GENERAL PHYSIOLOGY

Introduction

Physiology is studied through the study of individual systems the body is formed of; like the digestive system, respiratory system, etc. These systems function on the basis of some fundamental principles which are common to all of them. General physiology includes these fundamental principles which help a lot to understand the activity of the individual systems. This also helps to avoid repetition during discussion on the individual systems.

1 CHAPTER — Cell : the unit of Life

The cell is the structural and functional unit of the body. This means the body is formed of cells and its physiology means the sumtotal action of all the cells present in the body. So, a knowledge of cellular physiology is essential. The cells present in the human body are of innumerable types according to their functional specialities but the general description of a cell is as follows :

DESCRIPTION OF A CELL AND ITS COMPONENTS

A cell is composed of a small mass surrounded by a membrane called **cell membrane** or **plasma membrane**. This intracellular mass contains the cell nucleus and cytoplasm. The cytoplasm

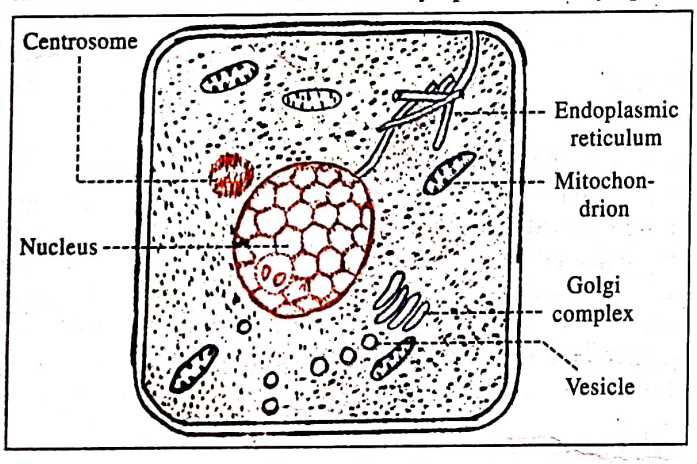


Fig. 1.1. *The cell.*

contains different cell organelles (Fig. 1.1). The fluid part of the cytoplasm which is present outside the organelles is called cytosol.

The Cell membrane

It forms the boundary of the cell and is a highly active functional component of the cell. It provides a selective barrier and maintains a specific environment within the cell which is very much different from outside. The intracellular organelles are also bound by the same type of membrane. The cell membrane (Fig. 1.2) is mainly composed of lipids and proteins along with some carbohydrates. It is 7.5 nm (75A^0) thick.

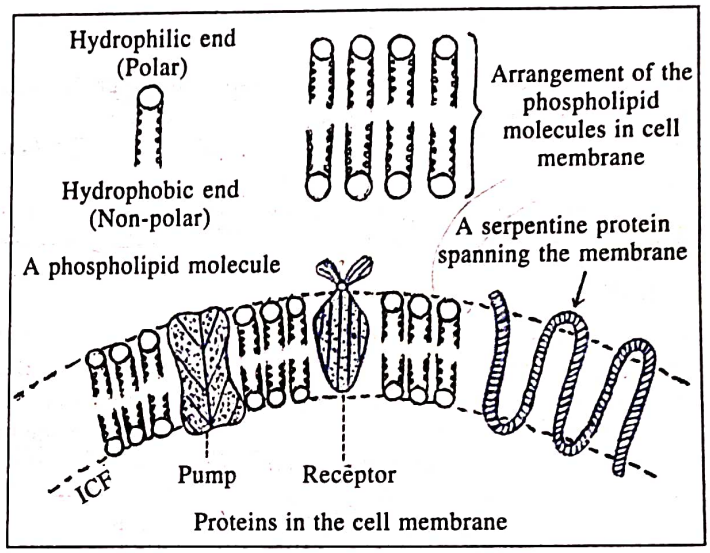


Fig. 1.2. *Structure of cell membrane.*

The **lipids** present in the cell membrane are mainly phospholipids (phosphatidyl choline, phosphatidyl ethanolamine) along with cholesterol and some other lipids. The phospholipid molecules are arranged in double layer with the hydrophilic ends (Phosphate part) outside and the hydrophobic ends in the middle of the membrane (Fig. 1.2). These molecules are not attached by any chemical bond but only by van der Wall forces. Hence, the molecules are highly mobile and impart fluidity to the membrane which is helped further by the presence of cholesterol.

The **proteins** are present on the outer surface, inner surface (peripheral proteins) and also through and through the membrane (transmembrane or integral proteins). These proteins are very important components of the cell membrane and serve the following purposes :

(i) They stitch the membrane through and through, and provide stability to the cell membrane.

(ii) Behave as water channels, ion channels and different pumps.

(iii) Work as permeases for sugars, *i.e.*, transporters.

(iv) Surface proteins are enzymes, act as receptors for hormone actions and also form the cell surface antigens.

(v) They also help to form the cytoskeleton (*e.g.*, spectrin, the proteins in the inner surface in the RBCs).

So, the proteins are **structural components, pumps, channels, receptors, transporters, antigens, enzymes,** etc. (see later for details). Concentration of these proteins determines the functional polarity of the membrane (*e.g.*, a portion of the membrane becomes suitable for Na^+ pumping when the Na^+-K^+ pumps are localised in that portion).

The **carbohydrates** present in the cell membrane are in the form of glycoproteins and glycolipids, and also form the glycocalyx. The glycocalyx layer on the outer surface of a cell is formed by the carbohydrate portions of the glycolipids and the glycoproteins present in the cell membrane on the luminal surface of many cells *viz.*, those lining the gut lumen. Carbohydrates on the RBC membrane help to form the blood group antigens.

Due to the lipid character of the membrane, the non-polar substances like lipids, steroids, O_2 and CO_2 can diffuse through it very easily. The polar substances pass through their channels or are transported by carriers but water can pass also through the lipid portion of the membrane so also through its channels (aquaporins).

The cell membrane is under continuous turnover through the processes of exocytosis and endocytosis (see below). It is folded at different sites to form brush border, T-tubules, and other such structures. The cell membrane is also responsible for electrical properties like membrane potential, action potential, etc. (see Section V).

Nucleus

It is the most important component of a cell (Fig. 1.3) and contains **chromatin,** the genetic material. It also contains the nucleoli and is covered by a unit membrane (*i.e.*, a lipid bilayer). The nuclear membrane is double layered and is permeable to larger molecules like RNA through the nuclear pore complex.

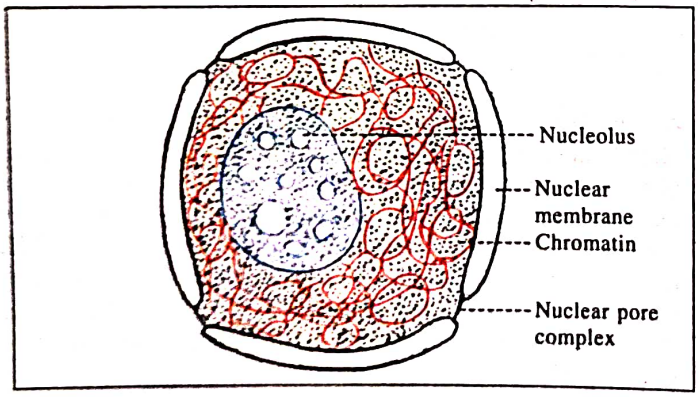


Fig. 1.3. *Nucleus.*

It contains nucleoli which are round structures and are prominent in rapidly growing cells. These are attached to that part of the chromatin which is involved in synthesis of ribosomal RNA. They produce the ribosomes.

The chromatin is composed of DNA and proteins. It is a highly complex structure and it is coiled four times *e.g.*,

(i) primary coil of DNA.

(ii) DNA on nucleoproteins,

(iii) with histone,

(iv) the total structure is further coiled.

The DNA molecules carry all the heritable characters of the species and of the individual. The chromatin materials become distinct rod-shaped structures during cell division and are called **chromosomes.** Each chromosome contains one DNA molecule which is about 2 metre long. This DNA is highly coiled as stated above. The portion coiled around histone forms a bead like structure called nucleosome and the chromosome looks like a string of beads due to these nucleosomes. The chromosome (chromatin) contains the **genes,** the units of heredity. These genes are responsible for regulation of the functions of all the cells in the body. The genes are represented by a segment of DNA. The DNA replicates during cell division. Each cell contains 23 pairs of chromosomes (Diploid) but the germ cells contain half of it (Haploid).

Endoplasmic Reticulum (ER)

It is a system of elongated cavities formed of unit membrane (Fig. 1.4) and forms an extensive network within the cell. It is attached to the nucleus or to the cell membrane or to both.

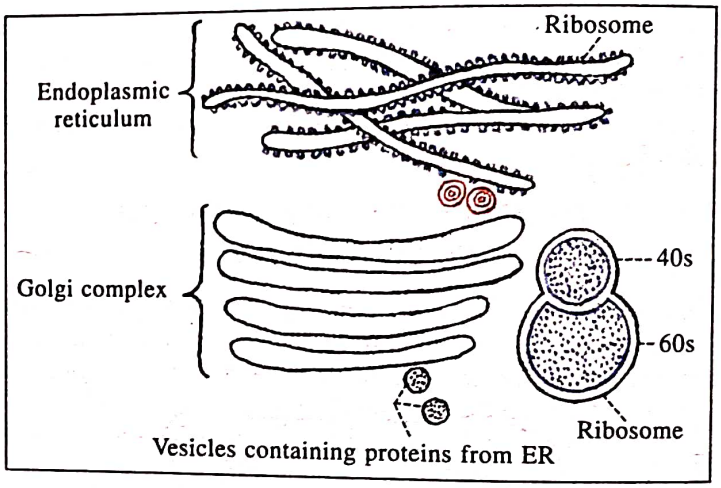


Fig. 1.4. *Organelles for protein synthesis.*

It is sometimes fragmented to form small vesicles called microsomes. In muscle cells it is called **sarcoplasmic reticulum (SR)** and plays important role in muscle contraction through regulation of intracellular Ca^{2+} concentration. The ER with ribosomes on its surface is called **rough ER** and is involved in protein synthesis. The ER without ribosomes is called **smooth ER** and is involved in synthesis of steroids, lipids, etc., and performs other functions like detoxification.

Ribosomes

These are present on the surface of ER (Fig. 1.4) and are composed of two parts : 60S and 40S. These are composed of 65% RNA and 35% protein. The ribosomes are involved in protein synthesis for incorporation in the cell membrane, in the lysosome or to be secreted by a cell. The 40S unit is attached to the mRNA during protein systhesis and the 60S unit is attached to the nascent protein. In some cases many ribosomes are attached to a single mRNA, then it is called **polysome** (see protein synthesis). Free ribosomes are also found in cytoplasm which are used for synthesis of proteins like haemoglobin which are found free in the cytoplasm.

The Golgi apparatus

It is also called Golgi complex and is composed of six or more flat sacs (Fig. 1.4) located near the nucleus. It receives the proteins synthesised in ER, modifies them suitably for different destinations and then releases all of them in the form of vesicles, granules or lysosomes. It therefore forms the packaging-labelling industry of a cell. The modifications of the carbohydrate moieties of the glycoproteins are completed in the Golgi complex.

Mitochondrion

It is the powerhouse of the cell as it is involved in electron transport and ATP formation. It is an oblong structure lined by a double membrane (Fig. 1.5). The inner membrane is thrown into folds or shelf-like structures (cristae) which divide

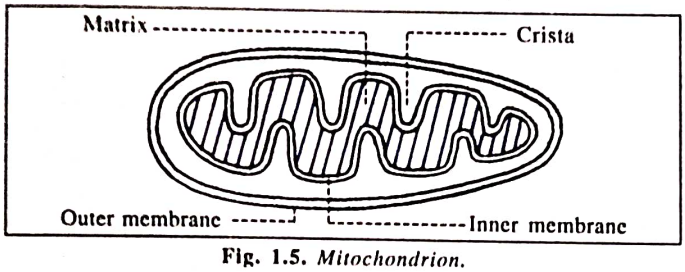


Fig. 1.5. *Mitochondrion.*

the interior in to different compartments containing matrix. The matrix contains DNA, RNA and granules which are enzyme complexes involved in electron transfer and oxidative phosphorylation. Enzymes on the outer membrane are also for biologic oxidation. Mitochondrial DNAs are used for synthesis of rRNAs, tRNAs and some mitochondrial proteins.

The Cytoskeleton

It means the skeleton of a cell, *i.e.*, the structure which supports a cell. It maintains the shape of a cell and is also responsible for cell movements. The cytoskeleton is formed of proteins like actin, tubulin, myosin, etc. Examples of cytoskeletons are microtubules, microfilaments, intermediate and thick filaments. The molecular motors move materials within the cell along the cytoskeleton *e.g.*, kinesin moves materials along the microtubules.

Microtubules : These are elongated tubular structures (Fig. 1.6). These are involved in **oriented movements** like axonal transport, movement of materials and organelles within the cell. They also provide support to the cell and help to maintain the shape of the cells. These are responsible for chromosome movement during cell division by forming the threads of the mitotic spindle. The cilia and the flagellae are formed of microtubules and so also their basal bodies. The microtubules are made up of a protein called tubulin. Thirteen globular tubulin molecules are organised to form rings and these rings are stacked to form the microtubules (Fig. 1.6).

Microfilaments : These are non-tubular dynamic structures composed of globular actin molecules polymerised into filaments. These filaments form the core of the microvilli. These are also present at desmosomes and hemidesmosomes. These are present in plenty inside the cells and are randomly arranged inside the cytoplasm. Highest amount of micro-filament is found in the fibrocytes. Thick filaments are formed of myosin molecules, *viz.*, the thick filaments of muscle cells. There are also intermediate filaments, found particularly in the areas of stress and strain of some cells to provide mechani-cal support as in the desmosomes.

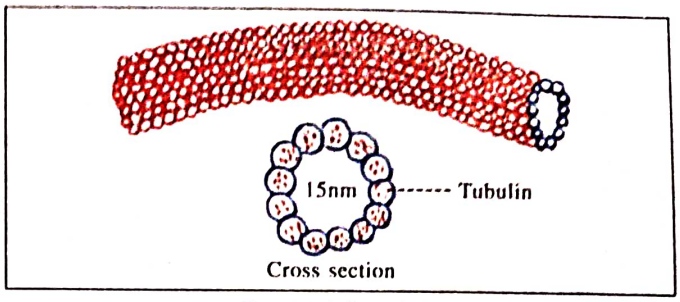


Fig. 1.6. *Microtubule.*

Centrioles : These are two cylindrical structures present in the **centrosome** associated with the nucleus of the cell (Fig. 1.1). During cell division the centrosomes duplicate and form the poles of the mitotic spindle.

Lysosomes

These are packets of enzymes with hydrolysing activity. These enzymes are used to digest different materials within the cells. These are also called suicidal bages, because the enzymes if get released within the cell, the cell itself will be destroyed. Some of the granules in the granulocytes are lysosomes.

Peroxisomes

These organelles contain enzymes like catalase which are involved in peroxidase metabolism, *e.g.*, destruction of H_2O_2, H_2O_2 is also synthesised here. The more important function of peroxisomes seems to be the β-oxidation of long chain fatty acids. Peroxisomes of liver cells catabolise alcohol by H_2O_2 and catalase.

The Cilia and the Microvilli

The cilia are the projections from a cell (Fig. 1.7). These are formed of microtubules and are covered by a layer of the cell membrane. These are rapidly beating structures producing waves as seen in a cornfield formed by wind and move materials on the surface of a cell (**escalator action**, p. 111).

The microvilli are formed by infolding of the cell membrane (Fig. 1.7). Their core structure is made up of microfilaments. These are present in the brush borders of the cells as in the enterocytes (cells of the mucous membrane of gut), renal tubular epithelium, etc. Microvilli help to increase the surface area of the cell.

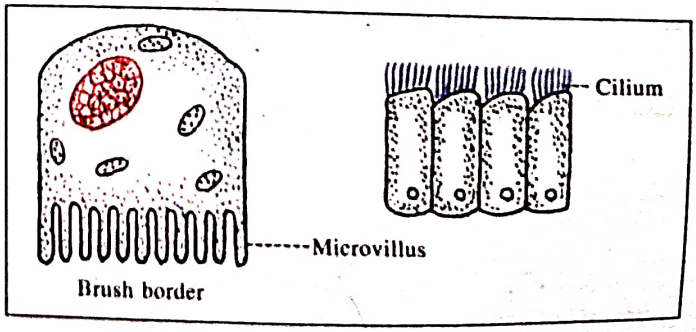


Fig. 1.7. *Microvilli and Cilia.*

ION CHANNELS, RECEPTORS AND CARRIERS

These are membrane proteins. These are very much important for the activities of the cells. There are intracellular receptors also but only the membrane receptors will be discussed here.

Ion channels

These transmembrane proteins provide aqueous pathways or channels to different ions (Fig. 1.8). These may be either continuously open (**leak channels**), or may open and close (**gated channels**). These gated channels may open either due to change in the membrane voltage (**voltage-gated**) or may

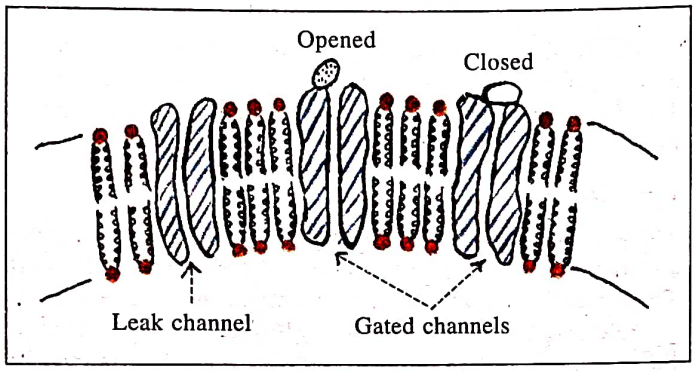


Fig. 1.8. *Ion channels.*

open after binding to chemicals/ligands(**ligand-gated**). Some channels open when the membrane is stretched; these are called mechanosensitive channels. Many of these proteins may be highly selective and will allow only a specific substance, *e.g.*, K^+ channels will allow only K^+ and not others. Some of the channels allow more than one ion. When a channel is opened, ions pass through it along their concentration or electrical gradient. Different ion channels are as follows :

Na^+ channels : These proteins are of different types. Most of the Na^+ channels are composed of large molecules with several membrane spanning segments. These channels have multiple subunits which encircle a central pore (Fig. 1.9).

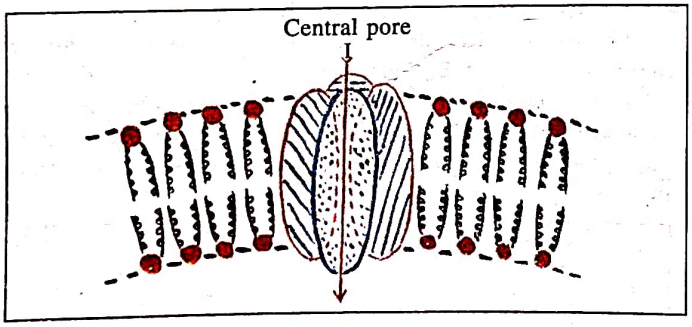


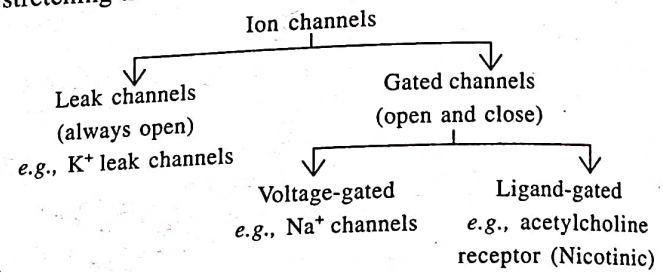
Fig. 1.9. *A Na^+ channel with four units.*

These are voltage-gated and open when the membrane voltage is lowered. They provide aqueous pathways through which Na^+ can pass. The Na^+ channels can be blocked by TTX (Tetrodotoxin) and STX (Saxitoxin). Once these are opened, close automatically. These volage-gated Na^+ channels are responsible for production of action potential.

K^+ channels are of many types, some of them are continuously open and are called leak channels, majority of the channels are voltage-gated or ligand-gated but some are gated by Ca^{2+}. These channels are also named according to their effect on K^+ conductance *e.g.*, inward rectifier, transient outward, delayed rectifier etc.

Chloride channels : These are of two types, one is voltage-gated and the other is gated by Ca^{2+} ion. These are also large protein molecules. GABA and glycine receptors are Cl^- channels.

Ca^{2+} channels : There are three types of Ca^{2+} channels voltage-gated, ligand-gated and another variety which opens on stretching the cell membrane.



Receptors

Most of the receptors are membrane proteins but some are also situated inside the cells. The receptors on a cell bind to different chemicals which are to act on that cell (Fig. 1.10).

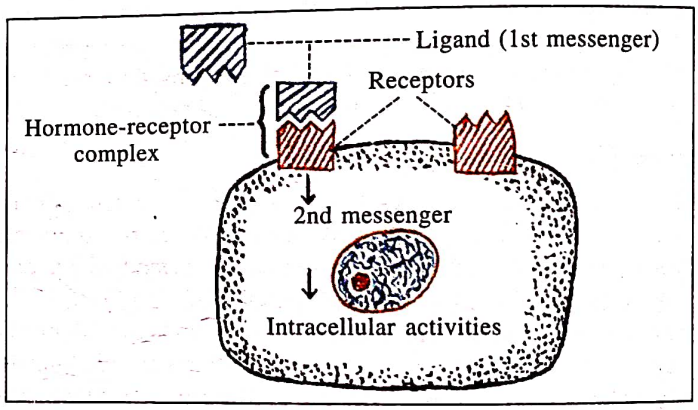


Fig. 1.10. *Receptor.*

This binding is not by formation of chemical bonds but by electrical or van der Waals forces. The receptors are highly specific, *i.e.*, a particular receptor will bind only to a particular substance (ligand) and not to others. When the specific chemical binds to its receptor the latter is activated and results in opening of ion channels or activation of enzymes or protein synthesis or endocytosis, etc. The chemical-receptor complex in many cases releases another group of substances like Ca^{2+},cAMP, etc. These are called **second messengers** which bring about the final activity.

The receptors which behave as ligand-gated channels are the nicotinic receptors of acetylcholine, receptor of GABA, glycine, angiotensin II, etc. The muscarinic acetylcholine receptors, peptide hormone receptors, adrenergic receptors, etc., lead to alteration of enzymatic activity. Receptors for LDL, transferrin, etc., lead to endocytosis (for details see respective chapters).

Carriers

These trans membrane proteins are also called transporters as they transport materials across the cell membrane. This type of transport by carriers when needs energy is called **active transport**, and the carriers are called **pumps**. If energy is not required then the process is called **passive transport**.

The carriers in general act in three ways. One variety transports one substance in one direction and the process is called **uniport** (Fig. 1.11). A second process transports two substances in the same direction called **symport** (Fig. 1.11). The third variety

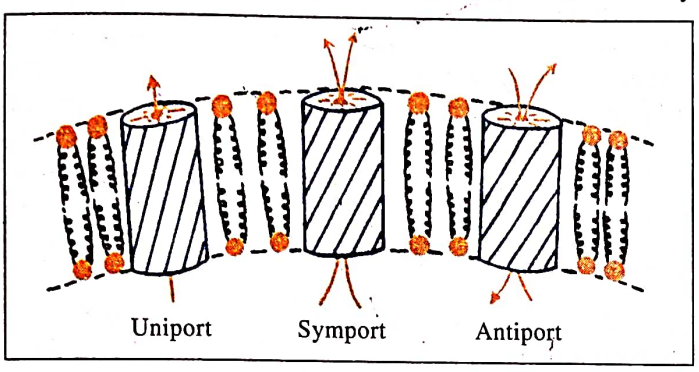


Fig. 1.11. *Transport proteins.*

is called **antiport** (counter transport) (Fig. 1.11) which is responsible for moving two substances in opposite directions. All these transport proteins bind to the substance to be transported across the membrane and these are also specific like the receptors in this respect.

Some of the carrier proteins are as follows :

(i) **Na^+-K^+ ATPase :** It is an enzyme which acts as a carrier. It can remove Na^+ from inside the cell against concentration and electrical gradient with expenditure of energy (Fig. 1.12). Simultaneously it introduces K^+ in to the cell. It has two subunits, α and β. Its action may be explained as follows :

When $3Na^+$ bind to the intracellular portion of the α unit, the latter binds to ATP (Fig. 1.12A). The ATP is then hydrolysed to ADP and the α unit is phosphorylated. This phosphorylated α unit undergoes conformational change and removes $3Na^+$ from the cell (Fig. 1.12B). In the next step $2K^+$ bind to the extracellular portion (Fig. 1.12C) of the α unit which is now dephosphorylated and then comes back to original position bringing $2K^+$ inside (Fig. 1.12D) the cell. This is an antiport and is activated by increased Na^+ concentration inside the membrane.

This pump can be inhibited by ouabain and also by other cardiac glycosides, *e.g.*, **digoxin**. It is responsible for maintenance of cell volume and membrane potential. It is an **antiport**. It is stimulated by Na^+ inside the cell also by CAMP and DAG (see below). Thyroxine and aldosteron increase the number and thus activity whereas dopamine inhibits. Insulin also increases the activity of the pump.

(ii) Ca^{2+} pumps are of two types, one is Ca^{2+} – ATPase which pump out Ca^{2+} from the cell and the other, an antiport, which uses Na^+ gradient for pumping out Ca^{2+} (Na^+-Ca^{2+} exchanger; removes one Ca^{2+} in exchange of three Na^+). There are also hydrogen pumps, *e.g.*, H^+-ATPase and H^+-K^+ ATPase.

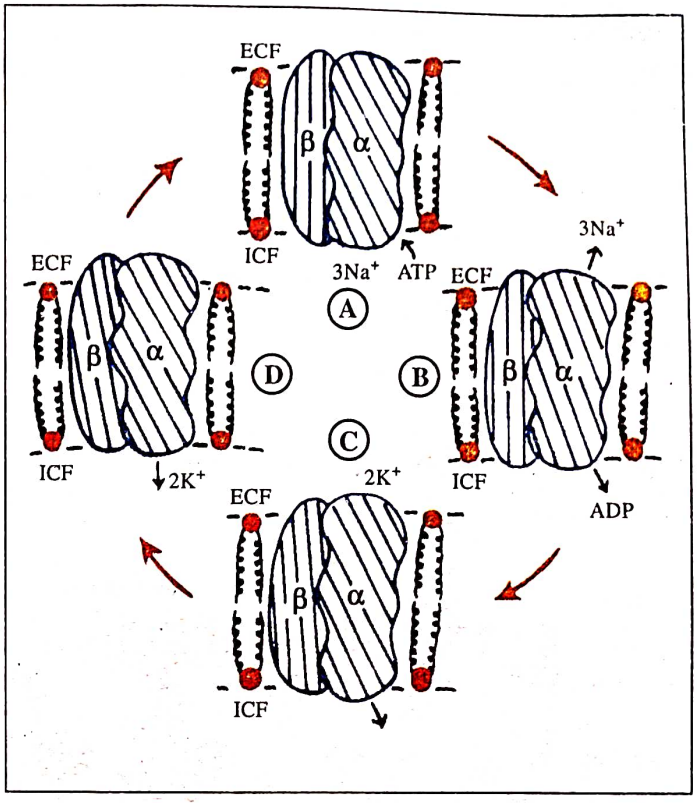


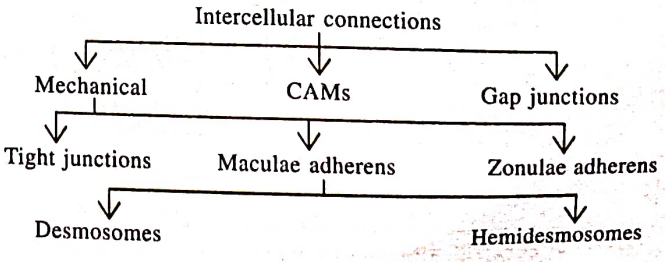
Fig. 1.12. *Na^+-K^+ ATPase.*

(iii) Simple carriers are the proteins which transport, for example, glucose into the cells down the concentration gradient, *viz.*, glucose transporters (GLUT), these are also called **uniport**.

(iv) Another type of carrier protein carries two substances at a time down the concentration gradient of one, *e.g.*, Na^+ and glucose, Na^+ and amino acid. These are called **symport**. Example is, sodium dependent glucose transporters (SGLT) which cause absorption of glucose in the kidney and intestine. This type of transport is called **secondary active transport** (p. 17) as energy is to be spent to maintain the concentration gradient of Na^+.

INTERCELLULAR CONNECTIONS

It means connections between the cells of a tissue. These connections are required to hold the cells of a tissue together or for communication between the cells. Sometimes, these connections make an impermeable barrier between an epithelial surface (lumen) and the interstitial space (*e.g.*, tight junctions in renal tubule). Intercellular connections are as follows :



Mechanical connections

(a) **Tight junctions** or zonulae occludens : This type of connections are formed by ridge-like structures (Fig. 1.13) contributed by the membranes of both the adjacent cells. The ridges are made up of proteins like cingulin, etc. Here the cells are bound together very close. This type of junction is found in between epithelial cells lining a lumen, *e.g.*, in intestinal mucosa, renal tubules, etc. The tightness of this junction varies in different situations, *e.g.*, the tight junctions are leaky in proximal part of the renal tubule but are very tight in the distal part.

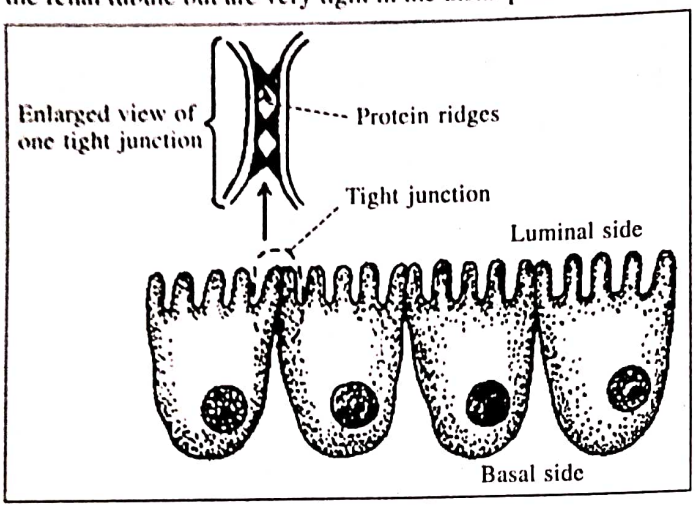


Fig. 1.13. *Tight junctions.*

These junctions are situated in the apical region of the cells and form a barrier between the two sides of the epithelial lining (Fig. 1.13). Due to this arrangement the substances are compelled to pass through the cells membrane, *i.e.*, the selective barrier. The tight junctions also help to maintain the functional polarity of a cell by localising the membrane proteins in one place.

(b) **Zonulae adherens :** This type of junctions are thought to be present in between epithelial cells and in continuation with the tight junction towards the basal side. These are made by the protein cadherin.

(c) **Desmosomes :** These are junctions, involving small areas, like rivets between two metal plates. Adjacent membranes become thickened and the space in between is filled with filament like material containing Cadherin and some other membrane proteins. From the thickened portions of the membranes, fibrils radiate to the interior of each cell (Fig. 1.14).

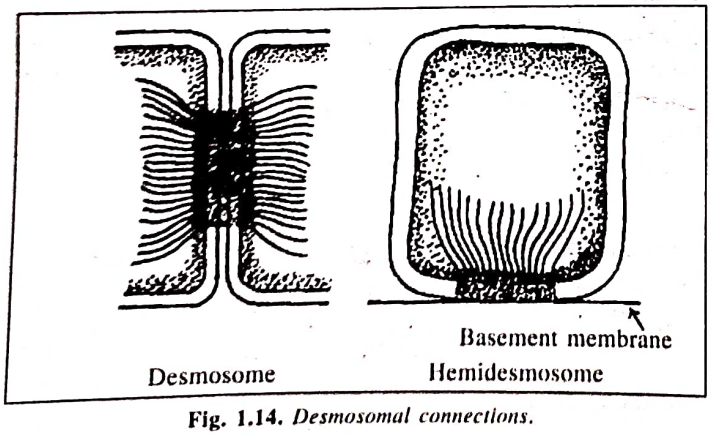


Fig. 1.14. *Desmosomal connections.*

(d) **Hemidesmosomes** are half desmosomes. They are found in the basal sides of the epithelial cells in contact with the basement membrane and attach the cell firmly to the basement membrane. There is no similar specialised structure in the basement membrane (Fig. 1.14).

Desmosomes and hemidesmosomes are also called **maculae adherens.**

The Cell adhesion molecules (CAMs)

Along with the specialised junctions stated above there are some protein molecules for binding the tissue cells in between; these are called CAMs. These CAMs of adjacent cells bind togehter giving stability to the tissue. These may be homophilic or heterophilic, *i.e.*, bind to same type or different types of molecules respectively. These molecules also play role in development, in inflammation, in wound healing and in metastasis of tumours. They include cadherins, selectins, etc.

Gap junction

It provides gaps in the membranes of the adjacent cells through which the cells can communicate with one another. The adjacent membranes come closer and membrane proteins called connexons make the pores. These protein molecules have a central hole which passes through and through the membrane (Fig. 1.15). When two such proteins of opposing membranes come in alignment, a pore is formed connecting the two cells.

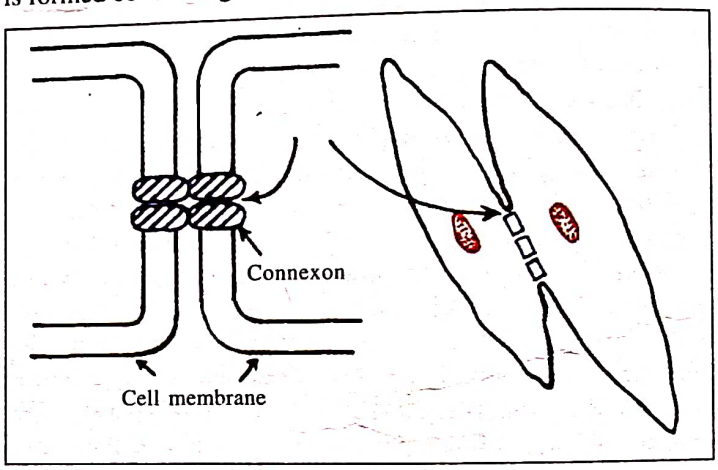
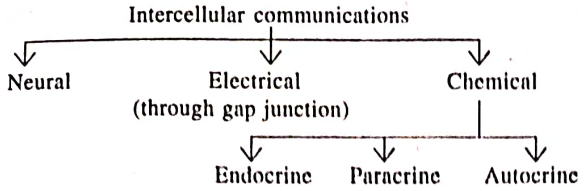


Fig. 1.15. *Gap Junction.*

These pores provide passage for transfer of ion, sugar, amino acid, chemical messengers, etc. Their pore diameter is regulated by Ca^{2+}, membrane voltage and pH. These gap junctions provide a nice low impedance electrical pathway in between cells and are of particular importance in cardiac muscle and single unit smooth muscles. They help to depolarise the whole tissue by conduction of electrical impulse in those tissues.

INTERCELLULAR COMMUNICATIONS

To achieve the physiology, *i.e.*, functions of the body, the cells of the body communicate with one another. This communication is effective enough to bring about a co-ordinated activity of the cells. The cells communicate with one another as follows :



In **neural communication** one cell informs the other by means of electrical impulse via nerves. Neural information is ultimately transformed into chemical communication due to release of neurotransmitters from the nerve endings (Fig. 1.16).

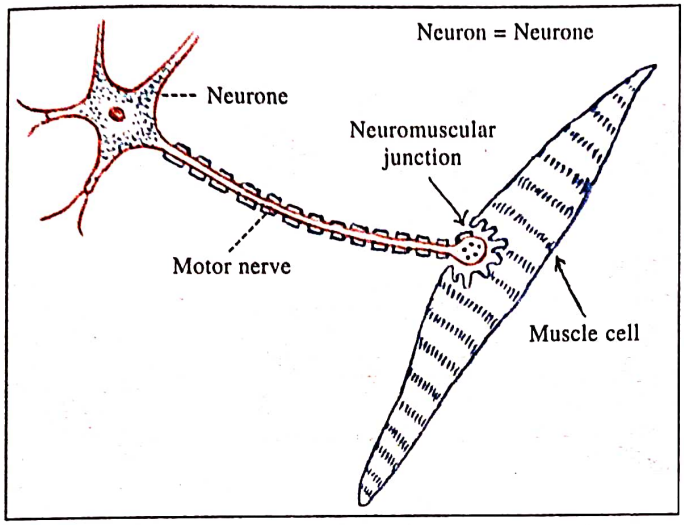


Fig. 1.16. *An example of neural communication.*

Suppose, a muscle is to be informed to contract. For this the nervous system communicates with the muscle via the motor nerve by **electrical** impulse. This impulse releases acetylcholine at the neuromuscular junction. The acetylcholine then acts on the muscle membrane and ultimately the muscle contracts.

Direct **electrical communication** between cells occurs through gap junctions (see above).

There are three types of **chemical communications** (Fig. 1.17). **Endocrine** communication involves the general hormones which are transported by blood to the cell to be communicated. For example, the thyroid gland is to be communicated to increase secretion of thyroid hormones. This information is sent as follows : thyroid stimulating hormone is secreted by the anterior pituitary. It then comes into the blood and circulates. Ultimately it reaches the thyroid gland and acts on the thyroid follicular cells to increase thyroid hormone secretion.

In **paracrine** communication, a local chemical passes through the extracellular fluid (ECF) to a nearby cell whereas in **autocrine** communication the chemical acts on the same cell from where it is produced. Example of paracrine communication is the glucagon from the α cells of the islets of Langerhans, which inhibits the β cells. Platelet activating factor (PAF) is the example of autocrine communication which is produced by and acts on the platelets. Similarly interleukin-2 is secreted by and acts on T cells.

These chemicals meant for communication with other cells, act via their **receptors**. These receptors may be some ion channels or may be proteins which are enzyme in nature and lead to chemical reactions. Receptor stimulation also lead to protein synthesis.

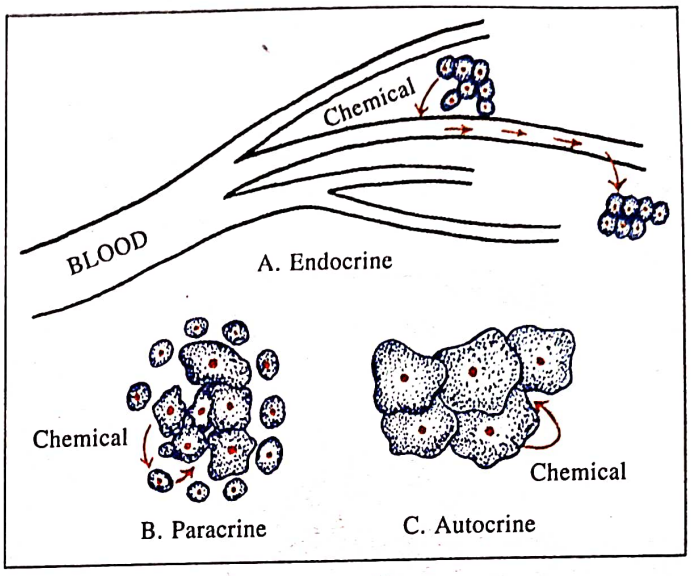


Fig. 1.17. *Chemical communications.*

This way, entry of ions, enzymatic activity or protein synthesis lead to change in the activity of the cells which receive the communication. These chemicals sent for communication are also called **first messengers.** First messengers in many cases lead to release of another set of agents inside the cells on which they act. These agents are called **second messengers** (Fig. 1.10). Examples of second messengers are Ca^{2+}, cyclic adenosine monophosphate (cAMP), cyclic guanosine monophosphate (cGMP), etc. These second messengers bring about the actions of the first messenger.

Note : Juxtacrine communication is another form of inter cellular communication where the cells communicate through interaction of specific cell surface proteins of the adjacent cells.

FUNCTION OF A CELL

Function of a cell means the functions of its components and as stated above, the function of cells means physiology. In general, functions of a cell include protein, fat, carbohydrate metabolism, detoxification, excretion, exocytosis, endocytosis, etc. Many of the substances required by the cell for its function are synthesised in the cell. Some of the functions of the cells are for their basic needs for survival while others are the part of the co-ordinated and combined function of cells as groups to achieve homoeostasis.

Protein synthesis

In the cells the key material is DNA. The DNA carries the hereditary properties. It is composed of two long chains of bases (adenine, guanine, thymine and cytosine). These chains are interconnected by hydrogen bonds (adenine to thymine, guanine to cytosine). Deoxyribose and phosphates are attached to the bases of each chain on the outer side (Fig. 1.18). Each chromosome has a part of this chain. A small segment of DNA called gene is

the ultimate unit of heredity, which carries all the information for the synthesis of a protein. (One gene may be responsible for synthesis of more than one protein). The specificity of a protein depends much on the sequence of amino acids in it. This sequence is determined by the sequence of the bases in DNA through codons, *i.e.*, base triplets, specific for each amino acid.

For synthesis of a protein, the specific mRNA is formed in the nucleus from the DNA template at the gene for that protein (Fig. 1.18). (RNA has single strand, the sugar is ribose and the bases are adenine, cytosine, guanine and uracil). This is called **transcription.** After the mRNA is formed, it is modified (unnecessary portions are removed) within the nucleus to produce the specific mRNA wanted (**post-transcriptional moodification**).

The mRNA then moves out to cytoplasm. There it is attached to the ribosomes on the endoplasmic reticulum (ER). Now according to the base sequence in the mRNA, a protein chain is synthesised (**translation**). The amino acids necessary are brought by tRNA. The new protein enters into the ER. There it is modified to suit the demand, or modification can also occur later on, this is called **post-translational modification.** This way the desired protein molecule is formed. But for this the proper gene is to be

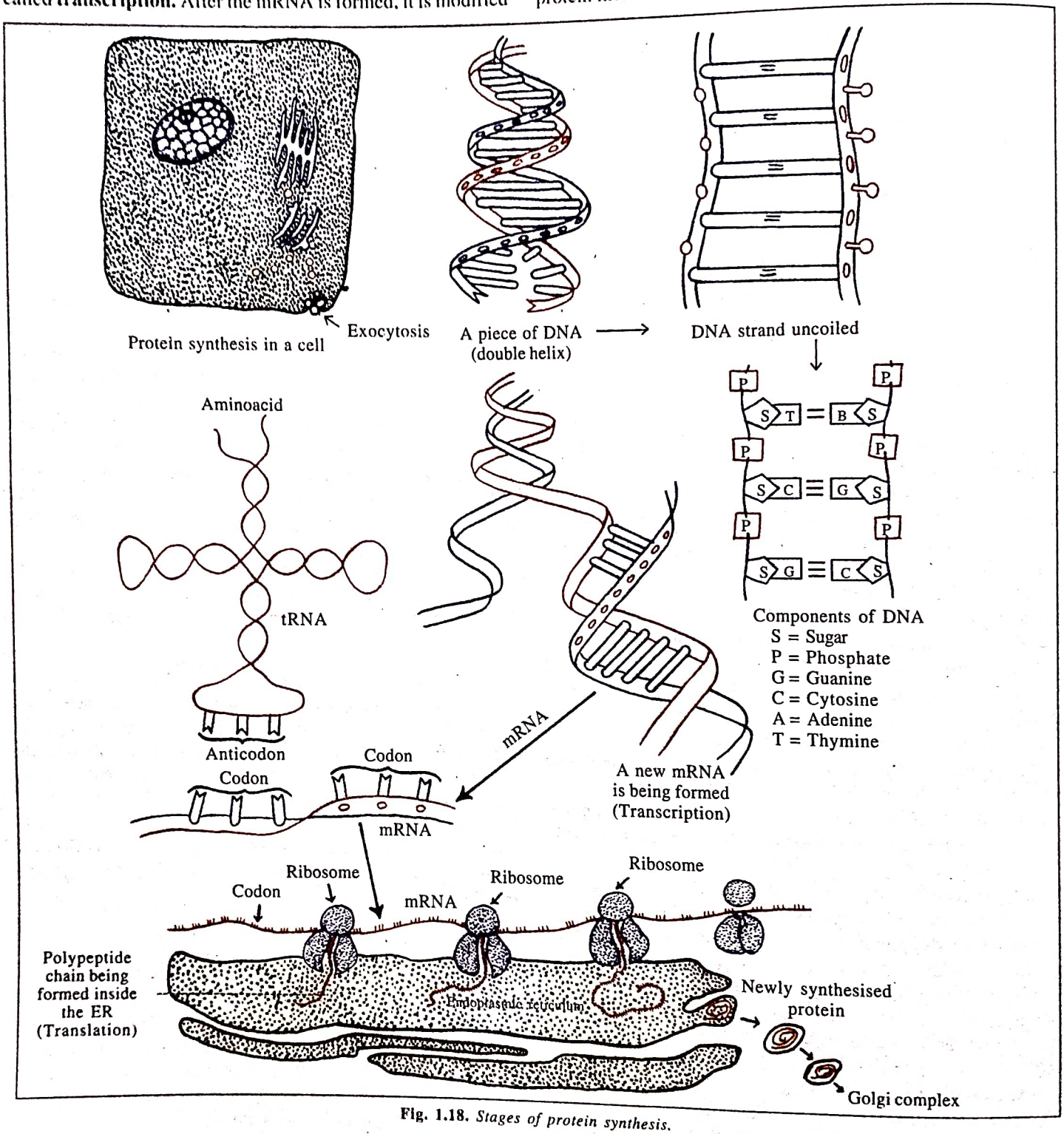


Fig. 1.18. *Stages of protein synthesis.*

transcribed by proper signal in the required cell by the correct transcription factor (*gene expression*).

This is a superficial description of protein synthesis, details of which should be read from biochemistry text book. This is important as the proteins not only control the metabolic reactions but are also responsible for the development of the whole organism from DNA via mRNA.

Exocytosis

It is the process by which materials are extruded from a cell, *e.g.*, during secretion by a cell (Fig. 1.19). The materials which cannot pass through the cell membrane are sent outside by this process. It mainly involves proteins. The protein synthesised at ER is moved to the Golgi apparatus. There it is packed into granules or vesicles. Many other cell products are also included in the vesicles for exocytosis. Exocytosis is initiated by increased intracellular Ca^{2+} concentration caused

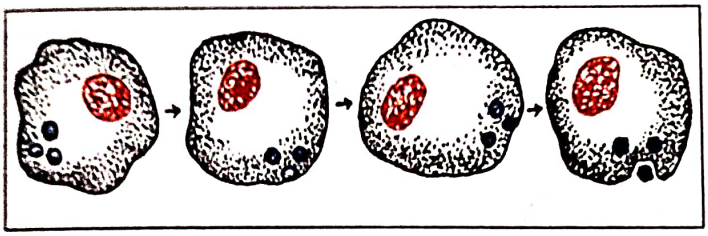


Fig. 1.19. *Exocytosis.*

by the stimulus for secretion. Intracellular contractile proteins and microtubules help in the process. The granules or the vesicles then move to the cell membrane and fuse with the latter. In the area of fusion the membrane breaks down and the contents of the granules or vesicles are released outside. Some materials may be exocytosed quickly without formation of true granules. Remnants of a phagocytic vesicle are also expelled from the cell by exocytosis.

Endocytosis

Endocytosis is the process by which various materials are taken inside the cells. It is thus the reverse of exocytosis. It occurs as follows : The material to be endocytosed first comes in contact with the cell. After this the cell membrane at that point invaginates and the material is then taken inside the cell with a layer of the cell membrane around it (Fig. 1.20). It is then separated from the cell membrane and released in to the cytoplasm as a membrane bound vesicle called **endosome**. The endosome is then handled according to the material it contains. In some case the content is exocytosed straightway through the opposite side of the cell, some are sent to golgi complex for processing, while some others fuse with the lysosome for digestion of the contents.

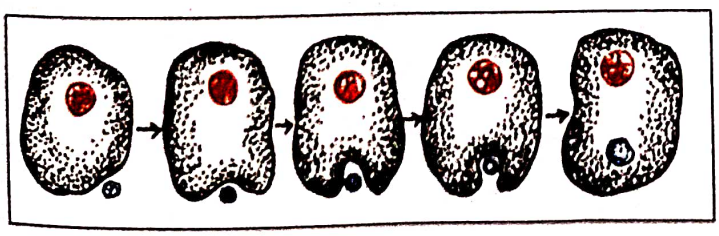


Fig. 1.20. *Endocytosis.*

The process of endocytosis involves various proteins at different stages. The proteins clathrins and caveolins are required for formation of the vesicles. Dynamin is related to its separation from the membrane and microtubules are involved in transport of the endosomes within the cell.

Endocytosis is basically of two types according to the contents of the endosome *viz.*, **pinocytosis** and **phagocytosis**. In **pinocytosis** the endocytosed material cannot be seen under microscope but in phagocytosis it can be seen. When pinocytosis involves only fluid it is called **fluid endocytosis** and it is called **adsorptive endocytosis** when the fluid contains some molecules in solution. Adsorptive endocytosis is receptor mediated and molecules endocytosed are many *e.g.*, low density lipoproteins and others. Endocytosis of large particles like bacteria, tissue debris by specialised cells like macrophage or microphage, is called **phagocytosis**.

CELL PROLIFERATION, GROWTH AND DIFFERENTIATION

Cells of the body grow in number, in size and are also modified to perform specific functions. Growing in number is called **multiplication**, increase in size of individual cell is called cell **growth** and modification to become capable of specific functions is called **differentiation**. These three processes make the complete human being from a single cell, *i.e.*, the fertilised ovum or the zygote.

This single cell through division and differentiation give rise to more than two hundered types of specialised cells, thus forming the cells of so many types of tissues present in the body. All these cells in adults do not show division, some have stopped dividing after birth and some before, while others continue to divide upto the death of the individual. Cells which do not divide after birth are the muscle cells and neural cells. Stem cells in bone marrow, enterocytes, etc, divide continuously. Some cells, *e.g.*, neutrophils stop dividing after maturation (differentiation) but others can divide even after maturation (lymphocytes).

The cell division is under the control of various protein factors *viz.*, growth factors, cyclins, cell division cycle kinase, (cdc kinase) and others. In the process, after adequate action of the growth factors the cyclins activate the cdc kinase which then activates the cell division.

Cell division

Division of a cell occurs by two processes : mitosis and meiosis. Meiosis is seen in the germ mother cells during the production of gametes. Mitosis is the process used by all other cells to increase their number.

Cell cycle

A dividing cell undergoes cyclical changes called cell cycle in which the cell remains silent (interphase) for some time and then divides; and again becomes silent to divide. This cell cycle can be subdivided as follows :

Osmosis

Osmosis means movement of water by diffusion. This movement occurs along the concentration gradient of water from a weak solution towards a strong solution. This is because the weak solution contains more water molecules and less solute whereas the strong solution contains more solute hence less water molecules. When water moves towards a concentrated solution through a semipermeable membrane which prevents movement of the solutes, the amount of pressure required to prevent this movement of water (osmosis) is called **osmotic pressure.** Osmotic pressure depends on the number of particles in the solution and not on the type or size or concentration of the substance. For example, 1 g of NaCl in 1 litre of water will exert more osmotic pressure than 1 g of glucose, as one NaCl molecule produces two particles ($NaCl=Na^+ + Cl^-$) and its mol. wt. is also less. So it provides more particles per gram than glucose.

Tonicity

The term tonicity is used to compare the osmolarity of a solution in respect of impermeant solutes with that of the plasma or extracellular fluid. **Isotonic** means the solutions of same osmolarity with plasma, *e.g.*, a 0.9% solution of NaCl, 5% glucose, etc. **Hypertonic** solutions have higher and **hypotonic** solutions have lower osmolarity than plasma. A cell placed in an isotonic solution will not change its size as there will be no net movement of water because the impermeant ions from the solution cannot move into the cell and water concentration in both remain same. When placed in hypotonic solution, the cell will swell but it will shrink in a hypertonic solution.

The term **isosmotic, hyperosmotic** and **hyposmotic** are used when the osmolarity is considered in total without regard to whether the solutes are permeant or impermeant.

Osmolarity of plasma is about 280 mosm/L. Of this, Na^+ contributes 143 mosm, Cl^- 108 mosm, HCO^-_3 24 mosm, glucose 5.6 mosm, urea 4 mosm, etc.

Note : Osmolarily of plasma is calculated from the freezing point depression as follows :

$$\text{mosm/litre} = \frac{\text{Freezing point depression}}{0.00186}$$. It can also be determined from the following formula : mosm/litre = 2 × [Na^+] in meq/litre + 0.055 × [Glucose] in mg% + 0.3 × [BUN] in mg%.

Osmotic tension

It is also called **osmotic pressure.** As the osmotically active particles may be crystalloids or colloids, osmotic tension also has two components : the crystalloid osmotic tension and colloidal osmotic tension. The total osmotic tension of plasma is 5450 mm of Hg (75% of this is due to NaCl). Osmotic pressure exerted by molar solution of a non-dissociable substance like glucose is 22.4 atmos but for a dissociable substance like NaCl it is higher depending on the number of particles produced by each mole in solution.

(i) **Crystalloid osmotic tension** : It is important in relation to the stability of RBC and also for the size of all the cells in the body. When the ECF becomes dilute (water enters inside) the cells swell up and when the ECF becomes concentrated (water goes out) the cells shrink.

(ii) **Colloidal osmotic tension** : It is the osmotic tension exerted by the colloids in a solution. The colloidal osmotic tension (COT) is of great importance in the body as the colloids in the body are not evenly distributed. For example, in plasma there are colloids like plasma proteins, plasma lipids, etc., but concentration of these colloids in ECF is negligible. So plasma has more COT than ECF which helps to keep water in it and thus to maintain its volume. It also regulates formation and absorption of tissue fluid.

Diffusion

It is the process by which molecules of a fluid or molecules of a substance in solution move to fill up all the available space. This is due to continuous random movement of all particles. This movement, also called thermal motion is shown by the molecules of all substances.

The diffusing particles can move with equal ease to high or to low concentration areas but the number of particles moving out of a high concentration area is more due to higher number of particles there (more from higher to lower). Thus the net flux is towards the less concentrated area; *i.e.*, along the concentration gradient or downhill (**flux** = amount of a substance passing in one direction in unit time). This movement in both directions continues until an **equilibrium** is reached, *i.e.*, when concentrations in both the sides become same and the number of particles moving from either side is same, *i.e.*, net flux is zero. So, it is a **dynamic equilibrium.**

Diffusion also occurs easily through biological membranes if they are permeable to the diffusing substances. But the rate of diffusion through a membrane is much less than that in water and far more less than in gaseous phase.

Diffusion is guided by **Fick s law** of diffusion (Fig.4.18) and the amount of substance diffused or passed through, is given by the equation :

$$Q = \frac{A}{T} . D . (C_1 - C_2)$$

Where Q = Amount of substance diffused or flux from higher to low concentration.
A = Area through which diffusion is occurring.
T = Thickness of the membrane.
$(C_1 - C_2)$ = Concentration difference.
D = Diffusivity of the substance in relation to the membrane through which diffusion occurs. It is the ratio of the solubility (S) of the substance in the membrane to the square root of the MW of the substance. *i.e.*,

$$D = \frac{S}{\sqrt{MW}}$$ (see, P. 122)

Diffusion is also effected by electrical gradient in case of charged particle like K^+, Na^+, (P. 155) so also by temperature. Many substances move by diffusion through capillary wall. These are oxygen, carbon dioxide, various nutrients and many others. Diffusion is an important mode of transport through the plasma membrane lining the cell or the organelles. Here the nonpolar substances can diffuse easily through the lipid portion of the membrane whereas the polar substances can not. Diffusion of many substances occurs through their channels. When channels are involved, the amount diffused will depend on the number of channels in open state.

GIBBS-DONNAN EQUATION

Diffusion of substances can occur through a membrane freely if the membrane is freely permeable to the substance and ultimately the concentration of the subtance becomes equal on either side of the membrane. A semipermeable membrane *e.g.*, cell membrane allows some particles to diffuse through it but not the others. If a semipermeable membrane (SPM) separates solutions containing both permeant and non-permeant ions, then diffusion of the ions will occur in a predictable manner, which can be expressed by Gibbs-Donnan equation.

Gibbs and Donnan proved that after equilibrium, the concentration ratio of the permeant ions in two sides (As shown below, in A and B) of the membrane will be equal (though, the side with impermeant ions will have more ions in total than the other), *i.e.*,

$$\frac{[\text{Cation}] \text{ in A}}{[\text{Cation}] \text{ in B}} = \frac{[\text{Anion}] \text{ in B}}{[\text{Anion}] \text{ in A}}$$

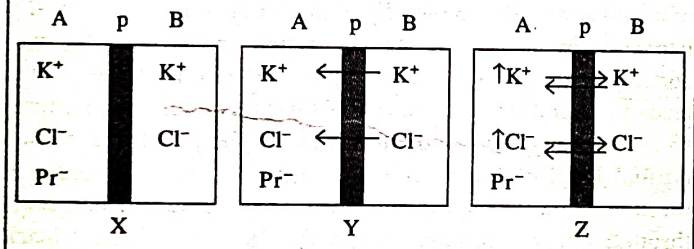
or, [Cation] × [Anion] in A = [Cation] × [Anion] in B.

This is **Gibbs-Donnan equation.**

Note : The product of concentration of ions on either side will be equal provided both the ions are monovalent or of same valency.

DONNAN EFFECT

Let us consider another situation with impermeant ions. The sides 'A' and 'B' are separated by a semipermeable membrane "p" in the systems X, Y and Z shown below. In X, both the sides are electrically neutral and [K^+] on either side is same.



(equilibrium)

So in the side B, there will be more Cl^- than in A as (Cl^- + Pr^-) in A = (Cl^-) in B. Now Cl^- will move down the concentration gradient to A and K^+ will follow to maintain the electrical neutrality, as shown in Y. The Pr^- can not move out due to its non-diffusibility through 'p', therefore the side A in Z will ultimately have more ions than in the side B (as it is gaining some Cl^- and K^+ but not losing any protein). Due to presence of slightly more ions on the side with non-permeant ions (*e.g.*, protein) there occurs a difference of osmotic pressure and due to this reason the cells swell up or the plasma volume increases (sides with protein), hence their volumes are maintained. This is called **Donnan effect.** Difference in the ion concentration as stated above also leads to electrical difference (see membrane potential). These effects are controlled by N^+–K^+ pumps, different ion channels and other mechanisms within limits of physiological advantage.

Note : The process of diffusion can cover only a small distance *e.g.*, within a cell or across the cell membrane. So this process can meet all the needs of an unicellular organism but cannot meet the demand of the whole human body. Here comes the role of circulation and other modes of transport.

Non-ionic diffusion

Suppose the molecules of some substances are soluble in a membrane but not its ions. So, once the molecules are ionised, the ions cannot diffuse through the membrane, *e.g.*, NH_3 can diffuse but not NH^+_4. Here NH_3 moves by non-ionic diffusion.

Mediated transport

This transport mechanism causes movement of substances with the help of carrier proteins. The amount transported depends on the concentration of the substance, number of transporters available and the behaviour (*i.e.*, the rate of conformational change) of the transporters. Unlike diffusion, it shows a highest limit which is reached when all the available carriers are engaged. There are mainly three types of mediated transport which are as follows :

Facilitated diffusion

Like diffusion, movement occurs here from higher to lower concentration but with the help of carrier and without any energy expenditure. In our body, glucose enters into the cells by this process with the help of glucose transporters (GLUT). Unlike simple diffusion, this process has a higher limit which is reached when all the carriers are pressed into action, *i.e.*, saturated. Like diffusion, it stops when the concentration gradient is lost.

Primary active transport

Transfer of materials against concentration and/or electrical gradient by protein pumps with expenditure of energy derived directly from ATP hydrolysis is called primary active transport, *e.g.*, Na^+ is pumped out of the cells by Na^+ pump.

Secondary active transport

It is the process where concentration gradient of one is utilised for the transport of another, *e.g.*, sodium dependent glucose transporter (SGLT) transports glucose into the cell along the concentration gradient of Na^+. Similarly Na^+-Ca^{2+} exchanger removes Ca^{2+} by using Na^+ gradient. As energy is spent to maintain the Na^+ gradient, this type of transport is called secondary active transport. If energy supply is stopped this system will also stop.

Note : (i) **Bulk flow** : When a fluid moves en masse (*i.e.*, all together) in one direction, then it is called bulk flow, *e.g.*, flow of blood in blood vessels, flow of air in the bronchi, movement of fluid during filtration, etc.

(ii) **Solvent drag** : When a solvent moves by bulk flow it tries to carry some solute with it and the process is called solvent drag *e.g.*, during filtration.

Applied Physiology

The knowledge about movement of substances in the body is utilised in clinical practice. For example, anaesthetic gases which can move into the brain freely are used to make anaesthesia during operation. If there is a disease in a part of the body we should select a drug which can move into the affected part. With this knowledge, the side-effects of the drugs are also avoided, *e.g.*, atenolol, a medicine for high blood pressure cannot enter brain, so it has less side-effects than the antihypertensive drugs which can enter the brain *e.g.*, reserpine.