# CELL PHYSIOLOGY

**Objectives after studying this chapter, you should be able to . . .**

1. Describe the structure and functions of the plasma membrane, glycocalyx, and ions channels.
2. Expound the functions of cilia and flagella.
3. Explain the means of cell-to-cell adhesion.
4. Describe how the cells communicate with each other (signal transduction or cell signaling).
5. Expound the ways by which cell regulates the intracellular [$Ca^{2+}$] and [$H^{+}$].

The basic anatomical and functional unit of the body is the cell, and each organ is an aggregate of many different cells held together by intercellular supporting structure. A human cell is enclosed by a cell (or plasma) membrane. Enclosed by that membrane are the cytoplasm, organelles, and a nucleus. There are many different types of cell, each with its own characteristic size, shape, and function.

**The chemical composition of the cell:** **Water** constitutes between 70 and 85 per cent of the total cell mass in which **electrolytes** (potassium, magnesium, phosphate, sulfate, bicarbonate, and small quantities of sodium, chloride, and calcium) are dissolved. In addition, cell contains **proteins** (10%-20% of the cell mass), **lipids** (such as phospholipids, cholesterol which constitute about 2% of the total cell mass), and **carbohydrates** (1% of the total mass).

**Cell membrane (plasma membrane):** The membrane made up **lipids** (primarily of phospholipids, **40%** of the membrane) and **protein** (**60%** of the membrane).

**Functions and characteristics of cell membrane:**

**1.** The **maintenance of cell shape and structure**.

**2. A transport function**. This is brought about by selective permeability to ions and macromolecules, allowing the maintenance of cytosolic ionic composition, osmotic pressure and pH (around 7.2–7.4) and guarding the contents of the cell, which are unique as compared to outside

**3**. **Intercellular communication**, involving signal transduction, i.e. the detection of chemical signals (messengers) from other cells. These signals mediate nerve transmission, hormone release, muscle contraction and the stimulation of growth. This is the result of the binding of signaling molecules by transmembrane receptors.

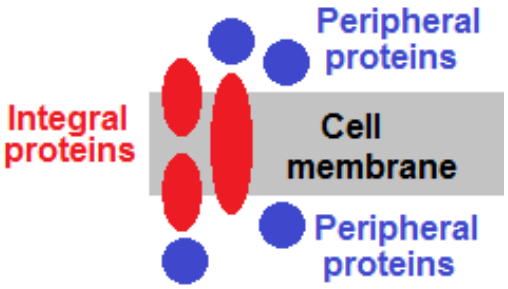
**4. Intercellular adhesion**. This is brought about by the fusion of the membrane with other cell membranes via specialized junctions.

**5. Directed cell movement**.

All these functions differ from cell-to-cell, time-to-time and on the inside as compared to outside the surface membrane,

**The membrane lipids:** The cell membrane consists of two layers of **phospholipids** with **cholesterol** in between the two layers (fluid mosaic model). The presence of cholesterol decreases the fluidity of the membrane, thus making it more stable. The hydrophilic (water-soluble) polar negatively charged heads of the phospholipids are facing the outer and the inner surfaces of the membrane while the two non-polar fatty acid tails of the phospholipids which are hydrophobic (water-insoluble) are facing the core of the membrane. Therefore, lipid-soluble substances (such as $O_2$, $CO_2$, nitrogen, anesthetic gases, steroid hormones, alcohol) cross cell membranes easily because they can dissolve in the hydrophobic lipid bilayer. In contrast, water-soluble substances (such as $Na^+$, $Cl^-$, glucose, urea, $H_2O$) cannot dissolve in the lipid of the membrane, but cross through water-filled channels, or pores, or may be transported by carriers.

The plasma membrane contains cholesterol. The cells in the body with the highest content of cell membrane cholesterol are the Schwann cells, which form insulating layers by wrapping around certain nerve fibers. Their high cholesterol content is believed to be important in this insulating function. Cholesterol has a rigid structure that stabilizes the cell membrane and reduces the natural mobility of the complex lipids in the plane of the membrane. Increasing amounts of cholesterol make it more difficult for lipids and proteins to move in the membrane. The ratio of cholesterol to phospholipids therefore helps in determining the flexibility of a plasma membrane. When there is an inherited defect in this ratio, the flexibility of the cell may be reduced. This could result, for example, in the inability of red blood cells to flex at the middle when passing through narrow blood channels, thereby causing occlusion of these small vessels.




**The membrane proteins:** They are of two types:

**[A] Integral proteins:** They are firmly inserted into the lipid bilayer. Some protrude from one membrane face only, but most are transmembrane proteins that span the entire membrane and protrude on both sides. Protein domains on the extracellular membrane surface are generally involved in cell-cell signaling or interactions. Domains within the membrane, particularly those that form channels and pores, move molecules across the membrane. Domains lying along the cytosolic face of the membrane have a wide range of functions, from anchoring cytoskeletal proteins to the membrane to triggering intracellular signaling pathways. Integral proteins include:

- **Ion channels proteins** permit the passage of ions into or out of the cell.
- **Pumps**, actively transporting ions across the membrane.
- **Transport proteins (carriers),** transporting substances down or against electrochemical gradients.
- **Receptors**, those bind neurotransmitters and hormones.
- **Cell adhesion molecules,** are proteins that attach cells to neighboring cells or provide anchors for the cytoskeleton that give stability to the cell.
- **Antigens and recognition proteins (identifiers).** The cells of the immune system recognize other cells as normal or abnormal based on the presence or absence of characteristic recognition proteins.
- **Enzymes** (catalyzing reactions at the surfaces of the membrane).

**[B] Peripheral (associated) proteins:** They are not embedded in the lipid bilayer, and are located on intra- or extracellular side of the cell membrane phospholipid bilayer. They do not interact with the hydrophobic core of the phospholipid bilayer. Instead they are usually bound to the membrane indirectly by interactions with integral membrane proteins or directly by interactions with lipid polar head groups. Examples of such peripheral membrane proteins are:

- **Cytoskeletal proteins** (spectrin and actin)
- Enzymes that are catalyzing reactions at the surfaces of the membrane such as **protein kinase C**.
- **Certain proteins of the extracellular matrix are localized to the outer surface of the plasma membrane.**

**The general characteristics of transmembrane ion channel proteins:** One of the main ways through which solutes can cross a cell membrane is through channel proteins. They are integral membrane proteins that form a membrane spanning pathway that allows movement of solute molecules across the membrane. The membrane ion channels are distinguished by two important characteristics:

**[1] Specificity:** They are often highly selective for the transport of one or more specific ions or molecules. This is due to the characteristics of the channel itself (such as its diameter, its shape, and the nature of the electrical charges along its inside surfaces).

**[2] Many of the channels can be opened or closed by gates:** Protein channels can be (figure 1):

➔ **Open channels**,

➔ **Gated channels**. Gating of protein channels provides a mean for controlling the permeability of the channels. Opening or closing the gates can be achieved by the conformational change in the shape of the protein molecule itself, this conformational change and consequently the opening and closing gates are controlled by three ways:

**(A) Voltage gating (voltage-gated channel):** In this instance, the molecular conformation of the gate responds to the

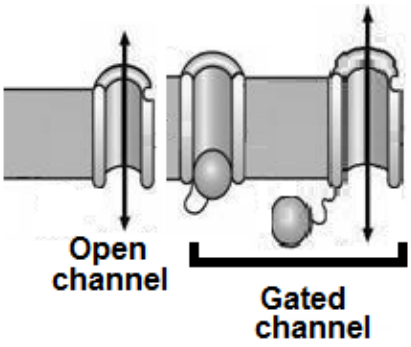



**Figure 1. Types of ion channel proteins.**

electrical potential across the cell membrane. Examples are voltage-gated Na channel, voltage-gated K channel.

**(B) Chemical or ligand gating (chemical or ligand-gated channel):** Some protein gates are opened or closed by the binding of another molecule with the protein, this binding may be directly or indirectly through receptors attached to the protein channel. By either way, this binding causes a conformational change in the protein molecule that opens or closes the gate. Examples of such channel are the acetylcholine-gated channels, Ca-sensitive k channel.

**(D) Physical gating (physical-gated channel):** Some protein channel gates are opened by physical stimulus such as stretch temperature, or pressure. Examples of such channels are those found in the membrane of pressure receptors.

**The receptors:** They are proteins or glycoproteins. They are located on the surface of cell, or within the cytoplasm or nucleus. Receptors have the properties of:

- **Specificity** and ensures that cells recognize and respond only to certain appropriate signals.
- **High affinity** (bind their agonists even the agonists are present at very low concentrations).
- **Limited capacity** and hence may become saturated when the concentration of agonist is high.
- **Down & up-regulation**, Current evidence suggests that when a chemical messenger is present in excess, the number of active receptors decreases (**down-regulation**), whereas in the presence of a deficiency of the chemical messenger, there is an increase in the number of active receptors (**up-regulation**). Prolactin, LHRH, and angiotensin II in its action on the adrenal cortex are exception; they increase rather than decrease the number of their receptors. These effects on receptors are important in explaining such phenomena as denervation hypersensitivity, tolerance to morphine, and decrease sensitivity to insulin in diabetes.

In addition, cells may temporarily activate or inactivate receptors by adding or removing phosphate or by sequestering them in vesicles to prevent access to agonists. Inactivation of receptors is called **adaptation** or desensitization.

**Receptor diseases:** Many diseases are due to mutation of genes: Receptor mutations that cause disease have been reported for vitamin D, Insulin receptor, Thyroid hormone receptor, Vasopressin receptor.

**Classification of cell membrane receptors:**

Cell membrane receptors are classified according to the signal transduction mechanism involved into Figure 2):

**1. Gated channel-linked receptors** (ionotropic), which are bonded directly to the gated ion channels. Examples include acetylcholine receptors, glutamate and gamma-aminobutyric acid (GABA) receptors.

**2. G-protein-linked receptors**, which are further discussed later.

**3 Catalysis-linked receptors**, which possess a cytoplasmic catalytic region that usually behaves as enzyme.

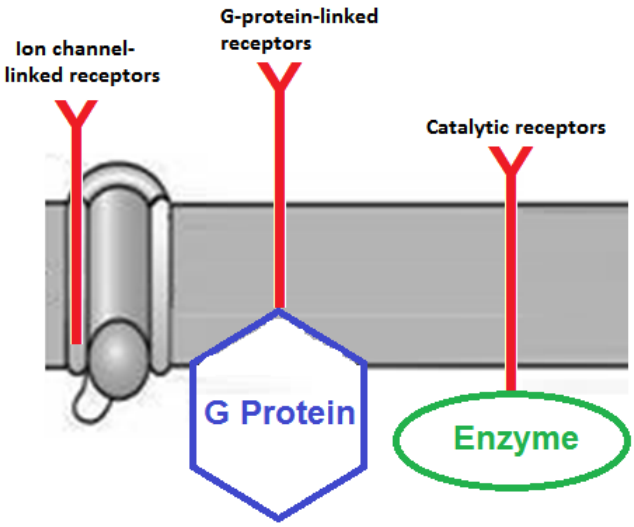



**Figure 2: Types of cell membrane receptors.**

**Glycocalyx:** The carbohydrate molecules attached to the integral or peripheral proteins (glycoproteins) and to the outer surface of cell membrane phospholipid (glycolipids) form a coat called glycocalyx (figure 3 which has several important functions such as:

**A.** Many of the carbohydrate moieties are negatively charged which gives most cells an overall negative surface charge that **repels other negative objects.**

**B.** The carbohydrate moieties of some cells attaches to the carbohydrate moieties of other cells, thus **attaching the cells to each other** as well.

**C.** Some carbohydrates act as **receptor** substance for binding hormones like insulin that stimulates specific types of activity in the cell.

**D.** Some **enter into immune reactions.** They are antigens markers that identify the cells of an individual as "self." It enables the immune system to recognize and selectively attack foreign organisms. Changes in the glycocalyx of cancerous cells enable the immune system to recognize and destroy them. In addition, glycocalyx forms the basis for compatibility of blood transfusions, tissue grafts, and organ transplants. Furthermore, it enables sperm to recognize and bind to eggs.

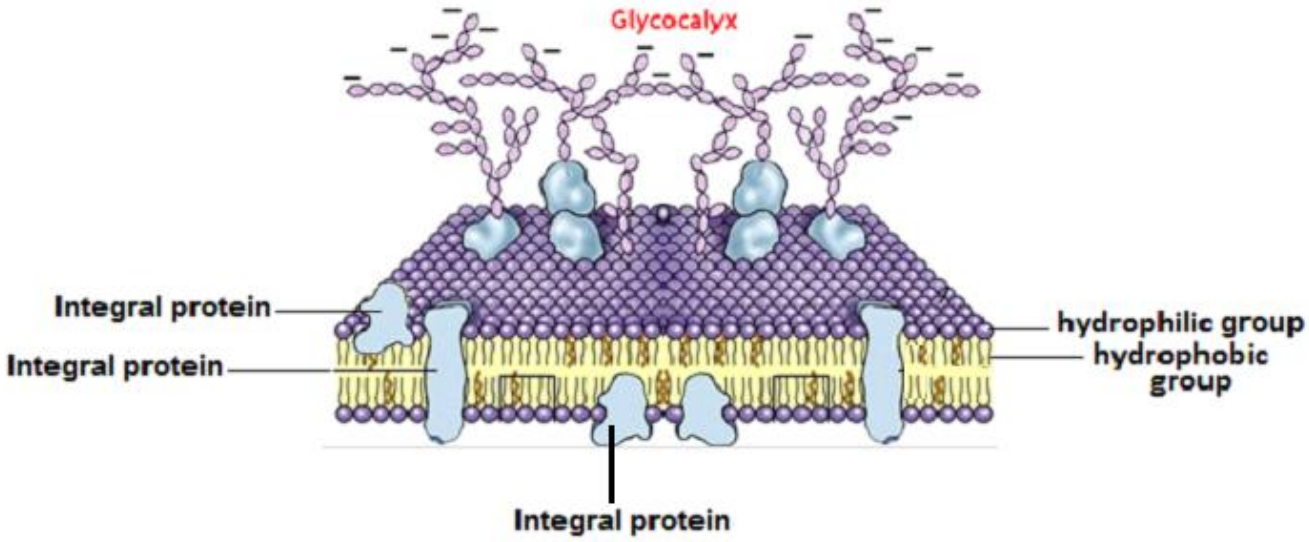



**Figure 3. The glycocalyx.**

**Cilia and flagella** are either non-motile or motile thread-like projections through the cell membrane; each is anchored by a basal body just within the membrane. Cilia are usually shorter than flagella, and an individual cell has many of them on its free surface.

- In the inner ear, cilia play a role in the sense of balance;
- In the retina of the eye, they are highly elaborate and form the light absorbing part of the receptor cells;
- Motile cilia are less widespread, occurring mainly in the respiratory tract and the uterine (fallopian) tubes. Cells lining the fallopian tubes, for example, have cilia to sweep the egg cell toward the uterus.

The only human cell with a flagellum is the sperm cell.

Motile cilia beat in waves that sweep across the surface of an epithelium, always in the same direction (figure 4). Cilia could not beat freely if they were embedded in sticky mucus. Instead, they beat within a saline (saltwater) layer at the cell surface. Chloride pumps in the apical plasma membrane produce this layer by pumping $Cl^-$ into the extracellular fluid. Sodium ions follow by electrical attraction and water follows by osmosis. Mucus essentially floats on the surface of this layer and is pushed along by the tips of the cilia.

**Cystic Fibrosis:** The significance of chloride pumps becomes especially evident in cystic fibrosis (CF), a hereditary disease especially affecting white children of European descent. CF is usually caused by a defect in which cells make chloride pumps but fail to install them in the plasma membrane. Consequently, there is an inadequate saline layer on the cell surface and the mucus is

dehydrated and overly sticky. In the respiratory tract, the mucus clogs the cilia and prevents them from beating freely. The respiratory tract becomes congested with thick mucus, often leading to chronic infection and pulmonary collapse. The mean life expectancy of people with CF is about 30 years.

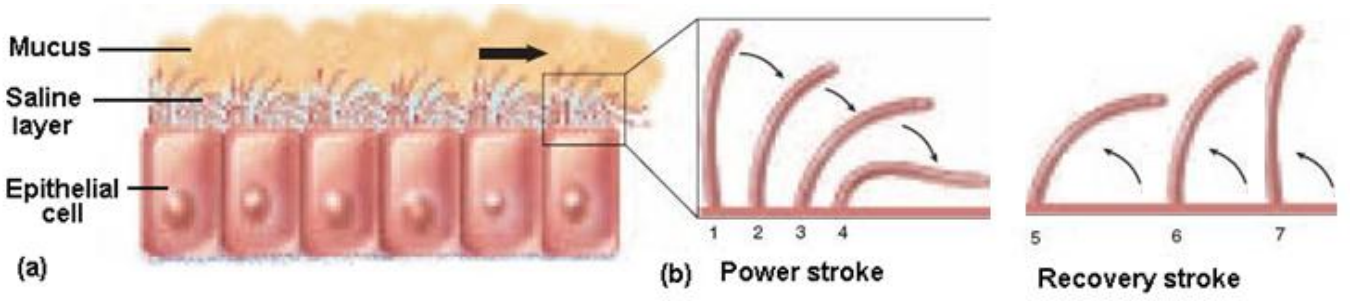



**Figure 4: Cilia and its movement.**

**Microvilli** are folds of the cell membrane on the free surface of a cell. These folds greatly increase the surface area of the membrane which is necessary for efficient reabsorption of useful materials back to the body.

**Cell-to-Cell adhesions:** Cells are held together by three different means: (1) Cell adhesion molecules (CAMs), (2) the extracellular matrix, and (3) specialized cell junctions.

**[A] Cell adhesion molecules (CAMs):** They are integral membrane proteins that have cytoplasmic, transmembrane and extracellular domains. The extracelluar domains of one cell bind (directly or indirectly) to the adjacent cell`s extracelluar domains (figure 5). Most of the CAMs belong to four protein families: **Immunoglobulin-like adhesion molecules,** the **integrins**, the **cadherins**, and the **selectins**.

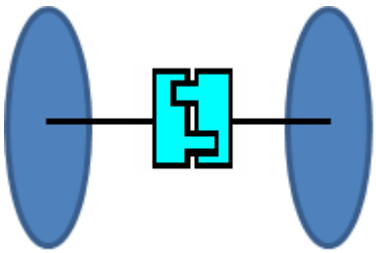


**Figure 5: Cell adhesion molecules.**

**[B] The extracellular matrix (ECM):** The extracellular matrix serves as the biological "glue". The ECM is composed of a **ground substance** of a gel-like substance and a **network of fibrous proteins**. The major types of protein fibers woven through the gel are:

- **Collagen** forms flexible but non-elastic fibers or sheets that provide tensile strength (resistance to longitudinal stress).
- **Elastin** is a flexible elastic protein fiber most plentiful in tissues that must easily stretch and then recoil after the stretching force is removed. It is found, for example, in the lungs, which stretch and recoil as air moves in and out.

Many people take extra vitamin C, for various reasons. Vitamin C has several functions, and an important one is the synthesis of collagen. Collagen formed in the absence of vitamin C is weak, and the effects of weak collagen are dramatically seen in the disease called **scurvy**.

**[C] Specialized membrane junctions:** Three types of junctions form between the cells that make up tissues. These junctions fasten the cells to one another and to surrounding tissues (figure 6).

**1. Tight junction:** It is an actual fusion of the outer surfaces of two adjacent plasma membranes by special proteins, so that there is no space between adjacent cells in the region of the tight junction (as those found between epithelial cells). Tight junctions may be:

- **Impermeable (non leaky)** these types of junctions form a barrier to the movement of ions and other solutes from one side of the epithelium membrane to the other which usually separate two compartments having different chemical composition.

- **Permeable (leaky)** these may form an intercellular pathway which allows substances to pass through depending on the size, charge, and characteristics of the tight junction.

**2. Gap junctions:** In which there is a gap (channel) between two adjacent cells and cytoplasm of the two cells are connected with each other by sort of channels made of connexin proteins. These junctions permit transfer of ions and other small molecules from one cell to another without entering the extracellular fluid. A variety of cell types possess gap junctions such as the muscle cells of the heart and smooth muscle cells.

**3. Adheren or Desmosome junctions:** These consist of two opposed thickening of the membranes of two adjacent and separated cells that are bounded together by filamentous protein materials. In addition, fibers (actin) extend from the inner surface of the desmosome into the cytoplasm and appear to be linked to other desmosomes of the cell. The function of the desmosome is to hold adjacent cells together in areas that are subjected to considerable stretching, such as in the skin and heart muscle.

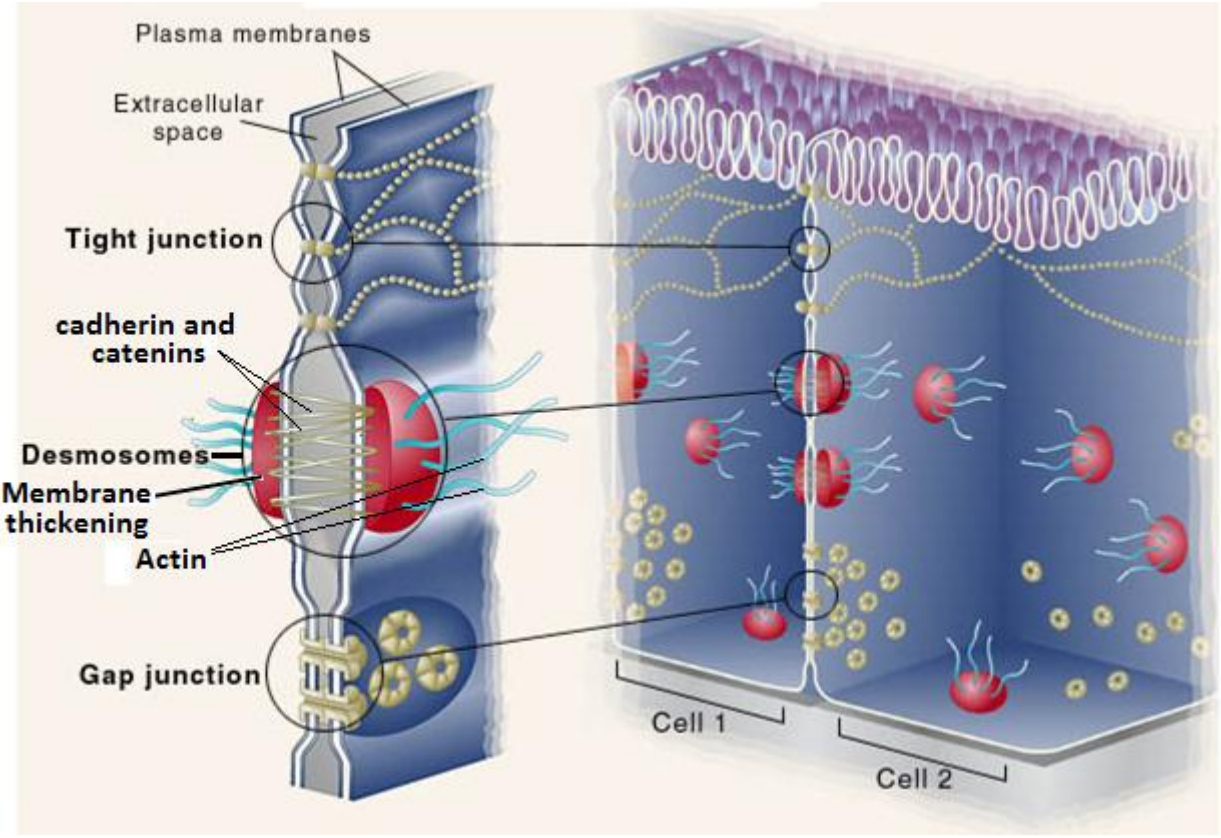



**Figure 6: Cell junctions.**

**Intercellular communication (signal transduction or cell signaling): It is the process by which a cell converts an input signal into a response**. The cell responses include a change in metabolic activity, contraction or relaxation, secretion, release of another signaling substance such as hormones, cell growth and division, and cell death (apoptosis). The cell response occurs as a consequence of changes in the chemical composition of the cell.

Input signal ➔ Changes in the chemical composition of the cell ➔ Cell response.

Cells communicate with each other via electrical signals (electrical communication) or through chemical messengers (chemical communication). In chemical communication, the target cells are affected by chemical messengers (ligand) when these messengers bind to receptors on the membranes of cells, in the cytoplasm, or in the nucleus. Therefore, cell communications are of two types:

**[A] Electrical communication:** It is a cell response due to an electrical signal (ions or electrons flow). As a result of flow of ions (or electrons) across the cell membrane, the cell membrane potential is

changed, this result in activation of voltage-gated channels (also see figure 7) resulting in inflow or outflow of ions through these voltage-gated channels. This will change the chemical composition of the cell which in turn triggers a response in the target cells. Such channels are found in the cell membrane of the neurons, muscles, and some gland cells. The change in the cell membrane potential and consequently the opening of voltage-gated ion channels can be achieved by a direct application of an **electrical stimulus** or through the **flow of ions** across other transmembrane channel proteins. This explains how the ion flows generate electrical signals in nerve, muscle, and some gland cells.

Flow of ions (or electrons) across cell membrane ➔ Change in the cell membrane potential ➔ Activation of voltage-gated ion channels ➔ Influx or efflux of ions ➔ Changes in the chemical composition of the cell ➔ Cell response.

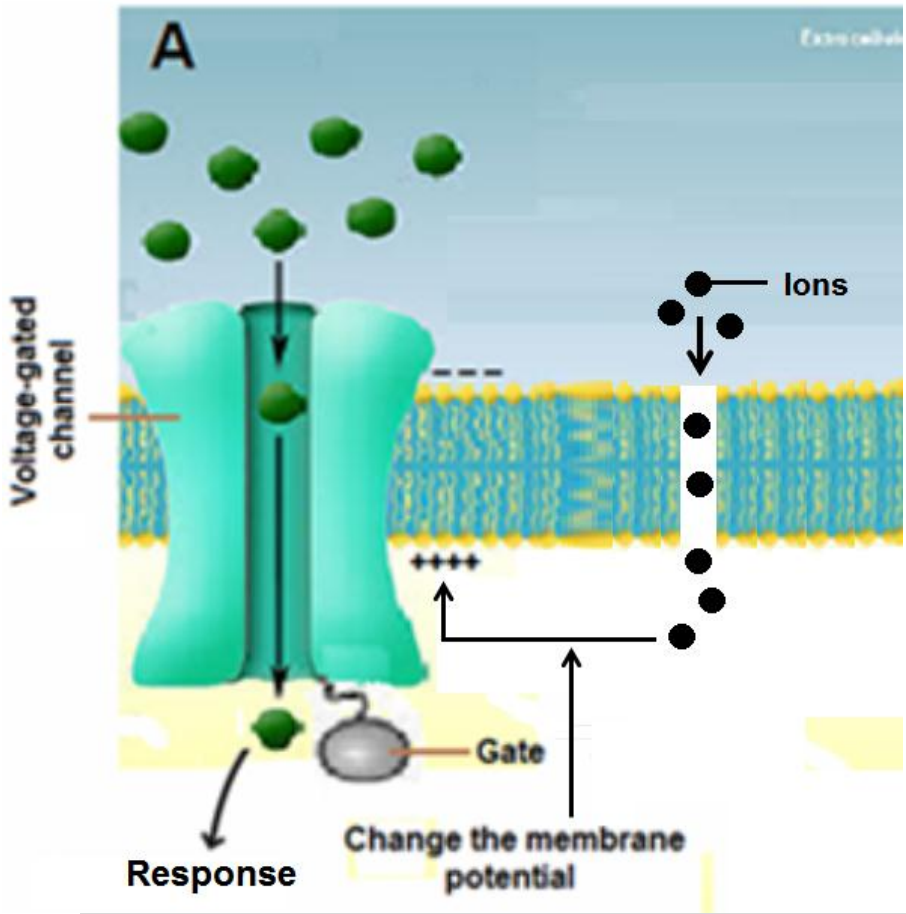



**Figure 7: Voltage-gated channel.**

**[B] Chemical Communication:** It is a cell response to a chemical messenger (**first messenger** or **ligand**). The chemical messenger could be a hormone, a neurotransmitter, or any other chemical substance. The response occurs after the binding of the chemical messenger to the membrane receptors. Chemical messenger approaches the target cell through four pathways:

**1. Endocrine pathway** (figure 8 a) involves a substance secreted by endocrine cells that is transported in the blood to distant target cells to elicit a response. For example, adrenocorticotropic hormone, which is released from the anterior pituitary into the blood, stimulates the release of cortisol from the adrenal gland.

**2. Paracrine pathway** (figure 8 b) involves a substance diffusing from the signaling cell that produced it to nearby target cells to elicit a response. For example, the gastrointestinal regulatory peptide somatostatin is produced by D cells in the stomach and diffuses to adjacent gastric acid cells to decrease secretion.

**3. Autocrine pathway** (figure 8 c) involves secreted substance acting on the same cell that produced it.

**4. Contact-dependent pathway** (figure 8 d) requires cells to be in direct membrane-membrane contact.

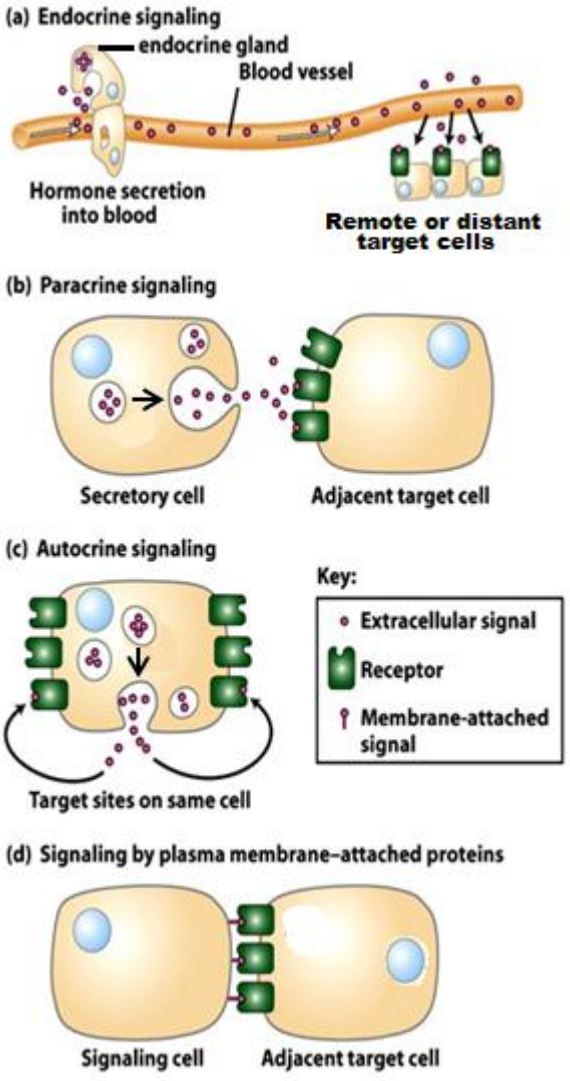



**Figure 8: Transportation pathways of chemical messenger.**

**Chemical Communication involves binding of first messenger (ligand) to the receptors on/in the target cell. The result of the binding of the first messenger to the receptor is one of the following:**

**[1] Open or close of gated channel-linked receptors:** The **binding of chemical messenger** (ligand) to membrane receptors will lead to conformational or structural change in the ion-gated channel protein attached to the receptor, the effect is to open or close the gate of the channel, which result in an increase or decrease in the diffusion of the ion (ions) specific to the channel across the plasma membrane (figure 9). The inflow or the outflow of these ions will change the chemical composition of the cell which in turn triggers a response in the target cells.

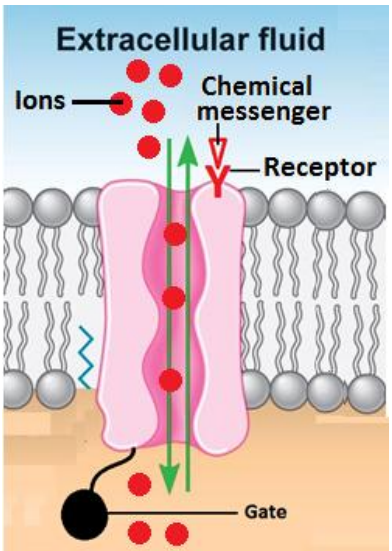



**Figure 9: Ion channel-linked receptors**

**[2] Activation or inhibition of G-protein-linked receptors:** G-proteins are integral transmembrane proteins and are of many types. The transmembrane portion of this protein is the receptor part, while within the inner surface of the membrane, three subunits (α, β and γ) of the G protein are located. Each of this subunit has different amino acid composition. In an inactive form, the largest subunit (the subunit) binds GDP (guanosine diphosphate), and all the three subunits associate together. When chemical messenger interact with transmambrane receptors, the result of this interaction is the activation of G-protein, located on the cytosolic side of the

receptors (figure 10). Activation of a G protein-linked receptor results in the G protein exchanging bound GDP for GTP, and this causes it to dissociate into two parts, the α subunit and the βγ subunit complex. The subunit can then migrate laterally in the plasma membrane to modulate the activity of:

- **G protein-linked ion channels** (figure 10), or
- **G protein-linked activation or inhibition of adenylate cyclases** (figure 11),
- **G protein-linked activation or inhibition of phospholipases C** (figure 12).

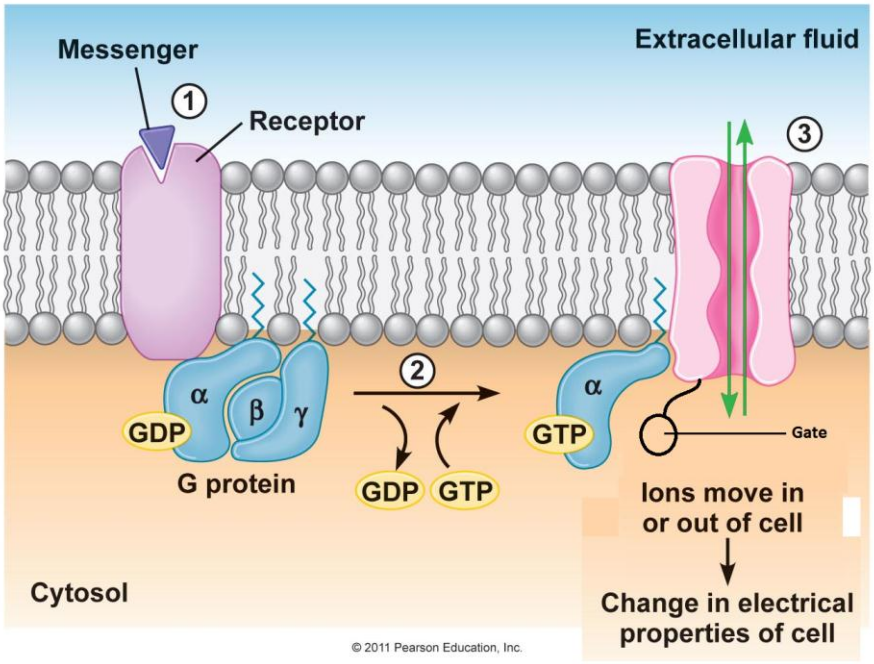



**Figure 10: G protein & G protein-linked ion channels**

The liberated beta/gamma (βγ) complex can also bind to cellular proteins and modify enzyme activities or membrane permeability to ions. The changes in the protein activity and the intracellular ion concentration will change the chemical composition of the cell which in turn triggers a response in the target cells leading ultimately to the cell's overall response. The subunit will eventually hydrolyze the attached GTP to GDP by its inherent GTPase enzymatic activity, allowing it to re-associate with βγ and starting a new cycle.

**[A] G protein-linked ion channels:** G protein-gated ion channels are a family of transmembrane ion channels in neurons and atrial myocytes that are directly gated by G proteins (figure 10). Ion channels allow for the selective movement of certain ions across the plasma membrane in cells.

**[B] Activation or inhibition of G protein-linked adenylate cyclases:** Adenylate cyclases are integral membrane proteins. Adenylate cyclase activity is regulated mainly by interactions with **alpha subunits of G proteins** (can also be activated by beta-gamma subunits of G proteins, and by protein kinase C, and by Ca ions). Binding of a stimulatory G alpha subunit enhanced activity while binding of an inhibitory G alpha subunit inhibited adenylate cyclase activity (figure 11). Activation of adenylate cyclase leads to an increase of intracellular cAMP (cyclic adenosine monophosphate). cAMP can then diffuse throughout the cell and

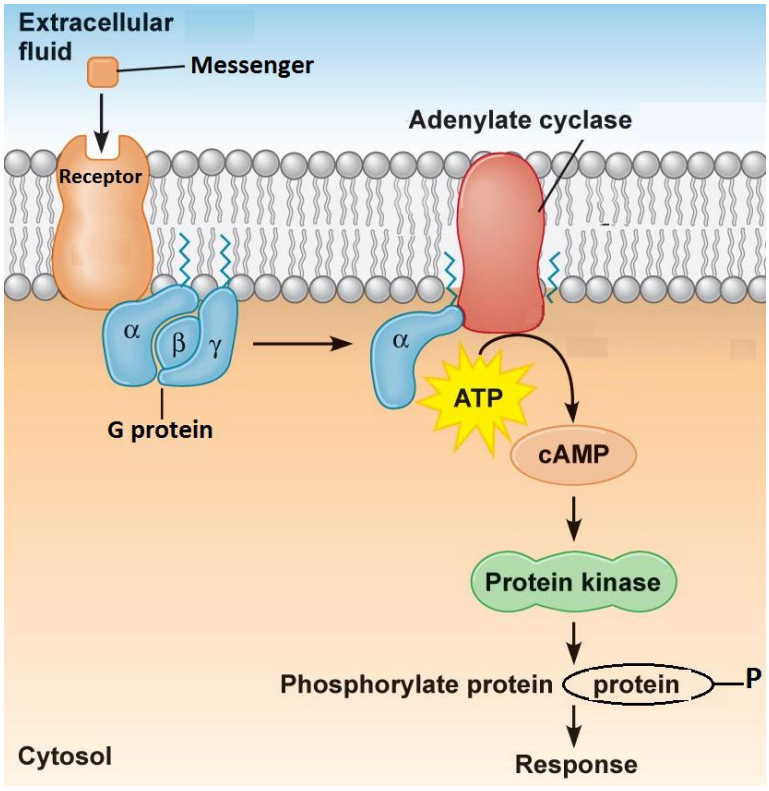



**Figure 11: G protein-linked activation or inhibition of adenylate cyclases.**

activates the **cAMP-dependent protein kinases (such as protein kinase-A)**, which in turn catalyze the phosphrylation of enzyme proteins causing an increase or decrease in their activity. The changes in the protein activity will change the chemical composition of the cell which in turn triggers a response in the target cells through changes in cell metabolism leading ultimately to the cell's overall response.

The $Cl^-$ secretion mechanism of small intestinal epithelial cells into the intestinal lumen, is associated with efflux of $Na^+$ and water, and is stimulated by cAMP which is regulated by G proteins. **Cholera toxin** inhibits the GTPase of the G proteins thereby blocking its deactivating effect on adenylate cyclase. This results in extremely high levels of intracellular cAMP and therefore a marked increase in $Cl^-$ secretion. In response to it, large quantities of water and $Na^+$ are secreted into the lumen, which can lead to severe diarrhea

**[C] Activation or inhibition of G protein-linked phospholipases C:** Phospholipases C are integral membrane proteins found in the inner surface of the cell membrane. Phospholipase C activity was regulated primarily by interactions with **alpha subunits of G proteins**, which in turn are activated through G protein-coupled receptors (figure 12).

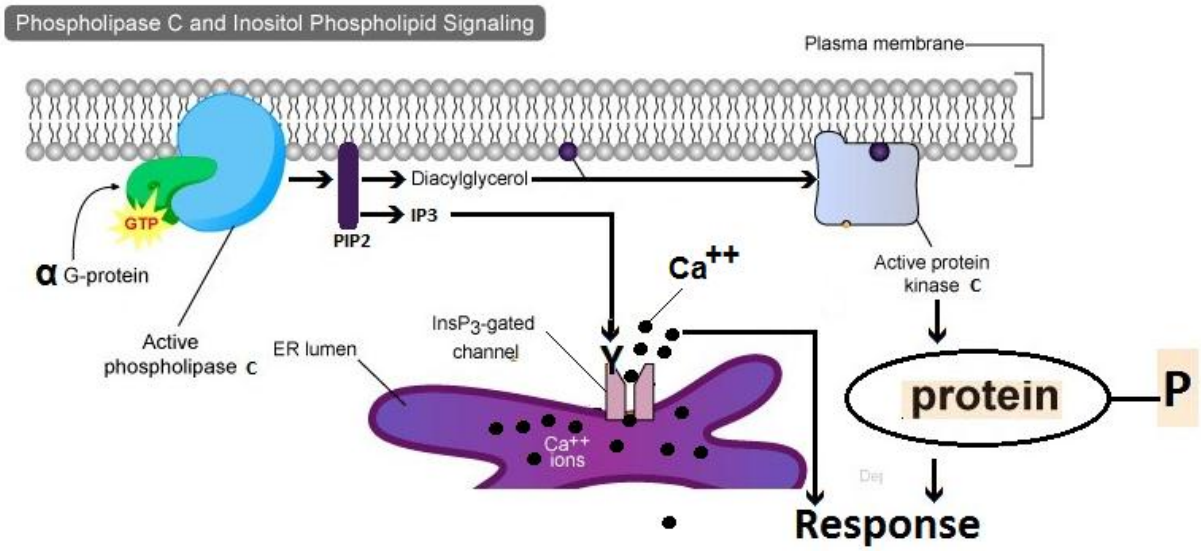



**Figure 12: G protein-linked activation or inhibition of phospholipases C.**

This enzyme in turn causes some phospholipids (mainly phosphatidyl insositol biphosphate [PIP2]) in the cell membrane itself to split into smaller substances (mainly inositol triphosphate [IP3] and diacylglycerol [DG]) that have widespread "second messenger". Intracellular effect of **IP3** is mediated by increasing the free intracellular $Ca^{2+}$ through the release of $Ca^{2+}$ ions from the intracellular stores. DAG can then diffuse throughout the cell and activates the **DAG-dependent protein kinases (such as protein kinase-C)**, which in turn catalyze the phosphrylation of enzyme proteins causing an increase or decrease in their activity. The changes in the protein activity and the intracellular ion concentration will change the chemical composition of the cell which in turn triggers a response in the target cells leading ultimately to the cell's overall response.

**[3] Activation or inhibition of receptor-linked guanylyl cyclase (catalysis-linked receptors):** Number of hormones and neurotransmitters (**ANP** = Atrial natriuretic peptide, or **BNP** = Brain natriuretic peptide, or **NO** = Nitric oxide) bind to specific membrane receptors and trigger specific responses but do not increase cAMP in their target cells, but instead, they may employ cGMP (cyclic guanosine monophosphate) (catalytic receptors). This is achieved through activation of **receptor-linked (membrane-bond) guanylyl cyclase** or **soluble guanylyl cyclase** (figure 13) which converts GTP into the second messenger cGMP, which in turn activates **protein kinase G**. cGMP exerts biochemical actions opposite to that cAMP. cAMP and cGMP serves as a "second messenger".

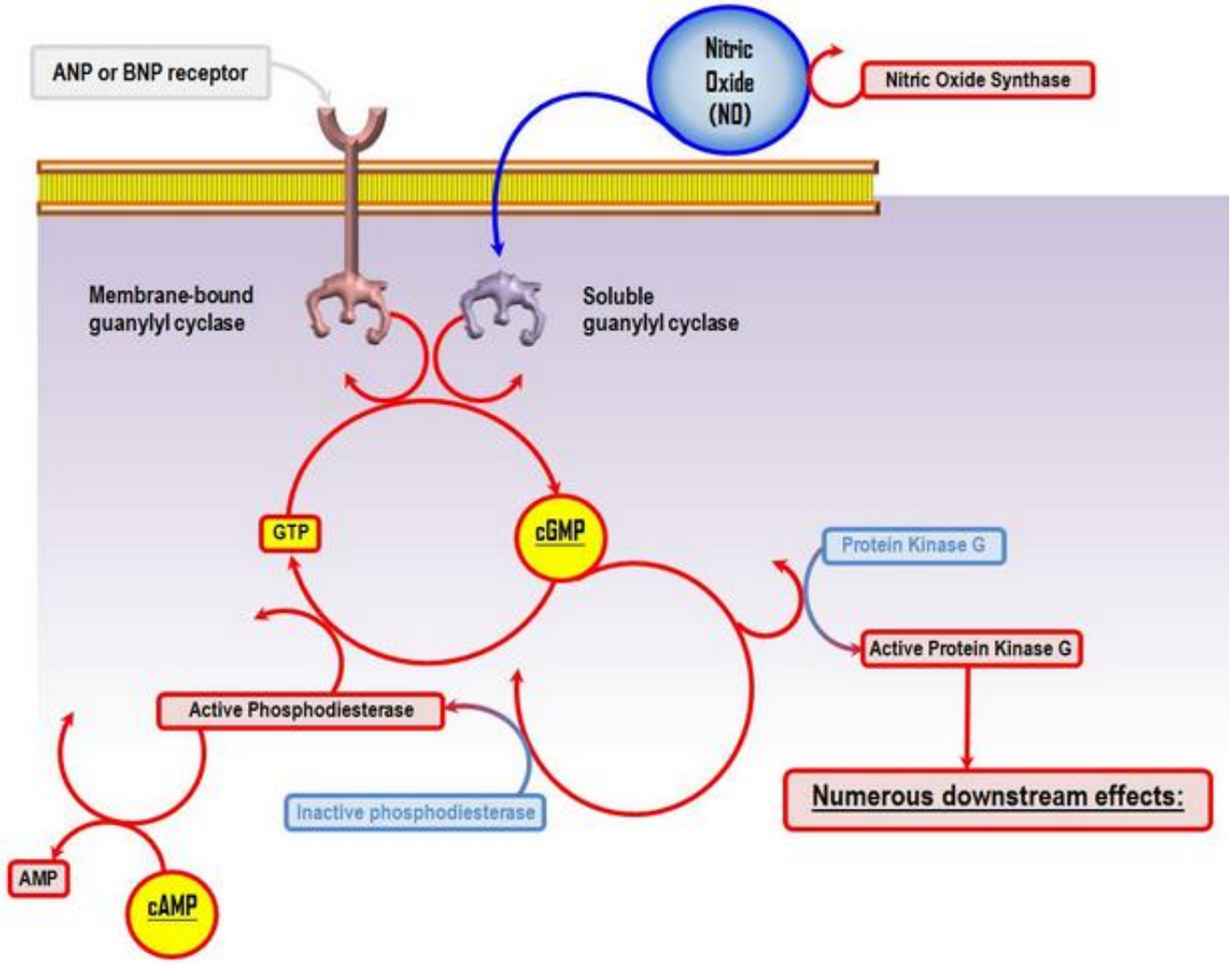



**Figure 13: Activation of guanylyl cycles.**

**[4] Activation or inhibition of receptor-linked tyrosine kinase (catalysis-linked receptors):** The tyrosine kinase receptors consist of a hormone-binding region that is exposed to the extracellular fluid, and transmembrane region where the intracellular portion of it has tyrosine kinase activity. Many of the receptors in this class of plasma membrane receptors have an intrinsic tyrosine kinase domain that is part of the cytoplasmic region of the receptor. Another group of related receptors lacks an intrinsic tyrosine kinase but once they are activated, they activate the cytoplasmic tyrosine kinase (figure 14). Tyrosine kinase phosphorylates the **tyrosyl residues** of proteins that have tyrosyl groups causing an increase or decrease in their activity. The changes in the protein activity will change the chemical composition of the cell which in turn triggers a response in the target cells leading ultimately to the cell's overall response. Typical agonists for these receptors include hormones (e.g., insulin), growth factors (e.g., epidermal, fibroblast, and platelet-derived growth factors), or cytokines.

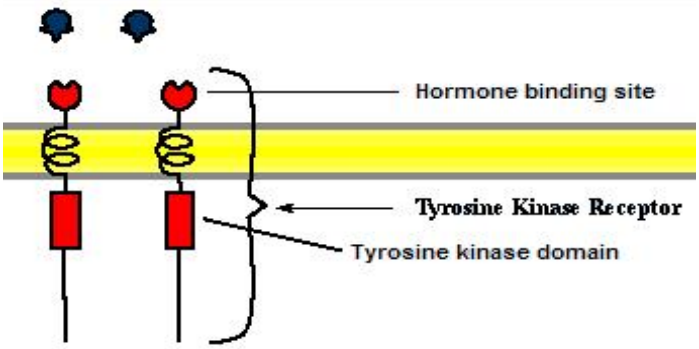



**Figure 14: Activation or inhibition of receptor-linked tyrosine kinase**

**[5] Gene modification:** The chemical messenger may enter inside the cell and bind to specific cytoplasmic receptor proteins. The binding changes the conformation of the receptor and then the "receptor protein-chemical messenger" complex then enter the nucleus where it binds reversibly to DNA. This binding generally influences the gene to make more of a particular mRNA, and the results is increased the formation of specific protein molecules with enzyme activity. An example of such reaction is the response of cell to steroid hormones. Gene modification can also occur by the binding of the chemical messenger directly to the receptors on the chromatin inside the nucleus with subsequent simulation of specific protein molecules with enzyme activity. Such response occurs as a result of thyroid hormone.

## Regulation of the intracellular $Ca^{2+}$:

$Ca^{2+}$ regulates a very large number of physiologic processes that are as diverse as proliferation, neural signaling, learning, contraction, secretion, and fertilization, so regulation of intracellular $Ca^{2+}$ is of great importance. The free $Ca^{2+}$ concentration in the cytoplasm at rest is maintained at about 100 nmol/L. The $Ca^{2+}$ concentration in the interstitial fluid is about 12,000 times the cytoplasmic concentration, ie, 1,200,000 nmol/L, so there is a marked inwardly directed concentration gradient as well as an inwardly directed electrical gradient. Much of the intracellular $Ca^{2+}$ is bound by the endoplasmic reticulum and other organelles and these organelles provide a store from which $Ca^{2+}$ can be mobilized via ligand-gated channels to increase the concentration of free $Ca^{2+}$ in the cytoplasm. Increased cytoplasmic $Ca^{2+}$ binds to and activates calcium-binding protein called calmodulin, which in turn activates a number of protein kinases (figure 15).

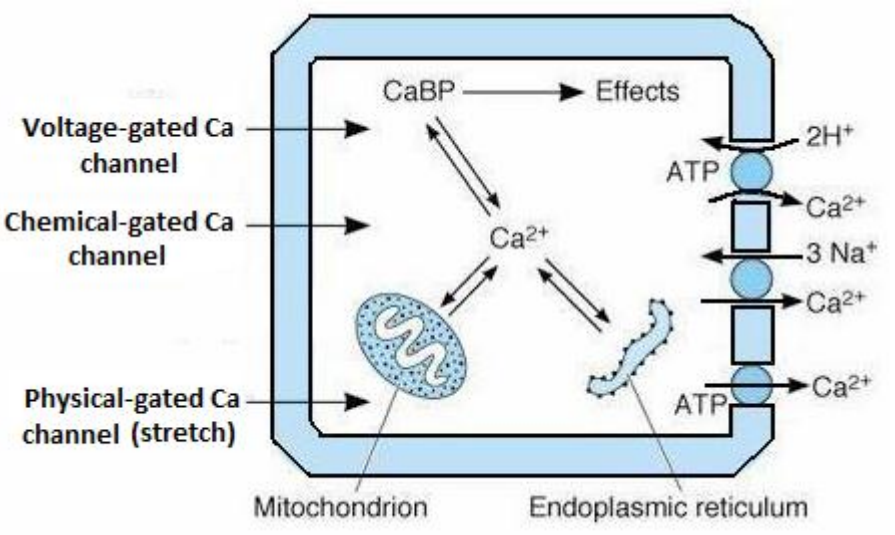



**Figure 15: Regulation of the intracellular $Ca^{2+}$.**

**Increase the free intracellular $Ca^{2+}$ can occur as a result of:**

**[1] $Ca^{2+}$ enters cells through many different membrane $Ca^{2+}$ channels.**

- Chemical (Ligand)-gated channels.
- Voltage-gated channels.
- Physical "Stretch" or "heat"-gated channels.

**[2] $Ca^{2+}$ release from endoplasmic reticulum (ER):** Channels on the ER membrane that mediate $Ca^{2+}$ release include the **IP3 (inositol triphosphate)-gated channels** and the **ryanodine-gated channels**.

**Decrease the free intracellular $Ca^{2+}$ can occur as a result of:**

**[1] $Ca^{2+}$ is pumped out of cells by**:

- $Ca^{2+}$-$2H^+$ countertransport ATPase pump
- $Ca^{2+}$-$3Na^+$ countertransport carrier protein
- $Ca^{2+}$-ATPase pump

**[2] $Ca^{2+}$ is sequestering into the ER** by the ER $Ca^{2+}$-ATPase pump.

Inhibition of $Na^+$-$K^+$-adenosine triphosphatase (ATPase) leads to an increase in intracellular $Na^+$ concentration. Increased intracellular $Na^+$ concentration decreases the $Na^+$ gradient across the cell membrane, thereby inhibiting $Na^+$–$Ca^{2+}$ exchange and causing an increase in intracellular $Ca^{2+}$ concentration. Increased intracellular $Na^+$ concentration also inhibits $Na^+$–glucose cotransport.

**Malignant hyperthermia** is a subclinical disease resulting from a genetic predisposition to react abnormally to volatile anesthetics such as halothane and muscle relaxants such as carbachol. Malignant hyperthermia is due to mutations in the ryanodine receptor (a family of $Ca^{2+}$ release channels found on intracellular $Ca^{2+}$ storage/release organelles) leading to an overactive receptor. The mutated ryanodine receptor is especially sensitive to the aforementioned anesthetics, resulting in increased $Ca^{2+}$ release from ER, and continuous activation of the ER $Ca^{2+}$-ATPase pump and a sustained muscle contraction, resulting in increased heat production and hyperthermia. Under severe conditions, extensive necrosis of

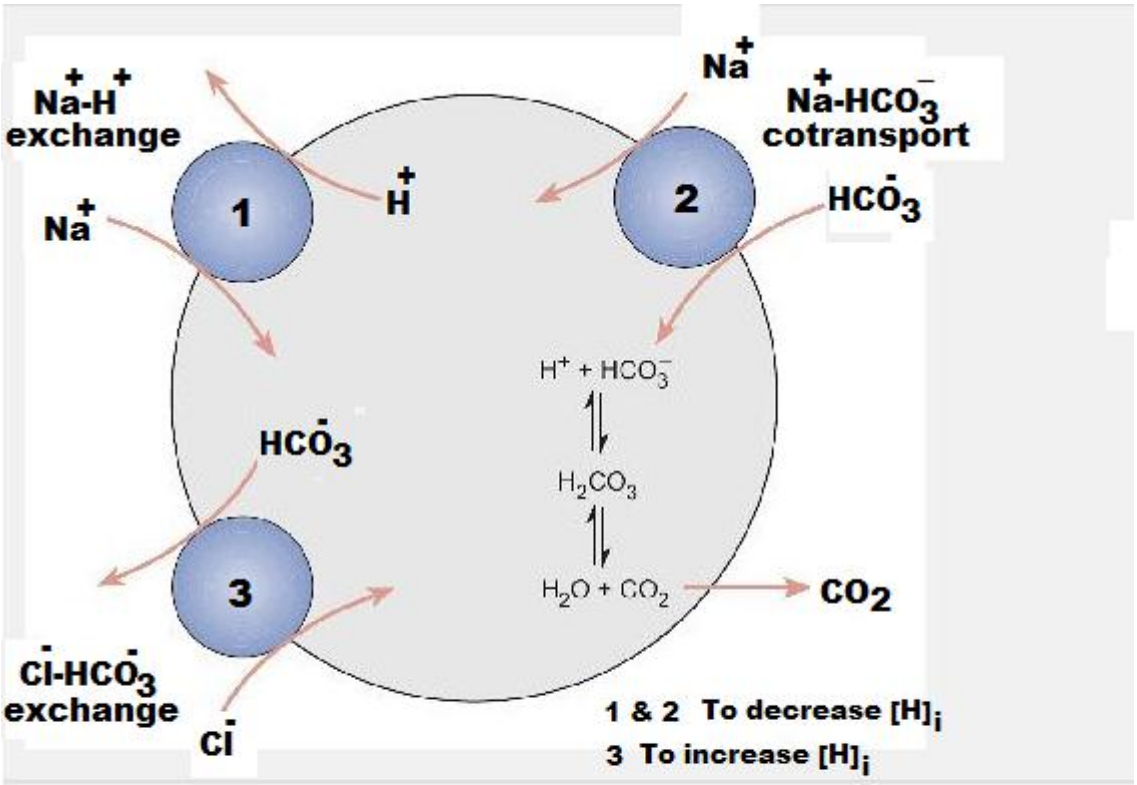
muscle cells follows, leading to release of large amounts of $K^+$, cardiac arrhythmias, and often-lethal ventricular fibrillation.

**Regulation of intracellular [$H^+$]:** All respiring cells continually produce metabolic acids (e.g. carbon dioxide and carboxylic acids) which are capable of altering the intracellular concentration of hydrogen ions [$H^+$]. Measurements have shown that cells maintain the hydrogen ion concentration of their cytoplasm close to a pH value of 7. This is higher than that of the extracellular fluid which is about a pH value of 7.4. The cells must actively regulate their intracellular hydrogen ion concentration to keep an optimal intracellular environment for enzymes and proteins to function.

For example, many enzymes work best at a particular hydrogen ion concentration (their pH optimum). Changes in intracellular hydrogen ion concentration also influence the function of other proteins such as ion channels, and the contractile proteins actin and myosin. When the hydrogen ion concentration rises during cellular activity, many hydrogen ions will bind to intracellular buffer systems (such as phosphate buffer system and protein buffer system), thus limiting the rise. However, buffering can only limit the change in hydrogen ion concentration. To restore its original hydrogen ion concentration a cell must pump out the excess hydrogen ions. To enable them to do so, cells have evolved a number of regulatory mechanisms, three of which are important and these are (figure 16):

- **Sodium-hydrogen ion exchange (counter transport)**
- **Co transport of $Na^+$ and $HCO_3^-$ into cells to increase intracellular $HCO_3^-$.**
- **Chloride-bicarbonate exchange (counter transport).**

Under most circumstances the cells are acting to prevent an increase in their hydrogen ion concentration. At high altitude, however, the extra breathing required to keep the tissues supplied with oxygen leads to a fall in the carbon dioxide concentration in the blood and tissues. This makes the cells more alkaline than they should be (i.e. they have a hydrogen ion deficit). To maintain the intracellular hydrogen ion concentration within the normal range, intracellular bicarbonate is exchanged for extracellular chloride. This mechanism (known as chloride-bicarbonate exchange) provides a means of defense against a fall in the intracellular hydrogen ion concentration. Chloride-bicarbonate exchange is freely reversible and plays an important role in the carriage of carbon dioxide by the red cells.




Cells regulate their internal $H^+$ concentration by three separate mechanisms: they exchange internal $H^+$ for external $Na^+$; they import $HCO_3$-ions to combine with $H^+$ to form carbonic acid and ultimately $CO_2$ which is able to cross the cell membrane; when the cell is alkaline (deficient in $H^+$), $HCO_3$- can be exchanged for $Cl^-$.

**Figure 16: Transport systems involved in the regulation of intracellular H ion concentration.**

**Apoptosis:** In addition to dividing and growing under genetic control, cells can die and be absorbed under genetic control. This process is called programmed cell death, or apoptosis. It can be called "cell suicide" in the sense that the cell's own genes play an active role in its demise. It should be distinguished from necrosis ("cell murder"), in which healthy cells are destroyed by external processes such as inflammation.

Apoptosis is a very common process during development and in adulthood. In the central nervous system, large numbers of neurons are produced and then die during the remodeling that occurs during development and synapse formation. In the immune system, apoptosis gets rid of inappropriate clones of immunocytes and is responsible for the lytic effects of glucocorticoids on lymphocytes. Apoptosis is also an important factor in processes such as removal of the webs between the fingers in fetal life and regression of duct systems in the course of sexual development in the fetus. In adults, it participates in the cyclic breakdown of the endometrium that leads to menstruation. In epithelia, cells that lose their connections to the basal lamina and neighboring cells undergo apoptosis. This is responsible for the death of the enterocytes sloughed off the tips of intestinal villi. Abnormal apoptosis probably occurs in autoimmune disease, neurodegenerative diseases, and cancer. It is interesting that apoptosis occurs in invertebrates, including nematodes and insects. However, its molecular mechanism is much more complex than that in vertebrates.

The final common pathway bringing about apoptosis is activation of caspases, a group of cysteine proteases. Thirteen of these have been characterized to date in mammals. They exist in cells as inactive proenzymes until activated by the cellular machinery. The net result is DNA fragmentation, cytoplasmic and chromatin condensation, and eventually membrane bleb formation, with cell breakup and removal of the debris by phagocytes.

Apoptosis can be triggered by external and internal stimuli. One ligand that activates receptors triggering apoptosis is Fas, a transmembrane protein that projects from natural killer cells and T lymphocytes but also exists in a circulating from. Another is tumor necrosis factor.

Between initiating stimuli and caspase activation is a complex network of excitatory and inhibitory intracellular proteins. One of the important pathways goes through the mitochondria, which release cytochrome c and a protein called smac/DIABLO. Cytochrome c acts with several cytoplasmic proteins to facilitate caspase activation. Smac/DIABLO binds to several inhibiting proteins, lifting the inhibition of caspase-9 and thus increasing apoptotic activity.