/L (35 mg/dL) produce glucose deficiencies in the brain, which can lead to coma and *hypoglycemic shock*. The **excessive intake of carbohydrates** can overload glycogen stores. The liver therefore starts to convert glucose into fatty acids, which are transported to and stored in fatty tissues in the form of *triacylglycerols***.**

Insulin causes K^+ to enter cells, with a resultant lowering of the extracellular K^+ concentration. Infusions of insulin and glucose significantly lower the plasma K^+ level in normal individuals and are very effective for the temporary relief of hyperkalemia in patients with renal failure.

Diabetes mellitus (DM).

The cause of clinical diabetes is always a deficiency of the effects of insulin at the tissue level, but the deficiency may be relative.

One of the common forms, **type 1,** or **insulin dependent diabetes mellitus (IDDM),** is due to insulin deficiency caused by autoimmune destruction of the B cells in the pancreatic islets; the A, D, and F cells remain intact. The second common form, **type 2,** or **non-insulin-dependent diabetes mellitus (NIDDM),** is characterized by insulin resistance.

In addition, some cases of diabetes are due to other diseases or conditions such as chronic pancreatitis, total pancreatectomy, Cushing syndrome, and acromegaly. These make up 5% of the total cases and are sometimes classified as **secondary diabetes.**

Type 1 diabetes usually develops before the age of 40 and hence is called **juvenile diabetes.** Patients with this disease are not obese and they

have a high incidence of ketosis and acidosis. Various anti-B cell antibodies are present in plasma, but the current thinking is that type 1 diabetes is primarily a T lymphocyte-mediated disease. Definite genetic susceptibility is present as well; if one identical twin develops the disease, the chances are 1 in 3 that the other twin will also do so. In other words, the **concordance rate** is about 33%.

Type 2 is the most common type of diabetes and is usually associated with obesity. It usually develops after age 40 and is not associated with total loss of the ability to secrete insulin. It has an insidious onset, is rarely associated with ketosis, and is usually associated with normal B cell morphology and insulin content if the B cells have not become exhausted. The genetic component in type 2 diabetes is actually stronger than the genetic component in type 1 diabetes; in identical twins, the concordance rate is higher, ranging in some studies to nearly 100%.

Glucagon, Somatostatin and Somatotropin

Glucagon

Released from A (α) cells; is a peptide hormone derived from *proglucagon*. The granules in which glucagon is stored are secreted by exocytosis. Secretion is **stimulated** by amino acids (AA) from digested proteins (especially alanine and arginine) as well as by hypoglycemia (e.g., due to fasting, prolonged physical exercise) and sympathetic impulses (via β2 adrenoceptors). Glucagon secretion is **inhibited** by glucose and SIH as well as by high plasma concentrations of free fatty acids. The **actions** of glucagon mainly antagonize those of insulin. Glucagon maintains a normal *blood glucose level between meals* and during phases of increased glucose consumption to ensure a constant energy supply. It does this

(a) By increasing glycogenolysis (in liver not muscle) and

(b) By stimulating gluconeogenesis from lactate, AA (protein degradation = catabolism) and glycerol (from *lipolysis*).

Somatostatin (SIH).

Like insulin, SIH stored in D cells; is released in response to increased plasma concentrations of glucose and arginine (i.e., after a meal). Through paracrine pathways (via Gi-linked receptors), SIH inhibits the release of insulin. Therefore, SIH inhibits not only the release of gastrin, which promotes digestion, but also interrupts the insulin- related storage of nutrients. SIH also inhibits glucagon secretion. This effect does not occur in the presence of a glucose deficiency because of the release of catecholamines that *decrease* SIH secretion.

Somatotropin (STH) = growth hormone (GH).

The short-term effects of GH are similar to those of insulin; its action is mediated by somatomedins. In the long-term, GH increases the blood glucose concentration and promotes growth.

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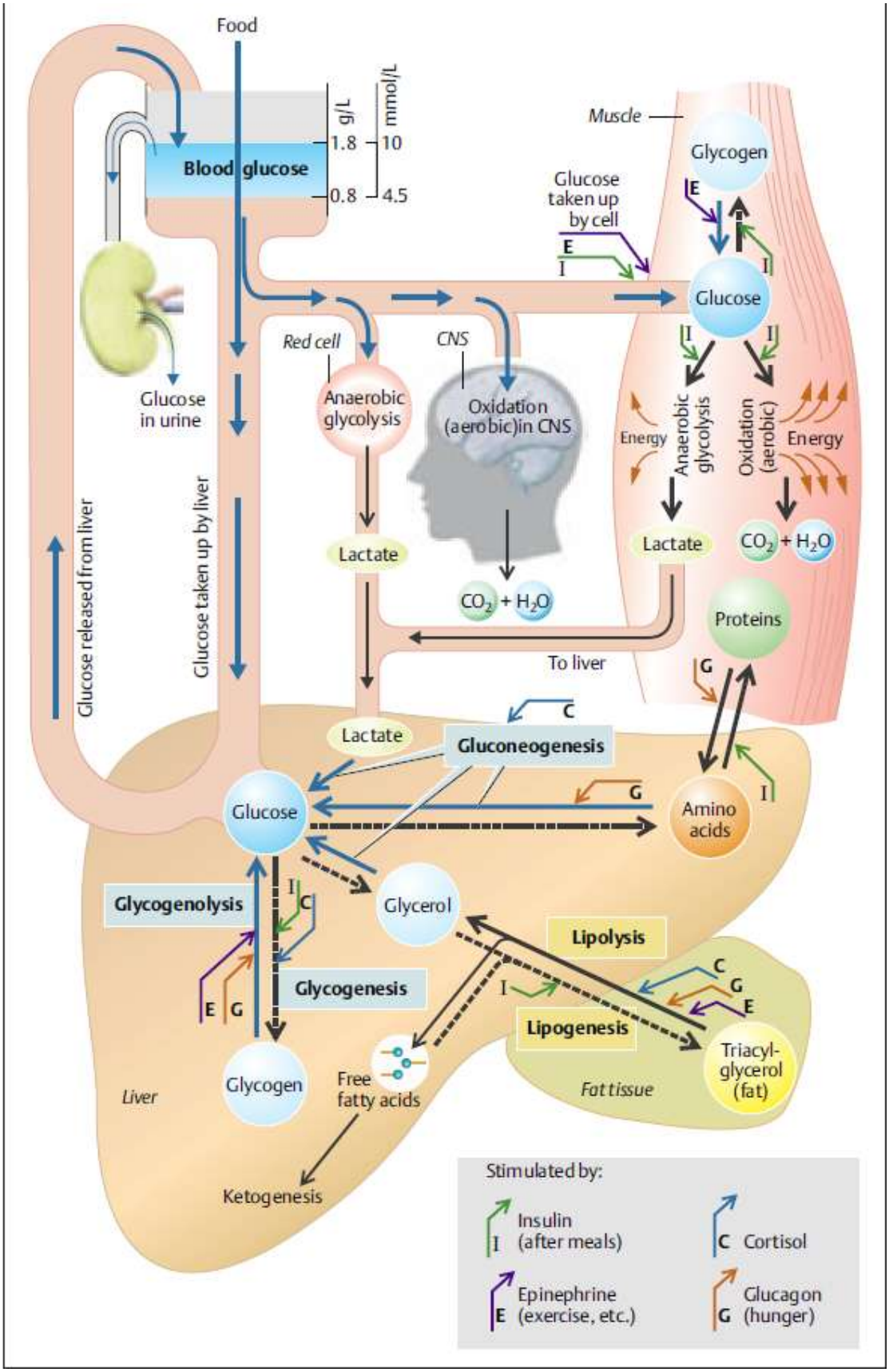

Food
g/L
mmol/L
1.8
10
0.8
4.5
Blood glucose
Glucose in urine
Glucose released from liver
Glucose taken up by liver
Red cell
CNS
Anaerobic glycolysis
Oxidation (aerobic)in CNS
Lactate
$CO_2 + H_2O$
Muscle
Glycogen
Glucose taken up by cell
Glucose
Energy
Anaerobic glycolysis
Oxidation (aerobic)
Energy
Lactate
$CO_2 + H_2O$
Proteins
To liver
Lactate
Gluconeogenesis
Glucose
Amino acids
Glycogenolysis
Glycerol
Lipolysis
Glycogenesis
Lipogenesis
Triacyl-glycerol (fat)
Liver
Glycogen
Free fatty acids
Fat tissue
Ketogenesis
Stimulated by:
Insulin (after meals)
Cortisol
Epinephrine (exercise, etc.)
Glucagon (hunger)

1st Lec.

Central Nervous System: Brain & Spinal cord

Physiology-2nd class

AHMED ATAIMISH

Neuronal Signaling and the Structure of the Nervous System

The various structures of the nervous system are interconnected, but for convenience we divide them into two parts:

(1) the **central nervous system** (**CNS**), composed of the brain and spinal cord; and

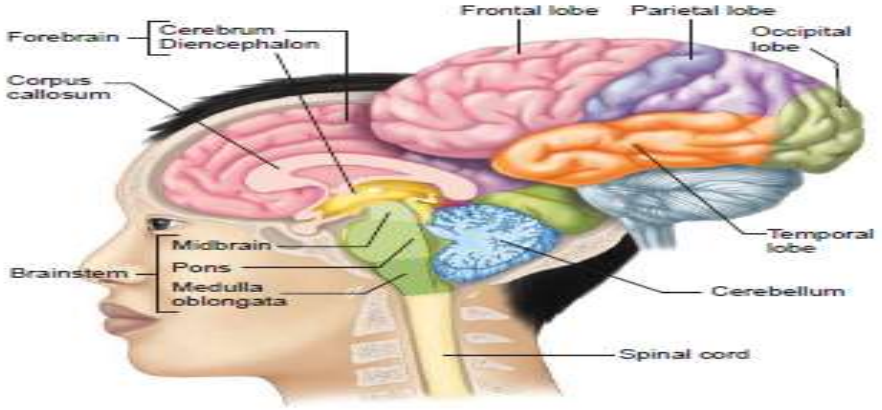
(2) the **peripheral nervous system** (**PNS**), consisting of the nerves that connect the brain and spinal cord with the body's muscles, glands, sense organs, and other tissues.

The basic unit of the nervous system is the nerve cell, or **neuron.** Neurons operate by generating electrical signals that move from one part of the cell to another part of the same cell or to neighboring cells. In most neurons, the electrical signal causes the release of chemical messengers—**neurotransmitters** —to communicate with other cells.

Central Nervous System:

Brain

The brain has four different regions: the **cerebrum, diencephalon, brainstem,** and **cerebellum**. The cerebrum and diencephalon together constitute the **forebrain.** The brainstem consists of the **midbrain, pons,** and **medulla oblongata.** The brain also contains four interconnected cavities, the **cerebral ventricles,** which are filled with fluid.



Forebrain

The larger component of the forebrain, the cerebrum, consists of the right and left **cerebral hemispheres** as well as some associated structures on the underside of the brain. The central core of the forebrain is formed by the diencephalon.

The cerebral hemispheres consist of the **cerebral cortex** —an outer shell of **gray matter** composed of cell bodies that give the area a gray appearance—and an inner layer of **white matter,** composed primarily of myelinated fiber tracts.

The cortex of each cerebral hemisphere is divided into four lobes: the **frontal, parietal, occipital,** and **temporal lobes.** Although it averages only 3 mm in thickness, the cortex is highly folded. This results in an area containing cortical neurons that is four times larger than it would be if unfolded.

The cerebral cortex is one of the most complex integrating areas of the nervous system. In the cerebral cortex, basic afferent information is collected and processed into meaningful perceptual images, and control over the systems that govern the movement of the skeletal muscles is refined. Some of the input fibers convey information about specific events in the environment, whereas others control levels of cortical excitability, determine states of arousal, and direct attention to specific stimuli.

The subcortical nuclei are heterogeneous groups of gray matter that lie deep within the cerebral hemispheres. Predominant among them are the **basal nuclei** (often, but less correctly referred to as **basal ganglia**), which play an important role in controlling movement and posture and in more complex aspects of behavior.

The diencephalon, is the second component of the forebrain. It contains the thalamus, hypothalamus, and epithalamus. The **thalamus** is a collection of several large nuclei that serve as synaptic relay stations and important integrating centers for most inputs to the cortex, and it plays a key role in general arousal. The thalamus also is involved in focusing attention. The **hypothalamus** lies below the thalamus and is on the undersurface of the brain. Although it is a tiny region that accounts for less than 1% of the brain's weight, it contains different cell groups and pathways that form the master command center for neural and endocrine coordination. Indeed, the hypothalamus is the single most important control area for homeostatic regulation of the internal environment. Behaviors having to do with preservation of the individual (for example, eating and drinking) and preservation of the species (reproduction) are among the many functions of the hypothalamus.

The hypothalamus lies directly above and is connected by a stalk to the **pituitary gland,** an important endocrine structure that the hypothalamus regulates.

The **epithalamus** is a small mass of tissue that includes the **pineal gland,** which has a role in regulating circadian rhythms through release of the hormone melatonin.

Summary of Functions of the Major Parts of the Brain

I. Forebrain

A. Cerebral hemispheres

1. Contain the cerebral cortex, which participates in perception; the generation of skilled movements; reasoning, learning, and memory

2. Contain subcortical nuclei, including those that participate in coordination of skeletal muscle activity

3. Contain interconnecting fiber pathways

B. Thalamus

1. Acts as a synaptic relay station for sensory pathways on their way to the cerebral cortex

2. Participates in control of skeletal muscle coordination

3. Plays a key role in awareness

C. Hypothalamus

1. Regulates anterior pituitary gland function

2. Regulates water balance

3. Participates in regulation of autonomic nervous system

4. Regulates eating and drinking behavior

5. Regulates reproductive system

6. Reinforces certain behaviors

7. Generates and regulates circadian rhythms

8. Regulates body temperature

9. Participates in generation of emotional behavior

D. Limbic system

1. Participates in generation of emotions and emotional behavior

2. Plays essential role in most kinds of learning

II. Cerebellum

A. Coordinates movements, including those for posture and balance

B. Participates in some forms of

III. Brainstem

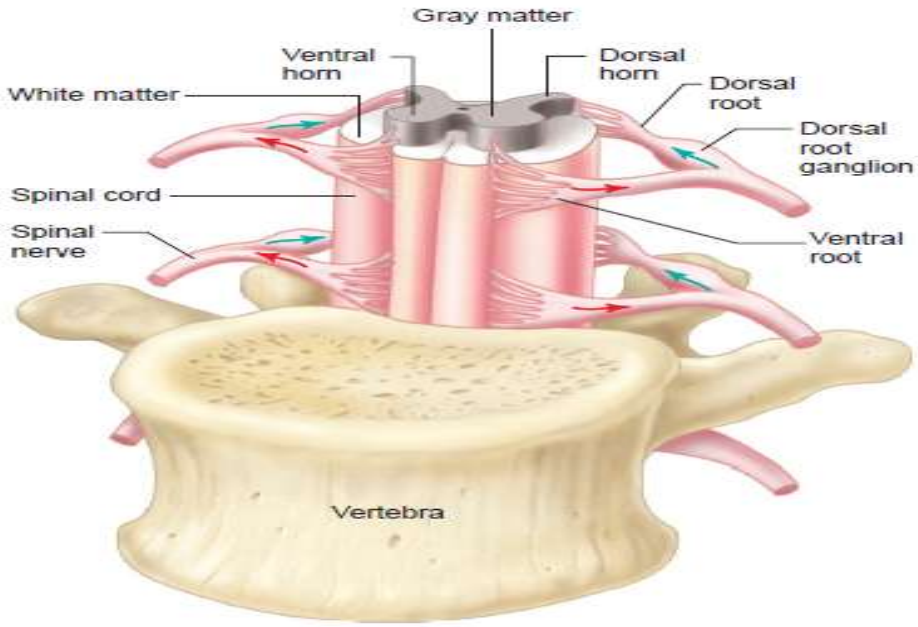
A. Contains all the fibers passing between the spinal cord, forebrain, and cerebellum

B. Contains the reticular formation and its various integrating centers, including those for cardiovascular and respiratory activity

C. Contains nuclei for cranial nerves III through XII

Spinal Cord

The spinal cord lies within the bony vertebral column. It is a slender cylinder of soft tissue about as big around as your little finger.

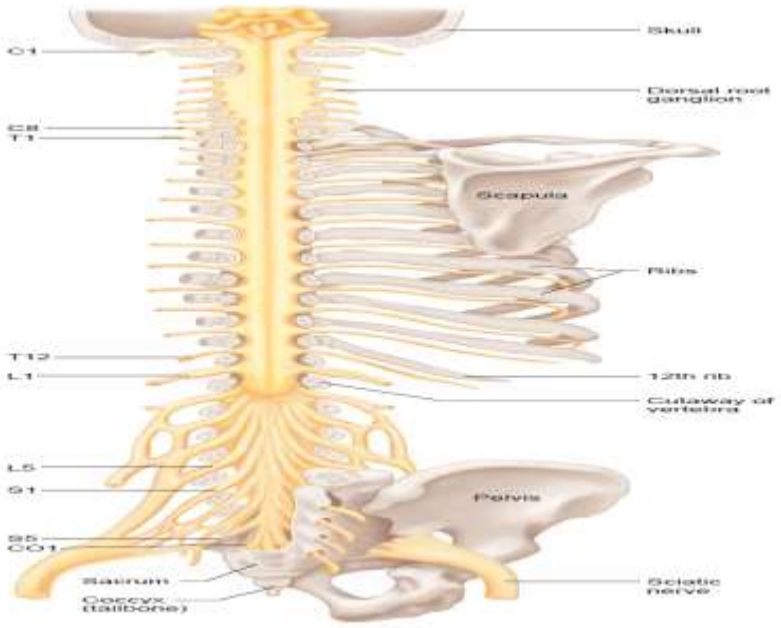


The central butterfly-shaped area (in cross section) of gray matter is composed of interneurons, the cell bodies and dendrites of efferent neurons, the entering axons of afferent neurons, and glial cells. The regions of gray matter projecting toward the back of the body are called the **dorsal horns,** whereas those oriented toward the front are the **ventral horns.** The gray matter is surrounded by white matter, which consists of groups of myelinated axons. These groups of fiber tracts run longitudinally through the cord, some descending to relay information *from* the brain to the spinal cord, others ascending to transmit information *to* the brain. Pathways also transmit information between different levels of the spinal cord. Groups of afferent fibers that enter the spinal cord from the peripheral nerves enter on the dorsal side of the cord via the **dorsal roots.** Small bumps on the dorsal roots, the **dorsal root ganglia,** contain the cell bodies of these afferent neurons. The axons of efferent neurons leave the spinal cord on the ventral side via the **ventral roots.** A short distance from the cord, the dorsal and ventral roots from the same level combine to form a **spinal nerve,** one on each side of the spinal cord.

Peripheral Nervous System

Neurons in the PNS transmit signals between the CNS and receptors and effectors in all other parts of the body. The axons are grouped into bundles called nerves.

The PNS has 43 pairs of nerves: 12 pairs of cranial nerves and 31 pairs of spinal nerves that connect with the spinal cord.



The 31 pairs of spinal nerves are designated by the vertebral levels from which they exit: **cervical, thoracic, lumbar, sacral, and coccygeal**. Neurons in the spinal nerves at each level generally communicate with nearby structures, controlling muscles and glands as well as receiving sensory input. The eight pairs of cervical nerves innervate the neck, shoulders, arms, and hands. The 12 pairs of thoracic nerves are associated with the chest and upper abdomen. The five pairs of lumbar nerves are associated with the lower abdomen, hips, and legs; the five pairs of sacral nerves are associated with the genitals and lower digestive

tract. A single pair of coccygeal nerves associated with the tailbone brings the total to 31 pairs.

These peripheral nerves can contain nerve fibers that are the axons of efferent neurons, afferent neurons, or both. Therefore, fibers in a nerve may be classified as belonging to the **efferent** or the **afferent division** of the PNS. All the spinal nerves contain both afferent

and efferent fibers, whereas some of the cranial nerves contain only afferent fibers (the optic nerves from the eyes, for example) or only efferent fibers (the hypoglossal nerve to muscles of the tongue, for example).

Efferent neurons carry signals out from the CNS to muscles, glands, and other tissues. The efferent division of the PNS is more complicated than the afferent, being subdivided

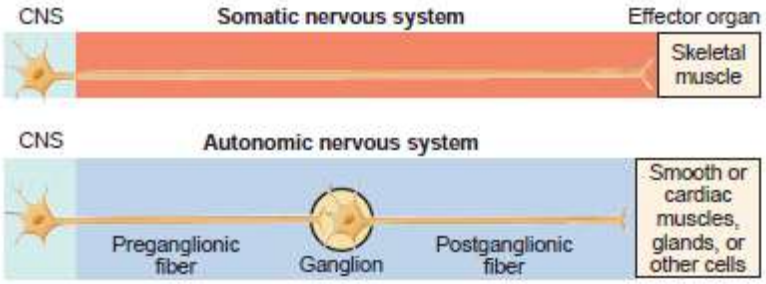
into a **somatic nervous system** and an **autonomic nervous system.** These terms are somewhat misleading because they suggest the presence of additional nervous systems distinct from the central and peripheral systems. Keep in mind that these terms together make up the efferent division of the PNS. The simplest distinction between the somatic and autonomic systems is that the neurons of the somatic division innervate skeletal muscle, whereas the autonomic neurons innervate smooth and cardiac muscle, glands, neurons in the gastrointestinal tract, and other tissues.

The somatic portion of the efferent division of the PNS is made up of all the nerve fibers going from the CNS to skeletal muscle cells. The cell bodies of these neurons are located in groups in the brainstem or the ventral horn of the spinal cord. Their large-diameter, myelinated axons leave the CNS and pass without any synapses to skeletal muscle cells. The neurotransmitter these neurons release is acetylcholine. Because activity in the somatic neurons leads to contraction of the innervated skeletal muscle cells, these neurons are called **motor neurons.** Excitation of motor neurons leads only to the *contraction* of skeletal muscle cells; there are no somatic neurons that inhibit skeletal muscles. Muscle relaxation involves the inhibition of the motor neurons in the spinal cord.

Autonomic Nervous System

The efferent innervation of tissues other than skeletal muscle is by way of the autonomic nervous system. A special case occurs in the gastrointestinal tract, where autonomic neurons innervate a nerve network in the wall of the intestinal tract. This network is called the **enteric nervous system,** and although often classified as a subdivision of the autonomic efferent nervous system, it also includes sensory neurons and interneurons.

In contrast to the somatic nervous system, the autonomic nervous system is made up of two neurons in series that connect the CNS and the effector cells.



The first neuron has its cell body in the CNS. The synapse between the two neurons is outside the CNS in a cell cluster called an **autonomic ganglion.** The neurons passing between the CNS and the ganglia are called **preganglionic neurons;** those passing between the ganglia and the effector cells are **postganglionic neurons.**

Anatomical and physiological differences within the autonomic nervous system are the basis for its further subdivision into **sympathetic** and **parasympathetic divisions.**

The neurons of the sympathetic and parasympathetic divisions leave the CNS at different levels—the sympathetic fibers from the thoracic (chest) and lumbar regions of the spinal cord, and the parasympathetic fibers from the brainstem and the sacral portion of the spinal cord. Therefore, the sympathetic division is also called the thoracolumbar division, and the parasympathetic division is called the craniosacral division.

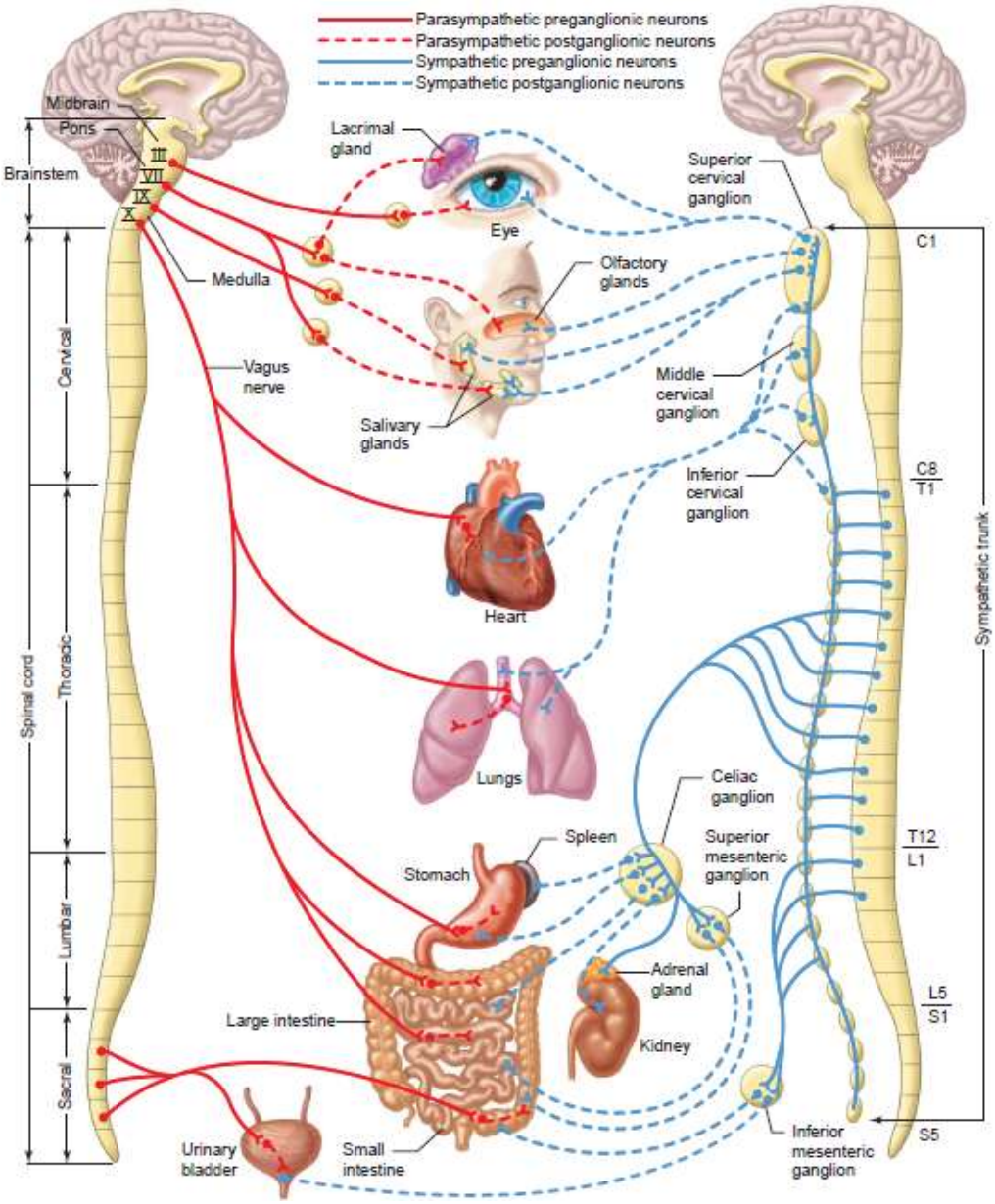
The two divisions also differ in the location of ganglia. Most of the sympathetic ganglia lie close to the spinal cord and form the two chains of ganglia—one on each side of the cord known as the **sympathetic trunks**.

In contrast, the parasympathetic ganglia lie within, or very close to, the organs that the postganglionic neurons innervate. Preganglionic sympathetic neurons leave the spinal cord only between the first thoracic and second lumbar segments, whereas sympathetic *trunks* extend the entire length of the cord, from the cervical levels high in the neck down to the sacral levels. The ganglia in the extra lengths of sympathetic trunks receive preganglionic neurons from the thoracolumbar regions because some of the preganglionic neurons, once in the sympathetic trunks, turn to travel upward or downward for several segments before forming synapses with postganglionic neurons.

In the parasympathetic division, acetylcholine is the neurotransmitter between the postganglionic neuron and the effector cell. In the sympathetic division, norepinephrine is

usually the transmitter between the postganglionic neuron and the effector cell. We say "usually" because a few sympathetic postganglionic endings release acetylcholine (e.g., sympathetic pathways that regulate sweating).

Many of the drugs that stimulate or inhibit various components of the autonomic nervous system affect receptors for acetylcholine and norepinephrine. Recall that there are several types of receptors for each neurotransmitter. A great majority of acetylcholine receptors in the autonomic ganglia are nicotinic receptors. In contrast, the acetylcholine receptors on cellular targets of postganglionic autonomic neurons are muscarinic receptors. The cholinergic receptors on skeletal muscle fibers, innervated by the *somatic* motor neurons, not autonomic neurons, are nicotinic receptors.


Parasympathetic preganglionic neurons
Parasympathetic postganglionic neurons
Sympathetic preganglionic neurons
Sympathetic postganglionic neurons
Midbrain
Pons
Brainstem
III
VII
IX
X
Medulla
Cervical
Thoracic
Lumbar
Sacral
Spinal cord
Lacrimal gland
Eye
Olfactory glands
Vagus nerve
Salivary glands
Heart
Lungs
Stomach
Spleen
Large intestine
Urinary bladder
Small intestine
Adrenal gland
Kidney
Superior cervical ganglion
Middle cervical ganglion
Inferior cervical ganglion
Celiac ganglion
Superior mesenteric ganglion
Inferior mesenteric ganglion
C1
C8
T1
T12
L1
L5
S1
S5
Sympathetic trunk

2nd Lec.

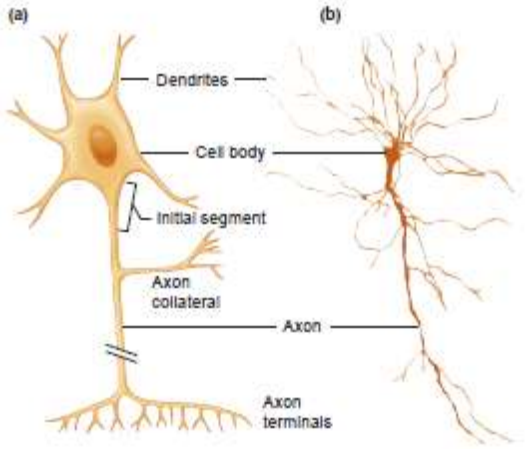
Nervous System: Neuronsand Action Potentials

Physiology 2nd class

AHMED ATAIMISH

Structure and Maintenance of Neurons

Neurons occur in a wide variety of sizes and shapes, but all share features that allow cell-to-cell communication. Long extensions, or **processes,** connect neurons to each other and perform the neurons' input and output functions. Most neurons contain a cell body and two types of processes—dendrites and axons.

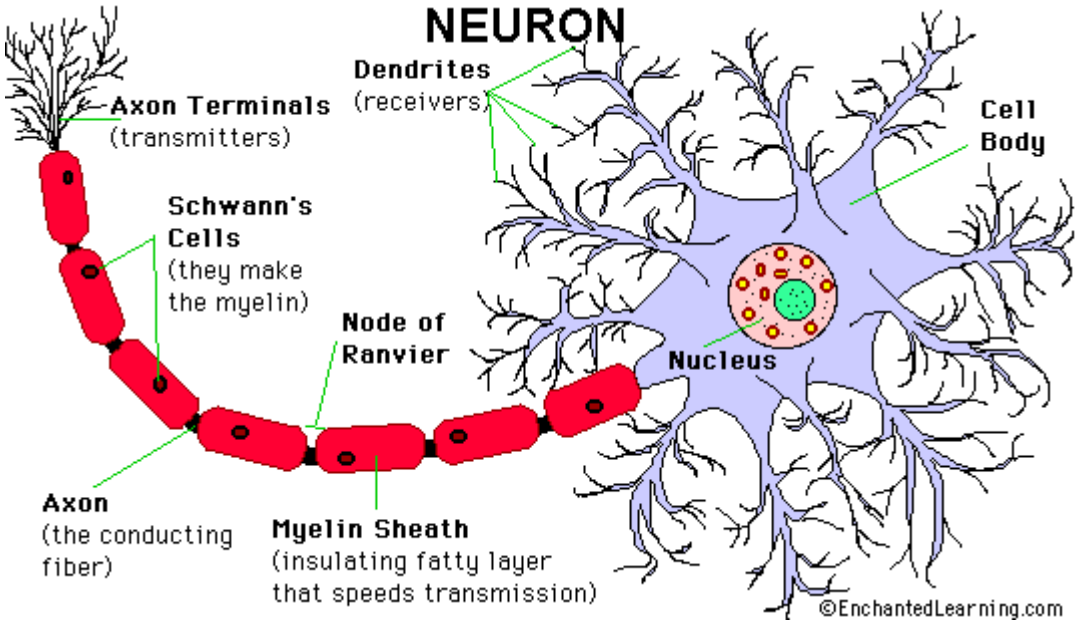


As in other types of cells, a neuron's **cell body** (or **soma**) contains the nucleus and ribosomes and thus has the genetic information and machinery necessary for protein synthesis. The **dendrites** are a series of highly branched outgrowths of the cell body. In the PNS, dendrites receive incoming sensory information and transfer it to integrating regions of sensory neurons. In the CNS, dendrites and the cell body receive most of the inputs from other neurons. Branching dendrites increase a cell's surface area—some neurons may have as many as 400,000 dendrites. Knoblike outgrowths called **dendritic spines** increase the surface area of dendrites still further, and there are often ribosomes present. The presence of protein synthesis machinery allows dendritic spines to remodel their shape in response to variation in synaptic activity, which may Thus, the structure of dendrites in the CNS increases a cell's capacity to receive signals from many other neurons.

The **axon,** sometimes also called a **nerve fiber,** is a long process that extends from the cell body and carries outgoing signals to its target cells. In humans, axons range in length from a few microns to over a meter. The region of the axon that arises from the cell body is known as the **initial segment** (or **axon hillock**).

The initial segment is the "trigger zone" where, in most neurons, propagated electrical signals are generated. These signals then propagate away from the cell body along the axon or, sometimes, back along the dendrites.

Each branch ends in an **axon terminal,** which is responsible for releasing neurotransmitters from the axon. These chemical messengers diffuse across an extracellular gap to the cell opposite the terminal. The axons of many neurons are covered by sheaths of **myelin**, which usually consists of 20 to 200 layers of highly modified plasma membrane wrapped around the axon by a nearby supporting cell. In the brain and spinal cord, these myelin-forming cells are the **oligodendrocytes.**



Each oligodendrocyte may branch to form myelin on as many as 40 axons. In the PNS, cells called **Schwann cells** form individual myelin sheaths surrounding 1- to 1.5-mm-long segments at regular intervals along some axons. The spaces between adjacent sections of myelin where the axon's plasma membrane is exposed to extracellular fluid are called the **nodes of Ranvier.**

The myelin sheath speeds up conduction of the electrical signals along the axon and conserves energy. To maintain the structure and function of the cell axon, various organelles and other materials must move as far as 1 meter between the cell body and the axon terminals. This movement, termed **axonal transport,** depends on a scaffolding of

microtubule running the length of the axon and specialized types of motor proteins known as **kinesins** and **dyneins**.

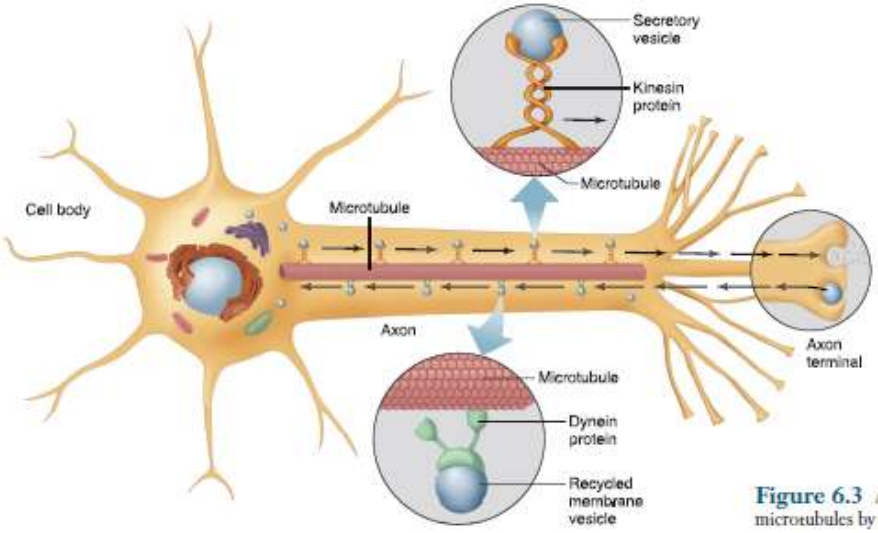
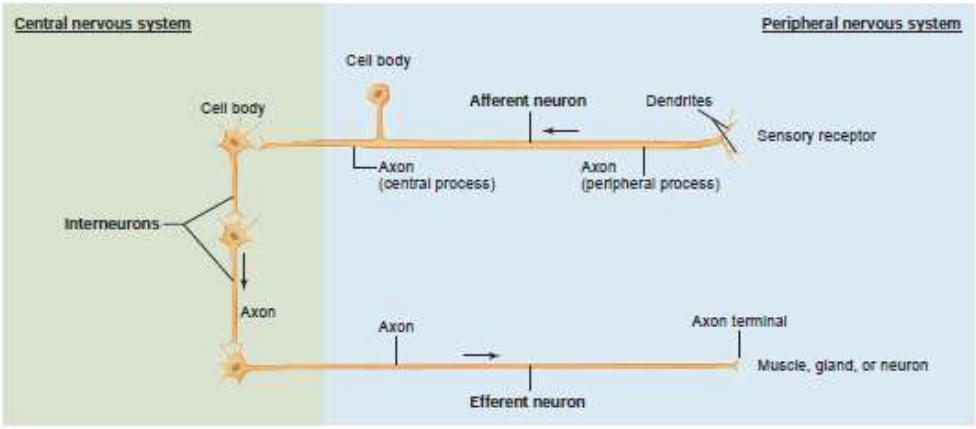


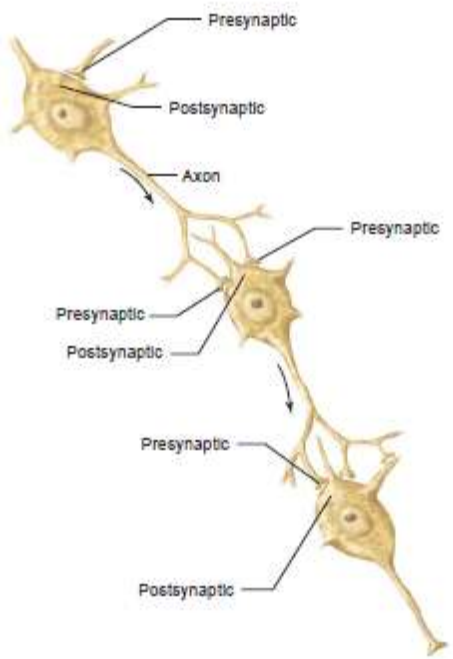
Figure 6.3 Axonal transport along microtubules by dynein and kinesin.



At one end, these double-headed motor proteins bind to their cellular cargo, and the other end uses energy derived from the hydrolysis of ATP to "walk" along the microtubules. Kinesin transport mainly occurs from the cell body toward the axon terminals (**anterograde**) and is important in moving nutrient molecules, enzymes, mitochondria, neurotransmitter-filled vesicles, and other organelles. Dynein movement is in the other direction (**retrograde**), carrying recycled membrane vesicles, growth factors, and other chemical signals that can affect the neuron's morphology, biochemistry, and connectivity. Retrograde transport is also the route by which some harmful agents invade the CNS, including tetanus toxin and the herpes simplex, rabies, and polio viruses.

Functional Classes of Neurons

Neurons can be divided into three functional classes: afferent neurons, efferent neurons, and interneurons.



Afferent neurons convey information from the tissues and organs of the body *toward* the CNS. **Efferent neurons** convey information *away from* the CNS to effector cells like muscle, gland, or other cell types. **Interneurons** connect neurons *within* the CNS. As a rough estimate, for each afferent neuron entering the CNS, there are 10 efferent neurons and 200,000 interneurons. Thus, the great majority of neurons are interneurons.

At their peripheral ends (the ends farthest from the CNS), afferent neurons have **sensory receptors,** which respond to various physical or chemical changes in their environment by generating electrical signals in the neuron. The receptor region may be a specialized portion of the plasma membrane or a separate cell closely associated with the neuron ending.

The anatomically specialized junction between two neurons where one neuron alters the electrical and chemical activity of another is called a **synapse.** At most synapses, the signal

is transmitted from one neuron to another by *neurotransmitters,* a term that also includes the chemicals efferent neurons use to communicate with effector cells (e.g., a muscle cell). The neurotransmitters released from one neuron alter the receiving neuron by binding with specific protein receptors on the membrane of the receiving neuron.

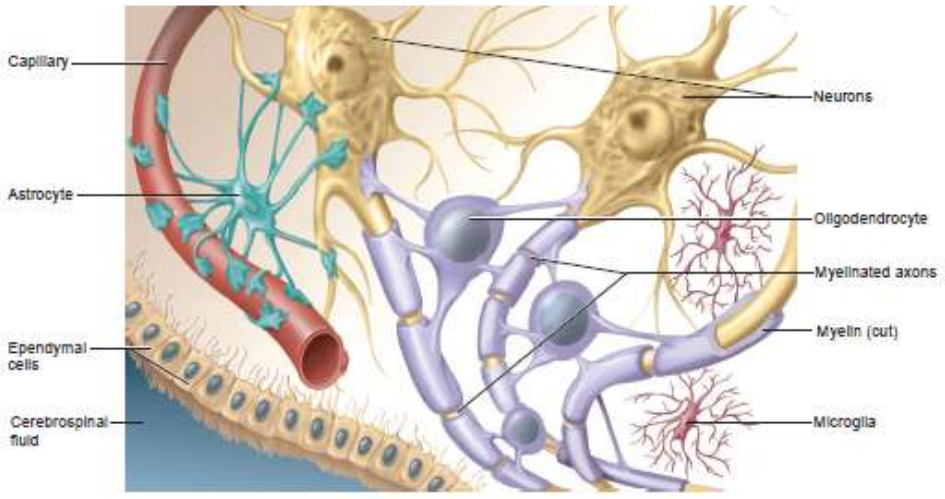
Most synapses occur between an axon terminal of one neuron and a dendrite or the cell body of a second neuron. Sometimes, however, synapses occur between two dendrites or between a dendrite and a cell body or between an axon terminal and a second axon terminal. A neuron that conducts a signal toward a synapse is called a **presynaptic neuron,** whereas a neuron conducting signals away from a synapse is a **postsynaptic neuron.**

A postsynaptic neuron may have thousands of synaptic junctions on the surface of its dendrites and cell body, so that signals from many presynaptic neurons can affect it.

Glial Cells

Neurons account for only about half of the cells in the human CNS. The remainder are **glial cells** (*glia,* "glue"). Glial cells surround the soma, axon, and dendrites of neurons and provide them with physical and metabolic support. Unlike most neurons, glial cells retain the capacity to divide throughout life. Consequently, many CNS tumors actually originate from glial cells rather than from neurons.

There are several different types of glial cells found in the CNS.



One type is the oligodendrocyte, which forms the myelin sheath of CNS axons.

A second type of glial cell, the **astrocyte,** helps regulate the composition of the extracellular fluid in the CNS by removing potassium ions and neurotransmitters around synapses. Another important function of astrocytes is to stimulate the formation of tight junctions between the cells that make up the walls of capillaries found in the CNS. This forms the **blood–brain barrier,** which is a much more selective filter for exchanged substances than is present between the blood and most other tissues. Astrocytes also sustain the neurons metabolically—for example, by providing glucose and removing ammonia. In developing embryos, astrocytes guide neurons as they migrate to their ultimate destination, and they stimulate neuronal growth by secreting growth factors. In addition, astrocytes have many neuronlike characteristics. For example, they have ion channels, receptors for certain neurotransmitters and the enzymes for processing them, and the capability of generating weak electrical responses. Thus, in addition to all their other roles, it is speculated that astrocytes may take part in information signaling in the brain.

The **microglia,** a third type of glial cell, are specialized, macrophage-like cells that perform immune functions in the CNS, and may also contribute to synapse remodeling and plasticity. Lastly, **ependymal cells** line the fluid-filled cavities within the brain and spinal cord and regulate the production and flow of cerebrospinal fluid. Schwann cells, the glial cells of the PNS, have most of the properties of the CNS glia. Schwann cells produce the myelin sheath of the axons of the peripheral neurons.

Neural Growth and Regeneration

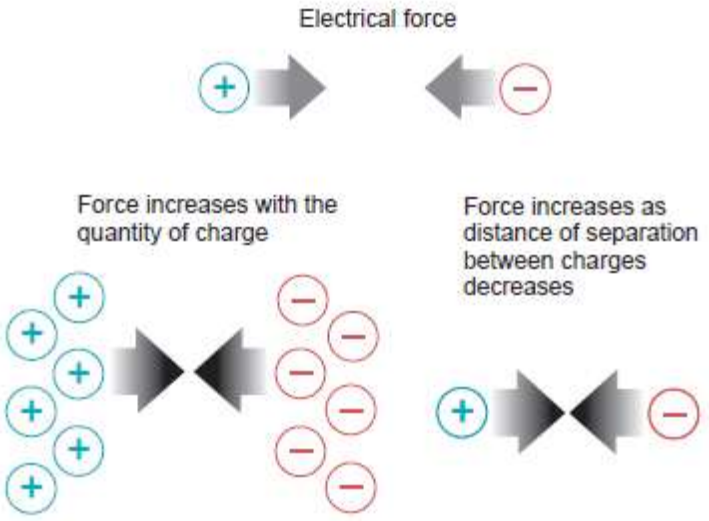
A surprising aspect of development of the nervous system occurs after growth and projection of the axons. Many of the newly formed neurons and synapses degenerate. In fact, as many as 50% to 70% of neurons undergo a programmed self-destruction called **apoptosis** in the developing CNS. Exactly why this seemingly wasteful process occurs is unknown, although neuroscientists speculate that this refines or make small adjustments in order to achieve the best or a desired performance connectivity in the nervous system. Throughout the life span, our brain has an amazing ability to modify its structure and function in response to stimulation or injury, a characteristic known as **plasticity.** This involves both the generation of new neurons and remodeling of synaptic connections, and

is stimulated by exercise and by engaging in cognitively challenging activities. The degree of neural plasticity varies with age. For example, an infant suffering from seizures (uncontrolled excessive neural activity) can have nearly half of the brain removed, and because of extensive remodeling the brain can recover full functionality into adulthood. If the same procedure were performed on an adult, it would result in permanent deficits in the functions served by the excised brain regions. For many neural systems, the critical time window for development occurs at a fairly young age. In visual pathways, for example, regions of the brain involved in processing visual stimuli are permanently impaired if no visual stimulation is received during a critical time, which peaks between 1 and 2 years of age.

Basic Principles of Electricity

The predominant solutes in the extracellular fluid are sodium and chloride ions. The intracellular fluid contains high concentrations of potassium ions and ionized non-penetrating molecules, particularly phosphate compounds and proteins with negatively charged side chains. Electrical phenomena resulting from the distribution of these charged particles occur at the cell's plasma membrane and play a significant role in signal integration and cell-to-cell communication, the two major functions of the neuron.

A fundamental physical principle is that charges of the same type repel each other—positive charge repels positive charge, and negative charge repels negative charge. In contrast, oppositely charged substances attract each other and will move toward each other if not separated by some barrier.

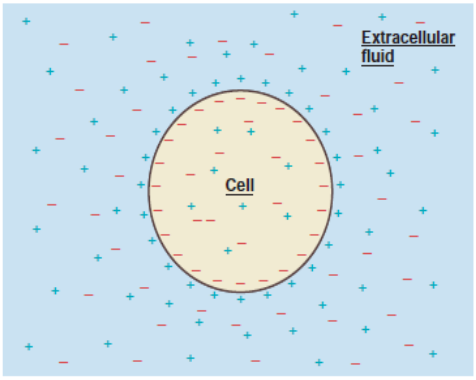


The intracellular and extracellular fluids contain many ions and can therefore carry current. Lipids, however, contain very few charged groups and cannot carry current. Therefore, the lipid layers of the plasma membrane are regions of high electrical resistance separating the intracellular fluid and the extracellular fluid, two low-resistance aqueous compartments.

The Resting Membrane Potential

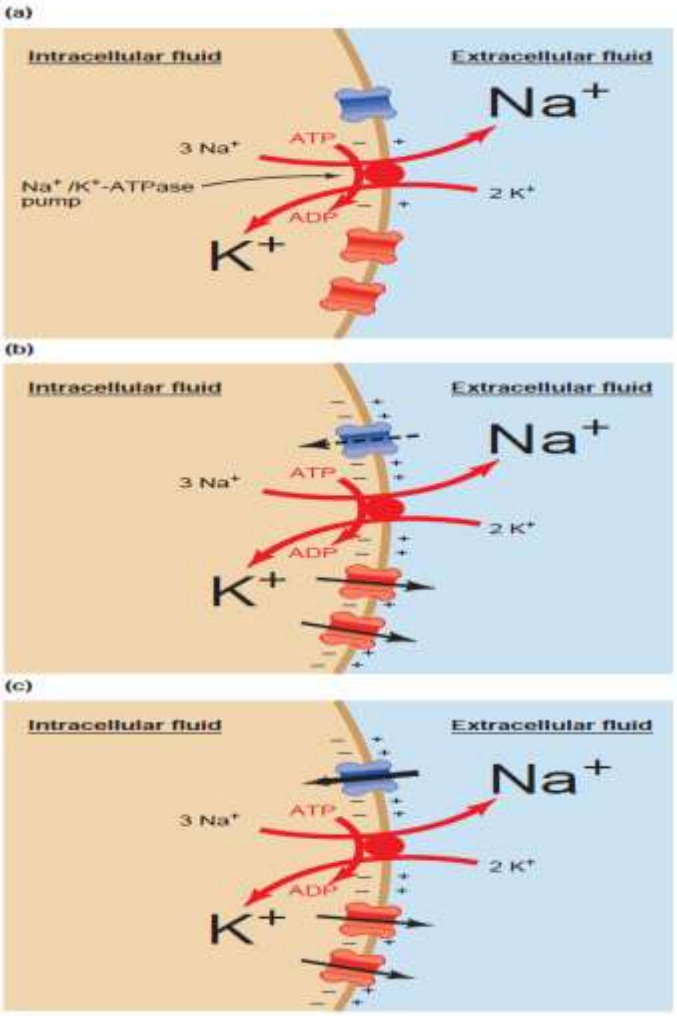
All cells under resting conditions have a potential difference across their plasma membranes, with the inside of the cell negatively charged with respect to the outside.
This potential is the **resting membrane potential.**
The **resting membrane potential** of a neuron is about -70 mV (mV=millivolt) - this means that the inside of the neuron is 70 mV less than the outside The resting membrane potential holds steady unless changes in electrical current alter the potential.

The resting membrane potential exists because of a tiny excess of negative ions inside the cell and an excess of positive ions outside. The excess negative charges inside are electrically attracted to the excess positive charges outside the cell, and vice versa. Thus, the excess charges (ions) collect in a thin shell tight against the inner and outer surfaces of the plasma membrane, whereas the bulk of the intracellular and extracellular fluid remains electrically neutral.



In a resting cell, the number of ions the pump moves equal the number of ions that leak down their concentration and/or electrical gradients. As long as the concentration gradients remain stable and the ion permeability of the plasma membrane do not change, the electrical potential across the resting membrane will also remain constant.

Thus far, we have described the membrane potential as due purely and directly to the passive movement of ions down their electrochemical gradients, with the concentration gradients maintained by membrane pumps. However, the Na /K -ATPase pump not only maintains the concentration gradients for these ions but also helps to establish the membrane potential more directly. The Na /K -ATPase pumps actually move three sodium ions out of the cell for every two potassium ions that they bring in. This unequal transport of positive ions makes the inside of the cell more negative than it would be from ion diffusion alone. When a pump moves net charge across the membrane and contributes directly to the membrane potential, it is known as an **electrogenic pump.**



First, the action of the Na /K -ATPase pump sets up the concentration gradients for Na and K (**a**). These concentration gradients determine the equilibrium potentials for the two ions— that is, the value to which each ion would bring the membrane potential if it were the only permeating ion. Simultaneously, the pump has a small electrogenic effect on the membrane due to the fact that three sodium ions are pumped out for every two potassium ions pumped in. The next step shows that initially there is a greater flux of K out of the cell than Na into the cell (**b**). This is because in a resting membrane there is a greater permeability to K than there is to Na. Because there is greater net efflux than influx of positive ions during this step, a significant negative membrane potential develops, with the value approaching that of the K equilibrium potential. In the steady state resting neuron, the flux of ions across the membrane reaches a dynamic balance (**c**).

Because the membrane potential is not equal to the equilibrium potential for either ion, there is a small but steady leak of Na into the cell and K out of the cell.

The concentration gradients do not dissipate over time, however, because ion movement by the Na /K -ATPase pump exactly balances the rate at which the ions leak in the opposite direction. Now let's return to the behavior of chloride ions in excitable cells. The plasma membranes of many cells also have Cl channels but do not contain chloride ion pumps. Therefore, in these cells, Cl concentrations simply shift until the equilibrium potential for Cl is equal to the resting membrane potential. In other words, the negative membrane potential determined by Na and K moves Cl out of the cell, and the Cl concentration inside the cell becomes lower than that outside. This concentration gradient produces a diffusion of Cl back into the cell that exactly opposes the movement out because of the electrical potential.

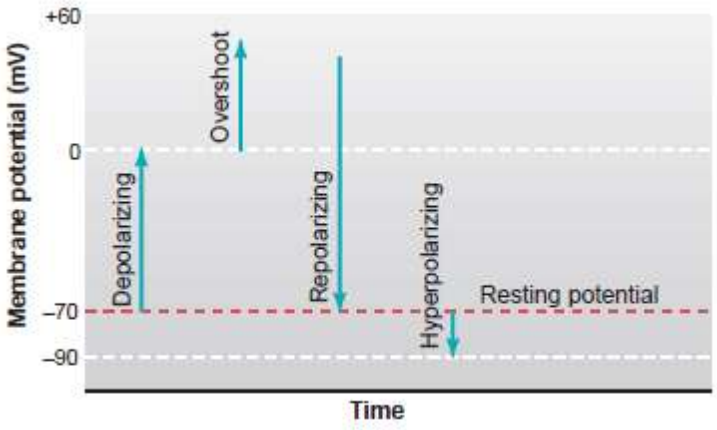
In contrast, some cells have a non-electrogenic active transport system that moves Cl out of the cell, generating a strong concentration gradient. In these cells, the Cl equilibrium

potential is negative to the resting membrane potential, and net Cl diffusion into the cell contributes to the excess negative charge inside the cell; that is, net Cl diffusion makes the membrane potential more negative than it would be if only Na and K were involved.

Action Potentials

You have just learned that all cells have a resting membrane potential due to the presence of ion pumps and leak channels in the cell membrane. In addition, however, some cells have another group of ion channels that can be gated (opened or closed) under certain conditions. Such channels give a cell the ability to produce electrical signals that can transmit information between different regions of the membrane. This property is known as **excitability,** and such membranes are called **excitable membranes.** Cells of this type include all neurons and muscle cells, as well as some endocrine, immune, and reproductive cells. The electrical signals occur in two forms: graded potentials and action potentials. Graded potentials are important in signaling over short distances, whereas action potentials are long-distance signals that are particularly important in neuronal and muscle cell membranes.

The terms *depolarize*, *repolarize*, and *hyperpolarize* are used to describe the direction of changes in the membrane potential relative to the resting potential.



The resting membrane potential is "polarized," simply meaning that the outside and inside of a cell have a different net charge. The membrane is **depolarized** when its potential becomes less negative (closer to zero) than the resting level. **Overshoot** refers to a reversal of the membrane potential polarity—that is, when the inside of a cell becomes positive relative to the outside. When a membrane potential that has been depolarized is returning toward the resting value, it is **repolarizing.** The membrane is **hyperpolarized** when the potential is more negative than the resting level. The changes in membrane potential that the neuron uses as signals occur because of changes in the permeability of the cell membrane to ions. When a neuron receives a chemical signal from a neighboring neuron, for instance, some gated channels will open, allowing greater ionic current across the membrane. The greater movement of ions down their electrochemical gradient alters the membrane potential so that it is either depolarized or hyperpolarized relative to the resting state.

In addition to the movement of ions on the inside and the outside of the cell, charge is lost across the membrane because the membrane is permeable to ions through open membrane

channels. The result is that the change in membrane potential decreases as the distance increases from the initial site of the potential change.

In fact, plasma membranes are so leaky to ions that these currents die out almost completely within a few millimeters of their point of origin. Because of this, local current

is **decremental;** that is, the flow of charge decreases as the distance from the site of origin of the graded potential increases.

Because the electrical signal decreases with distance, graded potentials (and the local current they generate) can function as signals only over very short distances (a few millimeters). However, if additional stimuli occur before the graded potential has died away, these can add to the depolarization from the first stimulus. This process, termed **summation,** is particularly important for sensation.

Action potentials are very different from graded potentials. They are large alterations in the membrane potential; the membrane potential may change by as much as 100 mV. For example, a cell might depolarize from -70 to +30 mV, and then repolarize to its resting potential. Action potentials are generally very rapid (as brief as 1–4 milliseconds) and may repeat at frequencies of several hundred per second. The propagation of action potentials down the axon is the mechanism the nervous system uses to communicate over long distances. What properties of ion channels allow them to generate these large, rapid changes in membrane potential, and how are action potentials propagated along an excitable membrane? These questions are addressed in the following sections.

4nd Lec.

Smooth Muscle

Physiology 2nd year students

AHMED HAMED ATAIMISH

Smooth Muscle

Two characteristics are common to all smooth muscles. They lack the cross-striated banding pattern found in skeletal and cardiac fibers (which makes them "smooth"), and the nerves to them are part of the autonomic division of the nervous system rather than the somatic division. Thus, smooth muscle is not normally under direct voluntary control.

Smooth muscle, like skeletal muscle, uses cross-bridge movements between actin and myosin filaments to generate force, and calcium ions to control cross-bridge activity. Smooth muscle can generally be divided into two major types:

1- *Multi-unit smooth muscle* and
2- *Unitary* (or *single-unit*) *smooth muscle.*

Multi-Unit Smooth Muscle

This type of smooth muscle is composed of discrete, separate smooth muscle fibers. Each fiber operates independently of the others and often is innervated by a single nerve ending, as occurs for skeletal muscle fibers. Furthermore, the outer surfaces of these fibers, like those of skeletal muscle fibers, are covered by a thin layer of basement membrane-like substance, a mixture of fine *collagen* and *glycoprotein* that helps insulate the separate fibers from one another.

The most important characteristic of **multi-unit smooth muscle** fibers is that each fiber can contract independently of the others, and their control is exerted mainly by nerve signals. In contrast, a major share of control of

unitary smooth muscle is exerted by non-nervous stimuli.

Some examples of multi- unit smooth muscle are the ciliary muscle of the eye and the iris muscle of the eye

Unitary Smooth Muscle

This type is also called *syncytial smooth muscle* or *visceral smooth muscle.* The term "unitary" is confusing because it does not mean single muscle fibers. Instead, it means a mass of hundreds to thousands of smooth muscle fibers that contract together as a single unit. The fibers usually are arranged in sheets or bundles, and their cell membranes are adherent to one another at multiple points so that force generated in one muscle fiber can be transmitted to the next. In addition, the cell membranes are joined by many *gap junctions* through which ions can flow freely from one muscle cell to the next so that action potentials or simple ion flow without action potentials can travel from one fiber to the next and cause the muscle fibers to contract together. This type of smooth muscle is also known as *syncytial smooth muscle* because of its syncytial interconnections among fibers. It is also called *visceral smooth muscle* because it is found in the walls of most viscera of the body, including the gastrointestinal tract, bile ducts, ureters, uterus, and many blood vessels.

One additional characteristic of single-unit smooth muscles is that a contractile response can often be induced by stretching the muscle. In several hollow organs—the stomach, for example—stretching the smooth muscles in the walls of the organ as a result of increases in the volume of material in the lumen initiates a contractile response.

Smooth muscle contains both *actin* and *myosin filaments*, having chemical characteristics similar to those of the actin and myosin filaments in skeletal muscle. It does not contain the normal troponin complex that is required in the control of skeletal muscle contraction, so the mechanism for control of contraction is different. The thin filaments are anchored either to the plasma membrane or to cytoplasmic structures known as **dense bodies,** which are functionally similar to the Z lines in skeletal muscle fibers.

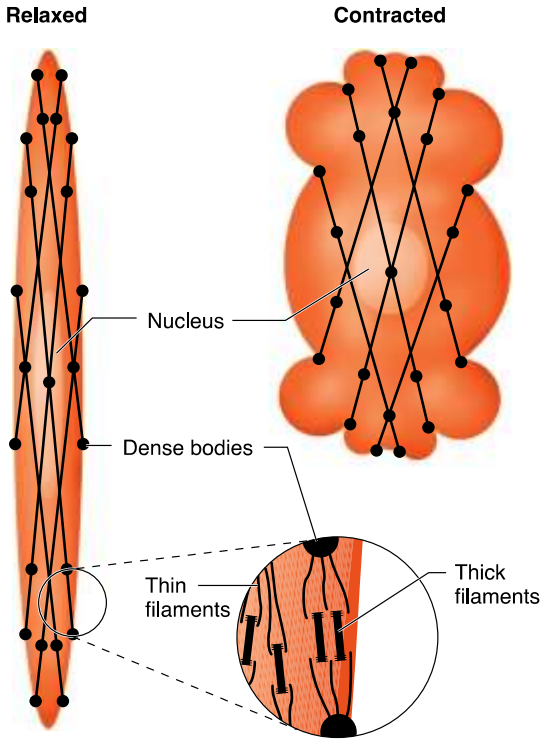
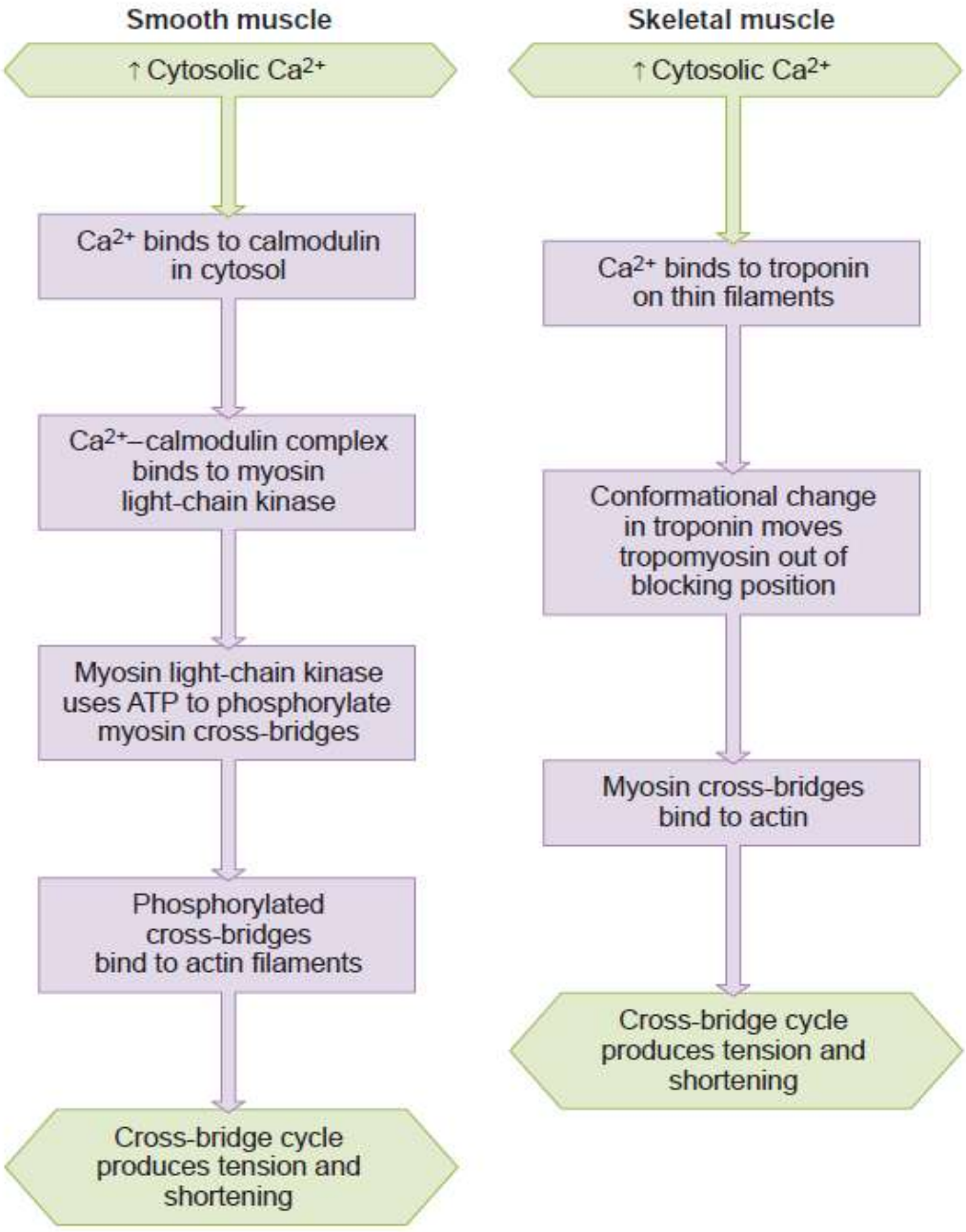


Figure 1: *Thick and thin filaments in smooth muscle are arranged in diagonal chains that are anchored to the plasma membrane or to dense bodies within the cytoplasm. When activated, the thick and thin filaments slide past each other, causing the smooth muscle fiber to shorten and thicken.*



Chemical studies have shown that actin and myosin filaments derived from smooth muscle interact with each other in much the same way that they do in skeletal muscle. Further, the contractile process is activated by calcium ions, and adenosine triphosphate (ATP) is degraded to adenosine diphosphate (ADP) to provide the energy for contraction.

Smooth Muscle Contraction and Its Control

Because smooth muscle lacks the Ca^{++}-binding protein troponin, tropomyosin is never held in a position that blocks cross-bridge access to actin. Thus, the thin filament is not the main switch that regulates cross-bridge cycling. *Instead, cross-bridge cycling in smooth muscle is controlled by a Ca^{++}-regulated enzyme that phosphorylates myosin.* Only the phosphorylated form of smooth muscle myosin can bind to actin and undergo cross-bridge cycling.

The following sequence of events occurs after an increase in cytosolic Ca^{++} in a smooth muscle fiber:

(1) Ca^{++} binds to calmodulin, a Ca^{++}-binding protein that is present in the cytosol of most cells and whose structure is related to that of troponin.

(2) The Ca^{++}–calmodulin complex binds to another cytosolic protein, **myosin light-chain kinase,** thereby activating the enzyme.

(3) Active myosin light-chain kinase then uses ATP to phosphorylate myosin light chains in the globular head of myosin.

(4) Phosphorylation of myosin drives the cross-bridge away from the thick filament backbone, allowing it to bind to actin.

(5) Cross-bridges go through repeated cycles of force generation as long as myosin light chains are phosphorylated.

A key difference here is that Ca^{++}-mediated changes in the thick filaments turn on cross-bridge activity in smooth muscle, whereas in striated muscle, Ca^{++} mediates changes in the thin filaments.

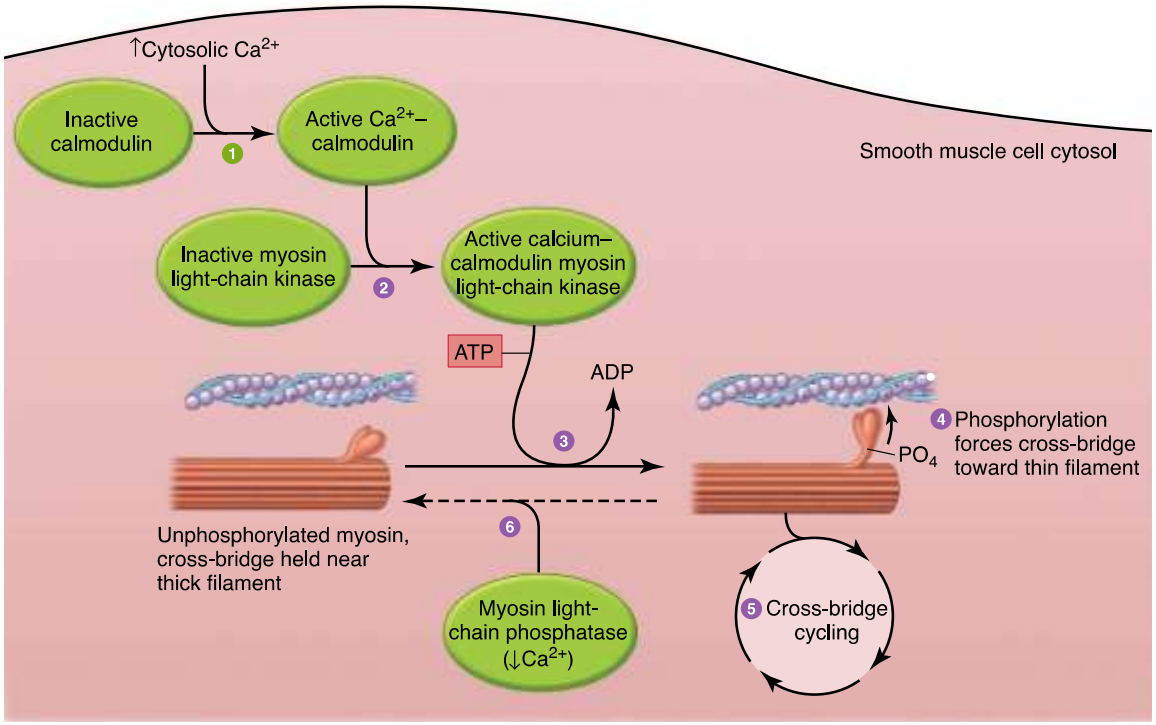


Figure : *Activation of smooth muscle contraction by* Ca^{++}

The smooth muscle form of myosin has a very low rate of ATPase activity, on the order of 10 to 100 times less than that of skeletal muscle myosin. Because the rate of ATP hydrolysis determines the rate of cross-bridge cycling and shortening velocity, smooth muscle shortening is much slower than that of skeletal muscle. Due to this slow rate of energy usage, smooth muscle does not undergo fatigue during prolonged periods of activity.

To relax a contracted smooth muscle, myosin must be dephosphorylated because dephosphorylated myosin is unable to bind to actin. This

dephosphorylation is mediated by the enzyme **myosin light-chain phosphatase,** which is continuously active in smooth muscle during periods of rest and contraction. When cytosolic Ca^{++} concentration increases, the rate of myosin phosphorylation by the activated kinase exceeds the rate of dephosphorylation by the phosphatase and the amount of phosphorylated myosin in the cell increases, producing an increase in tension. When the cytosolic Ca^{++} concentration decreases, the rate of phosphorylation decreases below that of dephosphorylation and the amount of phosphorylated myosin decreases, producing relaxation.

In some smooth muscles, when stimulation is persistent and the cytosolic Ca^{++} concentration remains elevated, the rate of ATP hydrolysis by the cross-bridges declines even though isometric tension is maintained. This condition is known as the **latch state** and a smooth muscle in this state can maintain tension in an almost rigor like state without movement. Dissociation of cross-bridges from actin does occur in the latch state, but at a much slower rate. The net result is the ability to maintain tension for long periods of time with a very low rate of ATP consumption. A good example of the usefulness of this mechanism is seen in sphincter muscles of the gastrointestinal tract, where smooth muscle must maintain contraction for prolonged periods.

Removal of Ca^{++} from the cytosol to bring about relaxation is achieved by the active transport of Ca^{++} back into the sarcoplasmic reticulum as well as out of the cell across the plasma membrane. The rate of Ca^{++} removal in smooth muscle is much slower than in skeletal muscle.

The degree of activation also differs between muscle types. In skeletal muscle, a single action potential releases sufficient Ca^{++} to saturate all troponin sites on the thin filaments, whereas only a portion of the cross-bridges are activated in a smooth muscle fiber in response to most stimuli. Therefore, the tension generated by a smooth muscle cell can be *graded* by varying cytosolic Ca^{++} concentration. The greater the increase in Ca^{++} concentration, the greater the number of cross-bridges activated and the greater the tension.

Membrane Activation

Many inputs to a smooth muscle plasma membrane can alter the contractile activity of the muscle. This contrasts with skeletal muscle, in which membrane activation depends only upon synaptic inputs from somatic neurons. Some inputs to smooth muscle increase contraction, and others inhibit it. Moreover, at any one time, the smooth muscle plasma membrane may be receiving multiple inputs, with the contractile state of the muscle dependent on the relative intensity of the various inhibitory and excitatory stimuli. All these inputs influence contractile activity by altering cytosolic Ca^{++} concentration.

Smooth muscle is different from skeletal muscle in another important way with regard to electrical activity and cytosolic Ca^{++} concentration. Smooth muscle cytosolic Ca^{++} concentration can be increased (or decreased) by graded depolarizations (or hyperpolarizations) in membrane potential, which increase or decrease the number of open Ca^{++} channels.

Whereas some neurotransmitters enhance contractile activity, others decrease contractile activity. This is different than in skeletal muscle, which receives only excitatory input from its motor neurons; smooth muscle tension can be either increased or decreased by neural activity.

Moreover, a given neurotransmitter may produce opposite effects in different smooth muscle tissues. For example, norepinephrine, the neurotransmitter released from most postganglionic sympathetic neurons, enhances contraction of most vascular smooth muscle by acting on α adrenergic receptors. By contrast, the same neurotransmitter produces relaxation of airway (bronchiolar) smooth muscle by acting on B2 - adrenergic receptors. Thus, the type of response (excitatory or inhibitory) depends not on the chemical messenger, but on the receptors the chemical messenger binds to in the membrane and on the intracellular signaling mechanisms those receptors activate.

In addition to receptors for neurotransmitters, smooth muscle plasma membranes contain receptors for a variety of hormones. Binding of a hormone to its receptor may lead to either increased or decreased contractile activity.

Local Factors

Local factors, including **paracrine signals**, **acidity, oxygen and carbon dioxide concentration, osmolarity**, and the **ionic composition** of the extracellular fluid, can also alter smooth muscle tension. Responses to local factors provide a means for altering smooth muscle contraction in response to changes in the muscle's immediate internal environment, which can lead to regulation that is independent of long-distance signals from nerves and hormones.

Many of local factors induce smooth muscle relaxation. Nitric oxide (NO) is one of the most commonly encountered paracrine compounds that produce smooth muscle relaxation. NO is released from some axon terminals as well as from a variety of epithelial and endothelial cells. Because of the short life span of this reactive molecule, it acts in a paracrine manner, influencing only those cells that are very near its release site. Some smooth muscles can also respond by contracting when they are stretched. Stretching opens mechanically gated ion channels, leading to membrane depolarization. The resulting contraction opposes the forces acting to stretch the muscle.

Table 1: *Inputs Influencing Smooth Muscle Contractile Activity*

Spontaneous electrical activity in the plasma membrane of the muscle cell
Neurotransmitters released by autonomic neurons
Hormones
Locally induced changes in the chemical composition (paracrine factors, acidity, oxygen, osmolarity, and ion concentrations) of the extracellular fluid surrounding the cell
Stretch

Lec. 5

Cardiac Muscle

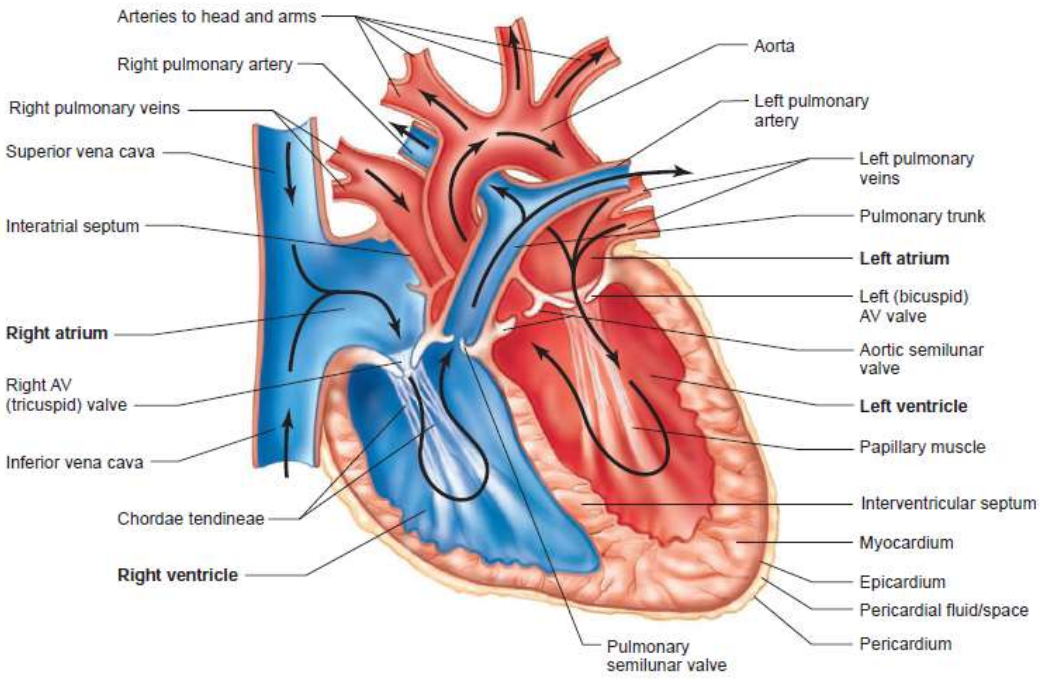
2nd year Students

Ahmed Hamed Ataimish

Anatomy of the Heart

The heart is a muscular organ enclosed in a protective fibrous sac, the **pericardium,** and located in the chest. A fibrous layer is also closely affixed to the heart and is called the **epicardium.** The extremely narrow space between the pericardium and the epicardium is filled with a watery fluid that serves as a lubricant as the heart moves within the sac.

The wall of the heart, the **myocardium,** is composed primarily of cardiac muscle cells. The inner surface of the cardiac chambers, as well as the inner wall of all blood vessels, is lined by a thin layer of cells known as **endothelial cells,** or **endothelium.**



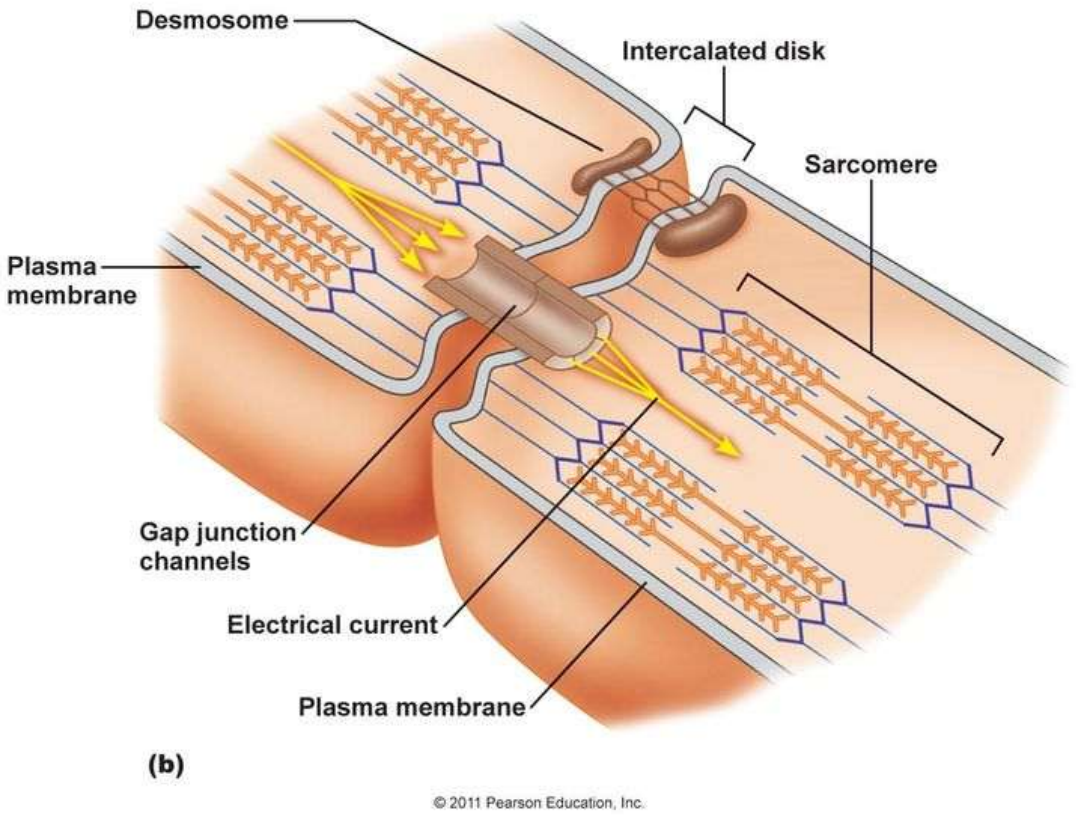
Cardiac Muscle

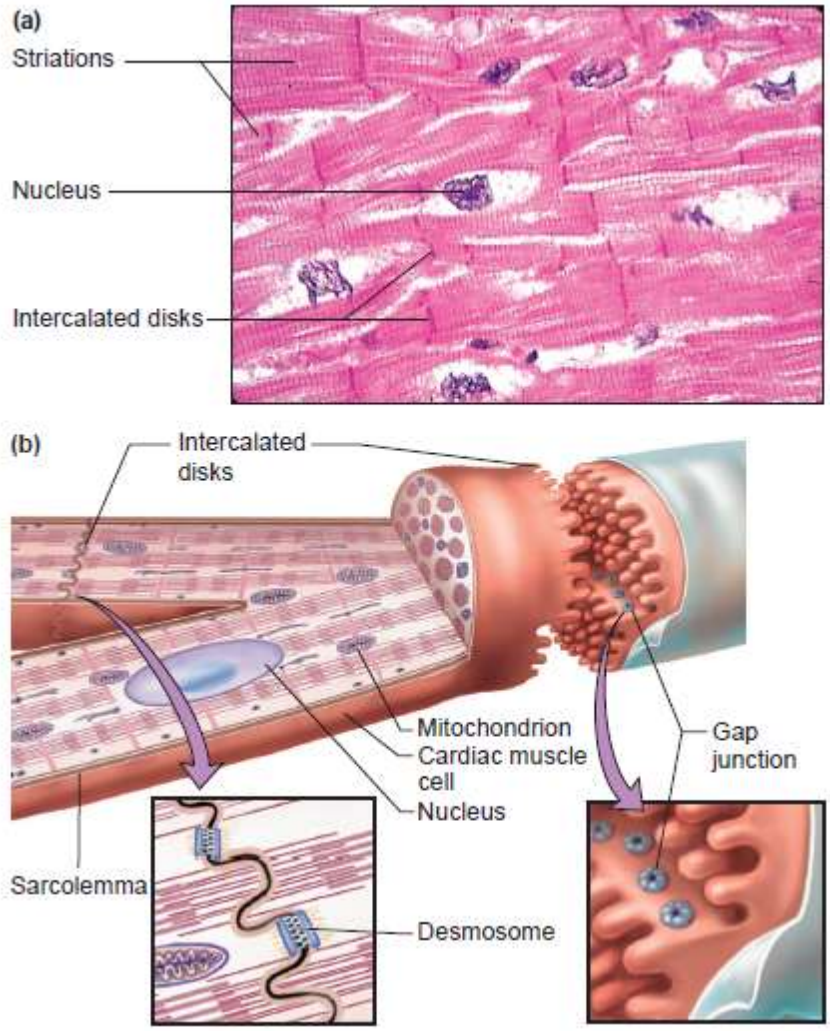
Cellular Structure of Cardiac Muscle

The third general type of muscle, cardiac muscle, is found only in the heart. Cardiac muscle combines properties of both skeletal and smooth

muscle. Like skeletal muscle, it has a striated appearance due to regularly repeating sarcomeres composed of myosin-containing thick filaments interdigitating with thin filaments that contain actin. Troponin and tropomyosin are also present in the thin filament, and they have the same functions as in skeletal muscle. Cellular membranes include a T-tubule system and associated Ca^{++} -loaded sarcoplasmic reticulum.

Like smooth muscle cells, individual cardiac muscle cells are relatively small (100 mm long and 20 mm in diameter) and generally contain a single nucleus. Adjacent cells are joined end to end at structures called **intercalated disks,** within which are desmosomes (also known as a **macula adherens)** which is a cell structure specialized for cell-to-cell adhesion that hold the cells together and to which the myofibrils are attached.

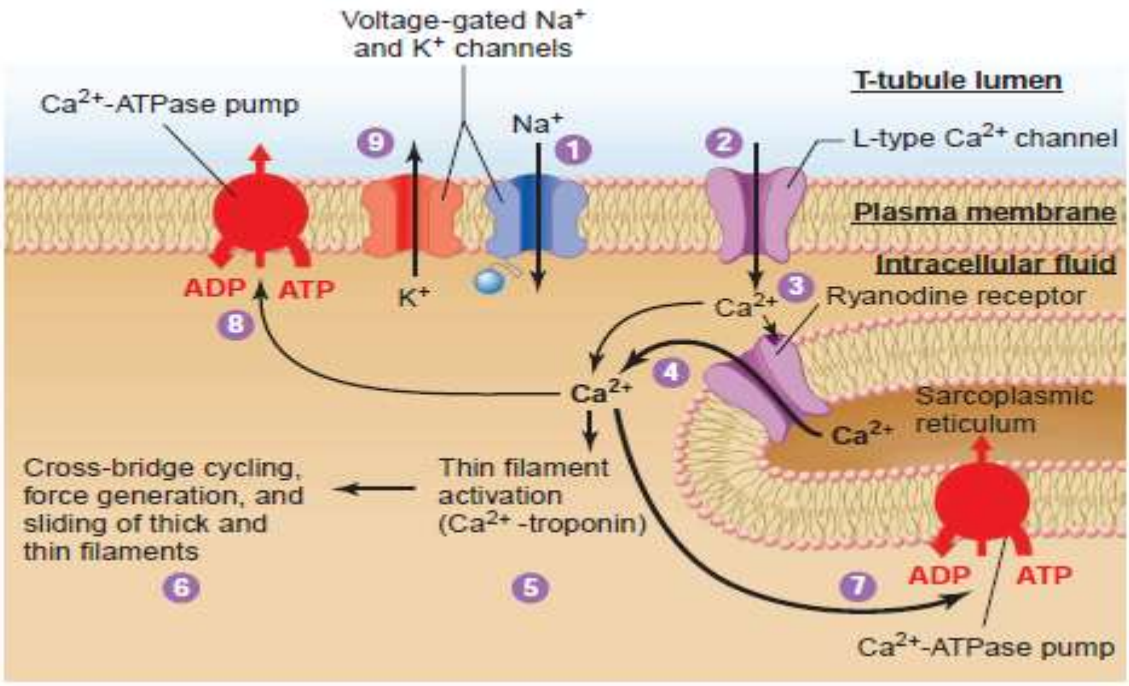




Also found within the intercalated disks are gap junctions similar to those found in single-unit smooth muscle. Cardiac muscle cells also are arranged in layers and surround hollow cavities—in this case, the blood-filled chambers of the heart. When muscle in the walls of cardiac chambers contracts, it acts like a squeezing fist and exerts pressure on the blood inside.

Excitation–Contraction Coupling in Cardiac Muscle

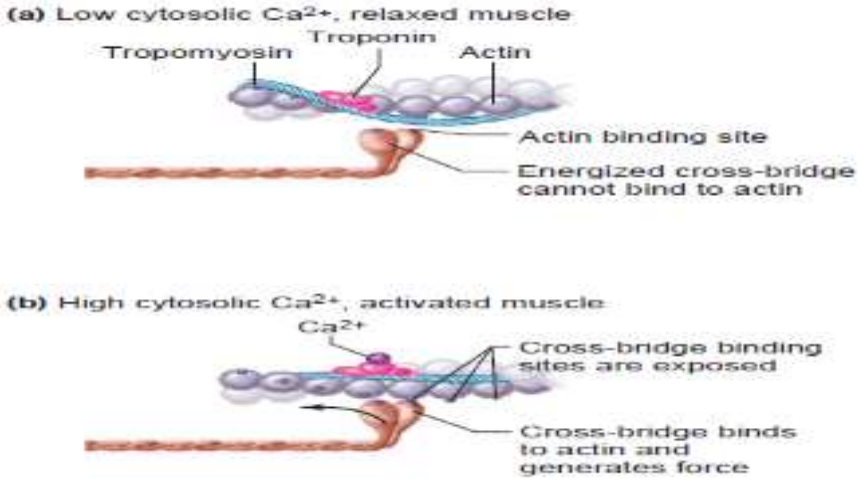
As in skeletal muscle, contraction of cardiac muscle cells occurs in response to a membrane action potential that propagates through the T-tubules, but the mechanisms linking that excitation to the generation of force exhibit features of both skeletal and smooth muscles.

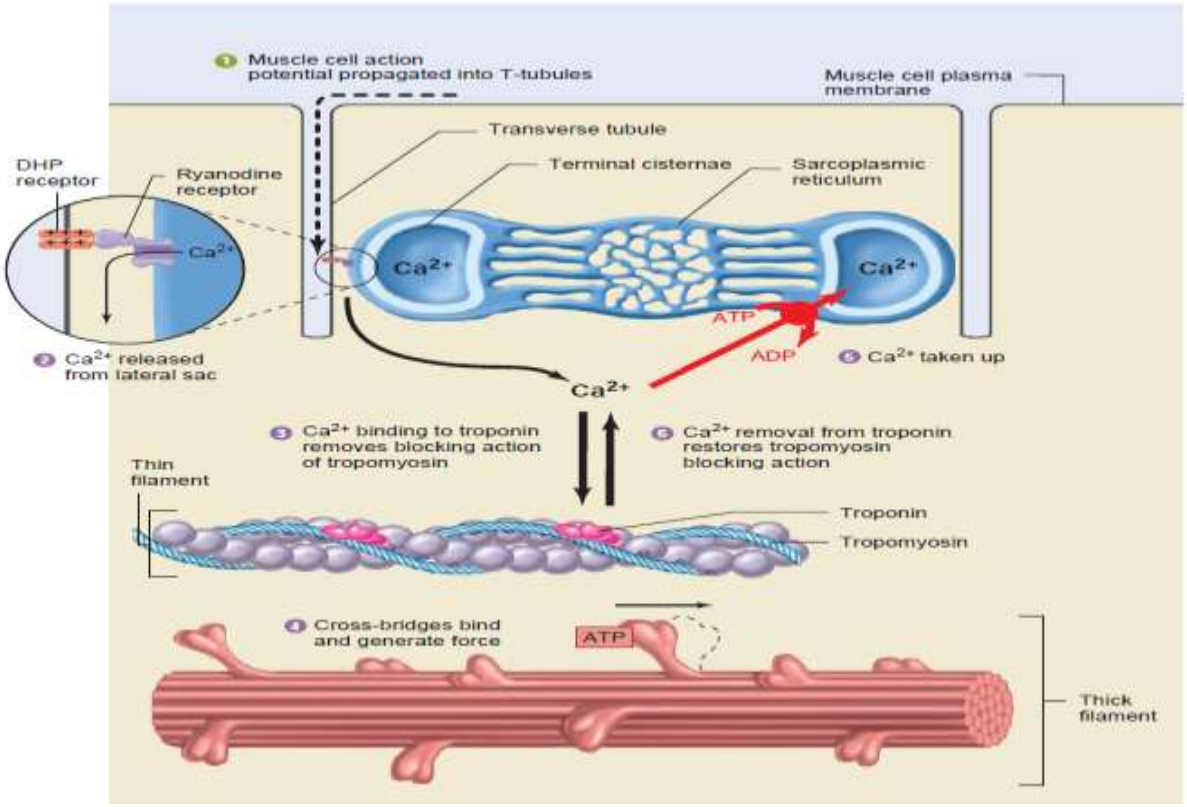


1- The membrane is depolarized by Na+ entry as an action potential begins.
2- Depolarization opens L-type Ca2+ channels in the T-tubules.
3- A small amount of "trigger" Ca2+ enters the cytosol, contributing to cell depolarization. That trigger Ca2+ binds to, and opens, ryanodine receptor Ca2+ channels in the sarcoplasmic reticulum membrane.
4- Ca2+ flows into the cytosol, raising the Ca2+ concentration.
5- Binding of Ca2+ to troponin exposes cross-bridge binding sites on thin filaments.
6- Cross-bridge cycling causes force generation and sliding of thick and thin filaments.
7- Ca2+-ATPase pumps return Ca2+ to the sarcoplasmic reticulum.
8- Ca2+-ATPase pumps (and also Na+/Ca2+ exchangers) remove Ca2+ from the cell.
9- The membrane is repolarized when K+ exits to end the action potential.

Depolarization during cardiac muscle cell action potentials is in part due to an influx of Ca++ through specialized voltage-gated channels. These Ca++ channels are known as **L-type Ca++ channels** (named for their Long-lasting current)

Not only does this entering Ca++ participate in depolarization of the plasma membrane and cause a small increase in cytosolic Ca++ concentration, but it also serves as a trigger for the release of a much larger amount of Ca++ from the sarcoplasmic reticulum. This occurs because ryanodine receptors in the cardiac sarcoplasmic reticulum terminal cisternae are Ca++ channels; but rather than being opened directly by voltage as in skeletal muscle, they are opened by the binding of trigger Ca++ in the cytosol. Once cytosolic Ca++ is elevated, thin filament activation, cross-bridge cycling, and force generation occur by the same basic mechanisms described for skeletal muscle.





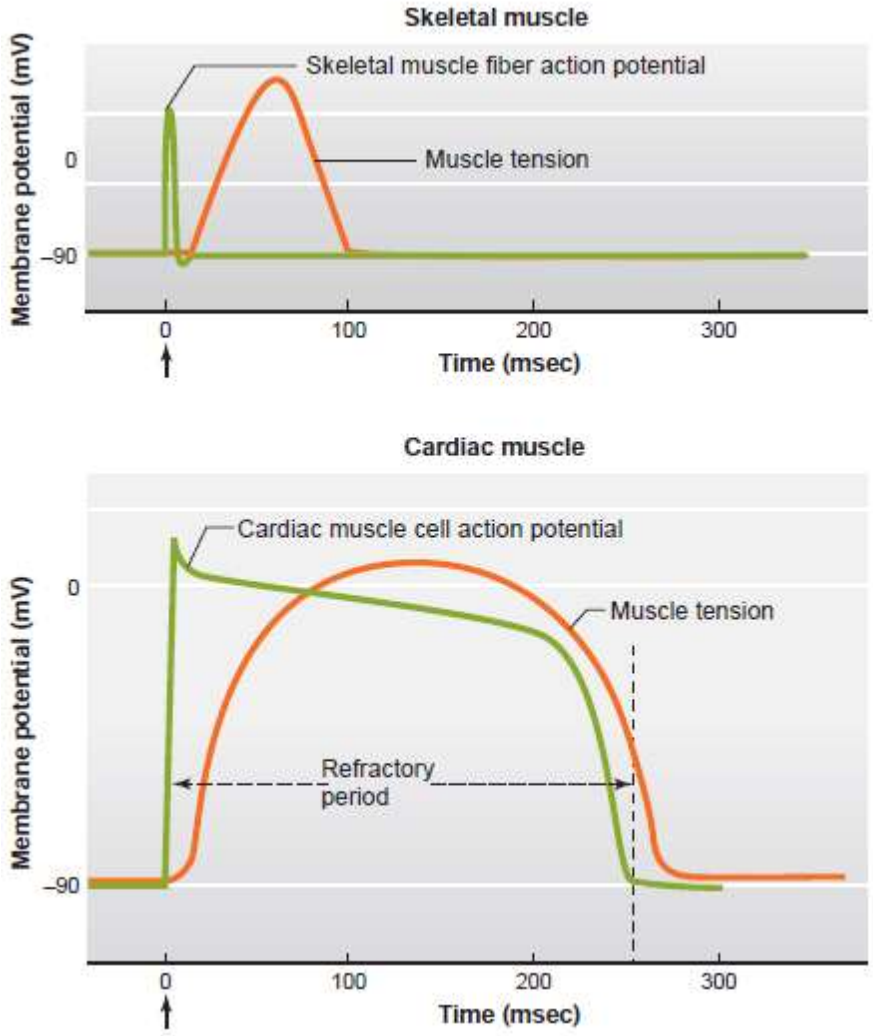
Thus, even though most of the Ca++ that initiates cardiac muscle contraction comes from the sarcoplasmic reticulum, the process—unlike that in skeletal muscle—is dependent on the movement of extracellular Ca++ into the cytosol.

Contraction ends when the cytosolic Ca++ concentration is restored to its original extremely low resting value by primary active Ca++-ATPase pumps in the sarcoplasmic reticulum and sarcolemma and Na/Ca++ counter-transporters in the sarcolemma. The amount of Ca++ returned to the extracellular fluid and into the sarcoplasmic reticulum exactly matches the amounts that entered the cytosol during excitation.

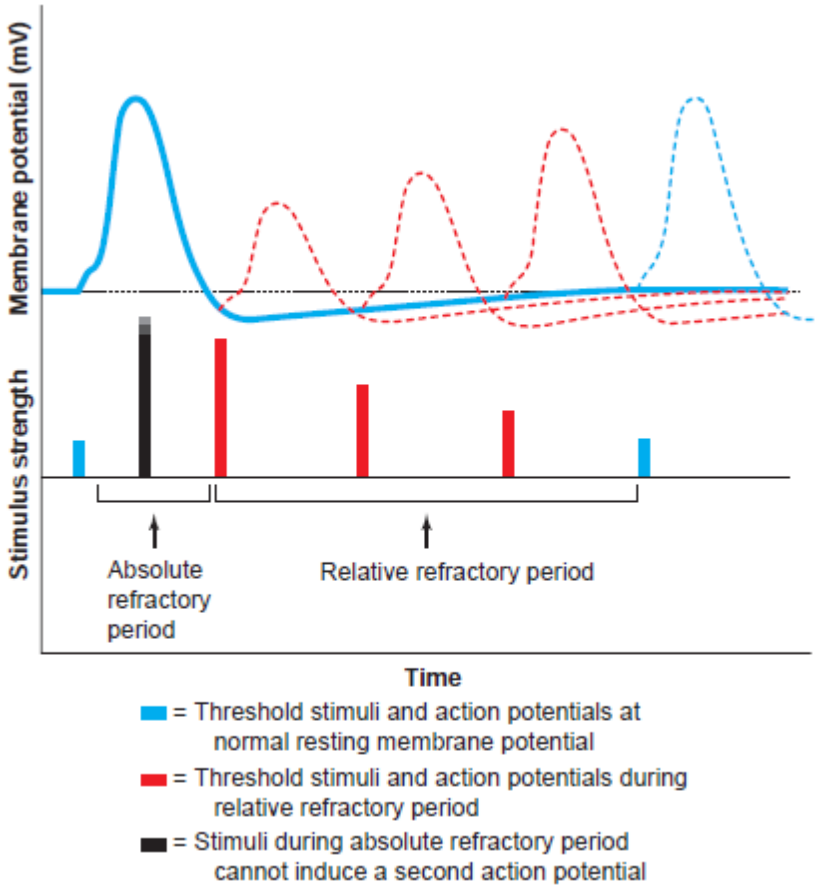
During a single twitch contraction of cardiac muscle in a person at rest, the amount of Ca++ entering the cytosol is only sufficient to expose about 30% of the cross-bridge attachment sites on the thin filament.

However, hormones and neurotransmitters of the autonomic nervous system modulate the amount of Ca++ released during excitation–

contraction coupling, enabling the strength of cardiac muscle contractions to be varied. Cardiac muscle contractions are thus graded in a manner similar to that of smooth muscle contractions. The prolonged duration of L-type Ca++ channel current underlies an important feature of this muscle type—cardiac muscle cannot undergo tetanic contractions. Unlike skeletal muscle, in which the membrane action potential is extremely brief (1–2 msec) and force generation lasts much longer (20–100 msec), in cardiac muscle the action potential and twitch are both prolonged due to the long-lasting Ca++ current.



Because the plasma membrane remains refractory to additional stimuli as long as it is depolarized,



It is not possible to initiate multiple cardiac action potentials during the time frame of a single twitch. This is critical for the heart's function as an oscillating pump, because it must alternate between being relaxed—and filling with blood—and contracting to eject blood.

Every heart cell contracts with every beat of the heart. Beating about once every second, cardiac muscle cells may contract almost 3 billion times in an average life span without resting! Remarkably, despite this enormous workload, the human heart has a limited ability to replace its muscle cells. Recent experiments suggest that only about 1% of heart muscle cells are replaced per year.

A final question to consider is: What initiates action potentials in cardiac muscle?

Certain specialized cardiac muscle cells exhibit pacemaker potentials that generate action potentials spontaneously. Because cardiac cells are linked via gap junctions, when an action potential is initiated by a pacemaker cell, it propagates rapidly throughout the entire heart. A single heartbeat corresponds to the initiation and conduction of a single action potential.

Innervation

The heart receives a rich supply of sympathetic and parasympathetic nerve fibers, the latter contained in the vagus nerves. The sympathetic postganglionic fibers innervate the entire heart and release norepinephrine, whereas the parasympathetic fibers terminate mainly on cells found in the atria and release primarily acetylcholine.

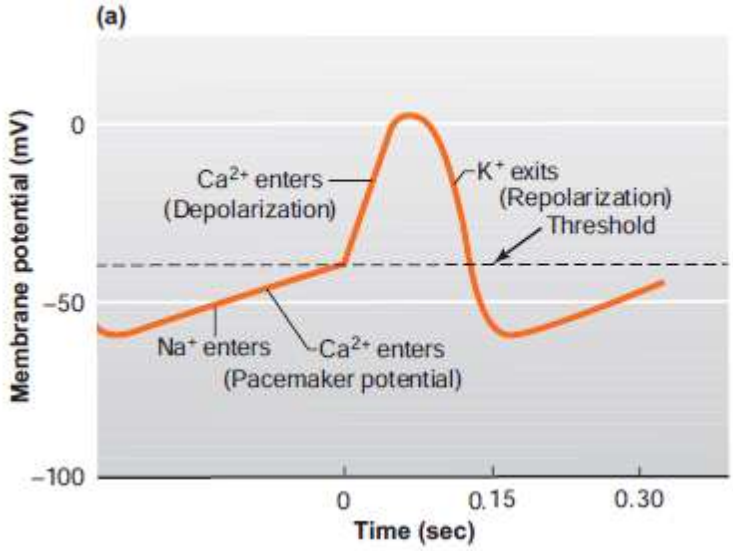
The receptors for norepinephrine on cardiac muscle are mainly B-adrenergic. The hormone epinephrine, from the adrenal medulla, binds to the same receptors as norepinephrine and exerts the same actions on the heart. The receptors for acetylcholine are of the muscarinic type.

In myocardial cells, membrane depolarization causes voltage-gated Ca++ channels in the plasma membrane to open, which results in a flow of Ca++ ions down their electrochemical gradient into the cell. These channels open much more slowly than do Na channels, and, because they remain open for a prolonged period, they are often referred to as **L-type Ca channels** (L long lasting).

The flow of positive calcium ions into the cell just balances the flow of positive potassium ions out of the cell and keeps the membrane depolarized at the plateau value. Ultimately, repolarization does occur due to the eventual inactivation of the L-type Ca++ channels and the

opening of another subtype of K channels. These K channels are similar to the ones described in neurons and skeletal muscle; they open in response to depolarization (but after a delay) and close once the K current has repolarized the membrane to negative values.

In contrast, there are extremely important differences between action potentials of cardiac muscle cells and those in nodal cells of the conducting system.



Three ion channel mechanism, contribute to the pacemaker potential.

First is a progressive reduction in K permeability. The K channels that opened during the repolarization phase of the previous action potential gradually close due to the membrane's return to negative potentials. **Second**, pacemaker cells have a unique set of channels that, unlike most voltage-gated channels, open when the membrane potential is at *negative* values. These nonspecific cation channels conduct mainly an inward, depolarizing, Na current and, because of their unusual gating behavior, have been termed "funny," or **F-type channels.** The third pacemaker channel is a type of Ca++ channel that opens only briefly but contributes inward Ca++ current and an important final depolarizing boost to the

pacemaker potential. These channels are called **T-type Ca++ channels** (T transient). Although SA node and AV node action potentials are basically similar in shape, the pacemaker currents of SA node cells bring them to threshold more rapidly than AV node cells, which is why SA node cells normally initiate action potentials and determine the pace of the heart.

Once the pacemaker mechanisms have brought a nodal cell to threshold, an action potential occurs. The depolarizing phase is caused not by Na but rather by Ca++ influx through L-type Ca++ channels. These Ca++ currents depolarize the membrane more slowly than voltage-gated Na channels, and one result is that action potentials propagate more slowly along nodal-cell membranes than in other cardiac cells. This explains the slow transmission of cardiac excitation through the AV node. As in cardiac muscle cells, the

Long-lasting L-type Ca++ channels prolong the nodal action potential, but eventually they close and K channels open and the membrane is repolarized. The return to negative potentials activates the pacemaker mechanisms once again, and the cycle repeats.