

MOVEMENTS |

Structure

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5.1 INTRODUCTION

In the previous Block you have read about the physiology of nutrition, respiration, circulation, and excretion in animals. In this unit of Block 2 of Volume 2, you will learn about the physiology of movement in animals. Animals sense the changes in the environment and respond accordingly and appropriately. These responses usually are in the form of movement of some sort. From one celled organisms to humans, all respond to external and internal stimuli and the response is usually in the form of movement. Often we consider movement in connection with locomotion, i.e., an organism moving from place to place, or a cell moving away from or towards a source of stimulus. It is a characteristic and fundamental property of animals. However, even animals that remain attached and never show locomotion, such as corals and sponges; barnacles and sea anemones exhibit a variety of movements. They rely on the movement of their individual cells to accomplish circulation and respiration.

There are three basic mechanisms used by animals and individual cells to achieve motion. These are: i) muscular movement, ii) amoeboid movement, iii) ciliary and flagellar movement.

Muscular movement is the fundamental mechanism used in the majority of animals for a variety of movements. Muscle has the ability to exert force by shortening which is called 'muscle contraction'. This force is the basis of all kinds of movements internal as well as external in animals. Individual cells also move: their internal movement is referred to as cytoplasmic streaming and their external locomotion is brought about by amoeboid movement (which derives its name from the locomotion in *Amoeba*), or by cilia and flagella. Cilia are found in all animal phyla and serve a variety of functions. Cilia (sing: cilium) enable movement of entire cells such as seen in the movement of single celled paramecium in water, set up currents that move water through the water vascular systems of various invertebrates of which echinoderms are a good example. Ciliated cells also line the lungs and respiratory tract of vertebrates and slowly remove the foreign particles that lodge on cell surfaces. The sperms move with the aid of a tail that is a flagellum.

In this unit you will learn about structure of different types of muscles and the mechanism of muscle contraction involved in movement of muscles. You will also learn about the cytoplasmic streaming involved in amoeboid movement as well as the structure of cilia and flagella and the mechanisms involved in ciliary movements.

Objectives

After studying this unit you should be able to:

- ❖ differentiate between the structure and function of skeletal, cardiac and smooth muscles;
- ❖ explain the molecular basis of muscle contraction;
- ❖ describe the mechanisms that regulate muscle contraction;
- ❖ identify the components of the neuromuscular junction, and summarize the events involved in the neural control of skeletal muscle contraction and relaxation; and
- ❖ explain the physiology of amoeboid movement, ciliary and flagellar movements.

5.2 TYPES OF MUSCLES

Before we start our study of muscle movement we must learn about the muscle tissue present in animals. Muscles cells or myocytes have the special ability to contract in order to produce movement in the body organs and in the body as a whole. The contractile proteins actin and myosin are present in these cells that grant them their contractability. Vertebrate muscles can be categorized into three types: **skeletal muscles, cardiac muscles and**

smooth muscles (Fig 5.1 and 5.2). Each type of muscle has a unique structure and specific role. However, all three muscle tissue have the property of excitability- that is, their plasma membranes can change their electrical states (from polarized to depolarized) and send an electrical wave called an action potential along the entire length of the membrane that causes contraction of the muscle. Differences among the three muscle types include the microscopic organization of their contractile proteins, their location in the body, and their control mechanisms. Morphologically vertebrate muscle tissue can be distinguished as **striated** and **smooth**.

Striated muscles when seen under a microscope appear to **have alternating transverse dark and light bands**, and hence they are named as striated muscles. **Striated muscles** can be **divided** into two types of muscles: **skeletal** and **cardiac**.

5.2.1 Skeletal Muscles

Skeletal muscles are attached to the bones in the arms, legs, vertebral column and other parts of the skeleton. The skeletal muscles cells are long and multinucleated showing regular stripes or striations under the microscope (Fig.5.1 A). These striations are due to the regular arrangement and alignment of contractile myofibrils actin and myosin present in them. Skeletal muscles are the major muscles in the body and are responsible for all the activities like walking, movements of the head, hand, etc. These muscles are usually under **voluntary** control of the individual and get their signals to contract exclusively through spinal or cranial nerves. We will learn about their structure and working in greater detail in the next section.

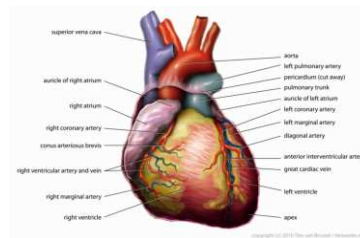
5.2.2 Cardiac Muscles

Cardiac muscles, as the name suggests are the muscles of the heart. Cardiac muscles are also striated however; the striations in them are not aligned as seen in skeletal muscles. Cardiac muscles are not as long as the skeletal muscle fibre. They contain a large number of mitochondria and abundant reserves of myoglobin as they solely depend on aerobic metabolism for their energy for contraction.

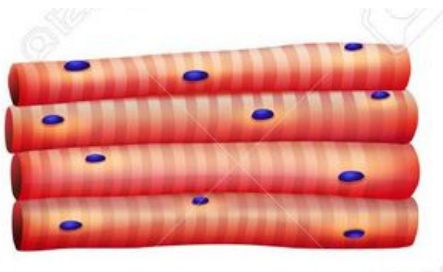
Cardiac muscle cells are branched and mononucleated although a few may have 2 or more nuclei (Fig.5.1B). One end of a cardiac muscle fibre (cell) is connected to another cardiac muscle fibre by means of intercalated discs. The branching of the cardiac muscle ensures that there is swift communication between the cells, allowing coordinated wave like contractions. Thus, as a result they are specialized for continuous rhythmic contractions of the heart needed for pumping blood. **Cardiac muscles are not under voluntary control and so are involuntary muscles.** Their rhythmic contractions (as you will recall from earlier “Unit 3- Circulation” of this course) are regulated by the sinoatrial node of the **heart**, which serves as the **heart's** pacemaker.



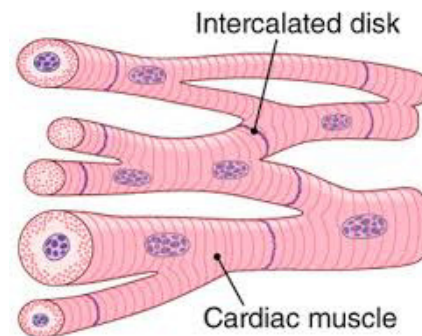
(a)



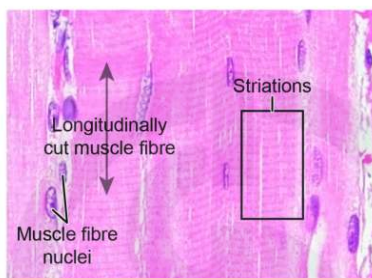
(a)



(b)

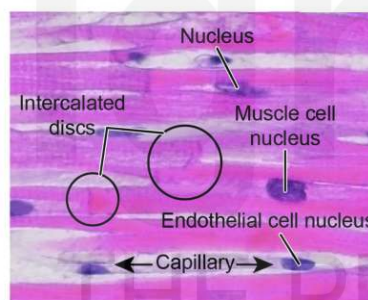


(b)



(c)

A SKELETAL MUSCLE



(c)

B CARDIAC MUSCLE

Fig. 5.1: Striated muscles: A) Skeletal muscle (a) are attached to bones; (b) external appearance of skeletal muscles;(c) photomicrograph of a longitudinal section of a vertebrate skeletal muscle tissue showing muscle cells or fibers that are multinucleated with definite striations.(B) Cardiac muscles(a)are present only in the heart; (b) external appearance of cardiac muscles;(c) photomicrograph of a longitudinal sections of vertebrate cardiac muscle cells which usually have one nucleus per cell. Cardiac cells are branched and have intercalated discs that connect the cells. (photomicrograph of muscle cells or fibers (Retrieved from Hill, M.A. (2020, April 27) Embryology ANAT2241 Muscle Tissue:from https://embryology.med.unsw.edu.au/embryology/index.php/ANAT2241_Muscle_Tissue

5.2.3 Smooth Muscles

Smooth muscle cells are **fusiform** and **uninucleated** (Figs. 5.2). Smooth muscle cells also contain the actin and myosin filaments which are however,

not arranged in a pattern in the cell, instead they are scattered in the cell. However the mechanism of contraction of smooth muscles is similar to the striated skeletal muscles. Smooth muscle cells show greater elasticity and can maintain their contractibility even when stretched. **A stretched smooth muscle adapts to its new length and retains its ability to contract on demand.** This ability of the smooth muscle cells is known as **plasticity** and is especially important in digestive organs which are subject to changes in volume (like the stomach). Smooth muscle contractions can be just as powerful as those of skeletal muscle cells.

Smooth muscles are present in the walls of internal organs such as large and small intestines, gall bladder and large blood vessels. Contraction of smooth muscles causes the diameters of blood vessels to increase or decrease and also helps propel the food down through the digestive tract. **Smooth muscles** are known as **involuntary** muscles as they are not under conscious control but are controlled by the autonomic nervous system.

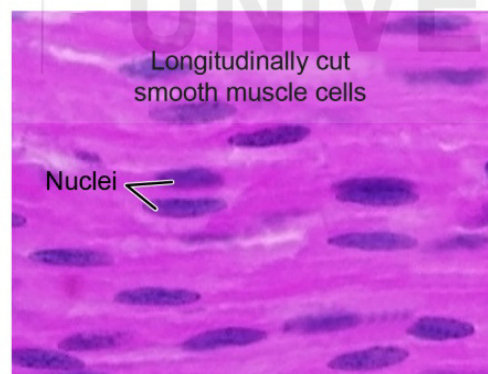
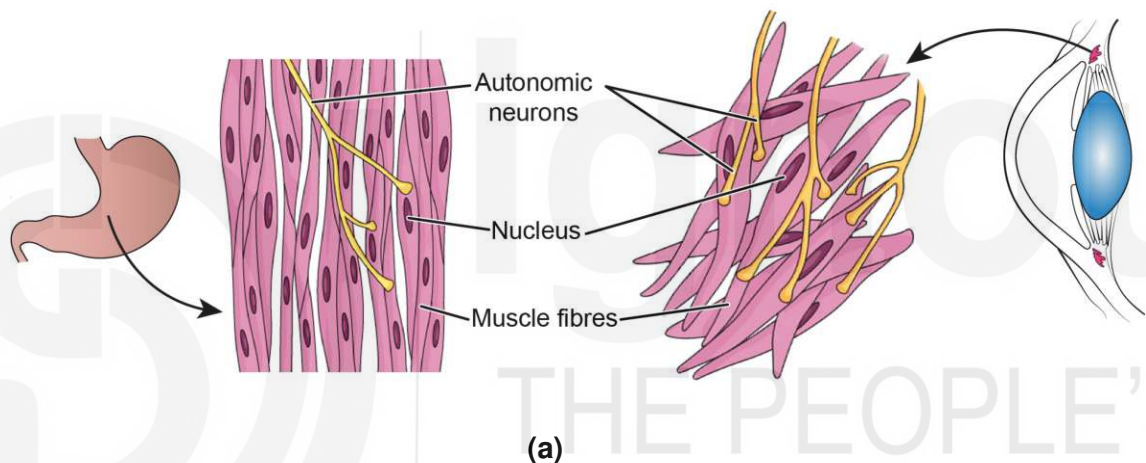


Fig. 5.2: (a) Smooth muscle cells are uninucleated and regulated by the autonomic nerves, therefore, not usually under voluntary control of the animal. (b) photomicrograph of a longitudinal sections of vertebrate. (photomicrograph of muscle cells or fibers (Retrieved from Hill, M.A. (2020, April 27) Embryology ANAT2241 Muscle Tissue:from https://embryology.med.unsw.edu.au/embryology/index.php/ANAT2241_Muscle_Tissue

SAQ 1

- a) List the three types of muscle tissue and give their major functions.
 - b) Fill in the blanks and compare your answers with those given at the end of this unit:
 - i) and are called striated muscles because under the microscope they exhibit transverse light and dark bands alternate to each other.
 - ii) muscles are under the control of will therefore are usually called while are not under the control of the conscious mind and are therefore called
-

5.3 STRUCTURE AND MOVEMENT OF MUSCLES

Let us now study the structure and functioning of skeletal muscles. Recall from the previous section that the most important property of skeletal muscle is contraction and the resulting movement. They not only cause movement but also stop movement and resist gravity to maintain the body's posture. Each skeletal muscle is made up of integrated tissue let us learn about the organization and ultra structure before we study the mechanism that causes it to contract.

5.3.1 Vertebrate Skeletal Muscles

Look at Figures 5.3 and 5.4 while you read this description of the structure of a skeletal muscle. A skeletal muscle contains connective tissues, blood vessels, nerves and the skeletal muscle tissue. The entire muscle is enclosed in a dense layer of collagen known as **epimysium** (epi=on mys=muscle). The epimysium separates the entire muscle from the surrounding tissues and allows it to contract and move powerfully while still maintaining its structure. If you cut a cross section of the muscle you will see that the muscle appears to be divided into compartments by another layer of connective tissue known as **perimysium**. The perimysium contains collagen, elastin and also encloses the blood vessels and nerves that supply the muscle. Each compartment formed by the perimysium contains a bundle of muscle fibers known as **fascicle**. This fascicular organization is common in muscles of the limbs and allows the nervous system to trigger a specific movement of a muscle by activating a subset of muscle fibers within a bundle, or fascicle of the muscle. Each fascicle is made up of a number of long, cylindrical **multinucleate muscle cells** or **muscle fibers**, arranged parallel to each other. Muscle fibers are the individual contractile units within a muscle. Individual muscle fibers in the fascicle are enclosed in a delicate connective tissue layer –the **endomysium** that interconnects adjacent muscle fibers. This endomysium layer contains the blood capillaries, and nerve fibers that supply the muscle fibers and also embryonic muscle cells that function in muscle repair. All these three connective tissue layers namely, **epimysium, perimysium and**

endomysium, are interwoven and together form the tendon at the end of the muscle, which connects to the bone. In addition, every muscle fiber in a skeletal muscle is supplied by the axon branch of a somatic motor neuron, which signals the fiber to contract. Unlike cardiac and smooth muscle, the only way to functionally contract a skeletal muscle is through signaling from the nervous system

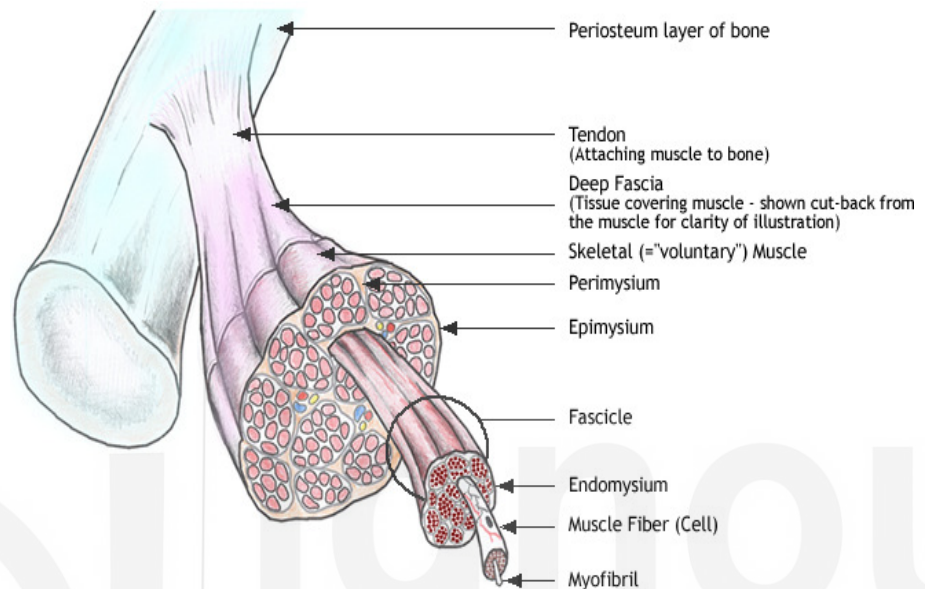


Fig: 5.3: Organization of the skeletal muscle.

Let us now examine the microscopic structure of the muscle cell or fiber as it will help you to understand the physiology of muscle contraction.

A muscle cell is different from a typical cell that you read about earlier. It is much larger and longer than most cells in the body and is multinucleate. The skeletal muscle fibers or muscle cells are arranged parallel to each other.

Each skeletal muscle fiber or muscle cell contains hundreds of nuclei scattered just beneath the cell membrane. The multinucleate structure of the muscle fibre is due to the fact that during the development of the muscle tissue, the individual precursor cells fuse together to form a new, combined structure with many nuclei—the mature muscle fiber. That is why muscle fibers do not follow the general rule of one nucleus per cell and each fiber is made up of several cells that are combined into one. Some adult muscle fibers still have one of these tiny precursor cells called **satellite cells** attached to their outer boundary. The **satellite cells** are stem cells that fuse with myocytes during strength training to make bigger muscle fibers. The satellite cells can also become active after a muscle injury to produce more muscle fibers. Scientists are still trying to understand this mechanism better in the hope of developing new therapies for replacing lost muscle tissues.

The advantage of the skeletal muscle fiber being multinucleate is that the multiple copies of genes in these nuclei can direct the production of proteins and enzymes needed for muscle function at a much faster rate than it could have done if there was only one nucleus per cell.

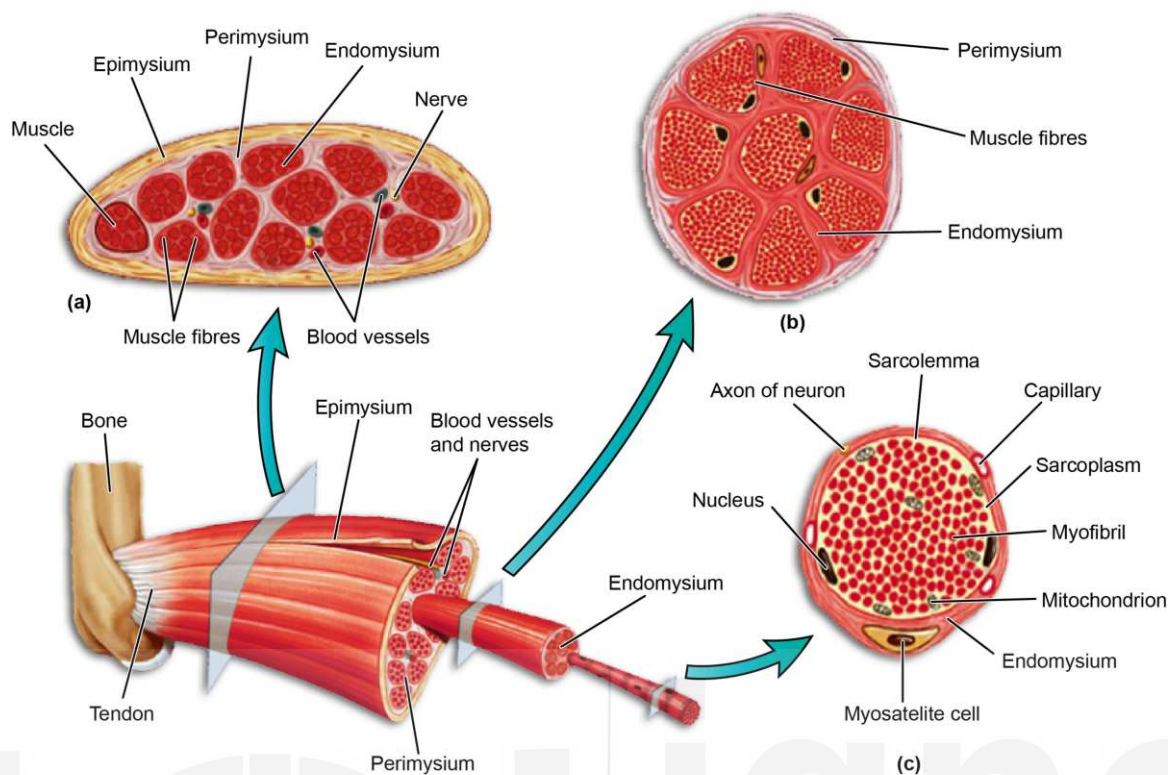


Fig: 5.4: Organization of the skeletal muscle. Cross section of: a) skeleton muscle (organ); b) bundle of fibres composing the muscle fascicle; c) individual muscle fibre (cell).

The plasma membrane of each fiber is known as a **sarcolemma** and the cytoplasm inside the cell is known as **sarcoplasm**. The sarcolemma like other plasma membranes has a transmembrane potential difference. A sudden change in its membrane potential causes the muscle fiber to contract. Even though the muscle fiber is quite long it is able to contract simultaneously and this can happen only if the signal is transmitted quickly throughout the muscle fiber. This is because a unique system of interconnecting **transverse tubules or T tubules are present in the muscle fibre (cell) and are responsible for the quick transmission of signal in them.**

The Transverse tubules are formed by inward extensions of the sarcolemma and extend transversely across the sarcoplasm, at right angle to the long axis of the cell (Fig 5.5). These tubules pass down into the muscle cell and go around the myofibrils (single unit of the muscle fiber). The T tubules DO NOT open into the interior of the muscle cell instead, after returning from the muscle they open somewhere else on the sarcolemma. Thus, these tubules do not function to get things into and out of the muscle cell, instead they function to conduct impulses from the surface of the cell into other structures present in the cell called the **sarcoplasmic reticulum**. The **sarcoplasmic reticulum (SR)** are similar to endoplasmic reticulum of cells and flank the T tubules. The SR expands on either side of the T tubule and forms chambers called **terminal cisternae**. Ca^{2+} are actively transported from the sarcoplasm and stored into the terminal cisternae. The concentration of bound and free Ca^{2+} in these cisternae can be up to 40,000 times than that in the surrounding sarcoplasm. These storehouses of calcium release the calcium ions in the region where the thick and thin filaments interact. **The combination of a pair of terminal cisternae plus T tubule is known as a triad.** The function of the

triad is to conduct electrical signals from the surface of the cell sarcolemma down and deeper into the muscle cell, and then specifically, into the **sarcoplasmic reticulum**.

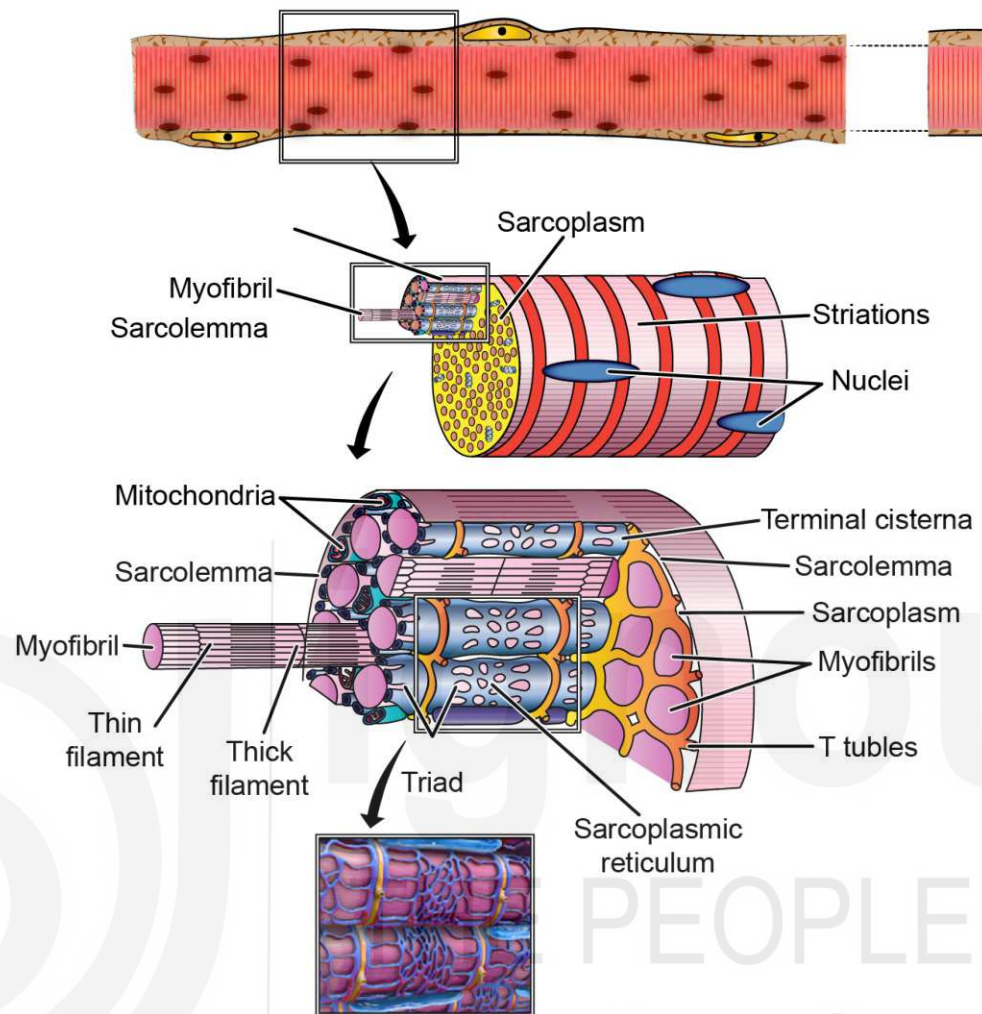


Fig. 5.5:a) Structure of a single muscle fiber,b) showing the organization of myofibrils and sarcoplasmic reticulum surrounding them. (based on Fig10.2 and 10.3 Martini).

An additional structure not found in other cells but present in skeletal muscle fibers **are the myofibrils**. Each skeletal muscle fiber is packed with a thousand or more of tightly packed contractile elements known as myofibrils. These myofibrils are 1-2 μm in diameter and are as long as the cell. Myofibrils, in turn, are made up of still finer fibers called **myofilaments which** are of two types: **thick filaments and thin filaments**. You can see in Figures 5.5 and 5.6 at a glance that some of the filaments are much thicker than others. Although they appear in contrasting colors in the diagram, they are actually colorless

Inside the muscle fibers the **myofibrils are** encircled by the T tubules. The T tubules attach to the **sarcoplasmic reticulum (SR)**, at the point at which they encircle the myofibril.

Each myofibril as you have learnt earlier is made up of bundles of myofilaments. The myofilaments are made up of (i) mainly two kinds of protein filaments **actin** known as thin filaments and a motor protein **myosin** or thick filaments; (ii) proteins that stabilize the position of these two filaments; (iii)

proteins that regulate the interactions between the thick and thin filaments. The myofilaments of the muscle fibers are organized into repeated units known as **sarcomeres** that are arranged end to end and are the functional units of the muscle fibers. The distribution, arrangement and size of the thick and thin filaments give the myofibril its typical banded or striated appearance. Figure 5.6 shows the composition of a resting sarcomere. You can see alternating dark and light bands in it. The dark band are known as the **A bands** and the light band are known as the **I bands**.

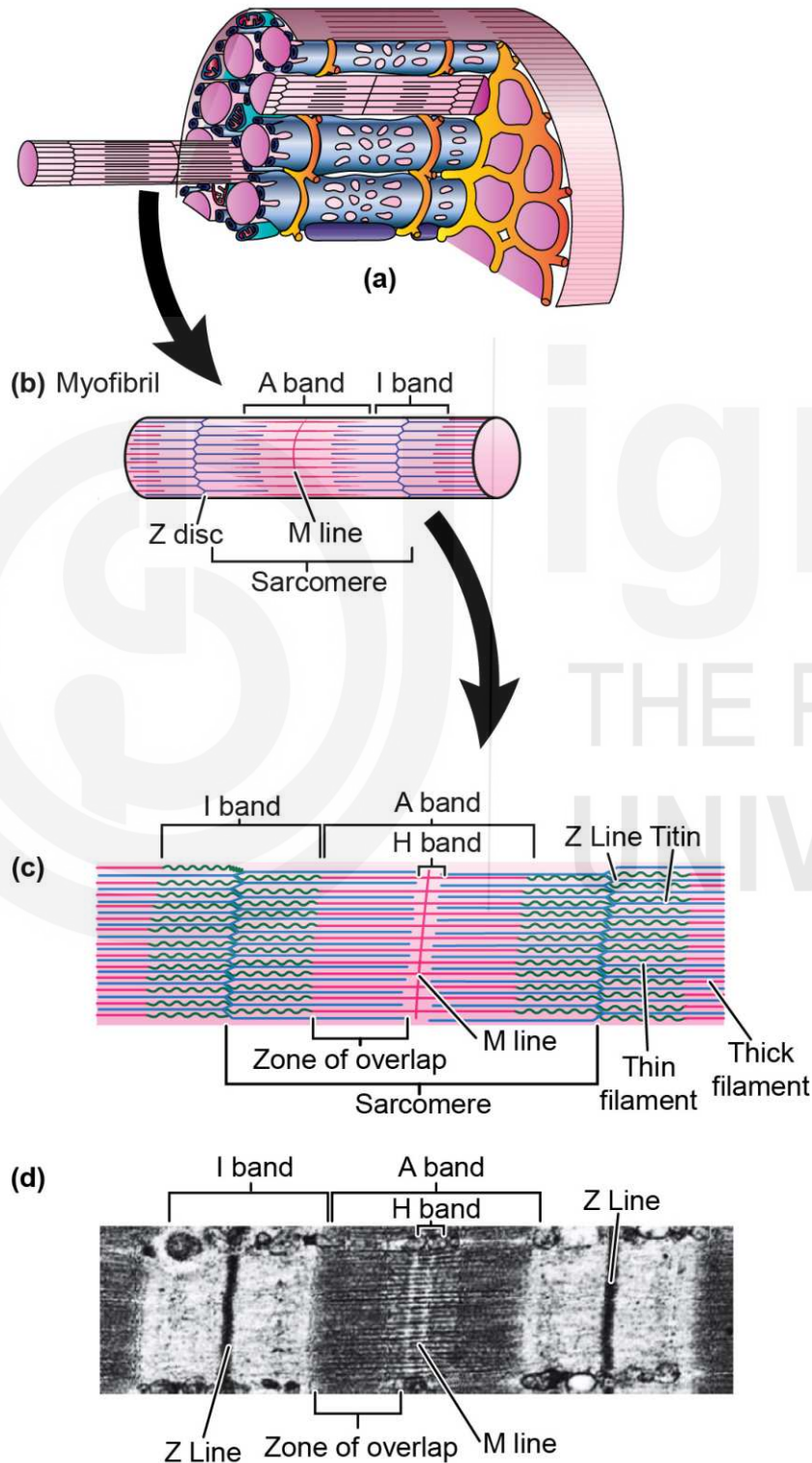


Fig. 5.6: Longitudinal view of sarcomere: a) diagrammatic representation and b) electron photomicrograph. (remove the matter written on the sides of the figure under a and b).

The A band of the myofibril contains myosin filaments in the center and the overlapping parts of actin filaments. The length of the A band is equal to the length of the myosin filaments and can be further divided into three regions (see Fig. 5.6 to understand the arrangement):

The central M line of the myofibril is made up of proteins that connect all the myosin filaments. These proteins stabilize the position of the myosin fibers.

The H zone in a resting sarcomere is a slightly lighter band on each side of the M line. This zone contains only myosin but no actin.

The zone of overlapping thick and thin filaments that gives the striated appearance to the muscle.

The I bands contain only the actin filaments and extend between the A band of one sarcomere and the A band of the next sarcomere.

The boundaries of each sarcomere are marked by the **Z lines** which are made up of a protein called **actinin**. The actin filaments of adjacent sarcomeres are attached to each other by actinin. Actin fibers extend on each side of the Z lines towards the center of the sarcomere making up the zone of overlap.

Strands of another protein **titin** extend from the tips of the myosin fibers and attach to the Z lines, keeping the thick and thin filaments aligned and preventing the sarcomere from stretching too far as this would disrupt the contraction mechanism.

At each end of the muscle fiber the myofibrils are attached to the inner surface of the sarcolemma. The outer surface of the sarcolemma is attached to the collagen fibers of the tendon by which the muscle is attached to the bone (Refer again 5.3 and 5.4). So when the myofilaments contract the entire cell shortens and the muscle is pulled. Scattered among the myofilaments in the muscle cell are mitochondria and glycogen granules (the storage form of glucose in animals) that provide the energy for the muscle activity. Let us now look at the molecular structure responsible for the mechanism of muscle contraction.

5.3.2 Molecular Basis of Muscle Movement

You have studied in the earlier section that the thick filament is made up of myosin and the thin filaments are mainly made up of actin. Each thick filament is 10-12 nm in diameter and 1.6µm in length. It is roughly composed of about 500 myosin molecules. A myosin molecule contains two heavy chains; part of a heavy chain makes up one head and the other part extends the length of the tail. The Myosin heads also contain four smaller light chains. Each myosin molecule thus is a double stranded globular protein twisted around each other, with a tail region and a head region. The tails of many myosin molecules in a thick filament are bound together and extend towards the M line in the center of the sarcomere. Whereas, the globular heads project to the side forming the cross bridges (Fig. 5.7).

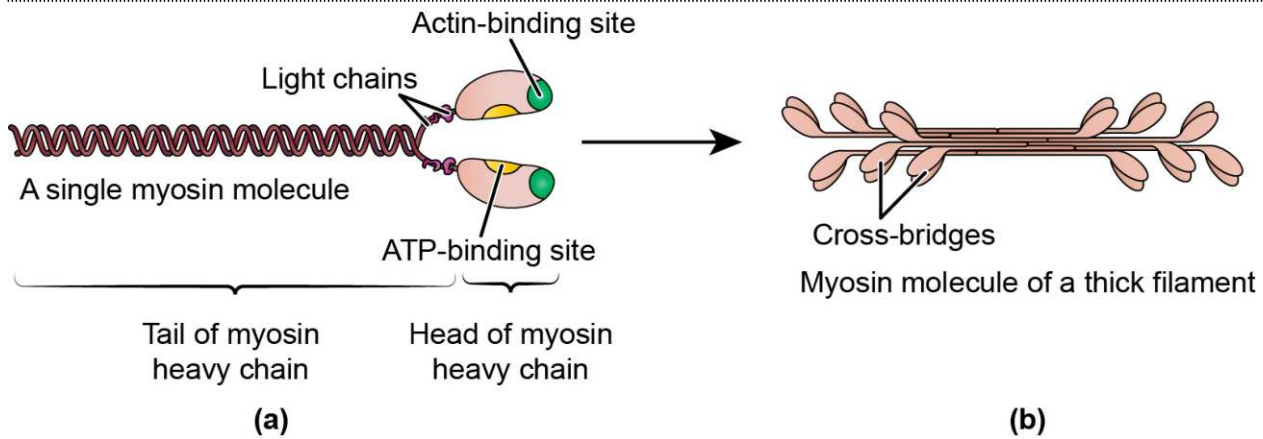


Fig. 5.7: Single myosin molecule consists of two heavy chains and four light chains making the two heads with the actin binding and ATP binding sites and the tails that combine with tails of other myosin molecules to form the thick filament.

The heads are arranged in a spiral, extending towards the nearest thin filament and placed away from the M line. Thus there is a central region in the H zone that appears lighter in colour as there are no heads in that area. The heads of the myosin molecules are formed of two subunits and interact with the thin filaments forming cross bridges during the contraction mechanism as we will see in the next section. The connection between the head and tail forms the pivot that swings the head to form the cross connections with the adjacent thin filament. In the center of each thick filament and extending from it on either side of the M line to the Z line, is present the thin strand of a protein -**titin**. The exposed part of titin protein in the I band is highly elastic and coiled. In the resting sarcomere this protein remains relaxed and becomes tense only when the sarcomere stretches. (See Fig 5.8).

The thin filaments are 5-6 nm thick and 1µm long. A single thin filament is actually made up of 4 different proteins namely, **Filamentous (F) actin** which is often simply referred to as actin, **nebulin**, and two regulatory proteins **tropomyosin** and **troponin** (Fig 5. 8). F actin is a linear polymer made up of two rows of 300-400 molecules of a globular protein G- actin which are twisted around each other in a helix . Each G-actin molecule contains an active site, where myosin heads (in the thick filaments) can bind. Nebulin protein extends in the cleft between the two strands of G actin molecules (that make up the F – actin). The nebulin molecule holds the two strands of G actin molecules together and the length of the F actin strand is determined by the length of the nebulin molecule. When the muscle is at rest, strand of tropomyosin cover the active sites and prevent the actin –myosin interaction. Each tropomyosin molecule is a double stranded protein and covers 7 active sites and is bound to one molecule of troponin in the middle of its length. A troponin molecule consists of three globular subunits one of which binds to tropomyosin forming the **tropomyosin- troponin** complex ; one subunit binds to one G actin molecule keeping the tropomyosin – troponin complex in position and one subunit has a receptor that binds to a Ca^{2+} . Since the Ca ion concentration in the resting sarcomere is very low this site remains empty before contraction starts.

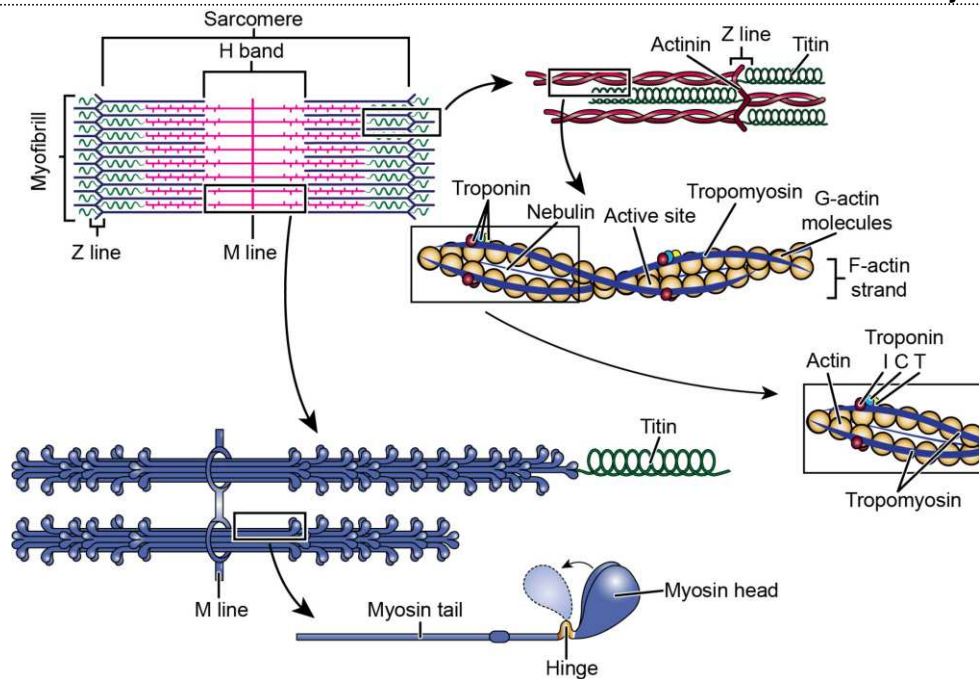


Fig. 5.8: Structure and arrangement of thick and thin myofilaments in the muscle cell.

SAQ 2

- a) Match the alphabet designating zones in the myofibril given in Column A with their description given in Column B :

Column A

- i) H- zone
- ii) A- band
- iii) M- line
- iv) Z- disc
- v) I- band

Column B

- a. central line of the sarcomere where myosin filaments are anchored
- b. the area where only actin filaments are present
- c. a line that separates one sarcomere from another
- d. the area where only myosin filaments are present
- e. includes overlapping myosin and actin filament

- b) Fill in the blanks and compare your answers with those given at the end of this unit:

- i) The entire muscle is covered by an
- ii) Bundles of muscle fibers (cells) are sheathed by a and each muscle fiber is surrounded by an
- iii) Myofibrils contain myofilaments called and filaments.
- iv) Thin myofilaments consist of, ..., - and

5.3.3 Sliding Filament Mechanism

Now that you know how the molecular structure of individual myofibrils let us see how they act to contract the muscle cells. Muscle contraction is a physical activity that generates force and causes the shortening of the muscle. In order for a muscle cell to contract, the sarcomere must shorten. A sarcomere is defined as you will recall from the earlier section of this unit as **“the distance between two consecutive Z discs or Z lines”**. When a sarcomere contracts the distance between the Z discs is reduced. In addition, some regions of the sarcomere shorten whereas others stay the same length when a muscle contracts.

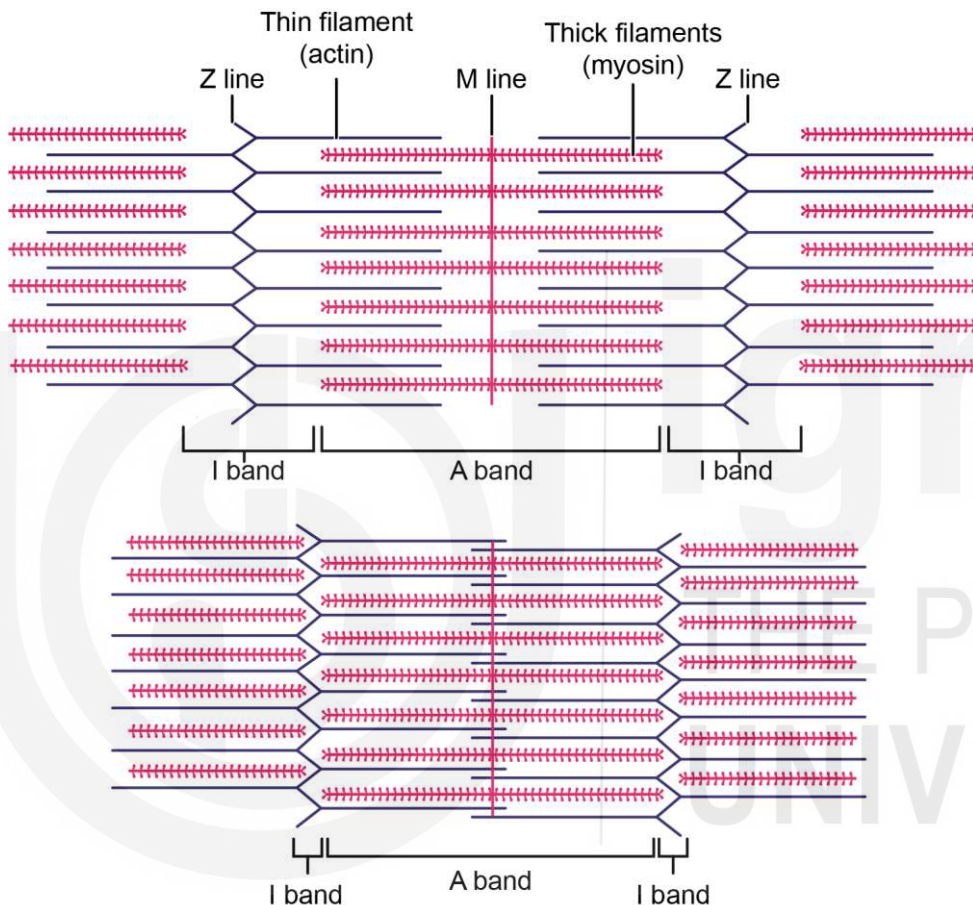


Fig. 5.9: Steps in contraction of skeletal muscles.

In this process of contraction of the sarcomere (See Fig. 5.9)

- the A band that contains thick filaments of myosin, remains constant in width while the width of other regions of the sarcomere shorten.
- The width of both H zone that contains only myosin filaments and the I band that contains only filaments of actin, decrease in length
- Furthermore, the zone of overlap, in which thin filaments and thick filaments occupy the same area, increases.
- The contraction weakens with the disappearance of the I bands, at which point the Z lines come in contact with the end of the thick filaments. The sarcomeres in the entire length of the myofibrils come closer to one another thus shortening the myofibril. All these changes during the

contraction of sarcomere can only be explained if we consider that the thin filaments are sliding past the thick filaments in order to move towards the center of the sarcomere.

These observations were first made in 1954 by two independent teams, H.E. Huxley and Hanson and A.W Huxley and Niedergerke who proposed the 'sliding filament model' which has been experimentally confirmed.

The next step in the study of muscle contraction was to find out what is the exact mechanism by which the actin molecules slide past the myosin molecules and what caused the muscle contraction? Let us first examine what causes the contraction.

5.3.4. Neural Control of Muscle Contraction

A normal skeletal muscle fiber contracts **only under the control of the nervous system**. Each muscle fiber receives midway along its length, an electrical signal by the axon of a motor neuron originating in the spinal cord or in the brain stem. The point where it receives the axon terminal is known as the **neuromuscular junction**. The axon of the neuron branches at this junction to form a fine network. Each branch of which, expands to form the synaptic terminal, making contact with the sarcolemma on the surface. The junction between the axon and the muscle fiber with which it communicates is called the **synapse**. The neuromuscular junction (NMJ) is a microstructure through which the process of contraction is initiated or halted in the muscles by the neurons. At the junction of the synaptic terminal and the sarcolemma, **acetylcholine** a neurotransmitter is released that changes the permeability of the muscle membrane. Both neurons and skeletal muscle cells are electrically excitable, meaning that they are able to generate action potentials across their membranes (you will learn in detail about this property in Unit 6). An action potential is a special type of electrical signal that can travel along a cell membrane as a wave. This allows a signal to be transmitted quickly and faithfully over long distances. The part of the synapse that is on the side of the axon is called the **presynaptic terminal** and the part on the side of the skeletal muscle cell is called the **postsynaptic terminal**. Between these terminals, there exists a gap, called the **synaptic cleft** (Fig 5.10 a).

Each pre-synaptic knob contains many mitochondria and secretory vesicles filled with neurotransmitter acetylcholine (ACh). The synaptic cleft allows the neurotransmitters to diffuse and reach the other side of the neuromuscular junction or the synapse. It also contains enzymes for the degradation of the excess or extra neurotransmitters (Fig 5.10 b).

The postsynaptic membrane (sarcolemma) of the skeletal muscle fiber lies directly under the nerve terminal and is characterized by extensive invaginations known as **postjunctional folds** which provide surface area for additional ACh receptors. These **postjunctional folds** often called the motor end plate. The neurotransmitter acetylcholine, released from the pre-synaptic knob diffuses across the space of the synaptic cleft and binds to its receptors in the sarcolemma changing the permeability of the muscle membrane (Fig.5.10 c).

This process takes place in the following steps :

1. An action potential arrives at the synaptic junction which stimulated the release of acetylcholine.

2. Acetylcholine molecules diffuse across the cleft and bind to receptors on the surface of the sarcolemma on the motor end plate, opening a channel in the receptor for positive ions and the membrane begins to depolarize (becoming less negative)
3. As the membrane depolarizes another set of ion channels known as voltage gates sodium ion channels open granting permeability to sodium ions

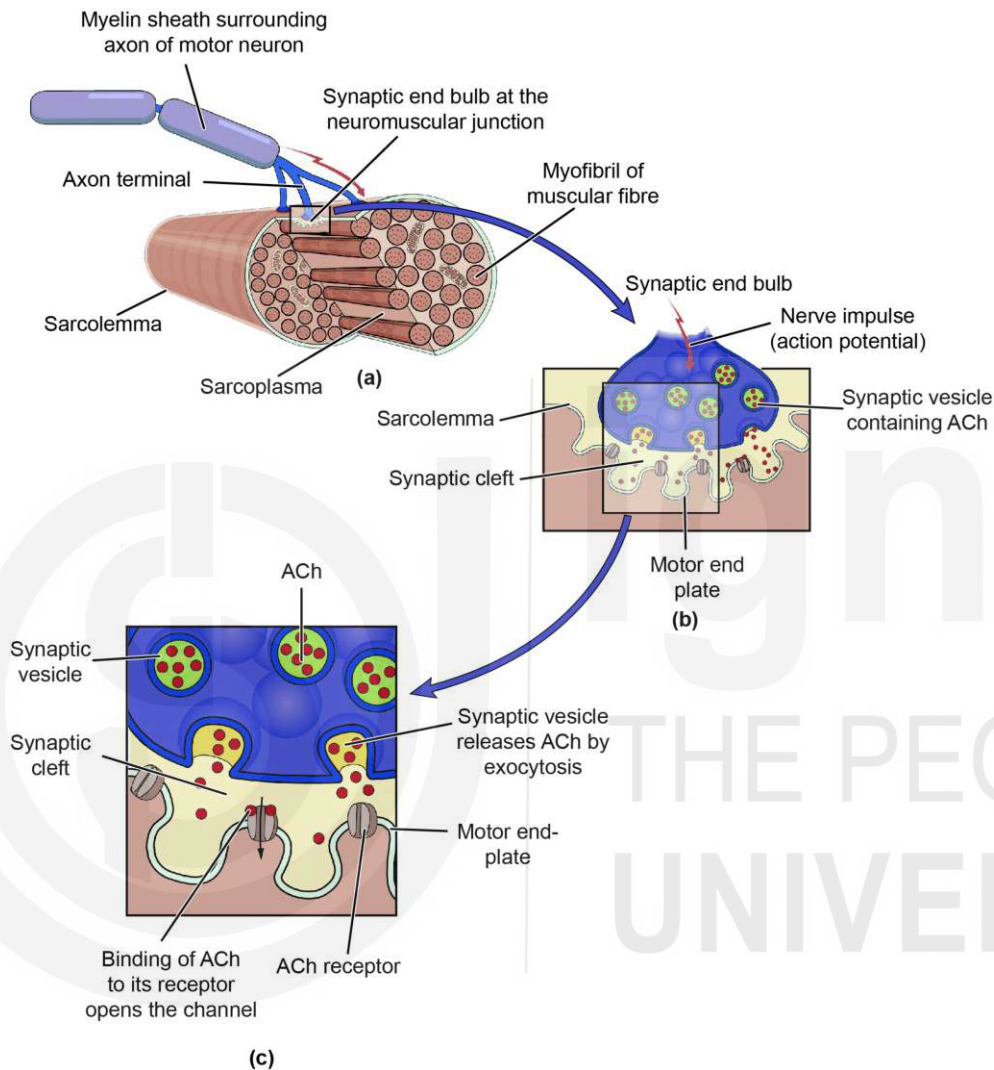


Fig 5.10: a) A diagrammatic representation of a muscle fiber with its neuromuscular junction; b) enlarged view of a neuromuscular junction; and c) detailed view of a terminal synaptic cleft and motor end plate. (add (a) ,(b), and (c) to the diagram, I prefer this one it is neater and less complicated that the one given before)

4. Sodium rushes in generating an action potential in the sarcolemma. The action potential thus generated travels along the surface of sarcolemma rapidly entering along the T tubules to initiate the “excitation-contraction coupling”
5. On reaching the cisternae of the sarcoplasmic reticulum, the action potential causes the release of Ca^{2+} which within a millisecond of release increases to 100 times the resting concentration. As the terminal cisternae are situated at the zone of overlap of the thick and thin filaments, the effect is instantaneous,

6. Even before the action potential has traveled through the sarcolemma surface the acetylcholine molecules are broken down by acetylcholinesterase. Some of these are reabsorbed by the synaptic membrane to be reused and the sequence of steps is ready to be repeated again.

The propagation of action potential along the sarcolemma is the excitation part of the excitation-contraction coupling. On reaching the cisternae of the sarcoplasmic reticulum, the action potential causes the release of Ca^{2+} which within a millisecond of release increases to 100 times the resting concentration. As the terminal cisternae are situated at the zone of overlap of the thick and thin filaments, the effect is instantaneous.

5.3.5 Role of Calcium and Regulatory Proteins

Recall from the earlier subsection 5.3.2 that troponin has an active site for binding calcium and a site that binds to tropomyosin. In a muscle at resting state tropomyosin prevents the interaction between the thick and thin filaments by blocking the cross bridge binding sites of F actin molecules (Fig. 5.11). The troponin which acts as a regulatory protein has a high affinity for calcium ion. Thus calcium acts as a key to unlocking those sites of F actin molecules. Ca^{2+} binds to the site on troponin and changes its shape. This weakens the bond between troponin and F actin. Troponin moves away pulling tropomyosin away from the active sites on F actin allowing the myosin heads to attach to the actin and the thin filaments slide past the thick filament towards the centre of the sarcomeres. But each head that attaches to actin can pull it a very short distance before it reaches its limit. So it needs to detach and 're-cock' or recharge itself to attach at the next site. This repeated attaching-detaching cycle also known as cross bridge cycle needs energy which is supplied by ATP.

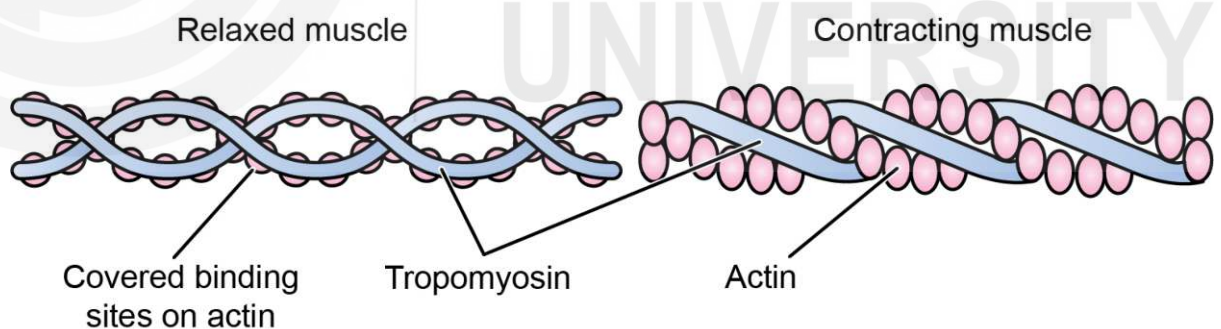


Fig.5.11: Action of Ca^{2+} in unlocking the active sites on actin filaments. In the relaxed muscle the tropomyosin lies on the outside blocking the myosin cross-bridge formation sites on the actin. In the contracting muscle tropomyosin is pulled into the groove of the actin filaments thus exposing the myosin binding sites.

Cross Bridge Cycle

In the resting sarcomere the myosin molecules are already charged with energy required for binding the actin molecules. This energy is obtained from the breakdown of ATP. At the start of the contraction cycle the myosin head splits a molecule of ATP into ADP and a phosphate (P) that remain attached to the myosin head (Fig 5.12a).

When the muscle is stimulated to contract, calcium ions enter the sarcoplasm and bind to the troponin molecules. The tropomyosin-troponin complex moves to expose the binding sites from the F actin molecule.

Myosin heads bind to the active sites on the F actin molecules, forming cross bridges (Fig. 5.12 b). In the resting sarcomere the myosin heads face away from the M line like a spring and is packed with energy obtained by the breakdown of ATP. In this position the ADP and P are still attached to the head. When the myosin heads forms the cross bridges this locked energy is released as the head pulls the F- actin molecules towards the M line . This action is known as the **power stroke**. After the power stroke ADP and P are released (Fig. 5.12c).

Another ATP molecule now binds to the myosin head and the link between the myosin head and the actin site is broken and this active site becomes free to bind with another myosin head (Fig.5.12d).

The myosin head that became free now gets recharged by splitting the bound ATP molecule into ADP and P and it becomes ready to attach to a new site on the actin filament (Fig.5.12e).

If calcium is sufficient and the supply of ATP is constant then myosin heads will repeat the cycle about 5 times per second. Each power stroke shortens the sarcomere by about 1 percent which means that per second the sarcomere can shorten by about 5 percent. Since all the sarcomeres shorten at the same time, the entire muscle shortens at the same rate.

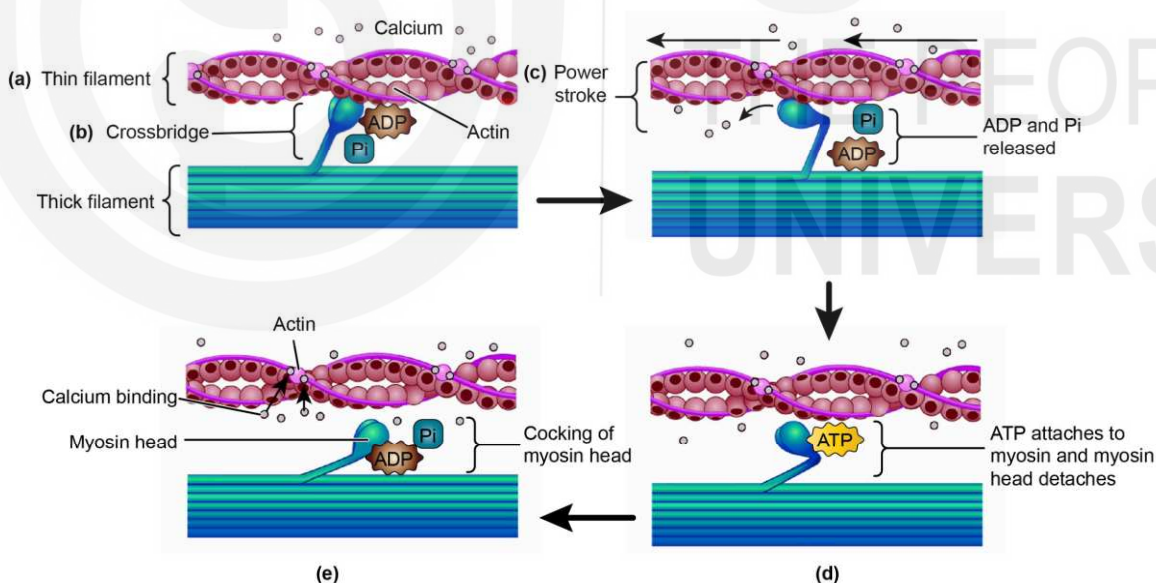


Fig. 5.12: Skeletal Muscle Contraction. a) The active site on actin is exposed as calcium binds to troponin; b) The myosin head is attracted to actin, and myosin binds actin at its actin-binding site, forming the cross-bridge; c) During the power stroke, the phosphate generated in the previous contraction cycle is released. This results in the myosin head pivoting toward the center of the sarcomere, after which the attached ADP and phosphate group are released; d) A new molecule of ATP attaches to the myosin head, causing the cross-bridge to detach; e) The myosin head hydrolyzes ATP to ADP and phosphate, which returns the myosin to the cocked position.

The time taken by a skeletal muscle fiber to sustain a contraction depends on : (a) the duration of nervous stimulation; (b) the amount of Ca^{2+} released and (c) the supply of ATP. Furthermore, contraction can be sustained only if there are repeated action potentials arriving at the neuromuscular junction. But if only one action potential arrives at the neuromuscular junction then the Ca^{2+} return to the resting concentrations by moving back into the extracellular fluid through active transport. In addition, the sarcoplasmic reticulum also pumps back the Ca^{2+} ions using Ca^{2+} ATPase. As the concentration of Ca^{2+} falls the Ca^{2+} ions detach from the troponin molecule and the troponin-tropomyosin complex reforms and the active sites on the actin molecule are again covered by tropomyosin and as a result the contraction ends. When the contraction ends some of the energy spent in stretching the elastic elements of the muscle is recovered as they recoil. This helps the muscle to relax gradually and come to the resting state.

Muscle Tone

All muscle fibers controlled by a single motor neuron form a motor unit. The size of the motor unit is indicative of the fineness of the motor control. For example, in the eyelid which requires fine muscle control, the motor unit controls 4-6 muscle fibers; in leg muscles a motor unit may control 1000-2000 muscle fibers as precise muscle control is not required. In a stimulated muscle, the contraction starts with the activation of the smallest motor unit and gradually the larger motor units are stimulated and tension rises steeply. This smooth and steady rise in muscular tension by increasing the number of activated motor units is known as **recruitment or multiple motor unit summation**. During a sustained contraction the motor units are activated on a rotating basis, so that some of them are resting while some are always active. This gives each motor unit some time to recover before it is stimulated again. However in any skeletal muscle some motor units are always active even if the entire muscle is not contracting. The activation may not cause movement but gives the muscle a firmness or **resting tension**. This resting tension is also known as **muscle tone**. Muscles with little tone appear limp and loose while those with moderate tone appear firm and solid and strong muscle tone makes the skeletal muscles appear well defined as we see in the muscle builders, weight lifters and Salman Khan!. The position of bones and joints in the body is maintained because of the resting muscle tone. At any given time some of the motor units are stimulated to produce this tension to maintain body posture.

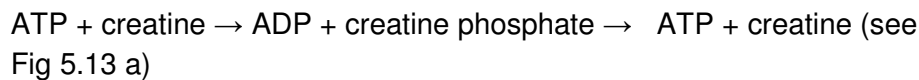
When muscle cells are damaged creatine phosphokinase leaks out of the cells into the blood stream. Thus any increase in creatine phosphokinase in the blood is indicative of serious muscle damage.

5.3.6 Energetics of Muscle Contraction

You know now that ATP is the immediate source of energy for muscle contraction. A single muscle fiber may contain 15 billion thick filaments and when that fiber is actively contracting then it uses up to 2500 ATP molecules per second. Recall that even a small muscle contains thousands of muscle fibers and therefore imagine the number of ATP molecules required even if the muscle was to contract for a short duration. Muscles in fact store enough ATP for them to contract only for a few seconds.

There are three ways that the muscle can obtain its needed ATP

1. **Through creatine phosphate** : At rest a skeletal muscle produces more ATP than it can use so where is this ATP stored in the muscles? ATP transfers energy into creatine to form another high energy compound molecule **creatine phosphate** in vertebrates and into **arginine** to form **arginine phosphate** in invertebrates. During contraction of skeletal muscles in vertebrates when ATP is broken down into ADP + P the energy required to recharge ADP comes from creatine phosphate which rephosphorylates ADP in a reversible reaction:



The enzyme that is required for this transformation is creatine phosphokinase. The pool of creatine phosphate in the muscle cell is about 10 times larger than the ATP present.

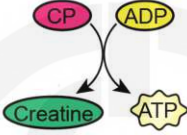
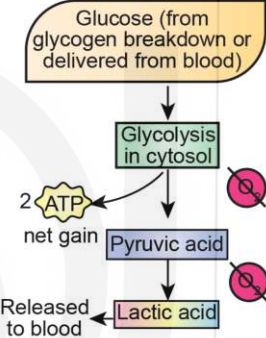
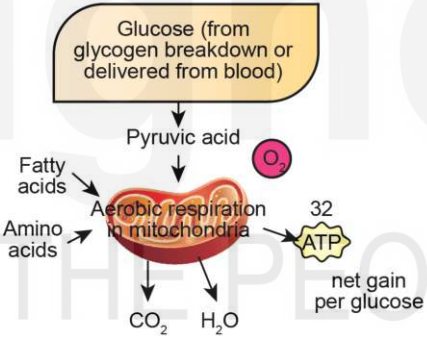
(a) Direct phosphorylation	(b) Anaerobic pathway	(c) Aerobic pathway
Coupled reaction of creatine phosphate (CP) and ADP  Oxygen use: None Products: 1 ATP per CP creatine Duration of energy provision: 15 seconds	Glycolysis and lactic acid formation Energy source: glucose  Oxygen use: None Products: 2 ATP per glucose lactic acid Duration of energy provision: 40 seconds or slightly more	Aerobic cellular respiration Energy source: glucose; pyruvic acid; free fatty acids from adipose tissue; amino acids from protein catabolism  Oxygen use: Required Products: 32 ATP per glucose CO₂, H₂O Duration of energy provision: Hours

Fig. 5.13: Requirements of ATP during muscle contraction are met by a) Stored ATP is in a resting muscle. As contraction starts, it is used up in seconds. More ATP is generated from creatine phosphate for about 15 seconds; b) In glycolysis each glucose molecule produces two ATP and two molecules of pyruvic acid, which can be used in aerobic respiration or converted to lactic acid. If oxygen is not available, pyruvic acid is converted to lactic acid; c) Aerobic respiration is the breakdown of glucose in the presence of oxygen (O₂) to produce carbon dioxide, water, and ATP. Approximately 95 percent of the ATP required for resting or moderately active muscles is provided by aerobic respiration, which takes place in mitochondria.

2. **Through glycogen**: As the source of ATP from creatine phosphate gets depleted, when muscles start to contract they obtain their ATP from the breakdown of pyruvic acid in the glycolysis pathway. Glycolysis is an anaerobic (non-oxygen-dependent) process that breaks down glucose to produce ATP; however, glycolysis cannot generate ATP as quickly as

creatine phosphate. The glucose used in glycolysis can be provided by blood glucose or by metabolizing glycogen that is stored in the muscle. The breakdown of one glucose molecule produces two ATP and two molecules of pyruvic acid, which can be used in aerobic respiration or when oxygen levels are low, converted to lactic acid (Fig. 5.13 b).

3. **Through aerobic respiration:** Normally 95% ATP demand of the contracting muscle fiber is met by aerobic metabolism that takes place in the abundant mitochondria present in the muscles cells. For aerobic respiration glucose, pyruvic acid and fatty acids are obtained from blood circulation. Aerobic respiration is much more efficient than anaerobic glycolysis, producing approximately 36 ATPs per molecule of glucose versus four from glycolysis (Fig. 5.13 c).

Let us see how the production and usage of energy for contraction changes as muscular activity increases with the help of Fig 5.14:

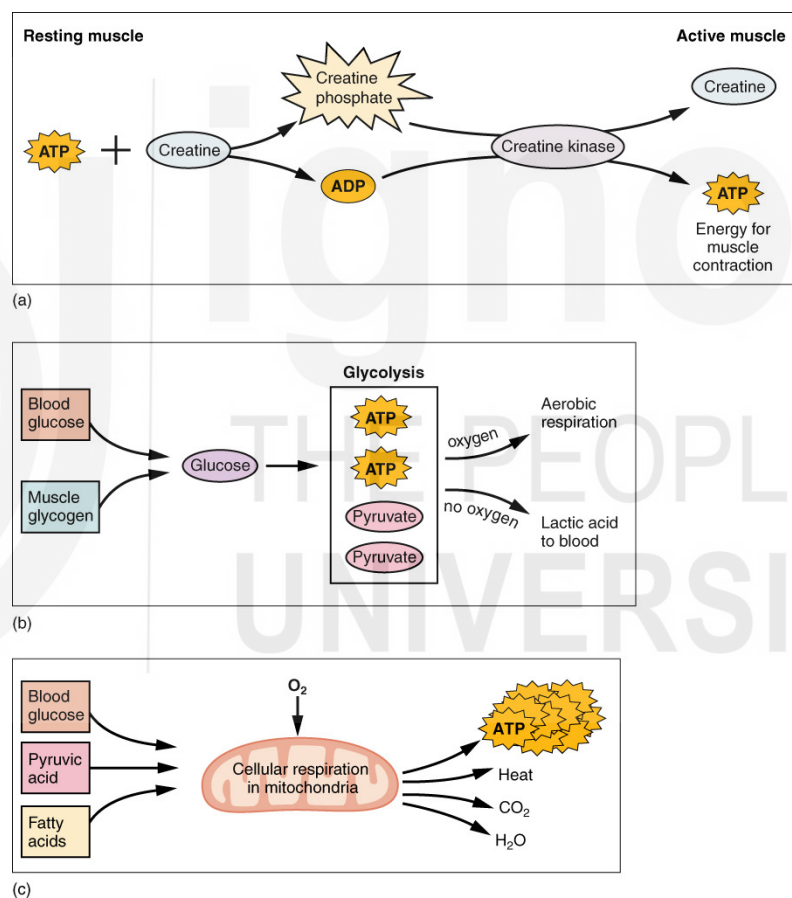


Fig. 5.14: Biochemical pathways producing ATP utilized during vertebrate muscle contraction:(a) Some ATP is stored in a resting muscle. As contraction starts, it is used up in seconds. More ATP is generated from creatine phosphate for about 15 seconds. (b) Each glucose molecule produces two ATP and two molecules of pyruvic acid, which can be used in aerobic respiration or converted to lactic acid. If oxygen is not available, pyruvic acid is converted to lactic acid, which may contribute to muscle fatigue. This occurs during strenuous exercise when high amounts of energy are needed but oxygen cannot be sufficiently delivered to muscle. (c) Aerobic respiration is the breakdown of glucose in the presence of oxygen (O₂) to produce carbon dioxide, water, and ATP. Approximately 95 percent of the ATP required for resting or moderately active muscles is provided by aerobic respiration, which takes place in mitochondria.

Recall that the demand for energy is low in a resting muscle and enough oxygen is available for aerobic metabolism of glucose. The cell absorbs glucose and fatty acids from the blood and is able to make enough ATP for its use and stores the surplus in the form of creatine phosphate and excess glucose is stored as glycogen.

At moderate levels of muscle activity ATP demand increases. As more mitochondrial ATP is formed oxygen consumption also increases which is easily met by more oxygen diffusing into the cell. However, no surplus ATP is available and the muscle now relies on the breakdown of glycogen and other substrates such as lipids and amino acids

When muscular activity is at peak the energy demand also reaches its maximum. The rate of ATP production is now limited by availability of oxygen and so now only a third of the ATP is obtained from aerobic mitochondrial activity and the rest is obtained from anaerobic conversion of pyruvate to lactate to glucose.

As more lactic acid is formed than is consumed, it accumulates in the muscle fiber and changes its pH which ultimately alters the activity of the key enzymes in the muscle fiber. As result the muscle fiber cannot continue to contract further. Once the muscle slows down it gets time for oxygen levels to be restored and lactates revert to pyruvate, allowing aerobic metabolism to resume and supply energy to the muscle cell. This build up of lactic acid in the muscle cells gives the body the sensation felt after vigorous exercise. The soreness felt after 24 hours of exercise is actually due to muscle damage and the inflammatory repair response leading to swelling and soreness that lasts for a few days.

SAQ 3

Choose the correct options:

- a) In a relaxed muscle fiber, the myosin-binding site on actin is blocked by
- i) titin
 - ii) troponin
 - iii) myoglobin
 - iv) tropomyosin
- b) According to the sliding filament model, binding sites on actin open when
- i) creatine phosphate levels rise
 - ii) ATP levels rise
 - iii) acetylcholine levels rise
 - iv) calcium ion levels rise

- c) The plasma membrane of a muscle fiber is called
- i) myofibril
 - ii) sarcolemma
 - iii) sarcoplasm
 - iv) myofilament
- d) Muscle relaxation occurs when
- i) calcium ions are actively transported out of the sarcoplasmic reticulum
 - ii) calcium ions diffuse out of the sarcoplasmic reticulum
 - iii) calcium ions are actively transported into the sarcoplasmic reticulum
 - iv) calcium ions diffuse into the sarcoplasmic reticulum
- e) During muscle contraction, the cross-bridge detaches when
- i) the myosin head binds to an ADP molecule
 - ii) the myosin head binds to an ATP molecule
 - iii) calcium ions bind to troponin
 - iv) calcium ions bind to actin
-

5.4 AMOEBOID MOVEMENTS

Amoeboid movement is the most basic type of movement and perhaps the least understood. It refers to the characteristic movement of some protists, slime moulds, and vertebrate white blood cells. It is the crawling movement seen in kupffer cells in the liver, metastasizing cancerous cells, in animal cells in tissue culture, in the cells of the developing embryo and in any other cells where the movement is effected by cytoplasmic streaming, constant changes in cell shape and extension of pseudopodia. These changes can easily be seen under the microscope.

Amoeboid movement begins in a cell or a single celled organism like the amoeba by extension, of an arm like structure called the **pseudopodium**, in the required direction into which, the cytoplasm of the single cell or single celled organism flows in (Fig.5.16). The newly formed pseudopodium enlarges and the cell finally occupies the space where previously the new pseudopodium had begun to form. As the cell moves, new pseudopodia form in the direction of the movement, while the posterior parts contract and are withdrawn. It is not known with certainty how the extension and retraction of the pseudopodium takes place. It appears that there is a conversion of the cytoplasm from fluid like sol state to the semi-solid gel state.

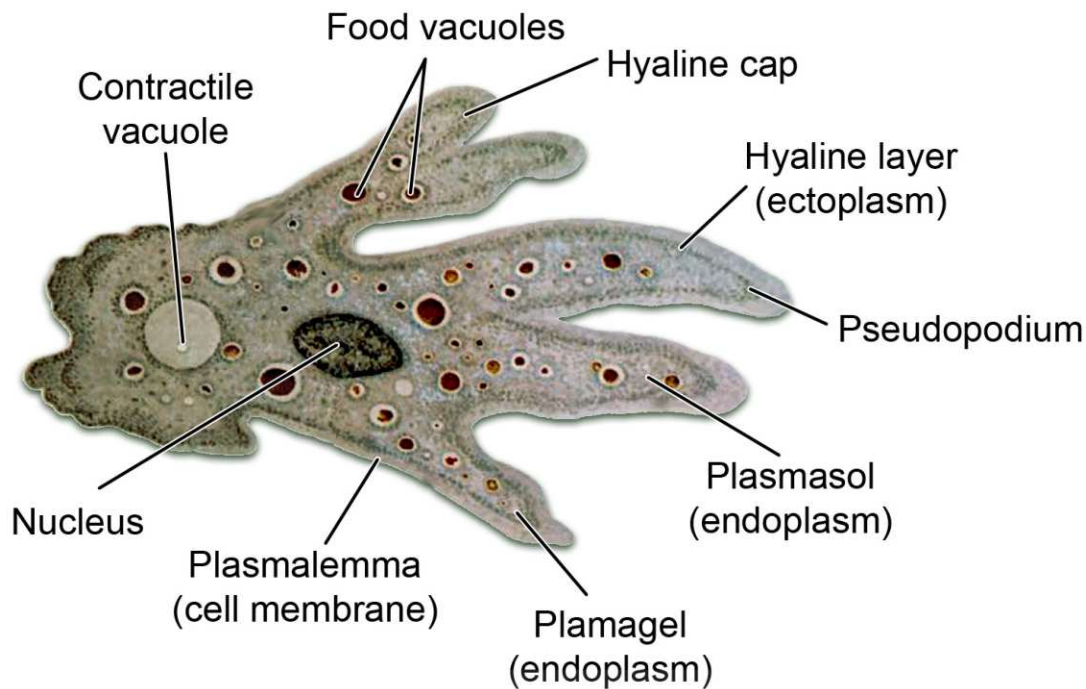


Fig.5.16: A moving amoeba cell showing the granular endoplasm and clear ectoplasm.

We can see two regions in the cytoplasm of the amoeba (Refer again to Fig. 5.13), under the light microscope, which are as follows:

The **central endoplasm** or granuloplasm which is fluid in nature and is also called **sol cytoplasm**. It contains granular inclusions and membranous particles that are in constant random motion, the **peripheral clear gel like part of the cytoplasm** called **ectoplasm** or hyaloplasm that contains a three dimensional network of actin and myosin filaments (actin and myosin are found in all eukaryotic cells and you have also learn about their role in muscle contraction earlier in this unit).

This gel like region apparently decides the shape of the pseudopodium and may transmit tension from the region of cellular contraction to the sites of contact with the substratum

Locomotion in amoeba is caused by continuous assembly and disassembly of the actin and myosin containing complexes. The ectoplasm at the front end becomes thin, causing a pseudopodium to bulge forward. The rear end of the amoeba contracts, and pushes the streaming endoplasm into the elongating pseudopodium. In the region near the tip of the pseudopodium the protein actin polymerizes to form a filamentous network. Cross linking of the actin protein and myosin protein cause the network to contract, pulling the cell in the direction of the pseudopodium. The energy required for this comes from ATP. It is not known how amoeboid movement is controlled or regulated. However, it is known that the amoebae cannot extend their pseudopodia in all directions simultaneously; if they could they would be ripped apart! It is known however, that the ability of many actin binding proteins to crosslink to actin is strongly dependent on calcium ion (Ca^{2+}) concentration and pH. Thus, Ca^{2+} and hydrogen ion (H^+) regulate the sol-to-gel transition. In low molar concentrations of Ca^{2+} (=ppm range), when pH is lowered to 6.8, the

cytoplasm of the amoeba begins to set as a gel while solution of the gel starts when pH or Ca^{2+} is raised. Studies suggest that proteins such as gelsolin or villin are responsible for gel-to-sol transition because these proteins fragment actin in the presence of micromolar free Ca^{2+} (10^{-6} moles). It has been suggested that directed growth of pseudopodia is due to differences in Ca^{2+} or H^+ concentration among various regions of the cytoplasm; whether this is the case, however, remains to be determined. In the next section you will learn about ciliary and flagellar movement.

SAQ 4

Fill in the blanks and compare your answers with those given at the end of the unit:

- Amoeboid movement is the characteristic of organisms , and
- When an amoeba has to move, it stretches its arm like extensions known as
- Locomotion in Amoeba is the result of continuous assembly and breakdown of and complexes.
- Under the light microscope the cytoplasm of the amoeba is distinguished into and regions.

5.5 CILIARY AND FLAGELLAR MOVEMENT

Cilia or flagella or their derivatives occur in all animal phyla. Historically, before their internal structure was known they were called cilia when many were present and were called flagella when present singly (flagellum) or in pairs. Cilia or flagella or their derivatives are microtubular structures formed by projections of the plasma membrane of the cell and basically have the same internal structure.. They both originate through the assembly of proteins onto a centriole-like basal body and they have the same internal arrangement of microtubules, motor proteins and accessory structures. The difference lies in their number, length and beating pattern (Fig 5.17).

Many cells are covered by numerous cilia which are about $10\mu\text{m}$ long. Cilia beat in a coordinated back and forth movement, moving the fluid over the cell or moving the cell through the liquid (Fig.5.17 a & b). For example, the cilia of *Paramecium* (Fig.5.18a) and some other protists are responsible both for cell motility and for sweeping across food organisms over the cell surface and into the oral cavity.

In animals, an important function of cilia is to move fluid or mucous over the surface of epithelial cell sheets. A good example is provided by the ciliated cells, lining the respiratory tract (see Fig.5.18 b) which clear mucous and dust from the respiratory passages. Derivatives of cilia occur in a wide variety of photoreceptor, mechanoreceptor, and chemoreceptor cells.

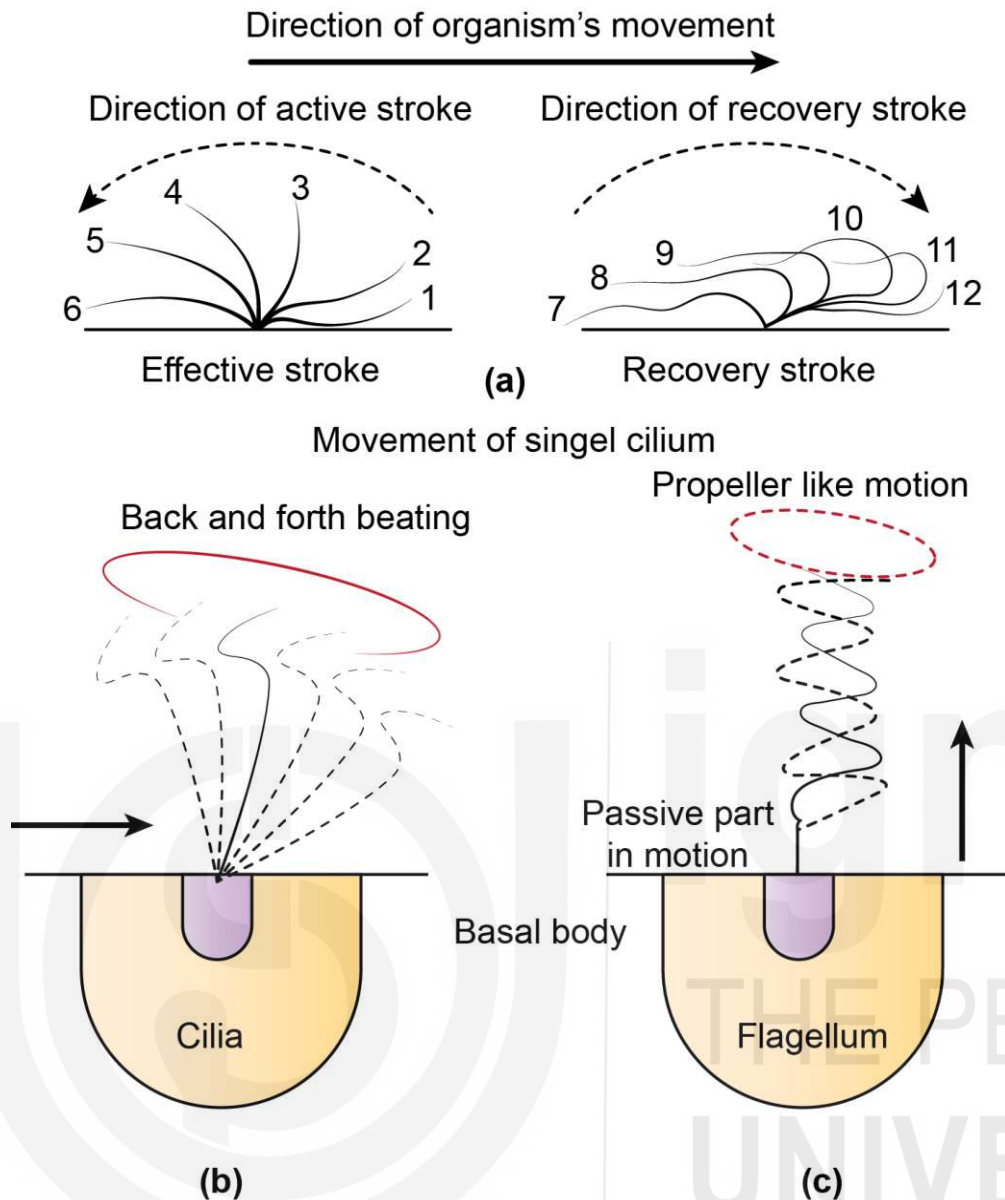


Fig.5.17: Cilia and flagella are hair-like appendages, which differ in their mode of beating, size, and number: a) The movement of cilia is like a flexible oar with alternating power and recovery strokes generating force perpendicular to the cilium's axis. The unidirectional movement of the cilium has a fast stroke in one direction followed by a slow recovery movement in which the bending cilium comes back to its original position; b) The beating of a cilium (propels water parallel to the surface to which the cilium is attached (arrow). c) Flagellum generates force parallel to its axis. The typical beat of a flagellum propels water parallel to the main axis of the flagellum (arrow). (add a,b,c to the diagrams well)

Flagella on the other hand are longer than cilia (Fig.5.17 c and Fig 5.18 c & d) and can be as long as 200 μm and beat in a wavelike pattern. Cells usually have only one (Refer again to Fig 5.17 c & d) or two flagella, which are responsible for the locomotion of a variety of protists and of sperm. A flagellum like the tail of a sperm beats in an undulating movement that is propagated as a wave along the length of the flagellum (Fig.5.17 d). To understand the mechanism of flagellar and ciliary movement we first must understand their internal structure.

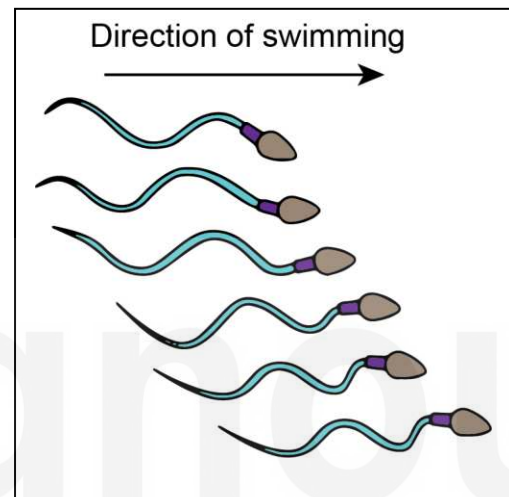
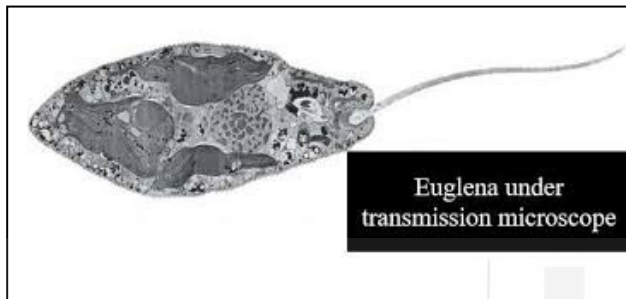
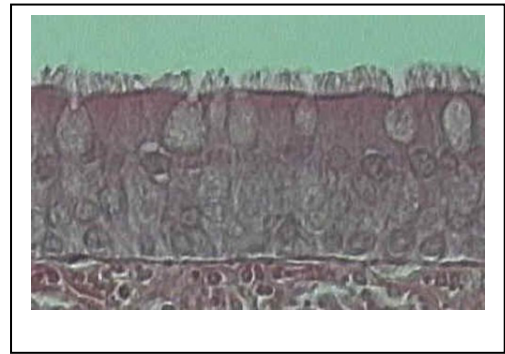


Fig 5.18: a) The entire body of *Paramecium caudatum* is covered by short, hair-like cilia which are present in large numbers (phase contrast microscopy-photo by Robert Berdan <http://www.canadiannaturephotographer.com/>); b) Ultra structure of the respiratory tract of human lined by ciliated cells in which the cilia helps to move mucous and debris; c) *Euglena* sp with a long flagella which is a long, hair-like complex structure (viewed by transmission electron microscope(TEM) [file:///C:/Users/Hp/Downloads/Lab-2-microscopes%20\(3\).pdf](file:///C:/Users/Hp/Downloads/Lab-2-microscopes%20(3).pdf)) and d) the flagellum like the tail of a sperm beats in an undulating movement that is propagated as a wave along the length of the flagellum (did you check if just giving the ref is enough if not then avoid giving photomicrographs especially these days the course will be uploaded before it is printed and freely available to download as well)

5.5.1 Structure of Cilia and Flagella

The basic structure of both cilia and flagella consists of a bundle of microtubules and their associated proteins forming the **axoneme** which extends from the base to the tip. The bundle of microtubules comprising the axoneme is surrounded by the plasma membrane of the cell as you can see in Figure 5.19 a.

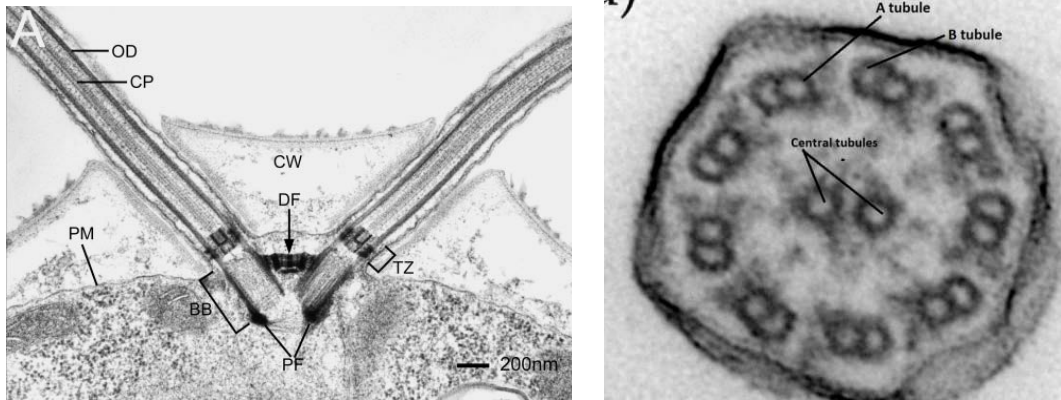


Fig 5.19: a) A Scanning electron micrograph of a longitudinal section through the basal bodies and flagella of plant like eukaryote protist *Chlamydomonas. reinhardtii*, showing the cell wall(CW) plasma membrane (PM), microtubules and the basal body (BB). (Image by Dr. William Dentler.) . Carolyn D. Silflow, and Paul A. Lefebvre Plant Physiol. 2001;127: 1500-1507) and b) Transmission electron microscopy cross section of a cilia (scale = 200 nm) showing the characteristic 9+ 2 arrangement of the filaments in cross-section of a cilium,; (Review Ciliary Proteins: Filling the Gaps. Recent Advances in Deciphering the Protein Composition of Motile Ciliary Complexes; Anna Osinka, et al.) (label (a) and (b).

The microtubules are arranged in a characteristic "9 + 2" configuration, consisting of a pair of microtubules in the center surrounded by nine outer or peripheral microtubule doublets b). Each microtubule is a hollow cylinder whose walls are composed of dimers of globular protein α and β tubulin(Fig. 5.20). If you look at a microtubule in cross section or top view, you will see it as a ring made of bead like structures, each of these beads in longitudinal section is a protofilament (see Figure 5.21). The inner two central tubules are linked to each other by periodic bridges like the rungs of a ladder and covered by a sheath. The two microtubules of each outer doublet are fused and consist of:1) one complete microtubule called the **A tubule** and 2) the other called the B tubule which is incomplete (see fig 5 .21 b again)

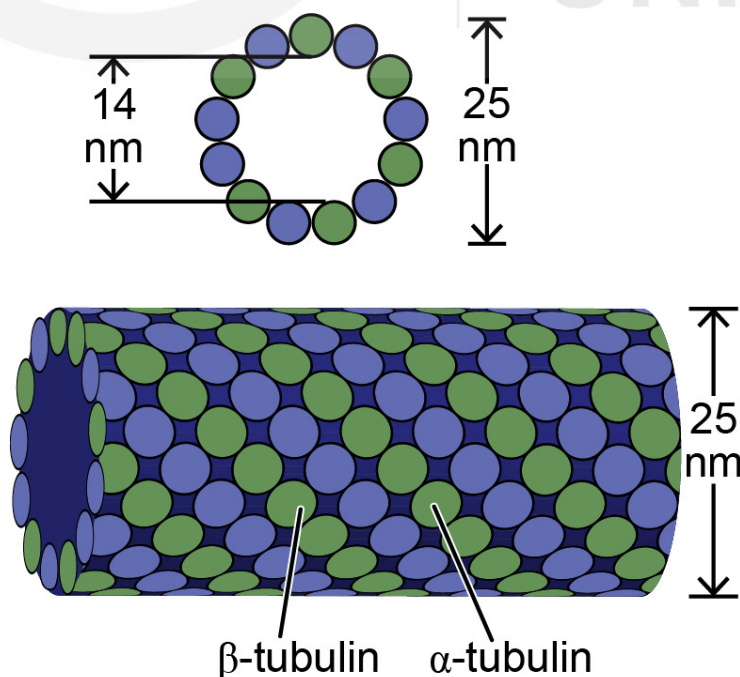


Fig.5.20: Structure of a microtubule.

The outer microtubule doublets are connected to the central pair by radial spokes formed of protein that extend from the A tubule to the sheath covering the two central tubule. The microtubule doublets are linked to each other by protein structures called **nexin** which are spaced along the microtubules to hold them together. In addition each A tubule bears two rows dynein arms, one on outer and one inner side, and it is the motor activity of these axonemal dynein arms that drives the beating of cilia and flagella (see Fig. 5.21). Dyneins are anchored with their globular part to the A microtubule of one peripheral pair or doublet and the tail part of dyneins attaches to the B microtubule of the adjoining pair of doublets during movement. The energy for the movement of cilia/flagella is provided by ATP.

At its point of attachment to the cell, the axoneme connects with the basal body (see Fig 5.21 a again). Like the centrioles, basal bodies are cylindrical structures, about 0.4 μm long and 0.2 μm wide, which contain nine triplet microtubules. Each triplet contains one complete A microtubule, fused to the incomplete B tubule, which in turn is fused to the incomplete C tubule (Fig.5.19 a). Basal bodies play a clear role in organization of the axoneme microtubules. Each of the outer microtubule doublets of the axoneme is formed by extension of two of the three microtubules (A and B) present in the triplets of the basal body. The C microtubule terminates in the transition zone between the basal body and the terminal shaft of the axoneme. The two central tubules also terminate in the transition zone. The growth of the axonemal microtubules starts at the basal body. Although the 9 + 2 pattern is the fundamental pattern of virtually all cilia and flagella, the axonemes of certain protists and some insect sperms show some variations.

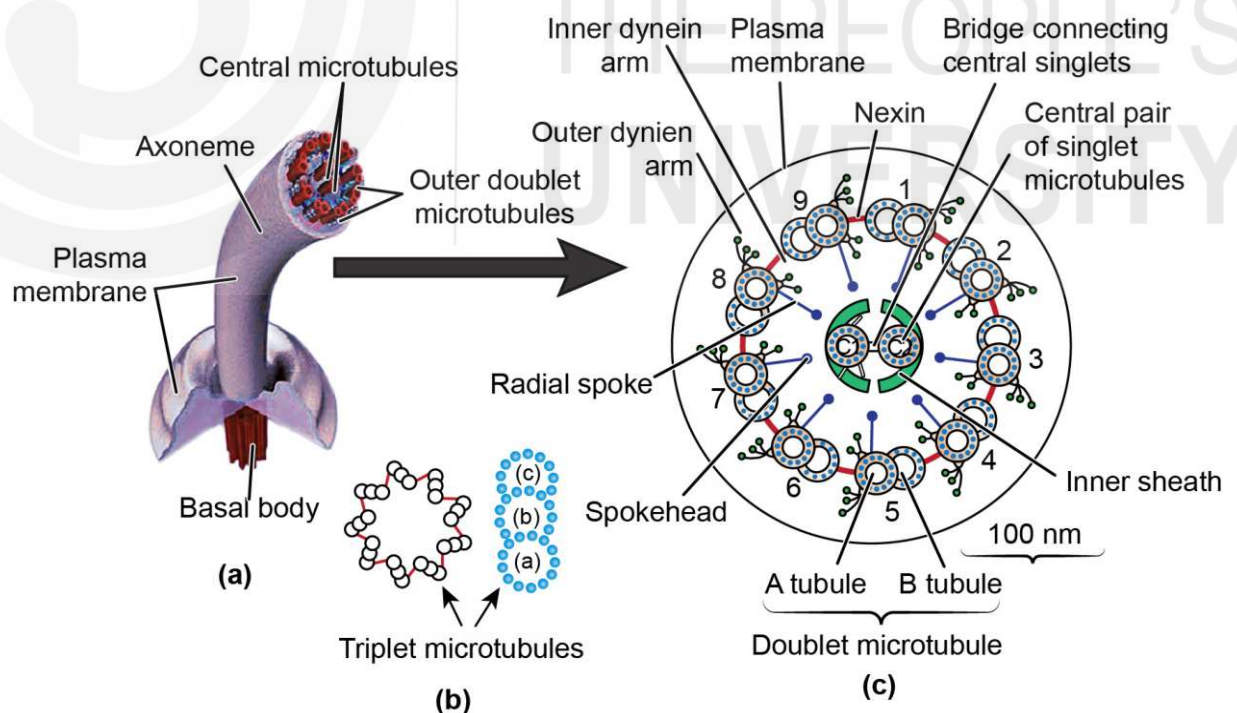


Fig: 5.21: a) Diagram showing the internal structure of the cilium attached to the basal body. the basal body in cross section show the triplets microtubules; b) cilium in cross section showing the major structural elements. The microtubules are connected by bridges and spokes and the entire structure is surrounded by plasma membrane (Adapted from Molecular cell biology W H Freeman and Company).

5.5.2 Mechanism of Movement of Cilia

As in muscle movement, the movement of cilia and flagella is due to sliding of the outer microtubule doublets relative to one another, being powered by the motor activity of axonemal dynein. Electron microscopic studies show that bending of a flagellum occurs when the **dynein arms** of the **A tubule of one doublet attach** to the **B tubule of the adjacent doublet**. The globular part of the dynein which form the base of dynein arm are bound to the A tubules, while the head groups also called tail end of the dynein bind to the B tubules of adjacent doublets during movement. The dynein arms on the A tubule of the doublet seem to walk along the B microtubule of the adjacent doublet towards its base.

This movement of the dynein head group causes the A tubule of the adjacent doublet to slide toward the basal end of the B tubule of the adjacent doublet. Because the microtubule doublets in an axoneme are connected by nexin links, they restrict, the sliding of one doublet along another and force them instead to bend. The bending forms the basis of the beating movements of cilia and flagella. Movement is achieved by the addition and removal to of a phosphate group from ATP to the dynein in the presence of Ca^{2+} and cyclic AMP. This causes conformation changes in the protein of the dynein molecules allowing it to attach, de-attach and again re-attach to the B tubule slightly closer to its base and the cycle continues inducing a sliding movement (see Fig.5.22).

The sliding on one side of the axoneme alternates with the sliding on the other side of the axoneme so that the cilium bends on one side and then in the opposite direction. This actually requires that the microtubules on one side are active while on the opposite side are inactive at the same time. Cilia beat 10 - 40 beats /sec and each stroke has a precise beat and thousands of cilia beat at the same time! The dynein arm activity has to be regulated because if all of them move at the same time then the organelle is paralyzed. The central tubules also play a role a regulating the movement of the cilia and flagella. It is thought that they determine which arm is active at a given time.

We had said earlier that cilia are just short flagella which beat stiffly, the power stroke pushing across the cell surface. Cilia show two types of coordinated rhythms or movement:

- i) Synchronous rhythm or beat, where the cilia beat simultaneously in a transverse row and
- ii) Metachronous rhythm or beating (Refer again to Fig 5.14 a) which is more common and in which cilia beat one after another in a longitudinal row. Thus, the cilia will beat slightly out of phase with their neighbors. In active cells, this appears like a wave passing across the body of the cell, with the crest of the wave being where the cilia are ready to begin their active beat.

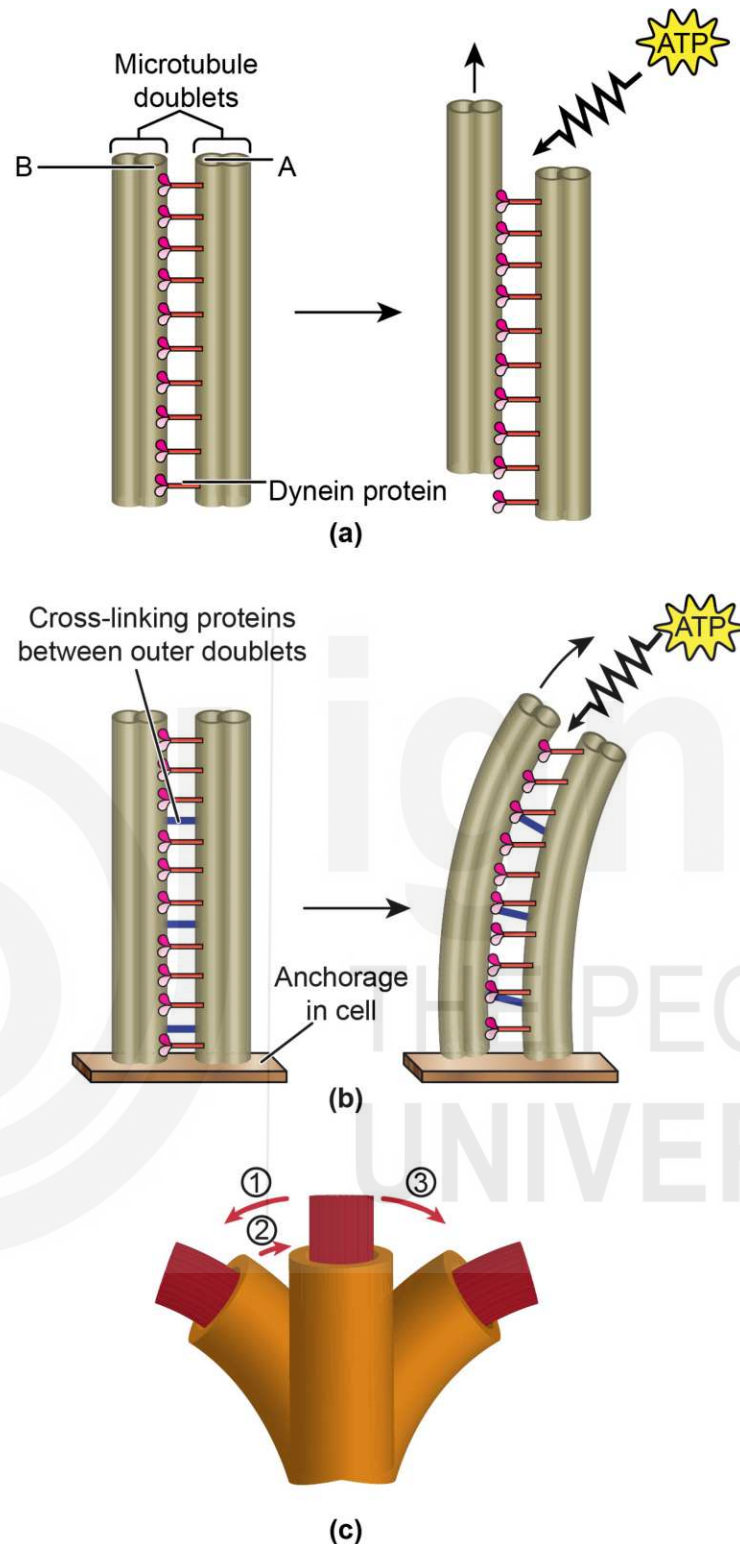
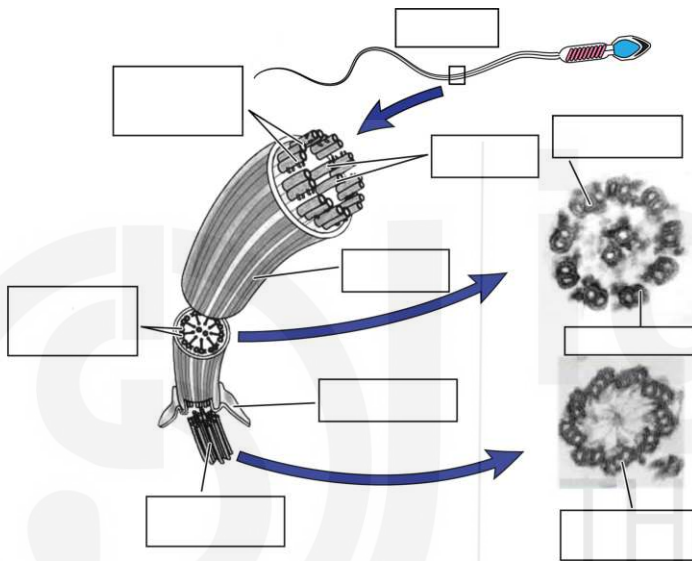


Fig.5.22: Diagram illustrating the sliding of outer microtubule doublets. The dynein arms attached to the A tubule of one microtubule walk along the B tubule of the adjacent doublet toward its basal end, moving this microtubule in the opposite direction (large arrow). When the nexin cross-links are broken, sliding can continue unimpeded as seen in (a). However, in the cilium the doublets are held by the cross links in the form of nexins (blue lines in the diagram) and so instead of sliding off microtubules it leads to bent formation of the microtubules as seen in (b). (c) shows the bending of the microtubules on one side and then back in position and bending on the other side.

SAQ 5

- a) Fill in the blanks and compare your answers with those given at the end of this unit :
- In the ciliated/ flagellated cell the basal bodies arise from the centrioles which have a 9+0 arrangement of
 - In cilia and flagella the microtubules are arranged in a characteristic configuration.
 - The energy for the sliding movement is provided by ATP and is regulated by and
- b) identify and label the given figure



5.6 SUMMARY

In this unit you have read about the physiology of movement in animals. You have read that :

- The primary function of muscle tissue is to produce movement. In vertebrates. There are three types of muscle cells in the vertebrate body skeletal, cardiac, and smooth. Their structures match their specific functions in the body. Skeletal muscle and cardiac muscles are striated and while skeletal muscle is multinucleated, voluntary and responds to conscious stimuli. Cardiac muscle is branched and uninucleated, found only in the heart and contracts autonomously and involuntarily. Smooth muscle is involuntary. Each cell is a spindle-shaped. No striations are evident.
- In skeletal muscle the sarcomere is the smallest contractile portion of a muscle. Myofibrils are composed of thick and thin filaments. Thick filaments are composed of the protein myosin; thin filaments are composed of the proteins Filamentous (F) actin nebulin, and two regulatory proteins iii) tropomyosin and iv) troponin.

- Contraction in skeletal muscles is brought about by sliding of the thin filaments past the thick filaments. A motor neuron controls the activity of contraction of a skeletal muscle fiber at a neuromuscular junction on skeletal muscle. When an action potential arrives at the neuron's axon (pre-synaptic) terminal, acetylcholine (ACh) is released into the synaptic cleft. The binding of ACh to its receptors on the post synaptic motor end plate on the sarcolemma leads to the generation of an action potential which travels along the sarcolemma to trigger calcium release from SR. The actin sites are exposed after Ca^{+} enters the sarcoplasm from its SR storage to activate the troponin-tropomyosin complex so that the tropomyosin shifts away from the sites. The cross-bridging of myosin heads docking into actin-binding sites is followed by the "power stroke"—the sliding of the thin filaments between the thick filaments. The power strokes are powered by ATP. Ultimately, the sarcomeres, myofibrils, and muscle fibers shorten to produce movement.
- Contraction of skeletal muscles requires large amounts of energy. Creatine phosphate can release stored energy to convert ADP to ATP. At rest or at moderate levels of activity, aerobic metabolism can provide most of the ATP needed to support muscle contractions. At peak levels of activity, the muscle cell relies heavily on anaerobic metabolism (glycolysis) to generate ATP.
- Movement in amoeba is due to cytoplasmic streaming, change in the cell shape and extension of pseudopodia.
- Cilia and flagella have a similar internal structure consisting of microtubules in 9+2 configuration. The microtubules in the cilium move past one another to produce movement similar to the sliding filaments of muscle contraction,

5.7 TERMINAL QUESTIONS

1. What is the role of nexin and the radial spokes in the structure and movement of cilia and flagella? What will happen if we were to remove the nexin links and radial spokes by means of protease?
2. Explain briefly the role of myosin in muscle contraction.
3. Describe the role of calcium in the regulating muscle contraction
4. Diagrammatically explain the biochemical pathways that produce ATP for vertebrate muscle contraction.

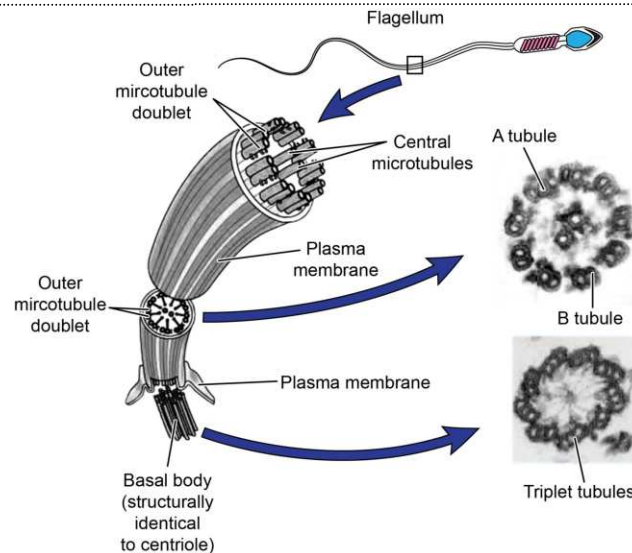
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5. What is the role of dynein in the motility of cilia and flagella?
6. What forms of energy reserves do resting skeletal muscle fibers contain?
7. What two mechanisms are used to generate ATP from glucose in muscle cells?

5.8 ANSWERS

Self-Assessment Questions

1. a) The three types of muscle tissue are skeletal muscle, cardiac muscle, and smooth muscle. Skeletal muscle tissue moves the body by pulling on our bones, cardiac muscle tissue pumps blood through the cardiovascular system, and smooth muscle tissue pushes fluids and solids along the digestive tract and other internal organs, and regulates the diameters of small arteries.
b) i) striated muscles, cardiac muscles
ii) Skeletal muscles, voluntary, smooth muscle, involuntary
2. a) i) the area where only myosin filaments are present
ii) includes overlapping myosin and actin filaments
ii) central line of the sarcomere where myosin filaments are anchored
iv) a line that separates one sarcomere from another
v) the area where only actin filaments are present
b) i) epimysium
ii) perimysium, endomysium;
iii) thin, thick;
iv) F-actin, nebulin, tropomyosin, troponin.
3. a) Tropomysin
b) calcium ions rise
c) sarcolemma
d) calcium ions are actively transported into the sarcoplasmic reticulum
e) myosin head binds to an ATP molecule.
4. a) Protozoan, slime molds and macrophages
b) pseudopodia
c) actin and myosin
d) ectoplasm, endoplasm
5. a) i) triplets
ii) $9 + 2$
iii) Ca^{2+} (calcium ion), cAMP
b) structure of cilia/flagella, showing the structure of axoneme



Terminal Questions

1. Nexin and radial spokes hold the outer doublets linked to each other at regular intervals and keep them anchored to the sheath of the central tubules. They thus keep the structure intact while bending. If these scaffolding proteins are removed by proteases then the nexin cross-links are broken, sliding can continue unimpeded. The doublets are held in the cilium by the cross links and if these are removed then the sliding will not lead to bend formation.
2. A myosin molecule contains two heavy chains; part of a heavy chain makes up one head and the other part forms the tail. The 'heads of the myosin molecules form cross bridges with the actin molecules. These cross bridges cyclically attach to actin molecules and swivel, acting as oars that pull the actin and myosin filaments past each other resulting in sliding movement.
3. The thin filaments of the myofibril consist of actin and two regulatory proteins, troponin and tropomyosin. In a resting state of the muscle, tropomyosin blocks the cross bridges binding sites of the actin molecules. When a muscle is stimulated the calcium ion concentration of the muscle fiber increases. The calcium ions bind to the troponin molecules. Binding of calcium ions to the troponin causes conformational changes in both troponin and tropomyosin, thereby uncovering the cross bridges binding sites of the actin molecules, causing muscle contraction.
4. Refer to Subsection 5.3.6 and Fig. 5.12.
5. Cilia/flagella beat because of the controlled dynein arms function just like the myosin heads of skeletal muscles. These arms are on A tubules and attach to the B tubules of the adjacent doublet walking along it thus causing bending and movement of the flagella/cilia. The force producing active sliding requires ATP and the successive binding and detaching of the dynein.
6. Resting skeletal muscle fibers contain ATP, creatine phosphate, and glycogen.
7. Glycolysis and aerobic metabolism generate ATP from glucose in muscle cells.

UNIT 6

COMMUNICATION: NERVE CELLS

Structure

6.1	Introduction	6.4	Synaptic Transmission
	Objectives		Chemical Synaptic Transmission
6.2	Nerve Cells		Postsynaptic Potential
6.3	Nerve Impulse		Electrical Synaptic Transmission
	Electric Activity of Membranes		
	Membrane Potential	6.5	Neurotransmitters
	Action Potential	6.6	Summary
	All or None Response	6.7	Terminal Questions
	Conduction	6.8	Answers

6.1 INTRODUCTION

In the previous units of this course you have studied that all multicellular animals possess organ systems of varying degrees of complexity to perform the physiological processes necessary for life. Such complexity requires an internal communication system that coordinates the activities of each system with those of the others and with the environmental conditions. Therefore, perception of environmental as well as internal information is necessary for the proper physiological functioning of an organism.

The nervous system and the hormonal system in animals perform the task of initiating and regulating internal communication and coordination necessary for the survival of the organism. You can think of the nervous system as a telephone exchange. When you dial a number, your message goes coded as an electric current to a specific place or 'target' where it is interpreted by the person who picks up the receiver of the telephone. Similarly in the nervous system messages are sent through cables i.e., from nerve cells via nerve to a specific site for an appropriate response.

All communication in the body starts at the cellular level. You have learnt in Unit -7 in the course on Comparative Anatomy and Developmental Biology of Vertebrates that the functional units that enable the animal to respond to internal and external environments are nerve cells or neurons that are organized into interconnected neuronal circuits and become increasingly complex through out evolution. You can realize the complexity of the system when you consider that the human brain alone contains 10^{15} nerve cells!

In this unit you will study about the structure and functioning of the nerve cells that are the basic units of any nervous system. Nerve cells or neurons are electrically active and release chemical signals to their target cells. You will learn how electrical signals or messages are generated and transmitted along these nerve cells to specific organs or cells in response to a stimulus or message received from the internal and external environment. The language in which the message is sent is the same regardless of the stimulus and the interpretation of the message lies in the brain which directs an appropriate response.

In the physiology of communication we have deliberately omitted certain functions of the central nervous system, the so called higher functions of the brain such as consciousness sleep, and memory. These topics can form a full course in their own right!

In the last unit of this block, we will deal with the complex of chemical messengers, called hormones that are secreted by endocrine glands. These form another communication system in the body.

Objectives

After studying this unit you should be able to :

- ❖ describe the parts of a neuron and their functional significance;
- ❖ explain resting membrane potential, action potential and significance of the all or none law;
- ❖ describe the conduction of action potentials along myelinated and non myelinated axons;
- ❖ describe the process of synaptic transmission;
- ❖ differentiate between graded potentials and action potential; and
- ❖ list some neurotransmitters according to their function.

6.2 NERVE CELLS

Living matter has the intrinsic capability to respond to changes in environmental (physical, biological and chemical) factors. Single cell organisms such as *Amoeba*, *Paramecium* also respond to the environment, interact with it and generate appropriate responses. With the advent of multicellularity and increase in the size of animals, arose the need for coordination and rapid conduction of information within the organism. To

Glial cells are about 5 times more than neurons. Brain tumors that occur in adults are usually composed of glial cells rather than neurons.

fulfill this need, some of the cells in the multicellular organisms became more and more specialized, acquired particular ability for receiving environmental information, for conducting it through the organism and finally for generating appropriate responses. And thus a cell type, **the nerve cell or neuron** came into being. The neuron itself underwent further morphological and physiological specialization resulting in the evolution of a great variety of neurons (nerve cells) differing markedly in size and morphological appearances according to the specialized job they were required to perform. These cells became organized in what is known as the nervous system.

Though neurons are considered the basis of the nervous system they are supported by another type of nervous tissue the **neuroglia** without which the neurons would not be able to perform their function. Recall from your study of Unit 7 of the course on Comparative Anatomy and Developmental Biology of Vertebrates the basic structure of nerve cells and other cell type - the **neuroglia or glial cells** which are present in large numbers and occupy practically all the space between the nerve cells. Neuroglia themselves are of several types better recognized in vertebrate nervous tissues than in the invertebrate nervous tissues. For your recapitulation, some categories of glial cells are listed in Table 6.1.

Table 6.1 : Some types of glial cells and their functions.

Neuroglia	Function
Schwann Cells	Surround axons of all peripheral nerve fibres, form the myelin sheath.
Oligodendrocytes	Form myelin sheath around central axons producing the white matter of central nervous system.
Astrocytes	Cover capillaries of brain to form the blood brain barrier and help regulate passage of molecules from blood to brain.
Ependyma	Line the ventricles or brain cavities and central canal of spinal cord.
Microglia	Phagocytic amoeboid cells in central nervous system that remove foreign and degenerate material from the brain.

Neuron Structure

As we learn about the functions of a nerve cell we must recall that although neurons occur in a great variety of sizes and morphological forms, they have a basic plan of structure representing certain common characteristics. The cell body of the neuron is called **perikaryon**. A large number of processes called **dendrites** emerge out of the perikaryon. These are relatively short, frequently branched, irregular in diameter and tapering. Besides these processes, there is another structure, the **axon** that emerges from the perikaryon. It is a relatively long process and branches at its tip into terminal processes. The neuron is covered all over by a cell membrane named **neurilemma** (Fig. 6.1)

Axons are of two types : i) myelinated and ii) nonmyelinated. In the case of **myelinated axons** the neurilemma is ensheathed by another covering, **the**

myelin sheath, composed of complex lipoproteins secreted by the Schwann cells in the peripheral nervous system and by another glial cell the oligodendrite in the axons of neurons in the brain. The terminal branches, dendrites, cell body (perikaryon) and the initial region of the axon (the axon hillock) are devoid of myelin sheath: Although the dendrites are relatively short, unsheathed, tapering, irregular in diameter, and branched in a wide array of patterns, the cell body cytoplasm extends into them. The dendrites receive synaptic endings over much of their surface and thus constitute the receptive surface of the neuron. They are like receiving antennae as a nerve cell receives messages along the dendrites but sends messages along the axon.

Another structural feature of unique importance in the nervous tissue is **the synapse**. A synapse is the anatomical site at which axon terminal processes of one nerve cell establish a functional contact with another nerve cell. At this contact site the membranes of the two cells in contact are separated by a physical space. Special mechanisms operate to transmit signal from one cell i.e. presynaptic to the other i.e. postsynaptic. Further description will be given when we deal with synaptic transmission.

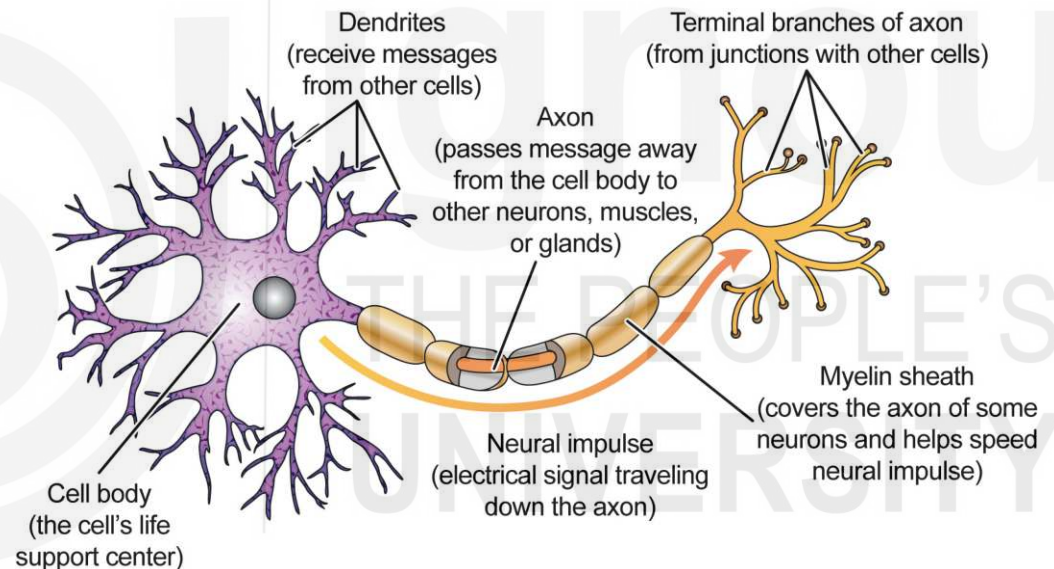


Fig.6.1: Vertebrate spinal motor neuron. The functions of different parts are indicated in the figure. Arrow shows the direction of conduction of message. (to be redrawn and add labeling of nodes of Ranvier)

The length of the axon provides one of the adaptive advantages of having neurons. The neurons that carry messages from the brain of giraffe to its toes are over 3 meters in length. The longest cells in the animal world.

The cell body constitutes the trophic apparatus of the neuron in which most biosynthetic activity occurs producing chemicals needed for other parts of the cell, for example, the axon. Rough endoplasmic reticulum is present in the cell body and dendrites but is absent in axon. Since rough endoplasmic reticulum is the principal protein-manufacturing machinery of the cell, the axon gets its proteins from the cell body. Movement of a large variety of substances from the perikaryon to and along the axon constitutes phenomenon of **axonal transport**. Extending throughout the cytoplasm from dendrites to the axon, are present fine fibrillar structures called **neurofilaments and microtubules**.

Axon is a relatively long process (also quite often referred to as nerve fibre) and can be considered as functionally specialized for conduction of excitation

or nerve impulse over considerable distance. We had said earlier that in vertebrates the axons of high velocity neurons are covered by insulating sheaths of lipid containing myelin. This myelin is made up of special glial cells – the **Schwann cells**. The myelin covering is not continuous. There are tiny uninsulated gaps between adjacent Schwann cells. These are the **nodes of Ranvier**. The myelin covering and nodes of Ranvier helps accelerate the speed of conduction of impulses by a mechanism which we will discuss later.

The terminal part of the axon branches, terminating into small ramifications whose tips form **end knobs** which synaptically contact with other nerve cells or muscles cells. In the end knobs are present characteristic structures called **synaptic vesicles** which contain and store chemical substances called **neurotransmitters**.

The diversity in neuron form, however, is so much that there can be many variations from the generalized description given above. For example, the nerve cells called **amacrine cells** found in retina contain processes without a specific axon.

SAQ 1

Pick the correct answer.

- a) In vertebrates myelin sheaths cover the
 - i) Nerve cell body
 - ii) Dendrites
 - iii) Axons
 - iv) All of the above
- b) Which of the following statements describes a synapse best?
 - i) A synapse is a point of contact between a nerve cell and another cell where messages are transmitted.
 - ii) A synapse is a functional connection between nerve cells where electrical messages are transmitted.
 - iii) A synapse is a functional connection between two nerve cells across which the message is sent from one cell to the other via a chemical substance.
 - iv) A synapse is a functional connection between two nerve cells across which the message jumps from one to excite the other.
- c) Give one word for the following statements:
 - i) A projection of the cell body of a neuron that is involved in carrying information away from the cell.
 - ii) A vertebrate glial cell that forms the myelin sheaths around the axons in the brain.

- iii) Branching extensions of the neuronal cell that carry information to the cell body.
- iv) Vertebrate glial cell that helps to regulate and support the neurons in the central nervous system.

6.3 NERVE IMPULSE

Neurons produce and conduct electrical signals or nerve impulses which are basic to all neurologic functions from sensory perception to physiological experiences. It is, therefore, of interest to understand as to how impulses are generated and conducted in the nerve cells. For instance how can pricking your finger with a sewing needle generate an electrical change that tells your brain to experience pain? The source of electricity is certainly not in the needle. It lies in the nerve cell itself. The property responsible for generation of electrical currents is largely in the neuron's plasma membrane which shows regional functional specialization. To understand this property of electric conduction in the membrane we have to first see what is responsible for creating it.

6.3.1 Electric Activity of Membranes

You might have studied in grade 12 in Cell Biology that all cell membranes have a charge built across them and the cell membrane uses this to regulate what substances can cross the membrane to enter the cell and what substances can cross it to go out. Since cell membranes are phospholipid bilayers only hydrophobic substances can cross it unaided. However, charged particles or ions being hydrophilic, are unable to pass through unless they are aided by transmembrane proteins that form **ion channels**. These proteins arrange themselves in the phospholipid bilayer so as to form a passageway or pore extending from one side of the membrane to the other. In these ion channel, protein molecules form a hole and the amino acids that line the hole are hydrophilic, while regions on the exterior that are in contact with the membrane phospholipids are hydrophobic. Research has shown that in excitable cells like neurons and muscle cells, most channels are gated, that is they open or close in response to binding of a particular molecule or to a change in the electrical charge on the outside of the membrane. There are various types of ion channels in the membrane that are responsible for building a charge difference across the membranes which have been summarized in Table 6.2. In the study of nerve cells we will be mainly concerned with, voltage gated ion channels and leakage channels and the carrier protein known as sodium/potassium pump (see Fig. 6.2 along with Table 6.2).

Table 6.2: Different types of ion channels and their role in nerve impulse generation and its conductance.

Type of Channel	Function
Charge specific, size exclusive	Selective for anions or cations

Nonspecific	Specific for a particular size of ion Specific for Na, K, and Ca ions but not anions
GATED	Open or close by binding of a molecule or by certain events. This controls the flow of ions
- Ligand gated	Ligand binds to extracellular part of channel, opens of gate for ions to cross over
- Voltage gated	Respond to changes in the electrical properties of membrane in which it is situated. Normally inner surface of the membrane is negative with respect to the outer surface, when voltage becomes less negative the channel opens to allow ions to cross over.
- Mechanically gated	Respond to physical distortion of cell membrane associated with sense of touch or temperature
- Leakage /randomly gated	Opens and closes randomly, has an inbuilt rate of switching on or off. Contributes to the resting membrane potential
Sodium/potassium pump	Imports ions against their electrochemical gradient and requires the use of energy in the form of ATP. Imports 3 Na ⁺ into the cell and exports 2 K ⁺ from the cytosol. Maintains the electrical and chemical gradient across the membrane

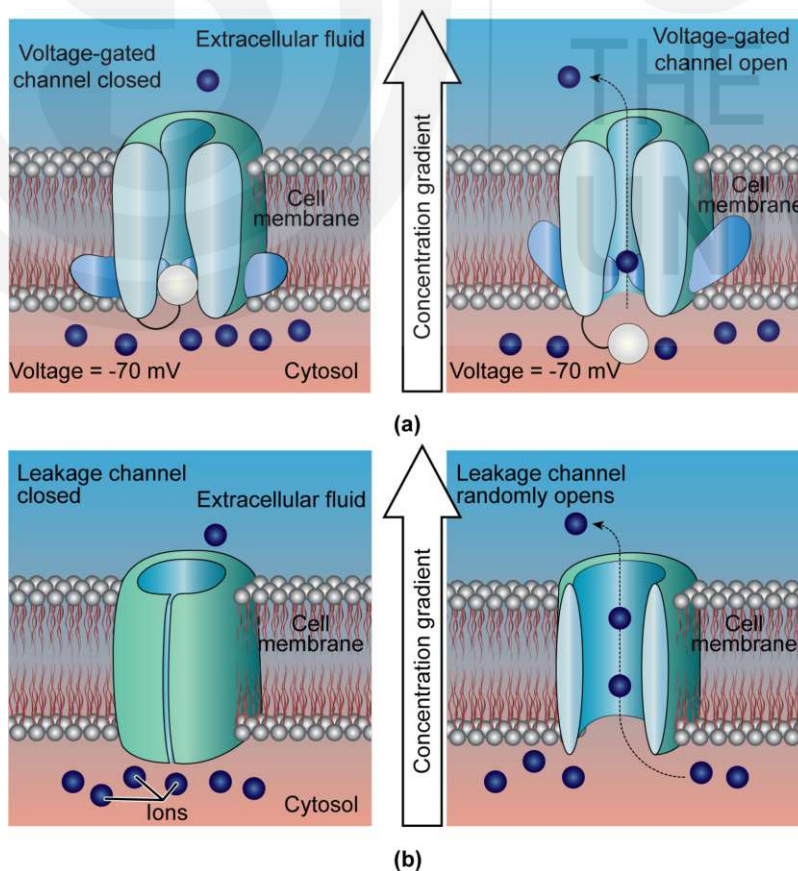


Fig.6.2: a) voltage gated ion channel. When open it allows the movement of ions according to the electrochemical gradient; b) leakage channel which open and close randomly allowing ions to flow through them.

6.3.2 Membrane Potential

You will recall that a difference between electric charge between two points creates difference in electric potential or a voltage. When an electric potential exists across a plasma membrane the separation of charge is known as **membrane potential**. The inside of the membrane is compared to the outside of the cell so that the membrane potential is really the charge on the intramembrane side if the charge on the extracellular side is considered zero. In virtually all cells, the distribution of ions is unequal in the extracellular fluid near the membrane and in the cytoplasm. The interstitial fluid around the cell has relatively higher concentration of sodium (Na^+) and chloride (Cl^-) ions, but low concentration of potassium ions (K^+). Inside the cell, the concentration of K^+ is more than Na^+ and Cl^- . These differences are pronounced as there is approximately 10 times more Na^+ outside the cell than inside and 25 to 30 times K^+ inside than outside the cell. Such differences create an **electrochemical gradient** (combination of chemical and charge gradient). The opening of the ion channels permits the ions on either side of the plasma membrane to flow down this dual gradient. This ion flow results in the production of an electrical signal. During the short time that the ion channel is open, the concentration of a particular ion in the cytoplasm as a whole does not change significantly. Only the concentration in the vicinity of the ion channel changes.

The basic functioning of all nerve cells, however, is the same. A.L Hodgkin and A.F. Huxley studied the giant axons of squids and received a Nobel Prize for showing how this potential difference contributes to the functioning of the nerve cells. The most dramatic experiment to show that nerve membrane is the essential element in generating a resting potential and not the axoplasm was shown by replacing the entire content of the axon with artificial salt solution. Such an axon behaves amazingly like a normal axon. It can remain excitable for several hours.

Even in their resting state i.e., when they are not conducting any impulses, nerve cells are generating an electric charge. Actually a resting neuron is not really resting but maintaining its **excitability** i.e., the capacity to conduct an impulse in response to a stimulus. The membrane potential can be measured using a voltmeter (Fig 6.3). A recording electrode is inserted into the cell and a reference electrode is placed outside the cell and the voltage can be measured as the value of the charge in the cytosol relative to the extracellular fluid.

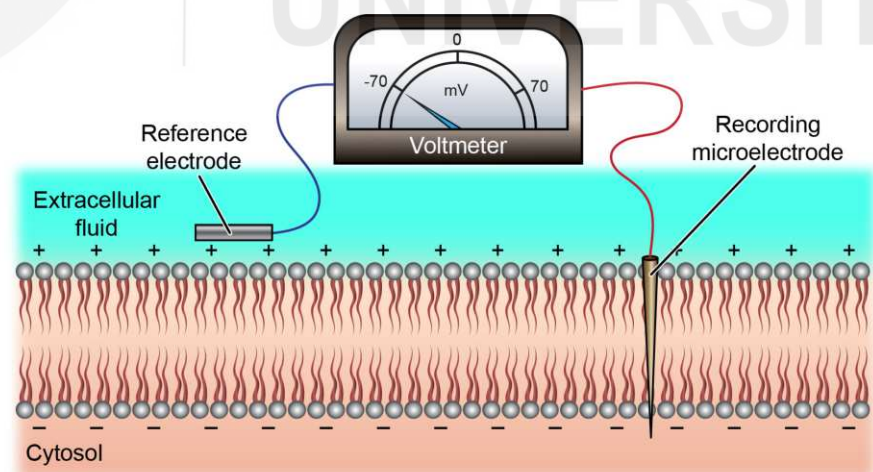


Fig.6.3: The membrane potential of a resting neuron can be measured by inserting a microelectrode inside the cell and a reference electrode in the extracellular fluid. The reading on the inside of the cell is compared to the reading outside the cell.

The nervous tissue's ability to accept and relay information results from difference in ion distribution between inside and outside the cell at rest and the

changed permeability of the plasma membrane when a stimulus is given. When at rest, the nerve cell is selectively permeable to K^+ , which can pass through the membrane through passive potassium ion specific channels (leakage channels) down its concentration gradient. The permeability to Na^+ and Cl^- at this time is almost zero because these channels are closed and there are very few leakage channels for sodium ions. Each K^+ that leaves the cell without Cl^- following it, gives a positive charge to the outside of the membrane. This positive charge quickly reaches a level that prevents further outflow of K^+ . The resting membrane attains equilibrium and the positive charge outside exactly balances the concentration gradient that drives the K^+ out. This gives the **resting membrane potential** which has been calculated to be $-70mV$ (negative sign preceding the value denotes that the inside of the cell is negative with respect to outside).

The concentration difference of ions inside and outside the nerve cell is due to:

- i) electrical attraction by negatively charged proteins and organic phosphates that are inside the cell and cannot move out,
- ii) the greater permeability of the cell membrane to K^+ than Na^+ . There are two types of channels for potassium ions. One, which lacks gates (leakage channels), the other type has gates that are closed in resting cell. As a result the resting cell is more permeable to K^+ as channels for Na^+ are always gated and these are closed in a resting cell,
- iii) active transport by Na^+ / K^+ pumps.

Now that we know how a resting membrane potential is maintained, let us see how the resting potential is disrupted by an event known as action potential which propagates along the axon as a nerve impulse.

6.3.3 Action Potential

When an appropriate stimulus interacts with the neurolemma, it is the resting membrane potential that is disturbed or changed temporarily. This rapid change in the membrane potential followed by its rapid return to the resting membrane potential is known as **action potential**. This was first recorded in the giant axon of the squid by Hodgkin and Huxley and it was found that the events that lead to its generation are the same for all nerve impulses. The action potential has three distinct phases as shown in Fig. 6.4 and Fig. 6.5:

- a) The initial event is the **depolarization** of the membrane. Recall that a membrane is said to be polarized if the charge on both sides of the membrane is different and depolarization means that the membrane becomes less polarized than before. When the stimulus is applied to the membrane the sodium ion channels open and Na^+ flows inside the cell through them along its concentration gradient. This makes the inside of the cell less negative and the membrane potential shifts from $-70mV$ to $-55mV$. If the stimulus is not able to bring the membrane potential to $-55mV$, the action potential will not start so this is actually the **threshold voltage**. Gated sodium ion channels have two types of gates, an activation gate and an inactivation gate. The activation gate is very sensitive to voltage changes and is the basis of the threshold. Once

threshold is reached, Na^+ rush in following their electrochemical gradient. Further depolarization occurs and eventually the inside of the membrane crosses zero and becomes positive with respect to the outside.

- b) When the membrane reaches +40mV, an abrupt change occurs, other voltage gated channels open. These allow only K^+ ions to leave the cell along their concentration gradient(remember that there are less potassium ions outside the cell). At the same time the inactivation gates for Na^+ channels are closed and no more Na^+ can enter the cell. In this second phase the membrane is rapidly approaching its resting potential of -70mV. This is the **repolarization** phase.
- c) The repolarization event actually results in the membrane becoming more negative than the resting potential for a very short time. It overshoots the resting potential that is it becomes more negative than -70 mV, this is a period of **hyperpolarization** in which the Na^+ are inactivated so no sodium gets inside the cell and though K^+ channels are closing as the membrane reaches its resting potential, some K^+ channels are still open. These K^+ channels are slightly delayed in closing, accounting for this short overshoot. Finally the inactivated Na^+ channels are reset so that they are ready for further depolarization and resting potential is restored.

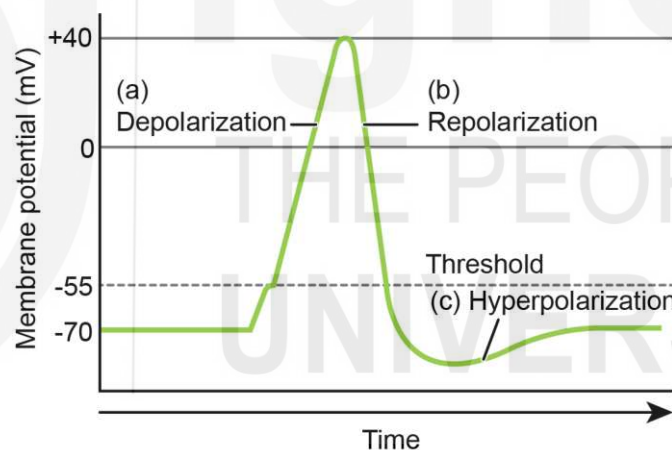


Fig. 6.4: The action potential is a change in the resting membrane potential. the action potential begins with depolarization, followed by repolarization, which goes past the resting potential into hyperpolarization, and finally the membrane returns to rest.

The entire sequence of action potential takes place in one thousandth of a second. The action potential is the electrical signal that the nervous tissue generates for communication. Throughout all this the Na^+/K^+ pump continues to work and extra Na^+ are pumped out and K^+ pumped into the cell. The Na^+/K^+ pump transports 3 Na^+ out of the cell for every 2 K^+ it brings inside the cell. Thus it actually helps to maintain the potential difference. Small amounts of Na^+ and K^+ , however, always diffuse out and the cell therefore, has a relatively constant intracellular concentration of ions and a constant resting membrane potential. You would notice after reading the above description that **active transportation processes are not directly involved in the production of action potential**. Giant axons which had been poisoned with cyanide to

disrupt the sodium pump continue to show normal excitability and action potentials for several hours. But the system finally collapses because of Na^+ accumulation in the cell. The Na^+/K^+ pumps are, therefore, needed to maintain the concentration gradients for diffusion of Na^+ and K^+ during the action potentials.

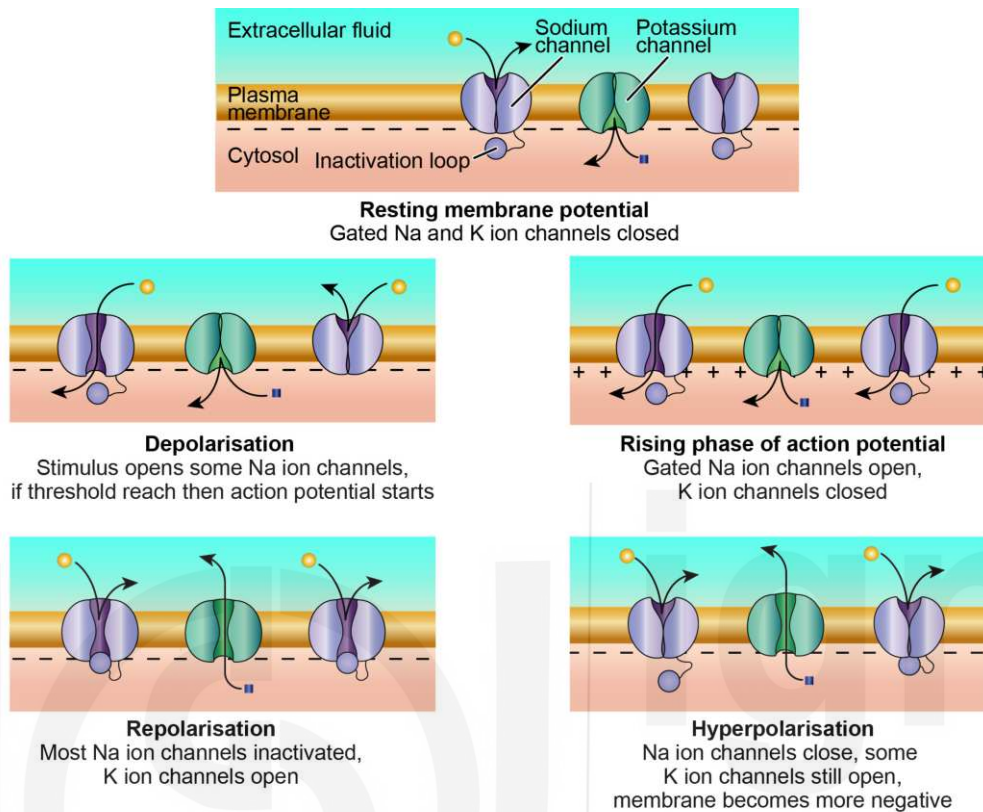


Fig.6.5: Phases in action potential generated by change in membrane potential.
After hyperpolarisation all gated K^+ channels close, Na^+ channels are reset and resting membrane potential is restored.

SAQ 2

a) Correct the following statements:

- Ion channel proteins span the membrane and are hydrophobic in the part lining the pore and hydrophilic on the part that is in contact with the phospholipid bilayer.
- Both Na^+ and K^+ ions pass only through gated channels at all times.
- Na^+/K^+ ion pump brings in 3 K^+ and 3 Na^+ ions inside the cell.
- Resting membrane potential on average is -55mV

b) Pick the correct answer:

- At the peak of action potential:
 - sodium channels are inactivated and potassium channels are opened.
 - all gated channels closed.
 - the membrane potential reaches its most negative value.

- d. the axon is hyperpolarized.
- ii) During the falling phase of the action potential the membrane repolarises beyond the resting voltage. This happens because:
 - a. calcium ions rush into the axons
 - b. large number of potassium channels are open
 - c. sodium ions rush in
 - d. delayed closing of potassium channels

6.3.4 All or None Response

In the earlier subsection we had said that a very weak stimulus does not result in an action potential. The stimulus must have certain strength to evoke an excitation. This you know is the **threshold value (-55mV)** below which no action potential results. Once generated, the size of the action potential is not influenced by the magnitude or amplitude of the stimulus. Even if we double or triple the strength of the stimulus, the action potential remains the same. The stimulus causes either a full response or non at all. In physiology, this type of response is called **all-or-none response**. When greater stimulus strength is applied to a neuron multiple but identical action potentials are produced more frequently.

Another important property of nerve impulse to be noted is that during the time that a patch of axon membrane is producing an action potential, it is incapable of responding to another stimulus i.e. it is in a refractory period. There are two phases in refractory period: (i) If the second stimulus is applied then no action potential can be started, this is **absolute refractory period**. The Na^+ gates are open the membrane is depolarized; (ii) but if the second stimulus is applied when the inactivated Na^+ channels are in resting configuration (-55mV) and K^+ gates are open, the membrane is in **relative refractory period** and can be depolarized only if the second stimulus is stronger than the initial stimulus that initiated the current action potential.

6.3.5 Conduction

An action potential occurs at one point along the beginning of the axon. There is a high density of voltage-gated Na^+ channels so that rapid depolarization can take place here yet we know that neurological impulses are not fixed, they travel along a neuron. So how can the action potential at one point excite a neuron at another point? We must realize that one particular action potential does not travel itself along the membrane but *each action potential activates voltage gated channels in the adjacent part of the membrane and a new action potential occurs there*. This triggers the next region and so on. Going down the length of the axon, the action potential is propagated because more voltage-gated Na^+ channels are opened as the depolarization spreads. This spreading occurs because Na^+ enters through the channel and moves along the inside of the cell membrane. As the Na^+ moves, or flows, a short distance along the cell membrane, its positive charge depolarizes a little more of the cell membrane

by the **cable properties** (the ability of a neuron to transmit charges through the cytoplasm) to the adjacent region that still has a membrane potential of -70mV . The limit of transmitting electric charge through cytoplasm is one to two millimeters. When the stimulus is of threshold value in the adjacent region it too produces an action potential. Therefore, an action potential is a self propagating event.

Because voltage-gated Na^+ channels are inactivated at the peak of the depolarization, they cannot be opened again for a brief time (the absolute refractory period). Because of this, depolarization spreading back toward previously opened channels has no effect. The potassium channels in that area are still open and carry this current out of the cell as an efflux of K^+ . The action potentials are, therefore, not really conducted but regenerated along the axons length. The last action potential has the same amplitude as the first. Thus they are said to be **conducted without decrement** and the action potential must propagate toward the axon terminals.

What we have describe above is the way action potential is propagated in unmyelinated fibers. The spread of conduction in ummyelinated fibres is faster if the axon is thicker because the ability of fibres to conduct by cable properties improves with increasing diameter as can be seen in the giant axons of squids in comparison to ordinary axons from the same animal.

Let us now see how this propagation occurs in myelinated fibers of vertebrates

Conduction in Myelinated Axons

In Section 6.2, we told you that myelin sheath provides insulation for the axon preventing movements of Na^+ and K^+ through the membrane. Therefore, if this myelin sheath was continuous no action potential would be generated. Fortunately, gaps or nodes of Ranvier occur in the myelin covering. Since the cable properties of axon can conduct depolarizations over very short distance (1-2 mm), the nodes of Ranvier must be close together (actually they are 1mm apart). Studies have shown that the Na^+ channels are concentrated at the nodes and absent from the regions between two nodes. Action potential therefore occurs only at the nodes of Ranvier and seems to leap from node to node (Fig.6.6). This is called **salutatory conduction** (saltutatory= latin for leaping). The spread of depolarization between the nodes is very fast and fewer action potentials are needed. Therefore, the rate of conduction is much faster than in unmyelinated fibres of the same diameter.

Imagine the size of the optic nerve in humans if a high conduction velocity were to be achieved without myelination. The optic nerve has a diameter of $3\mu\text{m}$, if it were to contain the same number of fibres without myelination and conduct at the same speed it would require a diameter of 300 mm.

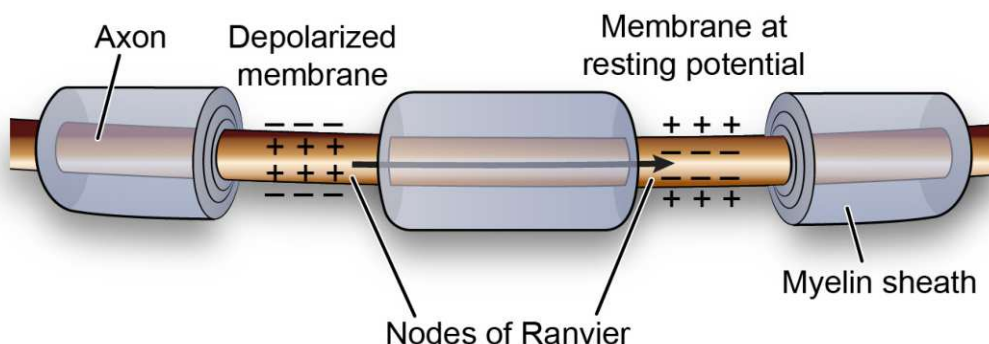


Fig.6.6: Nodes of Ranvier are gaps in the myelin sheath covering the axons of vertebrates. Only the gaps or nodes have sodium and potassium channels therefore the action potential leaps from one node to the other thus making the conduction fast.

This peculiar structure and mode of conduction in myelinated fibres is responsible for the fast conduction of impulses in motor nerves of vertebrates even though the nerves are very thin. The greatest advantage of myelinated fibres comes from their smaller size and so a highly complex nervous system with high conduction velocities can occur without occupying too much of space.

SAQ 3

- a) What would happen if we increase the strength of the stimulus to an axon?
- b) Fill in the blanks with suitable words:
 - i) The leaping of action potential between the nodes of Ranvier is called while conduction of action potential in unmyelinated axon happens through
 - ii) Action potentials are conducted without
 - iii) If a stronger stimulus is applied during the action potential, another impulse is generated if the membrane is in period.

6.4 SYNAPTIC TRANSMISSION

Now that you know how a nerve impulse is generated and conducted along the axon we come to the most important aspect of the functioning of the nervous system. The transfer of information from one neuron to another neuron or another cell after it reaches the end of the axon.

We mentioned in the beginning of the unit that the ends of axons split into fine extensions which form synapses with other cells. You also know that a synapse is an area where the membrane of the axon terminal lies very close to the membrane of the other neuron, muscle or gland. A synapse close to a muscle cell is called **neuromuscular junction**.

Information passes across a synapse in two ways: chemically or electrically. Chemical transmission, however, is more common and takes place through chemicals called **neurotransmitters** (we will learn more about neurotransmitters in section 6.5). The end of the axon terminals are known as **synaptic knobs** or **boutons** (bouton = button). The membranes of the synaptic knobs do not touch the membrane of the other cell but are separated by a narrow space, 20 nanometer (nm) apart, and known as **synaptic cleft**. The *sending* cell with the axon knob is referred to as **presynaptic neuron** and the dendrite or other cell with which it communicates is the *receiving* or **postsynaptic neuron** (see Fig. 6.7).

The appearance and width of synaptic cleft is remarkably similar throughout the animal kingdom but all the chemicals released in each cleft are not known as yet. The synaptic knob contains a large number of small vesicles that are usually 30-80 nm in diameter. These vesicles enclose the neurotransmitters.

The neurotransmitter molecules are synthesized in the Golgi apparatus in the soma and transported to the presynaptic terminal by current flow in the axon. For example, **acetylcholine** a neurotransmitter, is synthesized from choline and acetyl coenzyme A, the reaction being catalyzed by the enzyme **choline acetyl-transferase**. The newly synthesized acetylcholine is stored within the synaptic vesicles. Each vesicle may contain 10,000 to 50,000 molecules of a neurotransmitter. The whole neurotransmitter content of a vesicle represents one quantum of the neurotransmitter.

The postsynaptic membrane has molecular receptors that specifically interact with the released neurotransmitter molecules. Binding of the neurotransmitter molecules with the receptors on ligand gated ion channels causes changes in the membrane permeability.

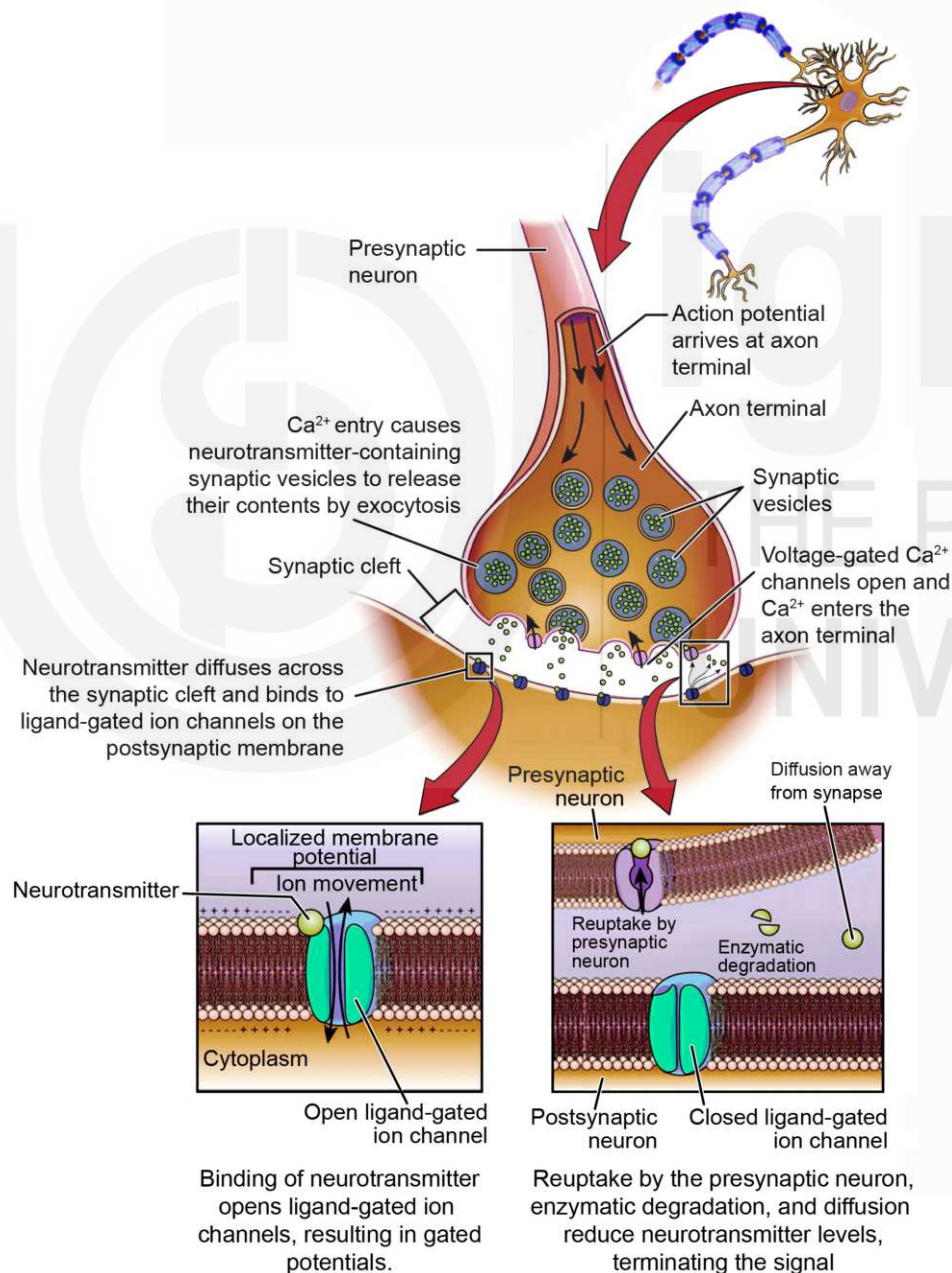


Fig.6.7:Transmission across a nerve ending. The synapse is the connection between a terminal axonal ending of a neuron with its target cell which could be the cell body or dendrites of another neuron or a muscle or gland. Steps 1 to 6 explain the functioning at the synapse.

6.4.1 Chemical Synaptic Transmission

Look at Fig. 6.7 again; the arrival of an impulse at the presynaptic terminal depolarizes the membrane. The depolarization opens voltage gated calcium channels allowing calcium ions to move through these channels into the axon terminal (step (2) in Fig 6.7). The elevated Ca^{2+} concentration causes the translocation (propulsion) of the synaptic vesicles toward the presynaptic membrane. The synaptic vesicles become oriented and aligned with the synaptic plasma membrane. A number of vesicles ultimately fuse with presynaptic membrane leading to the release of their neurotransmitter contents by exocytosis into the synaptic cleft (step(3) in Fig.6.7). After releasing their neurotransmitter, the synaptic vesicles merge with the membrane. New vesicles are formed from invaginations of the synaptic membrane, which are filled with the transmitter and can be reused again.

The released neurotransmitter diffuses across the cleft and binds with the specific receptor molecules (step (4) Fig 6.7). This process takes a fraction of a millisecond to occur. The neurotransmitter does not bind with its receptor irreversibly, they are quickly inactivated or broken down by enzymes and either taken up by the presynaptic cell to be recycled or nearby glial cells remove them from the cleft (step (6) of Fig.6.7). Binding of the neurotransmitter to a postsynaptic receptor causes the opening of ion channels (step(5) Fig.6.7). These channels are therefore **chemically gated** and not voltage dependent. Flowing of the ions across the postsynaptic membrane changes the potential of the postsynaptic membrane thus producing a new signal, the **postsynaptic potential (PSP)**, in the postsynaptic neuron. Our description about the transfer of information from a single synapse seems simple and does not reflect the complexity of the functions of the nervous system. You must recall that most axons are highly branched at their ends and may connect to a large number of other neurons. Similarly a single neuron would also receive branches from a large number of axons that terminate on its cell body or its dendrites.

Some specialized neurons are so densely covered with synaptic knobs that a single such neuron may have about 10,000 synaptic connections. You would appreciate the complexity of the central nervous system when you couple this with the number of neurons present which are more than 10^{11} . These connections are not random but highly specific and have been studied in great detail by neuroanatomists and neurophysiologists.

6.4.2 Postsynaptic Potential

Let us now examine the postsynaptic potential (PSP) in some detail. It has been found that axon of a neuron may carry inhibiting impulses or excitatory impulses to the post synaptic neuron. But you must remember that there is no difference in the impulse carried in excitatory and inhibitory impulses, the action potential is the same but opposing effects are achieved by the release of different chemical transmitters from the presynaptic endings. The ion gates that open up in the postsynaptic membrane depend upon the type of neurotransmitter involved.

As said in the earlier subsection, numerous synapses can be found in the same region of a dendrite or a cell body. These synapses can be of two types; if the receptors at the synapse admit Na^+ ions in response to the neurotransmitter then the postsynaptic membrane depolarizes in reaction to the action potential of the presynaptic neuron. In most cases, depolarisations are more likely to invoke an action potential in the postsynaptic cell. Changes in the postsynaptic membrane that lead to depolarization are **excitatory postsynaptic potentials (EPSP)**. On the other hand if, the neurotransmitter – receptor-interaction opens K^+ then some K^+ will leave the cell increasing the negative membrane potential i.e. hyperpolarisation. This increase in potential is **inhibitory postsynaptic potential (IPSP)**. If the channel opened by the neurotransmitter is for Cl^- , then also an IPSP will develop. It is critical to understand that unlike action potentials, EPSPs and IPSPs are not all or none events but are **graded in size and short lived**. (Fig. 6.8)

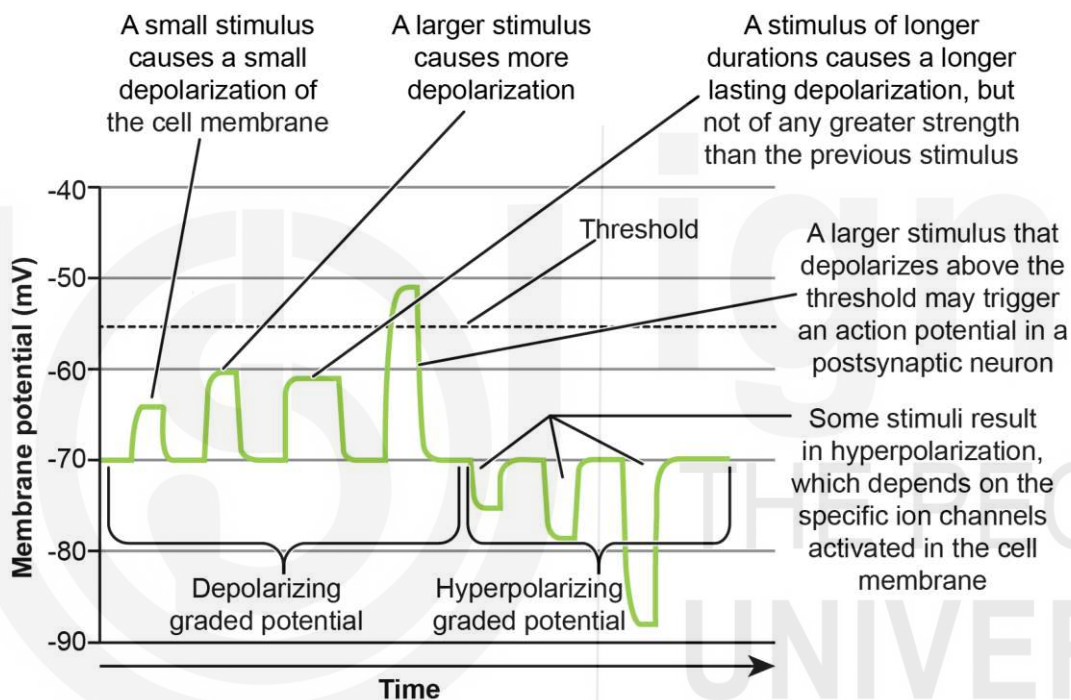


Fig. 6.8: Graded potentials depend on the size and duration of the stimulus provided by the presynaptic cell to the post synaptic cell. They can be depolarizing or hyperpolarizing potentials depending on the type of ion channels being opened by them.

Let us see how the postsynaptic potential (PSP) works by using the example of a well known neurotransmitter **acetylcholine** which has been studied at neuromuscular synapses. The interaction of acetylcholine results in the opening of both Na^+ and K^+ gates allowing the flow of ions simultaneously. The depolarisation effect predominates therefore this is an EPSP and the membrane potential takes a value of -45 mV which is nearer zero but does not reach threshold and the characteristic overshoot of action potential is not achieved (the magnitude of the PSP at the synapse is dependent on the amount of neurotransmitter released). Acetylcholine must also be removed quickly or there would be a continuous PSP. An enzyme **acetylcholinesterase** present at the synapse removes the transmitter.

Now if a second impulse arrives before the first one dies off, it adds to the first one evoking a stronger depolarising potential (see Fig. 6.9). If more EPSPs

arrive one after the other all of them add up and may cross the threshold to generate an action potential. This effect of adding up the PSPs is known as **summation** and in the example given above is known as **temporal summation** (many signals received from the same neuron at different times). Now if two separate neurons have synapse with the same postsynaptic neuron, the PSPs generated by the different sites of synapse will also add up. These could be two or more IPSPs or EPSP and IPSP depending on the neurotransmitters and accordingly the response could be excitatory or inhibitory. This kind of summation is known as **spatial summation**. The PSP is a direct expression of the impulse frequency in the axon. These two types of summation – temporal and spatial form the basis for computation in each neuron and so the entire nervous system.

Thus, excitatory (EPSP) and inhibitory (IPSP) postsynaptic potentials are constantly developing at many points on the surface of the postsynaptic cell. Summation occurs at the axon hillock. The two types of postsynaptic potentials will have opposing effects on the net membrane potential. If the postsynaptic potential at the axon hillocks is of sufficient size to reach threshold value, an action potential is initiated and travels along the axon of the receiving neuron. If inhibitory inputs prevail then no action potential is generated. Thus synapses act as relay stations in the line of communication in the nervous system.

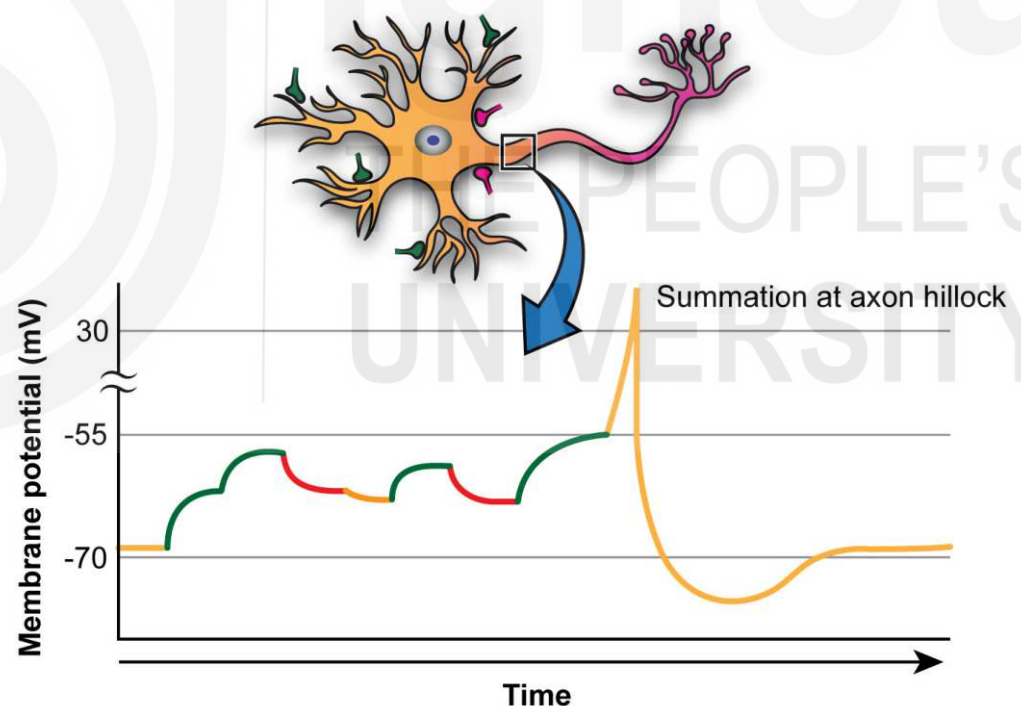


Fig. 6.9: Postsynaptic membrane potential summation. A combination of EPSPs and IPSPs lead to the membrane potentials adding up at the axon hillock of the cell to generate a membrane potential in the postsynaptic cell.

6.4.3 Electrical Synaptic Transmission

Electric synapses are fewer in number than chemical synapses though they are found in all nervous systems. As described above, the mode of chemical synaptic transmission involves the secretion of a chemical transmitter from the

presynaptic terminal to affect the permeability of the postsynaptic membrane causing an action potential to develop in the postsynaptic neuron. The mode of electrical transmission, however, involves the direct spread of ionic current from the presynaptic terminal to the postsynaptic membrane to depolarize the postsynaptic cell to the threshold that would generate an electric potential.

Microstructure of the electrical synapses differs from that of the chemically transmitting synapses. In an electrical synapse, the extracellular space between presynaptic and the postsynaptic membrane is greatly reduced (about 2nm) making the cell membranes more closely approximated. Furthermore, the cleft width of 2-3 nm is bridged by the large tubular protein molecules which are embedded in the presynaptic and postsynaptic membranes, thus providing channels known as **gap junctions** through which inorganic ions can pass. This is indicative of some cytoplasmic continuity. These structural features make it possible for the current to flow readily from the presynaptic to postsynaptic side and there is essentially no delay between potential changes in the presynaptic and postsynaptic neurons making the two neurons electrically continuous. The electrical synapse can transmit equally well in both directions. In some electrical synapses, however, it has been found that current passes more easily in one direction than in the other. At chemical synapses the distance across the synaptic cleft is too large (20nm) to allow the presynaptic current to invade the postsynaptic membrane.

Properties and functions of synapses

There is an interval between depolarization of the presynaptic terminal and the earliest appearance of a postsynaptic response. This interval is called **synaptic delay**.

The synapse is the prime locus in the integration of neuronal signals. The synapse is also a site where functional properties are changed as a result of previous activity. For example, prolonged activity transmitted across a synaptic junction may result in a reduction of the threshold of firing of the neurons to further afferent inputs. This indicates that synapses are the site of changes in the storage of information (learning and memory). The synapse is thus modifiable i.e., it shows **plasticity**.

A variety of chemical agents (drugs etc.) act at synapses to alter nervous system's behaviour. A postsynaptic neuron is an integrator of information that is received from presynaptic neurons. Synaptic transmission is a one way process except in electric synapses.

Synapses are the site of several pathological disorders viz., Parkinsonism, myasthenia gravis, and psychiatric disorders like schizophrenia.

So far we have discussed the action potential and its effect at the synapse i.e. release of neurotransmitter. Acetylcholine is just one of the examples of a neurotransmitter. There are many more physiologically active chemicals that are produced by nerve cells. These have profound effects as hormones which we will study in Unit 7. In the next section we will learn about neurotransmitters.

SAQ 4

- a) What are the two main differences between chemical synapses and electrical synapses?
- b) What kind of channels must open for excitatory PSPs and inhibitory PSPs?
- c) Define the following:
 - i) Synaptic delay
 - ii) plasticity of synapse
 - iii) temporal summation
 - iv) spatial summation
- d) What is the role of voltage gated Ca^{+2} channels in the release of neurotransmitter in the synapse?

6.5 NEUROTRANSMITTERS

We know that transmission of signals from nerves to muscles is affected by acetylcholine a transmitter substance. Similarly neuron-neuron transmission is also achieved by acetylcholine. But there are several other biochemicals that function as neurotransmitters. A limited number has already been identified and new ones are being identified rapidly. Some of these are listed in Table 6.3

A chemical can be called a neurotransmitter in a given tissue only if it fulfills certain conditions like :

- When applied to the postsynaptic membrane it should be able to produce the same effect as does presynaptic stimulation
- It should also be released by the presynaptic membrane
- Its action should be blocked by the same agents that block neural transmission.

Table 6.3: Some common types of neurotransmitters and their effects (+ denotes excitatory, and – denotes inhibitory effects).

Neurotransmitter	Action + or-	Target Cells	Effect
Acetylcholine	+	Voluntary muscle neuromuscular junction	Stimulates muscle contraction
	–	Autonomic nervous system	Inhibitory at parasympathetic endings of vagus; vital for normal functioning of
		Vertebrate central	

		nervous system	muscles. In the brain it plays a role in memory , arousal and attention
		Heart muscle	
Norepinephrine	+	Neurons of central nervous system	Increases alertness and attention, prepares for muscular activity.
Epinephrine (adrenaline)		Sympathetic neurons	responsible for arousal, attention, moods; involuntary muscles
Dopamine	— or +	CNS pathways	Prevents overactivity of neurons that activate muscles, deficiency causes uncontrolled muscle contraction of Parkinson's disease. Has a role in schizophrenia
Glutamate	+	Central nervous system.	Ensures homeostasis with GABA, regulates excitability in CNS, learning process and memory
Serotonin	—	Neurons in the brain that maintain wakefulness.	Induces sleep, may modulate moods, emotions.
GABA (γ - aminobutyric acid)	—	Neurons in the brain.	Reduces neuronal excitability throughout the nervous system.

The neurotransmitters are either derived from the amino acid tyrosine, which include dopamine, norepinephrine, epinephrine and serotonin or from neuropeptides. Peptide neurotransmitters include the **endorphins** and **enkephalins** that reduce pain perception. Therefore, these are called natural opiates (morphine like substances).

The neurons that are involved in pain reception have receptor molecules to which internal opiates attach so that pain receptors are inhibited from releasing their own transmitter substance (substance P) on to neurons in the pain perception centers. Thus relay of information to the brain is blocked. The pain killing effectiveness of endorphins is similar to that of morphine.

Neurotransmitters have three mechanisms of action, namely **ionotropic**, **metabotropic**, and **modulatory**.

- Ionotropic (Fig.6.10 a): they induce the opening of specific ionic gates in the membrane. Glutamate, GABA, and acetylcholine are all ionotropic. Glutamate is excitatory as it opens Na⁺ gates, leading to depolarization. GABA opens Cl⁻ gates, thereby allowing the movement of Cl⁻ into the neuron and leading to hyperpolarization hence it is inhibitory. Acetylcholine is ionotropic at nicotinic synapses (acetylcholine has two types of receptors one that respond to nicotine and another type known as muscarine receptors that respond to muscarine a drug obtained from

The hallucinating effects of drugs like morphine, heroin, mescaline etc., are due to their competition with receptor sites of natural opiates.

certain types of mushrooms), inducing the opening of Na^+ gates. These ionotropic effects are rapid (occurring typically within 10 milliseconds after neurotransmitter release) and last from 1 to 20 milliseconds.

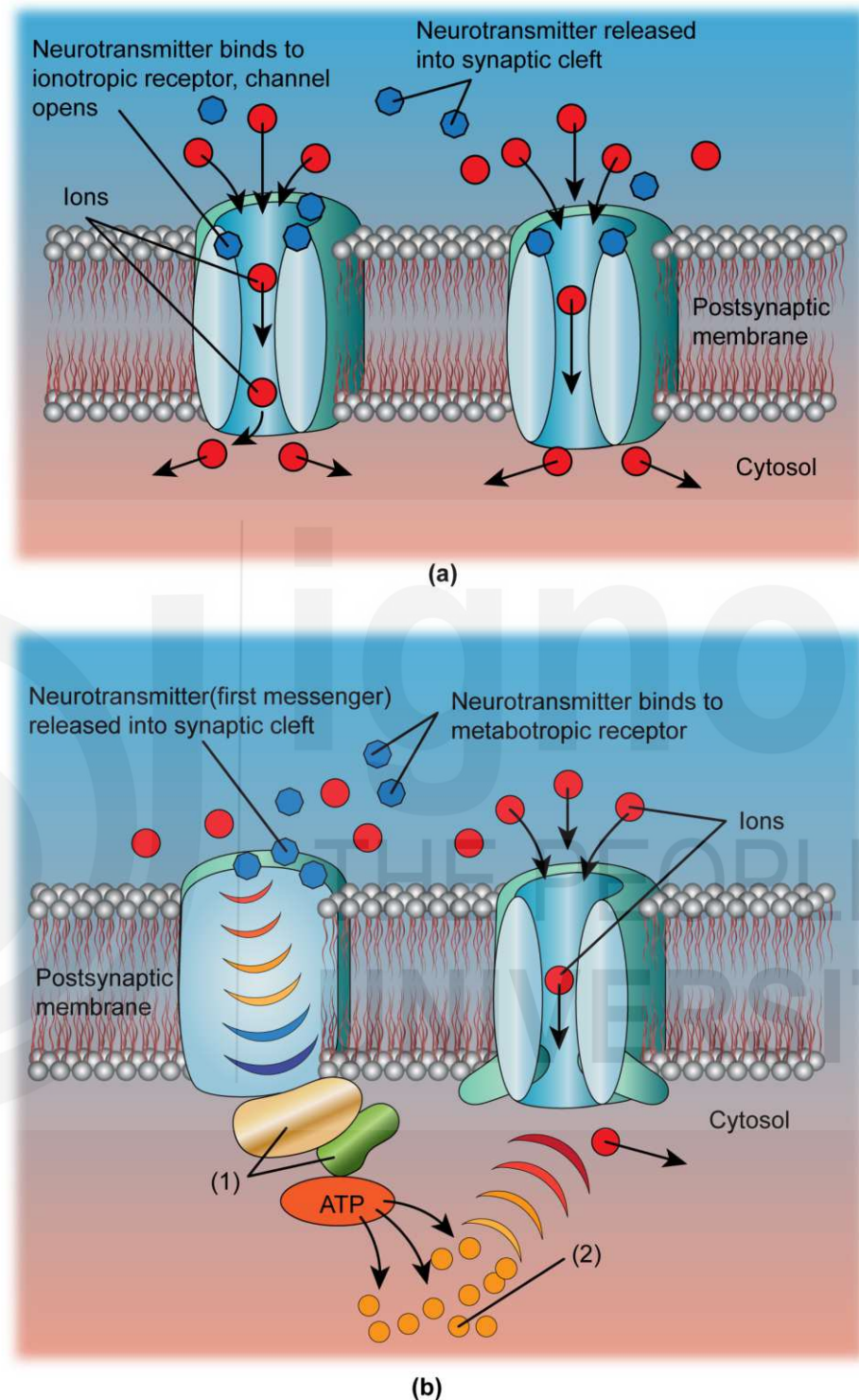


Fig. 6.10: a) An ionotropic receptor is a channel that opens when the neurotransmitter binds to it. This direct action brings immediate response; b) A metabotropic receptor is a complex that causes indirect action involving prolonged response when the neurotransmitter binds to it. After binding, the G protein hydrolyzes GTP and moves to the effector protein (1). When the G protein contacts the effector protein, a second messenger is generated, such as cAMP (2). The second messenger can then go on to cause changes in the neuron, such as opening or closing ion channels, metabolic changes, and changes in gene transcription.

- **Metabotropic (Fig.6.10 b):** and are more complicated involving a sequence of metabolic reactions. These effects typically involve a "second messenger", molecule that may open or close an ion gate, alter the production of proteins, or alter the structure of the postsynaptic cell. The biogenic amine, epinephrine, is a metabotropic transmitter. The effects are much slower to occur (30 milliseconds after neurotransmitter release), are longer-lasting (up to several seconds in duration).
- **Neuromodulators:** are peptide molecules (short proteins) whose function lie somewhere between that of a neurotransmitter and a hormone. Neuromodulators may influence a number of neurons in the region of release, including the releasing neuron. They act by prolonging or limiting the effects of a neurotransmitter. Their effects are slow to occur and long lasting (from seconds to minutes, and possibly hours). The endorphins are neuromodulators. Most neurons synthesize and release both neurotransmitters and neuromodulators. This combination supports a broader range of effects.

Neurons do not always function in the way they should. Things can go wrong in a deadly way if the synaptic cleft is occupied by chemicals that interfere with neurotransmission (see Box 6.1).

Box 6.1

Nerve Poisons

In general nerve poisons are the most toxic substances known. In minute quantities, they can interfere with acetylcholine activity and sabotage the normal functioning at the synapse.

Curare

Curare is a deadly extract of tropical plants of South America. The native hunters of South America dip their darts in this neurotoxin and blow it from their small blowguns. Curare blocks the neurotransmitter sites on the postsynaptic membrane so that the muscles stop contracting even though there is enough acetylcholine in the synaptic clefts. Death occurs quickly suffocation when the muscles used for breathing stop working.

Organophosphates and Nerve Gas

Organophosphates and nerve gas inhibit the enzymatic removal of acetylcholine so that the neurotransmitter remains in the cleft and the victim suffers from the spastic paralysis.

Tetanus

Tetanus also causes spastic paralysis and is associated with simple bacterial infection of wounds. The toxin released by the bacteria affects inhibitory synapses by blocking glycine sites on the postsynaptic membrane. The muscles become locked in permanent contraction. All voluntary muscles are eventually affected and the victim loses the ability to breathe and dies.

SAQ 5

- a) Which of the following neurotransmitters is associated with inhibition exclusively and which of them is exclusively excitatory?
- i) GABA

- ii) Acetylcholine
 - iii) Glutamate
 - iv) Dopamine
- b) Which of the following is **not true** for a neurotransmitter?
- i) They are biochemicals
 - ii) They are released into the synaptic cleft
 - iii) They increase the likelihood that the post synaptic membrane will generate an action potential
 - iv) They are stored in vesicles in the pre synaptic axon button.
-

6.6 SUMMARY

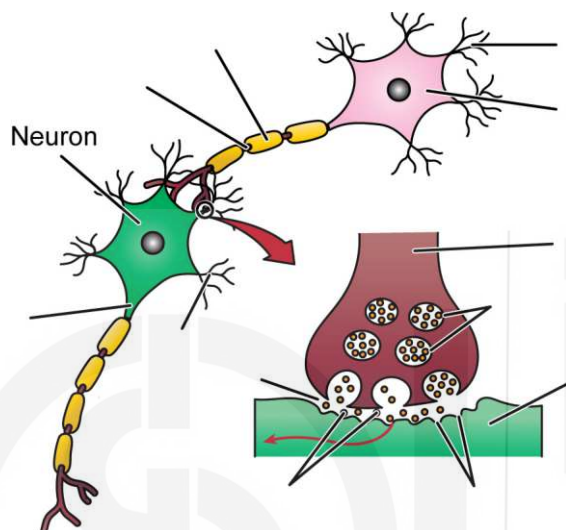
In this unit you have studied that :

- the functional unit of all nervous systems is the neuron which typically consists of a cell body containing the nucleus, a variable number of dendrites that receive inputs and a single axon that carries information in the form of the electrical impulses. These impulses are conveyed to other neurons or cells by release of neurotransmitters from the axon terminal ends or synaptic terminals.
- the nervous system functions as a result of differences in ion distribution across the neuron membrane at rest and after stimulation. Action potential (AP) is generated when the membrane is sufficiently depolarized in response to a stimulus to attain a threshold level. It is an all-or-none phenomenon. The AP is conducted due to the cable property of neurons in unmyelinated fibres and by salutatory conduction in myelinated fibres,
- synaptic transmission of information is mostly through chemical synapses and in some instances through electrical synapses. Chemical synapses involve neurotransmitter substances that are produced in presynaptic terminals and released in the narrow cleft that separates the presynaptic cell from postsynaptic cell. Receptors in the postsynaptic membrane pick up these transmitter molecules. These receptors are linked to chemically gated ion channels and change in membrane permeability generates a postsynaptic potential which may be inhibitory or excitatory. In excitatory postsynaptic potential the action of the transmitter molecules is to shift the membrane potential beyond the threshold for initiation of action potential in the axon hillock. Inhibitory postsynaptic potential changes ion conduction so as to counteract depolarization of the membrane.

- the neurotransmitter substance in the cleft is either destroyed or picked up by surrounding glial cells or reused by the presynaptic cell. Basically action potentials are the result of voltage regulated ion channels and postsynaptic potentials are due to chemically gated ion channels. Several chemicals are known to be neurotransmitters and they may have excitatory or inhibitory effect depending on the type of synapse from which they are released and the types of receptors they bind to.

6.7 TERMINAL QUESTIONS

- Label the figure of neurons and show the direction of flow of impulse.



- The resting membrane potential of an axon is normally -70mV . What would happen to the membrane immediately after the following events?
 - A sudden increase in Na^+ permeability
 - A sudden increase in Cl^- permeability
 - Arise in concentration of K^+ on the outside of the membrane
 - An accumulation of Na^+ on the outside of the membrane
- Data regarding velocity of conduction of action potential is given below for two species. Which of them is an invertebrate species and why is the velocity of conduction more in species B?

	Axon diameter (μm)	Velocity of conduction (ms^{-1})
Species A	500	33
Species B	15	90

- Explain why an action potential is all-or-none event.
- Write down the steps that take place when an action potential arrives in a presynaptic axon terminal and the generation of another action potential in the post synaptic neuron.
- Define a neurotransmitter.

6.8 ANSWERS

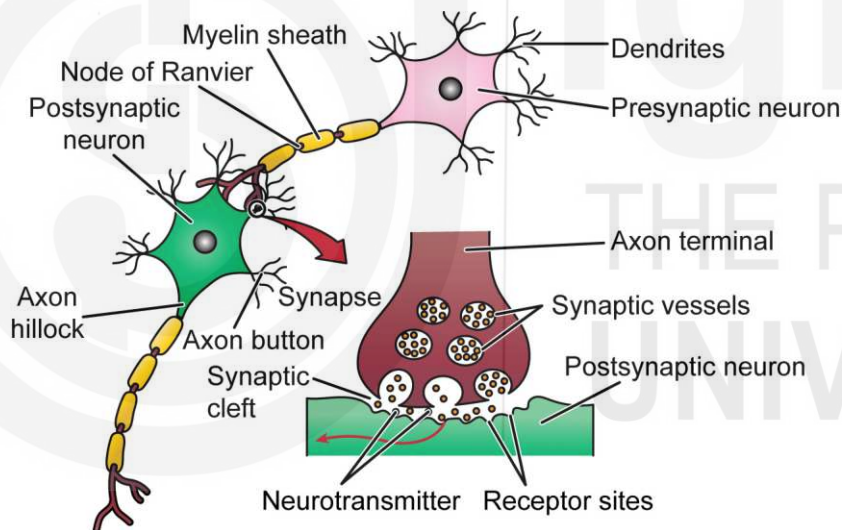
Self-Assessment Questions

1. a) Axons
b)
c)
2. a) i) Ion channel proteins are **hydrophilic** inside the channel and **hydrophobic** on the side that exposes them to the phospholipid bilayer.
ii) Both Na and K have gated ion channels, however, both also have leakage channels.
iii) Na^+/K^+ ATPase pump takes out 3 Na^+ from the cell and brings in 2 K^+ .
iv) Resting membrane potential on average is - 70mV.
b) i) sodium channels are inactivated and potassium channels are opened.
ii) delayed closing of potassium channels
3. a) If threshold level is already reached and action potential then increasing the strength of the stimulus would still produce the same action potential only frequency of action potential may increase.
b) i) Saltatory conduction; cable properties
ii) Decrement
iii) Relative refractory period
4. a) Chemical synapse: have a gap or cleft between the pre and post synaptic membrane in which the neurotransmitter is released; direction of signal is one way from pre to post synaptic cell. Electric synapse the pre and post synaptic membranes are connected by large proteins making gap junction, signal can travel in either direction.
b) Excitatory post synaptic signals open Na^+ and K^+ channels to cause depolarization while Inhibitory postsynaptic signals open channels for K^+ or only Cl^- that lead to hyperpolarisation.
c) i) **Synaptic delay** : the time interval between the arrival of an action potential at the axon terminal and generation of another signal in the post synaptic neuron.
ii) **Plasticity of synapse** : ability of change at a synapse activity based on its previous activity. The synaptic activity can weaken or strengthen over time.

- iii) **Temporal summation:** adding up of graded potentials from the same location that is same axon terminal arriving at short intervals.
 - iv) **Spatial summation :** combination of graded potentials across the neuronal cell membrane caused by signals from separate presynaptic axon terminals that add up to initiate an action potential.
 - d) Voltage gated Ca^{+2} channels open on the presynaptic membrane in response to the action potential to allow these ions to enter and they propel the synaptic vesicles to merge with the presynaptic membrane and release their neurotransmitter.
5. a) glutamate is exclusively excitatory and GABA is exclusively inhibitory.
- b) They increase the likelihood that the post synaptic membrane will generate an action potential.

Terminal Questions

1.



- 2. i) A sudden increase in Na^+ permeability results in depolarization
 - ii) A sudden increase in Cl^- permeability results in hyperpolarisation
 - iii) A rise in concentration of K^+ on the outside of the membrane results in start of repolarisation
 - iv) An accumulation of Na^+ on the outside of the membrane will bring the membrane back to resting potential.
3. Species A is invertebrate because only invertebrates have giant axons ($500\text{ }\mu\text{m}$). Species B though has thinner axon it still conducts at a faster rate than species A so it must be a vertebrate with myelinated axon.
4. Refer to Section 6.3.
5. Refer to Section 6.4 and Fig. 6.7 and 6.8.

Hint:

Calcium ion channels open in the presynaptic membrane → neurotransmitter released → attaches to receptors on the postsynaptic membrane suitable ionotropic or metabotropic channels activated → graded PSPs generated → and depending on their summation a new action potential is generated or inhibited.

6. A chemical that is released from a nerve cell which thereby transmits an impulse from a nerve cell to another nerve, muscle, organ, or other tissue. A neurotransmitter is a messenger of neurologic information from one cell to another.



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UNIT 7

COMMUNICATION: CHEMICAL SIGNALLING

Structure

7.1	Introduction	Factors Affecting Target Cell Response	
	Objectives		
7.2	Chemical Signalling	7.5	Neuroendocrine Connection
7.3	Endocrine Secretions		Hypothalamus and Pituitary Gland
	Chemical Nature of Hormones		Regulation of Hormone Secretion
	Synthesis and Secretion of Hormones	7.6	Pheromones
7.4	Action of Hormones	7.7	Summary
	Cell Surface Receptors for Hormones	7.8	Terminal Questions
	Intracellular Receptors for Hormones	7.9	Answers

7.1 INTRODUCTION

After studying through the earlier six units you would have realized that the success and survival of vertebrates has been enhanced due to the specialization of their cells into different types of tissue for different functions. In unit 6 you learnt how the nervous system communicates with the environment as well as with the various systems in the body in order to coordinate their activities and responses by means of electrical signals, generated in the nerve cells. These electrical signals conduct messages rapidly from one part of the organism to another part. The nervous system, however, is only able to innervate a small fraction of the cells in the body and the commands issued by the neurotransmitters are of a short duration and of a very specific nature. Many of the life processes are however not so short lived. They cover the entire life span of an individual, which may be several years, for instance, the reproductive life span of an average female may be 30 years

or more and that of the male even longer. Growth and development of an individual involves each and every cell of the body and would require regulation by a system that can exert long term controls instead of commands that are of a brief duration. This long term control is provided by the other system of communication in the body known as “the endocrine system” which uses chemical messengers known as hormones to transmit information between cells (Refer again to Volume I, Unit 9 - Endocrine system of the course BZYCT-133) which you studied in the second semester course. Thus the body's chemical messengers produced by the endocrine system together with the nervous system work to coordinate the activities of the different cells of the body.

Animal hormones are present in very small concentrations in the blood stream but have huge effects on the target tissues. Unlike action potentials that have a short term effect on the target cells or a group of cells, hormones affect many cells and have a longer lasting effect.

The goal of this unit is to learn how chemical signals in the form of hormones influence and coordinate the various functions in the body. We will consider the general chemistry of the hormone groups and then look into the different mechanisms that hormones use to affect the target tissue.

You have already learnt about the anatomy of the endocrine glands in Unit 9 of the Comparative Anatomy and Developmental Biology of Vertebrates (BZYCT-133) course that you took in second semester of your B.Sc. program. In this unit, we will discuss the functions of the secreted hormones briefly and learn how their secretion is stimulated and regulated so that optimum levels and homeostasis are maintained for the normal functioning of the organism's body.

Objectives

After studying this unit you should be able to :

- ❖ define the terms hormone, endocrine glands, exocrine glands and identify the sources of various hormones;
- ❖ describe the chemical classification of hormones and compare the action of protein and steroid hormones;
- ❖ discuss the neuroendocrine relationship and mechanism by which the hypothalamus regulates secretion from the pituitary gland;
- ❖ explain the negative and positive feedback in relation to hormone action; and
- ❖ describe the role of pheromones and compare their action with hormonal action.

7.2 CHEMICAL SIGNALLING

In the animal kingdom communications between cells can be of several types. Most of these communications between cells involve the secretion of chemical

molecules into the interstitial fluid or directly into the blood (recall Unit 10, entitled, “Cell signaling” which you studied in volume 2 of the BZYCT-133 course). The endocrine secretion is labeled **autocrine** (Fig. 7.1 a), when the cells secrete chemicals that affect the secreting cells themselves, that is, the secreting cells have receptors for their own secretion. The signaling (Fig. 7.1 b) can take place in adjacent cells connected by **gap junctions** (you have already read about this type of signaling when you studied electric synapses in the previous unit “Nervous system”).

When the secreted chemical affects the functioning of neighboring cells in the same tissue, the secretion is termed **paracrine** (Fig. 7.1c) and the chemicals involved are known as cytokines or local hormones. Prostaglandins and various growth factors are examples of such secretions. Paracrine factors are secreted into the blood but in such low quantities that they do not affect distant (faraway located) tissues. Several prostaglandins however, have primary effect on the tissue of their origin and secondary effects on more distant tissues, thus acting like hormones.

When the secretion from cells is carried by the bloodstream to distant target tissue in the body it is known as **endocrine** (Fig. 7.1d). These endocrine messenger molecules are termed as **hormones**. The special cells or tissues that secrete these hormones form the endocrine system. In contrast, when cells secrete chemicals on the epithelial surfaces including the gut, by means of a duct then the secretions are termed as **exocrine**. Examples are sweat glands, mammary glands, digestive glands etc. When a nerve cell secretes messenger molecules that are not carried across the synapse to an adjacent cell, but go directly into the blood stream and are carried via circulation to affect some distant target tissue then the secretion is termed as **neuroendocrine**.

The term hormone was first introduced by Earnst H. Starling in 1908 when he discovered the first hormone **secretin**. It has a Greek origin which means **I arouse**

Another set of chemical signals that are released into the environment and act upon a different individual is known as **pheromone**. In many species, mostly invertebrates, pheromones help to attract mates and coordinate reproduction.

The hormone molecules during their circulation throughout the body along with blood or interstitial fluid come in contact with every organ but affect only specific target tissues or organs. These target tissues have receptor molecules present on their cell surface or inside the cell that are specific to a particular hormone or group of hormones. Under normal conditions hormone concentrations in the blood are very low (in the range of nano 10^{-9} to pico 10^{-12}) and the target cells are exceptionally sensitive to the hormone.

Neural and Endocrine Signaling

We had seen in the previous unit that neurons communicate by two methods, by means of chemicals - the neurotransmitters that traverse short distances to activate receptors on post synaptic cells. Neurotransmitters act locally and rapidly. In contrast, endocrine secretions travel longer distances to activate receptors on their target tissue. Thus, as a result, endocrine signaling requires more time than neural signaling to prompt a response in target cells, though the precise amount of time varies with different hormones (Fig. 7.2). There is a close link between the activation of nervous secretion and endocrine

secretion. In both instances calcium ions are needed to release the neurotransmitters from the nerve cells as well as to release the secretion of the hormones from the endocrine cells. In case of endocrine secretion, Ca^{2+} enters the cell from extracellular spaces via calcium channels and also from intracellular calcium storage compartments. While in the case of neurosecretory cells an external stimulus generates an action potential, which opens calcium channels in the membrane of the synaptic knob, that causes an inward movement of calcium ions into the synaptic knob. Calcium ions trigger the release of neurotransmitter from synaptic vesicles into the synaptic cleft.

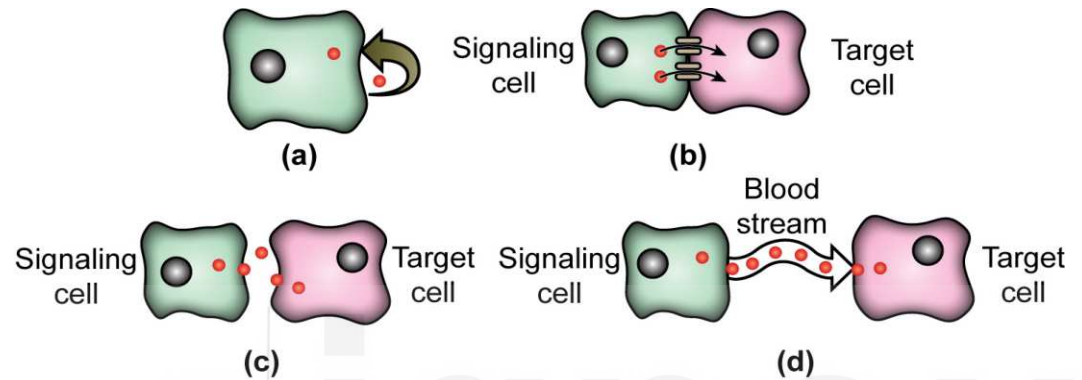


Fig. 7.1: Chemical signaling systems in metazoans. a) Autocrine signalling where the cell targets itself; b) cell to cell signaling where the signaling cell targets the other cell through gap junctions; c) paracrine signaling when signals reach nearby target cells; d) endocrine signaling where the signals travel through blood to distant target cells that have specific receptors for the hormone but other cells that come in contact with the hormones do not react as there are no receptors.

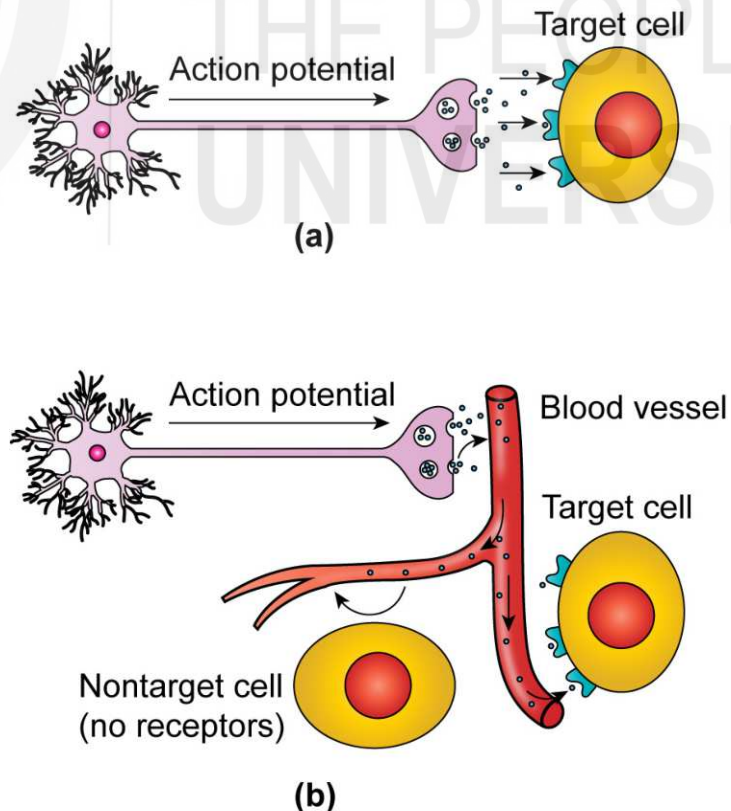


Fig. 7.2: a) neural secretion of neurotransmitter across the synaptic cleft; b) neural secretion of hormone that diffuses directly into the blood stream to a distant target cell.

Let us now learn about the major endocrine glands, chemical nature, method of synthesis and secretion of hormones.

SAQ 1

Match the following:

- | | |
|-----------------------------|---|
| a) Paracrine secretion | i) Signals affect the target cell over a large distance outside the body |
| b) Endocrine secretion | ii) Signals released from neurons and act on distant target cells via blood |
| c) Neuroendocrine secretion | iii) Signals affect locally placed cells |
| d) Pheromone | iv) Signals target cells locally or at a distance via blood |

7.3 ENDOCRINE SECRETIONS

Before we learn about the endocrine secretions and chemical nature of hormones, let us briefly recapitulate about the location of endocrine glands. The endocrine system consists of cells, tissues, and organs that secrete hormones as a primary or secondary function. The major mammalian endocrine glands are shown in Figure 7.3. Some of these glands have both endocrine and non-endocrine functions. For example, the pancreas contains cells that function in digestion as well as cells that secrete the hormones insulin and glucagon, which regulate blood glucose levels. The hypothalamus, thymus, heart, kidneys, stomach, small intestine, liver, skin, female ovaries, and male testes are other organs that contain cells with endocrine function. Moreover, adipose tissue has long been known to produce hormones, and recent research has revealed that even bone tissue has endocrine functions.

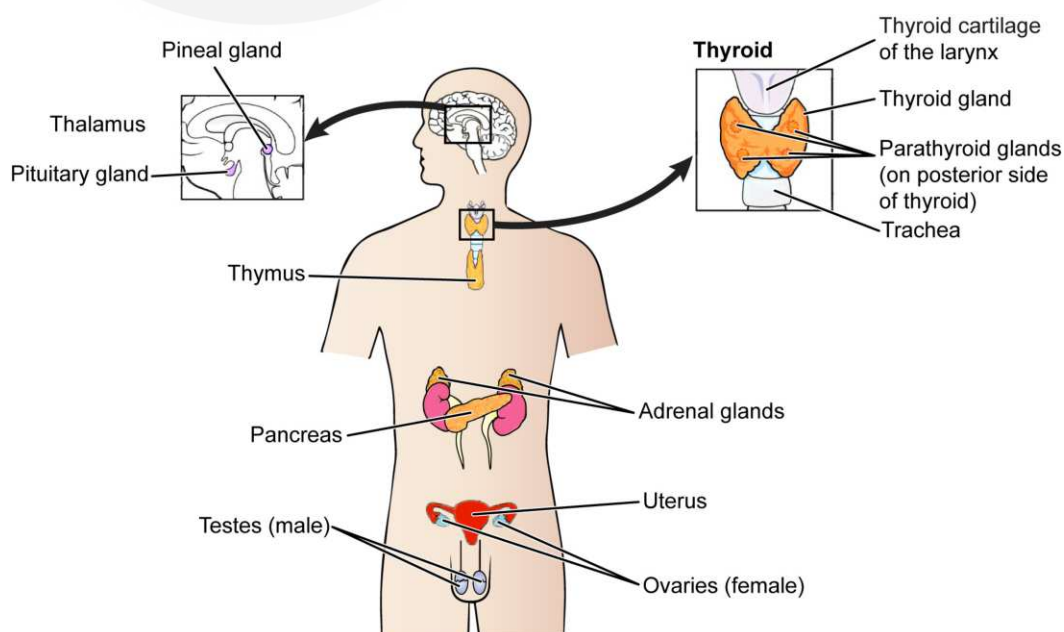


Fig. 7.3: Location of endocrine glands in humans

7.3.1 Chemical Nature of Hormones

All hormones are chemical compounds that can broadly be classified as:

- Amino acid derived hormones (amines)
- Lipid derived hormones (steroids)
- Peptides and Proteins.

The amine hormones also termed as amino acid derived hormones (end in '-ine'). The amino acid derived hormones are the simplest hormones and were the first to be discovered. These are relatively small molecules derived from individual amino acids tyrosine or tryptophan. The amino acid is modified so that the carboxyl group (COOH) is removed and the NH_3^+ remains. There are two groups of hormones derived from tyrosine (a) **catecholamines** that include epinephrine (which was the first to be described and its functions mentioned in early twentieth century) and norepinephrine which function both as hormones and neurotransmitter and (b) thyroxine (produced by the thyroid gland). Thyroid hormones are basically a "double" tyrosine with the critical incorporation of 3 or 4 iodine atoms. An example of tryptophan derived hormone is melatonin produced by the pineal gland.

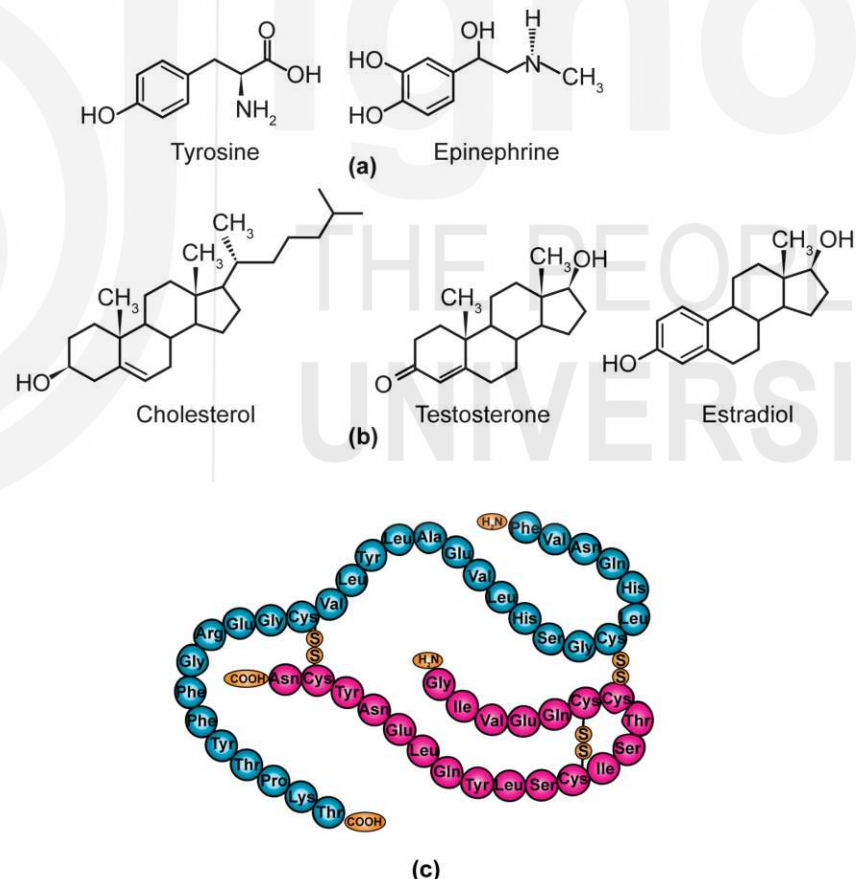


Fig. 7.4: Three general categories of hormones and some of their representatives. a) Epinephrine hormone (an amine hormone) derived from the source molecules tyrosine; b) reproductive hormones testosterone and estradiol hormone (steroid or lipid soluble hormones) derived source molecules cholesterol; c) Human insulin hormone a protein hormone formed from polypeptides. Human Insulin contains 51 amino acids, arranged in two polypeptide chains consisting of - Chain A with 21 amino acids and Chain B with 30 amino acids. The chains are linked by three disulfide bridges, two forming interchain cystines at A7-B7 and A20-B19, and one forming an intrachain cystine at A6-A11.

Lipid derived hormones are structurally similar to cholesterol and include the steroid hormones. The reproductive hormones testosterone and the estrogens—produced by the gonads (testes and ovaries respectively)—are steroid hormones. The adrenal glands produce the steroid hormones i) aldosterone which is involved in osmoregulation, and ii) cortisol which plays a role in metabolism.

Peptide and protein hormones are some of the most complex molecules. Where amines are derived from one amino acid the peptide and protein hormones are chains of several amino acids. Peptide hormones consist of short chains of amino acids, whereas protein hormones are longer polypeptides. Examples of peptide hormones include antidiuretic hormone (ADH), a pituitary hormone important in fluid balance, and atrial-natriuretic peptide, which is produced by the heart and helps to decrease blood pressure. Some examples of protein hormones include growth hormone, which is produced by the pituitary gland, and follicle-stimulating hormone (FSH), which has an attached carbohydrate group and is therefore, classified as a glycoprotein.

Figure 7.4 gives some representative structures of hormones from each of these categories. Even small differences in chemical structure make a great difference in the function of the hormone as we can note in the chemical structure of the steroid hormones estradiol and testosterone.

You have already studied the about the anatomy of the endocrine gland in unit 8 of the course on Comparative Anatomy and Developmental Biology. To help you recall the major hormones secreted by the endocrine glands we have given the important mammalian hormones, their chemical nature and major functions in Table 7.1 (most vertebrates have similar hormones with equivalent functions). **The table does not include the hormones secreted by the pituitary and hypothalamus as these will be dealt with later in the unit.** It is important to note, though major hormones and their functions in mammals have been identified, new hormones are being discovered, many with important functions that add to our understanding of endocrine physiology. An example is the discovery of the hormone leptin secreted by adipose tissue, which has enhanced our understanding of the mechanisms underlying growth, development, sexual function, food intake and also added the adipose tissue to the category of endocrine glands.

Table 7.1: Some mammalian hormones, their source, chemical nature and functions.

	Endocrine Source	Hormone	Chemical Nature	Action
1.	Thyroid	Thyroxine (T4) Triiodothyronine (T3)	Amine	Stimulates growth and metabolism and heart rate. Involved in amphibian metamorphosis.

2.	Thyroid	Calcitonin	Polypeptide	Reduces blood calcium levels by depositing calcium in bones
3.	Parathyroid	Parathyroid hormone (PTH)	Polypeptide	Increases blood calcium and phosphorus levels by causing their release from the bone. Prevents loss of calcium in urine by decreasing release of calcium from the kidneys.
4.	Pancreas (from B cells)	Insulin	Polypeptide	Decreases blood glucose, alters protein and lipid metabolism.
	(from A cells)	Glucagon	Polypeptide	Increases blood glucose levels by increasing glycogenolysis.
	(from G cells)	Gastrin	Polypeptide	Stimulates secretion of HCl from parietal cells in the stomach lining.
5.	Small intestine	Enterogastrone	Polypeptide	Inhibits acid secretion in the stomach
		Cholecystokinin (CCK)	Polypeptide	Stimulates gall bladder to release bile salts and the pancreas to secrete and digestive enzymes.
6.	Kidneys and Liver	Secretin	Polypeptide	Stimulates secretion of water and inorganic salts from pancreas.
		Erythropoietin (EPO), also known as haematopoietin,	Polypeptide	Increases RBC formation in the bone marrow.

		or haemopoietin		
7.	Kidney	Angiotensin I Angiotensin II	Small peptide	Stimulates aldosterone synthesis in adrenal cortex
8.	Adrenal medulla	Epinephrine or adrenalin Norepinephrine or noradrenalin	Amine Amine	Neurotransmitter causes contraction/relaxation of muscles. Causes dilation of blood vessels, increase in blood sugar and BP, increase in heart rate and cardiac output
9.	Adrenal cortex	Glucocorticoids (corticosterone, cortisol etc.) Mineralocorticoids (aldosterone) Small amount of sex hormones (androgens and progesterone)	Steroid Steroid Steroid	Involved in metabolism of protein, fat and carbohydrate in liver and in termination of pregnancy. Have anti-inflammatory action. Involved in resorption of Na^+ and K^+ in kidney, sweat glands and salivary glands and intestinal epithelial cells. Promotes secondary sexual characters
10	Testes	Androgens (Testosterone)	Steroid	Development and maintenance of male secondary sexual characters and behaviour.
11.	Ovaries	Estrogens	Steroid	Development and maintenance of female sexual characters and behavior.

	Corpus luteum	Progesterone	steroid	Maintenance of endometrium of uterus, stimulation of mammary gland formation; acts with estrogen to maintain the reproductive cycle.
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SAQ 2

- Which hormone/ hormones is/are mainly responsible for regulating the blood calcium levels?
- Which hormone is responsible for secondary sexual character in males?
- Which hormones regulate blood glucose levels?
- What functions of the body are regulated by thyroxine hormone?
- Synthesis of red blood cells is increased by which hormone? Where is it secreted from?

7.3.2 Synthesis and Secretion of Hormones

Amino acid hormones can act as either a steroid or peptide hormone. For example, thyroid hormone is an amino acid hormone which acts like a steroid, while epinephrine, which is also an amino acid hormone, acts as a peptide hormone.

The chemistry of the hormones determines how they are synthesized, stored, secreted and transported and also determines their mode of action. All hormones can be broadly segregated into two groups:

- Lipophilic or those soluble in lipids. These include the steroid hormones and the thyroid hormones.
- Hydrophilic or lipid insoluble hormones. These include the protein and peptide hormones and the catecholamines.

Steroid hormones are all made from cholesterol and are secreted by three “steroid glands” namely, the adrenal cortex, testes, and ovaries and during pregnancy by the placenta. The first step in the biosynthesis of steroid hormone is the cleavage of the side chain of cholesterol to form pregnenolone (Fig.7. 5). Pregnenolone is not a hormone but is the precursor for all steroid hormones. It is synthesized on the inner membrane of the mitochondria and is shuttled back and forth from the mitochondria to the smooth endoplasmic reticulum for further enzymatic transformations required for the synthesis of the derivative steroid hormones. As steroid hormones are lipophilic they cannot be stored in vesicles since they would diffuse out from the vesicles easily. Hence, they are secreted out soon after they are synthesized and the secretion is limited by the rate of synthesis.

The steroid hormones, being derived from cholesterol, are not soluble in plasma and other body fluids. They have to be transported in blood by being

bound to plasma carrier proteins. These carrier proteins may be specific or general plasma proteins like albumin.

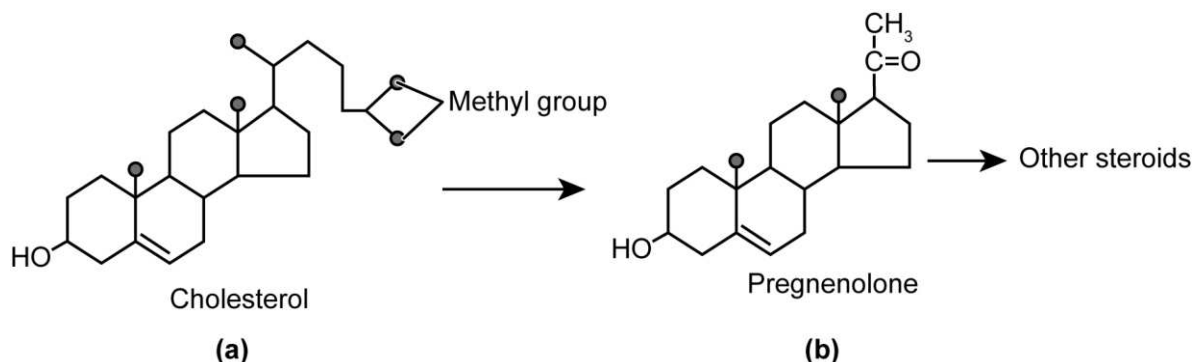


Fig.7.5: a) Cleavage of the side chain in the cholesterol molecule produces; b) pregnenolone which is precursor of all the steroid hormones.

Hormones based on amino acids, and protein as well as peptide hormones are products of translation and undergo post translational modification as given below, before they are secreted out of the cell

mRNA → prehormone → prohormone → hormone

Translation of the mRNA (messenger RNA), forms a large molecule called preprohormone or prehormone that is reduced to the active hormone before secretion from the cell. This is a method of keeping the protein hormone separated from the other cytosolic proteins (the cytosolic proteins do not have the signal segment and are synthesized on free ribosome). The 'pre' segment protein is synthesized first and is the signal that the ribosomal complex should be transported and attached to the rough endoplasmic reticulum. The newly synthesized protein is extruded and released into the lumen of the rough endoplasmic reticulum (Fig.7.5). The 'pre' segment is cleaved out in the rough endoplasmic reticulum and the prohormone thus formed is transported to the Golgi apparatus from where it is packaged into vesicles for secretion. The 'pro' segment is cleaved off either in the Golgi apparatus or in the secretory vesicles to give the active hormone. These vesicles migrate to the cell membrane and are secreted out by exocytosis. During the process of synthesis and secretion of protein hormones the packaging of hormones inside vesicles ensures that the contents are kept segregated from the cytoplasm as the entire contents of the vesicles are released. The empty vesicle then fuses with the plasma membrane.

The signal for exocytosis of the hormones is the increase in intracellular calcium. Recall that intracellular calcium is the trigger for the secretion for neurotransmitters and also for other hydrophilic hormones. The cells may accumulate the secretory vesicles and release them in bursts when stimulated. This allows the cell to secrete large amounts of hormone over a short period. Thyroid hormone is secreted in extracellular spaces of the follicles in the thyroid gland and can be stored for several months. However, some peptide hormones are not stored in the cells but are released from the vesicles as they are synthesized.

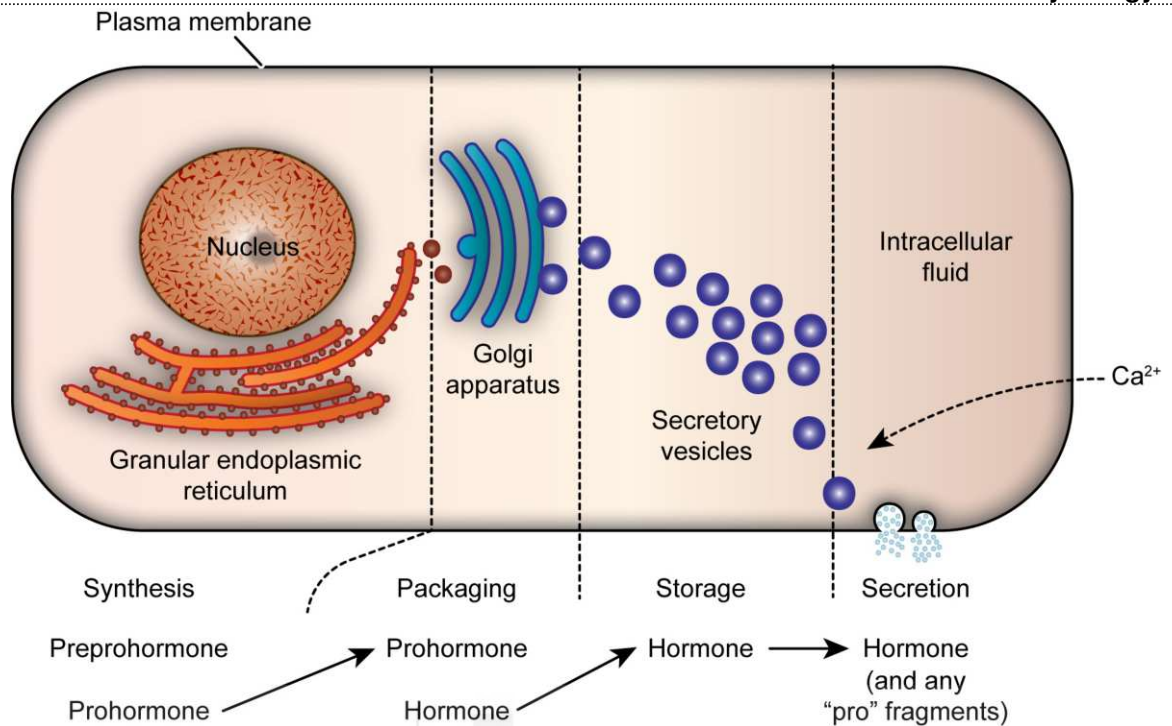


Fig 7.6: Synthesis of protein hormones.

The secretion of hormones is not a random process but follows a certain pattern, which may be circadian or seasonal or may be periodical (e.g. human menstrual cycle). Some hormones like the thyroid hormones are secreted continuously. The release of hormones from the endocrine glands is controlled by nervous, hormonal or metabolic stimuli, which also control the rate of release into the blood stream. As with neurotransmitters, Ca^{2+} plays an important role in the release of hormones. The duration of the circulating hormone in the blood stream is indicated by its 'half life' (time required for half the concentration of the hormone to degrade) which varies from a few minutes to over a week depending on the hormone.

Most peptide hormones circulate freely in the blood unbound to any other protein. A freely circulating hormone has a very short half life. It remains functional for less than an hour or even a few minutes. Catecholamines (tyrosine derived hormones) on the other hand have a very short half-life of only a few minutes. The peptide hormones are inactivated when they bind to the target cell receptors after which they are absorbed and broken down by cells of the liver or kidneys or are degraded by the enzymes in the plasma or interstitial fluid.

After steroid hormones are secreted into the circulation, most of them are bound to specific carrier proteins, forming aggregates. They can thus remain in circulation much longer because formation of aggregates prevents the hormones from being eliminated from the body via the kidneys, and also prevents rapid destruction by plasma enzymes. The carrier protein aggregate of the hormones are also responsible for the slow release of the hormone. Less than 1% of the hormone remains free in the blood and a state of equilibrium exists between the free and bound hormones. As the free hormone is removed from circulation by binding to the receptors the equilibrium shifts and more hormones dissociate from the protein carrier. In this way a steady trickle of the hormone is maintained in the bloodstream.

SAQ 3

- a) Compare the synthesis of steroid and protein hormones.
- b) Why do steroid hormones need a carrier molecule for transportation in the blood?

7.4 ACTION OF HORMONES

The way in which the hormones act upon their target cells is similar to the mechanism involved in the case of neurotransmitters. We must remember that the language used in both types of communication is chemical. Receptors for hormones can be located either on the surface of cell membrane or inside the cell. The lipid insoluble hormones have their receptors in the cell membrane of their target cells while the lipid soluble hormones have their receptors in the cytoplasm as these hormones can simply diffuse through the membrane of the target cells. Once the hormone reaches its target tissue it can change the functions of the target cells by:

- stimulating the synthesis of an enzyme or protein by activating an appropriate gene in the cell nucleus;
- increasing or decreasing the rate of synthesis of an enzyme or protein by altering the rate of transcription or translation;
- switching on or off an existing enzyme by changing its structure or shape;
- changing the permeability of the cell membrane.

The binding of the hormone to the receptor causes a cascade of enzymatic steps that lead to the amplification of the initial signal. The release of a few molecules of the hormone thus elicits a much larger response. We will discuss this with the help of examples later in the section. While the effects of one hormone may persist in the cell, the same cell may also encounter instructions from other hormones. The concerted effect of circulating hormones produces complex changes in the structure and physiological capabilities of the organism, an example of which can be seen in the process of embryological development, growth and puberty. We shall now consider the basic mechanism involved in hormone action by using some specific examples.

7.4.1 Cell Surface Receptors for Hormones

All amino acid based hormones (except for thyroid hormones) including catecholamines are hydrophilic and hence cannot cross the cell membrane. Their receptors are present in the cell membrane of their target cells on the extracellular surface. The binding of the hormone to the surface receptors leads to the activation of other substances that activate or inhibit enzymes or proteins or co- factors that change the metabolic activity of the target cell. In other words they initiate a signal transduction pathway that triggers intracellular activity, specific to the hormone. In this signal transduction

pathway, the hormone does not pass through the cell membrane; it remains bound at the surface of the cell and the intracellular product that is activated, remains inside the cell. This hormone or **first messenger** activates a **second messenger** inside the cell which initiates the action in the cell (see Fig. 7.6 which shows the action initiated by epinephrine). You know that cell surface receptors that are integral membrane proteins, can consist of three basic domains:

- **extracellular ligand binding domain** which is exposed to the outside of cell
- **transmembrane domain** which consists of hydrophobic stretches of amino acids that are embedded in the plasma membrane and help to anchor the receptor in the membrane and
- **Intracellular or cytoplasmic domain** consists of tails or loops of the receptors present within the cytoplasm. These tails or loops of the receptors react to the binding of the hormone by interacting with other molecules in the cytoplasm and generate second messengers. The residues of the receptor present in the cytoplasm are thus the **effector region** of the receptor molecule.

The cell surface receptors are linked either to a G protein (which is an enzyme complex coupled with a membrane receptor) or to protein kinases. The surface receptors may be stimulatory or inhibitory and can bind to respective stimulatory or inhibitory G proteins. When activated, G proteins bind to guanosine triphosphate (GTP), (hence the name G protein) and can activate or inhibit another membrane bound enzyme adenylyl cyclase. This leads to changed concentrations of the second messenger. There are several second messenger molecules and the 2 most commonly used in cells are cAMP and Ca ion based. Let us first see what happens if the second messenger is cAMP.

Cyclical AMP second messenger system

As mentioned before when the hormone binds to its receptor it activates the associated intracellular G protein which is actually separate from the receptor and is inactive until the hormone attaches to the receptor. Inactive G protein is bound to **guanine diphosphate** (GDP) and on activation by the binding of the hormone to it, binds **guanine triphosphate** (GTP) but only for a very short time after which it hydrolyses GTP to GDP again and becomes inactive.

The activated G protein, however, activates **adenylyl cyclase** a membrane bound enzyme with activity in the cytoplasm. Activated adenylyl cyclase begins to convert a nucleotide known as **cyclic adenosine monophosphate** (cAMP) that is produced from ATP by the action of an enzyme. cAMP activates a protein kinase called **protein kinase A** by removing the regulatory subunit from protein kinase A. The activated protein kinase phosphorylates other proteins and enzymes causing the activation or suppression of their activity, thus changing the metabolic activities of the cell. This can be understood by taking the example of hormone glucagon as illustrated in Figure 7.6.

1. Glucagon binds to the membrane receptors on the hepatocytes(liver cells)
2. The receptor linked G protein is activated
3. The activated G protein activates adenylyl cyclase
4. Adenylyl cyclase begins to convert ATP into the second messenger cAMP
5. The second messenger cAMP removes the regulatory subunit from protein kinase A leaving the activated catalytic subunit free to phosphorylate other proteins by using the energy from ATP.
6. The activated protein kinases phosphorylate other proteins in the cytoplasm that can change the activity of the cell.

The cAMP is eventually deactivated by the action of **cAMP-phosphodiesterase** which is always present in the cell: i) to control the activity of the hormone ii) to prevent over production of cellular products and iii) to cause inactivation of adenylyl cyclase.

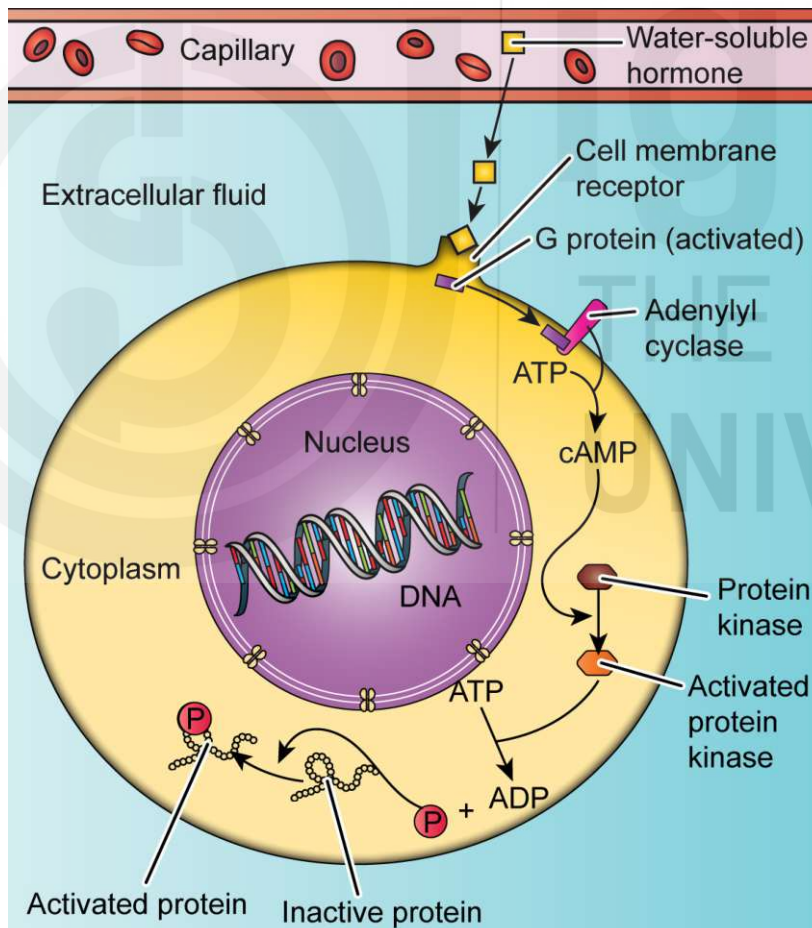


Fig. 7.7: Binding of a hydrophilic hormone (first messenger) to its receptor and the activation of the second messenger which is cAMP in this case. As a result there is change in the cell's activity.

The effect on the target cell depends on the proteins and enzymes that have been phosphorylated. For example, phosphorylation of membrane proteins results in the opening of ion channels and many cytoplasmic enzymes are activated only after phosphorylation.

In inhibitory action of hormones, the activation of the G protein can, however, decrease the concentration of cAMP in the cell by suppressing the activity of adenylyl cyclase and stimulating the activity of **phosphodiesterase** (PDE) instead. As a result the cAMP is converted to AMP and no new cAMP is formed. This decline in the concentration of cAMP has an inhibitory effect on the cell activity as the key enzymes are not phosphorylated. This is the mechanism behind the inhibitory effect of hormones epinephrine and norepinephrine which bind to the α_2 - receptors and stimulate them. Some examples of hormones that use cAMP are calcitonin, glucagon, epinephrine (adrenaline or adrenalin), norepinephrine (acts as both a hormone and neurotransmitter), thyroid stimulating hormone, antidiuretic hormone.

Box: 7.1: Discovery of the second messenger system in hormone action.

In the mid 1950s Earl W. Sutherland and associates discovered the role of cAMP as an intracellular regulatory agent. They studied the mechanism by which epinephrine regulates the degradation of glycogen to glucose in the liver. Sutherland first discovered that epinephrine acts by activating the enzyme (phosphorylase) which leads to the formation of glucose from glycogen. Later he found that this activation took place by means of an intermediate substance the cyclic AMP which was termed "the second messenger" by Sutherland. He noticed that the activity of adenylyl cyclase an enzyme that catalyses the conversion of ATP into cAMP was enhanced when certain hormones were added to the liver cell homogenate or intact liver cells. When he fractionated the cell – free liver homogenate he found that the fraction from which plasma membrane fragments were removed, showed no adenylyl cyclase activity. Ultimately it was discovered that adenylyl cyclase was closely associated with a membrane receptor for certain hormone and the hormones that activate adenylyl cyclase do not enter the cell. Also ATP as well as cAMP do not readily penetrate the cell membrane when placed in the extracellular fluid present outside the cell. Following Sutherland's discovery, It became known that **lipid insoluble hormones bind to receptors on the outside of cell membranes** which then activate adenylyl cyclase on the inside of plasma membrane initiating a cascade of events that makes up the response of the cell to the hormone.

Calcium as Second Messenger

Where calcium is used as a second messenger system in cells, the signaling pathway requires an extra stage. The hormone receptor linked to the G protein has another messenger that carries the signal from the G protein to all parts of the cell to trigger: (i) the release of calcium ions from intracellular calcium stores in the smooth endoplasmic reticulum (ER) or (ii) the opening of membrane channels for calcium. Figure 7.7 shows the steps involved.

1. The G protein activated by the binding of the hormone activates an enzyme phospholipase C (PLC) which functions similar to adenylyl cyclase.
2. Phospholipase C catalyses another membrane bound phospholipid called phosphatidyl-inositol-bisphosphate (PIP_2), cleaving it into two components to produce diacylglycerol (DAG) and inositol triphosphate (IP_3).
3. Inositol triphosphate (IP_3) diffuses into the cytoplasm to activate calcium channels in the ER membrane, which results in a rapid influx of Ca^{2+} in the cell.

4. Diacylglycerol (DAG) goes on to activate protein kinase C which triggers the cellular response by initiating a phosphorylation cascade.
5. The Ca^{2+} acts as the second messenger by either influencing the cellular activity directly or by binding to a calcium detecting and binding protein called **calmodulin**.
6. The **Ca^{2+} - calmodulin** complex binds to the regulatory subunit of the specific calmodulin dependent protein kinases (Cam kinases) which results in freeing and activating the specific calmodulin dependent protein kinases. Once free of the regulatory subunit the catalytic subunit of the Cam kinase can phosphorylate serine and threonine residues present on various proteins in the cell. The stimulatory effects of the hormones epinephrine and norepinephrine which bind and as a result activate their α_1 receptors follows this pathway. Calmodulin activation is also a response to stimulation by oxytocin and some other regulatory hormones of the hypothalamus.

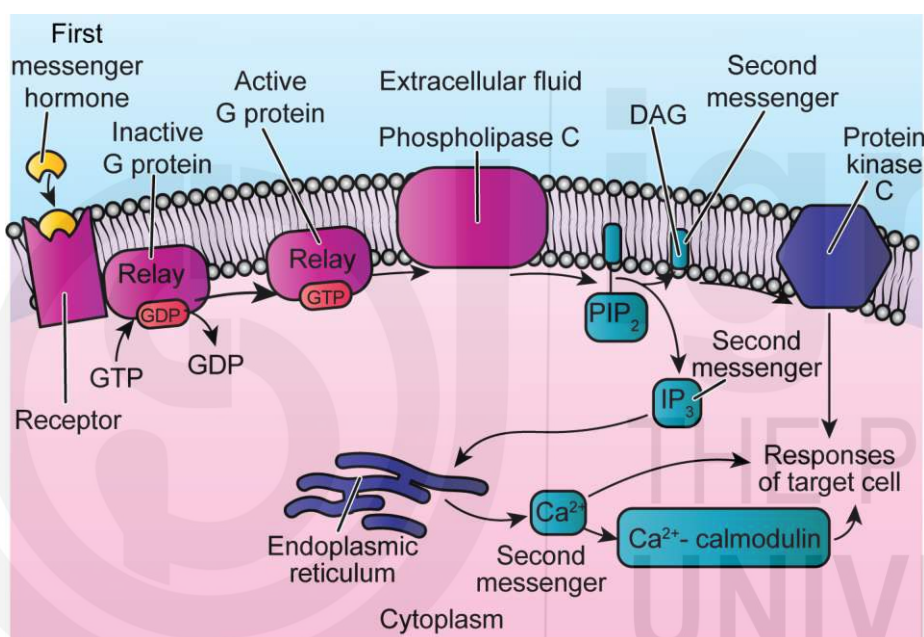
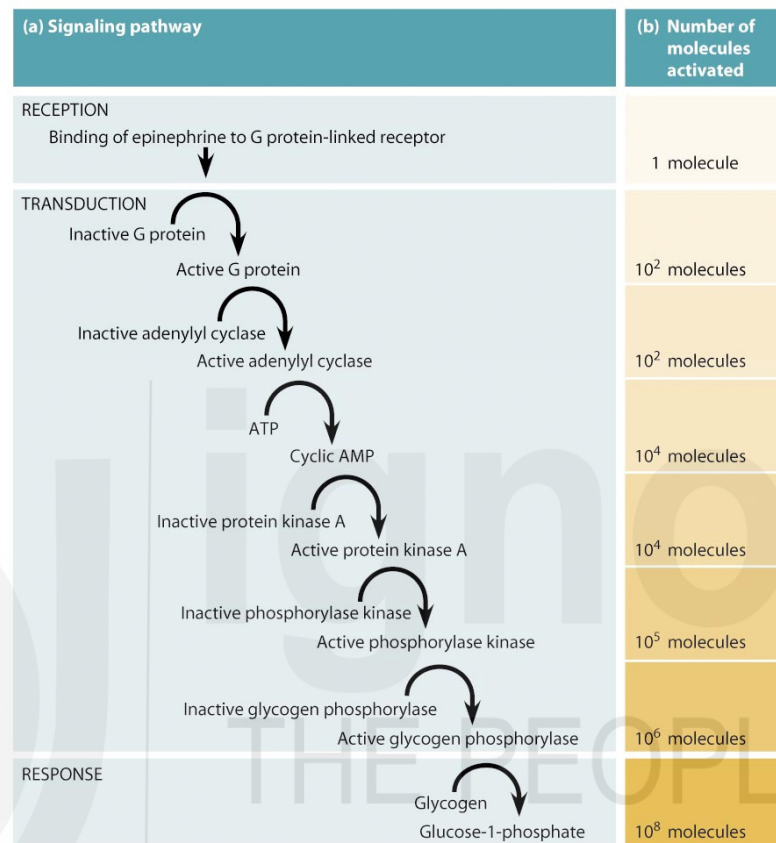


Fig. 7.8: Binding of a hydrophilic hormone to its receptor and the activation of second messengers DAG, IP_3 and Ca^{2+} -calmodulin complex. As a result there is change in the cell's activity.

Box 7.1: Modulation of calcium ion concentrations in the cell.

Calcium, as we have read so far is observed to be the central intracellular messenger in biological systems. It plays an important role in cell physiology, both as an intracellular regulatory agent as well as a messenger linking external signals to the cellular responses. This can happen because the cell has the ability to increase or decrease the concentration of Ca^{2+} over a wide range and the cell has a wide range of proteins whose activity is modulated by binding Ca^{2+} . Even though the total calcium content of most cells is about 1mM (10^{-3} M) the concentration of free Ca^{2+} is maintained at very low levels, usually below 10^{-7} M. The advantage of such low levels of free calcium is easy to see. Since the extra cellular concentration of Ca^{2+} is 10^{-3} M, the electrochemical gradient of calcium allows the flow of calcium into the cell. The cell on the other hand maintains low levels of calcium by active transport of calcium across the cell membrane and the movement of calcium ions into the endoplasmic reticulum through calcium pumps in the ER membrane. Also various proteins in the cytoplasm bind to calcium when the Ca^{2+} concentration in the cytoplasm increases and releases it when the level decreases.

Most animal cells also use **cyclical GMP as a second messenger** in addition to cAMP, though the concentration of cGMP is about one tenth of cAMP in the cell. Stimulation of the same type of receptor by a hormone can induce changes in the concentration of cAMP and cGMP at the same time in the cell. An example of this action is the increase in heartbeat by hormone epinephrine induced rise in cAMP and decrease in heartbeat by acetylcholine (neurotransmitter) induced rise in cGMP.



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Fig.7.9: Amplification of the hormone signal in second messenger system during hormone action. Hormones Glucagon and Epinephrine stimulate the breakdown of glycogen in the liver and the muscle respectively. Amplification of the initial signal occurs at many stages. The hormone binding to its receptor can activate several G protein molecules, which then activate many molecules of adenylyl cyclase. The hormone may be bound to the receptor for a very short time, but the G protein remains active for as long as the GTP is bound to it, which may be for several seconds, providing time for amplification. Each molecule of activated adenylyl cyclase catalyzes the conversion of many molecules of ATP to cAMP. Each molecule of cAMP binds the regulatory subunit of PKA, which activates several phosphorylase kinases. Each of these activated phosphorylase kinases activates several glycogen phosphorylase D that are responsible for converting glycogen molecules to glucose 1-phosphate. Thus, ultimately, several number of glucose molecules are released into the blood stream.

Some cell surface receptors signal the cell directly through their inherent enzyme activity. They have an external ligand binding domain and a catalytic domain on the inner side of the cell membrane. Binding of a hormone causes a conformational change that activates the catalytic domain. These receptors

are mostly **tyrosine kinases** themselves or bound to kinases intimately. When activated by binding of the hormone they activate a cascade of serine-threonine kinase activity which leads to the activation of more specific kinases or DNA binding proteins. Receptors that work in this way include those for insulin, growth factors and other vital hormones.

Each of these pathways involving a second messenger as discussed above has multiple steps that allow great amplification of a signal within the cell (See Fig .7.8). For example let us consider the binding of one molecule of hormone say epinephrine, to its receptor. This causes the activation of many G-proteins that will activate adenylyl cyclase. Each molecule of adenylyl cyclase then triggers the formation of many molecules of cAMP. Further amplification occurs as protein kinases, once activated by cAMP, can catalyze many reactions. In this way, a small amount of hormone can trigger the formation of a large amount of cellular product.

The important feature of second messenger systems is that the **target cells differ in the types of the receptors that are capable of activating the particular type of second messenger**. Thus the action of many hormones can be mimicked by raising the levels of the second messenger system (cAMP or Ca^{2+}) by means of various other drugs.

SAQ 4

- a) Arrange the following in its proper order and sequence:
- i) Activation of protein kinase
 - ii) Activation of G protein
 - iii) Activation of adenylyl cyclase
- A. i), ii) and iii)
B. ii), i) and iii)
C. ii), iii) and i)
D. iii), ii) and i)
- b) Which of the following is a definition of signal transduction?
- i) the binding of a hormone to its nuclear receptor.
 - ii) the changes in the cell as a result of the binding of hormone to the receptor
 - iii) the production of a second messenger inside a cell in response to a hormone binding to its cell surface receptor.
 - iv) the activation of a second messenger in response to a hormone binding to its intracellular receptor.
- c) The enzyme that deactivates cAMP is known as
-

7.4.2 Intracellular Receptors for Hormones

Lipid soluble steroid and thyroid hormones have their receptors inside their target cell located in the cytoplasm or in the nucleus and function as ligand (a molecule that binds to another usually larger molecule) binding transcription factors. Hormones that bind to Intracellular receptor must be able to cross the cell membrane. Steroid hormones are derived from cholesterol and therefore can readily diffuse through the lipid bilayer of the cell membrane to reach the intracellular receptor. Thyroid hormones, which contain benzene rings studded with iodine, are also lipid-soluble and can enter the cell. The location of steroid and thyroid hormone binding differs slightly: a steroid hormone may bind to its receptor within the cytosol or within the nucleus. In either case, this binding generates a hormone-receptor complex that moves toward the chromatin in the cell nucleus and binds to specific responsive genes or DNA sequences that stimulate or sometimes inhibit transcription of these genes. In contrast, thyroid hormones bind to receptors that are already bound to DNA and stimulate or sometimes inhibit transcription of specific responsive genes or DNA sequences. Thus, both steroid and thyroid hormones modulate gene expression in the target cell. The DNA sequence to which the receptor–ligand complex binds is generally the promoter region of the target genes and in the case of hormones, it is called a ‘hormone response element (HRE).

Recall that the steroid and thyroid hormones circulate in the blood bound to protein carrier molecules. Without these carriers only a small amount of the hormone would be able to circulate as being lipid soluble, it would be taken up by the first available tissue. These hormones thus, dissociate from the protein carrier molecules and readily diffuse through the plasma membrane only on reaching the target tissue. Within the cell the hormone binds to the receptor.

Steroid and thyroid hormone receptors are members of a large super-family of transcription factors that are of two types –Type I that are present in the cytosol and bind to steroid hormones and Type II that are present in the nucleus and bind to non-steroid lipid soluble hormones such as thyroid hormones and vitamin A and vitamin D.

All Intracellular receptors for hormones are composed of a single polypeptide chain that has four domains (Fig.7.9):

1. **Variable domain:** begins at the amino-terminal or N-terminal (A/B). The sequence of this domain is highly variable among different receptor (A/F)
2. . In most cases, this region is involved in activating or stimulating transcription by interacting with other components of the transcriptional machinery.
3. **DNA binding domain (DBD):** is centrally located and is a highly conserved domain that controls which gene will be activated (C). It reacts with the **hormone response element (HRE)** on the promoter region of the DNA.
4. **Hinge domain (D):** controls the movement of the receptor to the nucleus.

5. **Hormone or ligand binding domain:** is moderately conserved and is the ligand binding domain that can include amino-acid sequences known as **nuclear localization sequence**, which bind the protein to the nucleus. The **ligand** binding domain has a dimerization region, which is responsible for latching two receptors together in a homodimer form (protein composed of two polypeptide chains that are identical in the order, number, and kind of their amino acid residues) capable of binding DNA. The end of this **ligand binding domain** is the C-terminal also called carboxy-terminus or ligand-binding domain as this is the region that binds hormone.

There are two other regions Activation Function1 and 2 (AF1 and AF2). AF1 is ligand independent and is located in the variable domain while AF2 is located in the ligand binding domain and is regulated by hormone binding.

Only Type I receptors have a **heat shock protein** (HSP) associated with the inactive receptor. This heat shock protein is released when the receptor interacts with the ligand. Type II receptors have no HSP, and in contrast to the classical Type I receptor, they are already located in the cell nucleus.

A dimerisation is the joining of two subunits to form a single dimer. The subunits may be similar or dissimilar. These monomers will join usually upon binding of a signal to the receptor of each monomer.

Heat shock proteins are a family of proteins that are produced by the cell in response to stressful condition. They help to refold misfolded proteins and stabilise newly formed proteins.

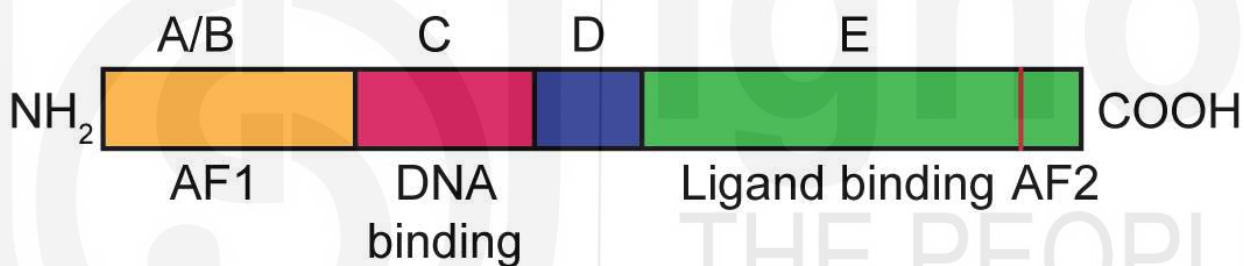


Fig.7.10: Steroid hormone receptor is a single polypeptide chain with four distinct domains: a) the variable N-terminal domain (A/B) of the protein which contains activation function 1 (AF1); b) the DNA binding domain; C) which is the highly conserved; d) the flexible hinge domain (D) which connects the DNA binding domain to (e) the hormone (ligand) binding domain (E) which contains the activation function 2 (AF2).

Let us see what happens when a free steroid hormone enters the cell cytoplasm (See Fig. 7.10)

1. It interacts with the Type I receptor, heat shock protein is dissociated, and the activated receptor-ligand complex is translocated into the nucleus after dimerisation.
2. The activated receptor binds to the specific **hormone response element** (HRE) on the promoter region of the DNA as a homodimer.
3. Receptor binding either stimulates or suppresses transcription of the gene. As a result messenger RNA is produced. The messenger RNA exits the nucleus and interacts with the ribosomes in the cytoplasm.
4. After translation of the genetic message, specific proteins are produced that alter the activity of the cell.

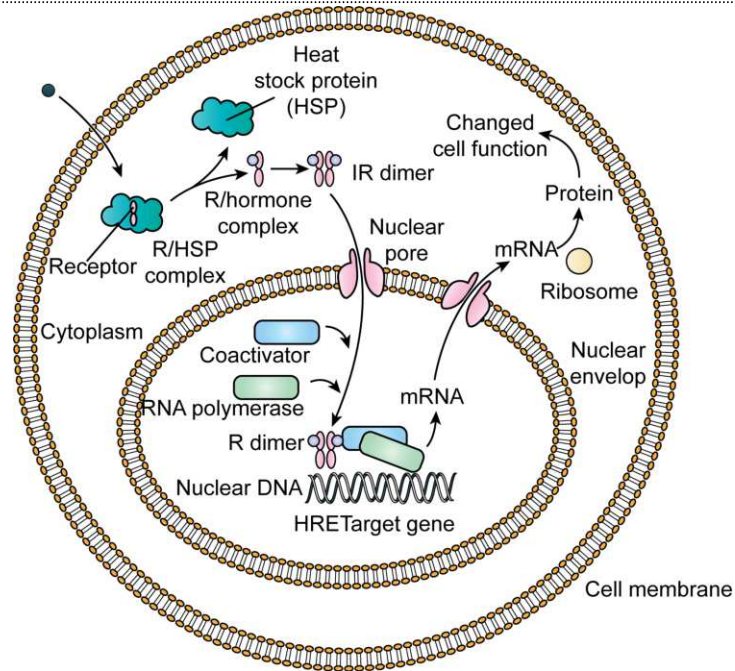


Fig: 7.11: An intracellular receptor (R) is located in the cytoplasm bound to a heat shock protein (HSP). Upon hormone binding, the receptor dissociates from the heat shock protein and dimerises and moves into the nucleus. In the nucleus, the hormone-receptor complex binds to a DNA sequence called a hormone response element (HRE), usually a promoter, which triggers gene transcription and translation. mRNA enters the cytosol and the corresponding protein products can then cause changes in cell function. (

Type II receptors are located in the nucleus. Their ligands pass through the cell wall and cytoplasm and enter the nucleus, where they activate the receptor without the release of HSP. The activated receptor interacts with the hormone response element, and the transcription process is initiated as with Type I receptors

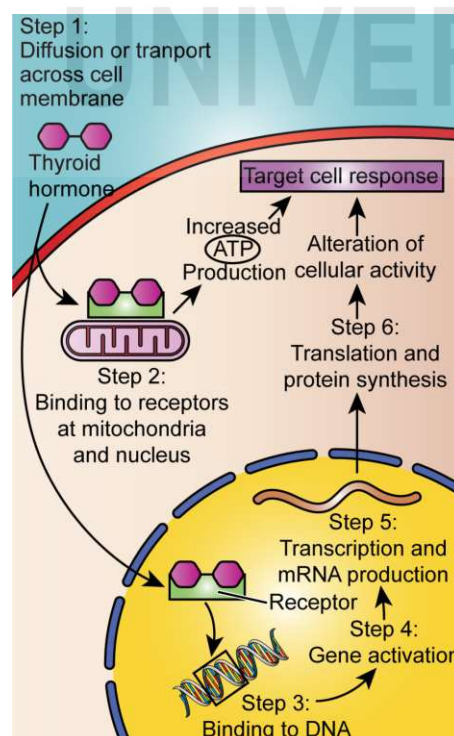


Fig. 7.12: Thyroid hormones bind to the mitochondria and receptors in the nucleus to change the metabolic activity of the cell.

Thyroid hormones cross the cell membrane to bind Type II receptors in the nucleus and to bind to receptors present on the mitochondria. The thyroid hormone – receptor complex in the nucleus, activates specific genes or changes the rate of transcription. The changes in the rate of transcription affect the metabolic activity of the cell. The hormone bound to the mitochondria increases the production of ATP (Fig.7.11).

7.4.3 Factors Affecting Target Cell Response

We had said earlier in the unit that target cells must have specific receptors for a given hormone as only then can the target cells respond to that hormone. Apart from the types of receptors there are other factors that affect the response of the target cell. For example, there can be a **downregulation** (decrease in number) of the receptors on the target cells if an excess amount of their particular hormone is circulating in the bloodstream. This allows cells to become less reactive to the excessive hormone levels. Similarly receptors of target cells can be **upregulated** (increase in number of receptors) when the level of their binding hormone is consistently low. This process allows cells to be more sensitive to the low levels of hormone that is present. In addition to this the sensitivity of the receptors themselves to various hormones can be altered by the cells.

The response of cells can also be affected by the combination of two or more hormones that act in different ways as given below:

- The effect of the action of two hormones is called **permissive** if the presence of one hormone enables another hormone to act. For example, thyroid hormones have complex permissive relationships with certain reproductive hormones. So if there is a dietary deficiency of iodine, which is a crucial component of thyroid hormones, then the development and functioning of the reproductive system is affected.
- The effect of the action of two hormones is called **synergistic** if two hormones with similar effects produce a more pronounced response. Infact, in some cases, two hormones are necessary for an adequate response. For example, both the reproductive hormones - follicle stimulating hormone (FSH) from the pituitary gland and estrogen from the ovaries-are required for the maturation of female ova.
- The effect of the action of two hormones is considered **antagonistic**, when the two hormones have opposing effects. The most familiar example is the effect of two pancreatic hormones, insulin and glucagon. Insulin increases the liver's storage of glucose as glycogen, decreasing blood glucose, whereas glucagon stimulates the breakdown of glycogen stores, increasing blood glucose.

In the next section we shall study the crucial connection between the **two communication systems** of the body - **the neuroendocrine connection**. We will also study the different stimuli for hormone production and how hormone production is regulated in the body.

SAQ 5

Which of the given statements are false and why?

- a) The number of receptors can increase or decrease affecting its response to the hormone.
- b) Depending on the nature of the protein receptor on the cell membrane and the nature of the steroid hormone, the cell's function is mediated by changes in the gene transcription.
- c) Type I intracellular receptors for steroid hormones are free receptors and Type II receptors are nuclear receptors bound to heat shock proteins.
- d) Receptors bound to heat shock proteins separate from them on binding of ligand and dimerize.

7.5 NEUROENDOCRINE CONNECTION

You have already learnt about the structure and histology of the various endocrine glands in Unit 9 of the course on Comparative Anatomy and Developmental Biology in your previous semester. You would recall that some endocrine glands such as the hypothalamus and the associated pituitary or the “master gland” are part of the nervous system. We had stated in the beginning of this unit that some neural cells secrete chemical messengers directly into the circulatory system which are carried to distant target cells. These specialised neural cells are termed **neurosecretory** cells and are similar to ordinary neurons except that they have some special properties. For instance the size of the neurosecretory vesicles is much larger (100-400nm in diameter) than the synaptic vesicles found in the neurons (30-80nm in diameter). The secretions of neurosecretory vesicles are termed as **neurohormones** and they move at a much faster rate in the axon. While the neurons form a synapse with other cells at the end of the axon terminal, the neurosecretory cells end in clusters of axon terminals near a bed of capillaries forming a **neurohaemal organ**. Neurohormones are released into the interstitial space near the capillary bed from where they diffuse into the blood and are carried to the target tissues. Let us now examine the neuroendocrine connection in greater detail.

7.5.1 Hypothalamus and Pituitary Gland

The most obvious neuroendocrine link is between the hypothalamus and the pituitary gland. You will recall that the hypothalamus is a small region of the brain that is connected to the small pea-sized endocrine organ, the pituitary gland that is situated at the base of the brain just above the roof of the mouth (Fig.7.12 a). The pituitary gland is also known as the **hypophysis**. It is composed of two embryologically different tissues. The anterior pituitary or **adenohypophysis** is derived from the roof of the mouth and the posterior pituitary or **neurohypophysis** is derived from neural tissue. The gland is joined to the hypothalamus by a slender stalk of neural tissue the **infundibulum**.

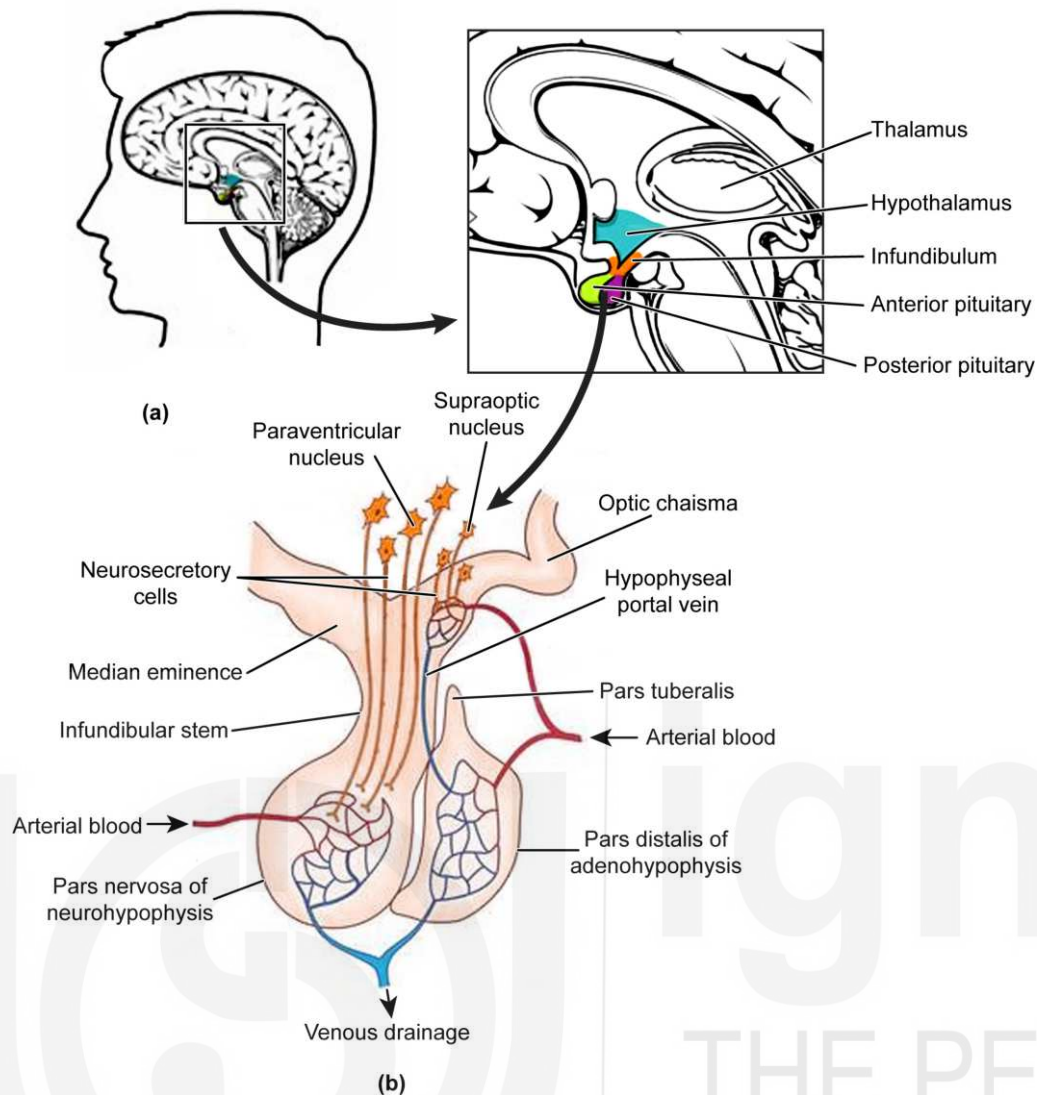


Fig. 7.13: a) Location of pituitary and hypothalamus; (b) Neurosecretory cells of the hypothalamus regulate secretion from the anterior pituitary via their secretions in the portal system and store their secretions in the posterior pituitary.

Secretion of neurohormones from the neurosecretory cells of the hypothalamus control the secretion of hormones originating from the anterior pituitary. Some of these cells located in the hypothalamus have their axons (neurosecretory nerve endings) situated in the posterior pituitary where the neurohormones are stored and released by them.

The anterior lobe of the pituitary is made up of a variety of endocrine cells where at least 7 hormones are synthesized. Table 7.2 gives a brief account of their structure and action on the target tissue. All except growth hormone (GH), prolactin and melanocyte stimulating hormone (MSH) are tropic hormones that is, they stimulate the secretion of other hormones from endocrine glands that are present in other parts of the body. GH, prolactin and MSH are direct acting hormones. As mentioned earlier, secretory activity of the anterior lobe is controlled by secretions of neurosecretory cells in the hypothalamus (see Box 7.1). These cells release their hormones through their axonal endings in the median eminence swelling at the part of the infundibulum that joins the pituitary to the hypothalamus. The walls of the capillary network in this area are fenestrated (with pores) and allow large

molecules to enter or leave the capillaries easily. The superior hypophyseal artery supplies blood to the capillary network and unites to form a series of vessels that wind around the infundibulum and enter the anterior pituitary to form an extensive second capillary bed amongst the endocrine cells, thus forming the hypophyseal portal system (see Fig.7.12b).

Table 7.2: Hormones which are synthesized in the anterior pituitary and those which are stored in posterior pituitary.

	Hormone	Chemical Nature	Action
1.	Growth Hormone (GH)	Protein	Stimulates liver to produce somatomedins that promote growth of body tissues, affects many other tissues
2.	Prolactin	Peptide	Promotes milk production in mammary glands; in liver stimulates production of pheromones in some mammals; maintains secretion of estrogen and progesterone by corpus luteum
3.	Melanocyte stimulating hormone (MSH)	Peptide	Promotes melanin synthesis; controls hair colouration in some mammals; affects activity of some neurons.
4.	Adrenocorticotrophic hormone (ACTH)	Peptide	Stimulates synthesis and release of corticosteroids from adrenal cortex
5.	Thyroid Stimulating Hormone (TSH)	Glycoprotein	Stimulates synthesis and release of thyroxin and triiodothyronine from the thyroid
6.	Follicle stimulating hormone (FSH)	Glycoprotein	Controls development and growth of germ cells in testes and ovary.
7.	Luteinizing hormone (LH)	Glycoprotein	Controls secretion of steroid hormones responsible for male and female sexual characters and triggers ovulation in females.
8.	Antidiuretic hormone (ADH) stored in posterior pituitary	Peptide	stimulates water reabsorption by the kidney by stimulating insertion of "water channels" or aquaporins into the membranes of kidney tubules
9.	Oxytocin stored in posterior pituitary	Peptide	Stimulates uterine contraction during childbirth. Ejection of milk during nursing.

The neurosecretory cells of the hypothalamus synthesise hormones that regulate the activity of pituitary gland. The neurohormones that control the secretion of hormones from the anterior pituitary are either releasing or release inhibiting hormones (Table 7.3). All of these except for one, are small peptides and are named according to their action on the anterior pituitary and are carried to the anterior pituitary through the portal vessels. However, they also secrete two hormones that are not tropic hormones, namely oxytocin and vasopressin or antidiuretic hormones that are transported along their axons and stored in the axon endings in the posterior pituitary (see Table 7.2again).

Box: 7.1

In the 1920s a German scientist Ernst Scharrer observed that the neurons of the hypothalamus in the brain of the bird minnow (*Phoxinus phoxinus*) were structurally similar to endocrine cells. The axons of these cells passed out of the hypothalamus into the pituitary gland and ended as large bulbous swellings that closely applied to certain blood capillaries in the pituitary. Scharrer concluded that at least some of the hormones secreted by the pituitary gland were actually secreted by these hypothalamic cells and that the pituitary was actually a storage place for these hormones. At that time this idea was rejected outright. However, Scharrer and his wife Berta persisted in their studies and by 1950s a considerable amount of evidence was collected in invertebrates that supported their hypothesis. This phenomenon came to be known as neurosecretion and the secretory products as neurohormones to indicate their origin from nervous tissue. The storage organs were known as neurohaemal organs because of the close connections between the nerve endings and the blood capillaries in these organs.

Table 7.3: Hypothalamic hormones that release or inhibit anterior pituitary hormones.

Hormone	Chemical Nature	Action
Corticotropin-releasing hormone (CRH)	Peptide	Stimulates (ACTH) release
Thyrotropin releasing hormone (TRH)	Peptide	Stimulates release of TSH and prolactin
Growth hormone releasing hormone (GRH)	Peptide	Stimulates GH release
Gonadotropin Releasing hormone (GnRH)	Peptide	Stimulates release of FSH and LH
GH Inhibiting hormone (GHIH) Somatostatin	Peptide	Inhibits GH release and interferes with TSH release
Prolactin release inhibiting factor also known as dopamine	Peptide	Inhibits prolactin release
MSH release inhibiting hormone (MIH)	Peptide	Inhibits MSH release

You can now appreciate that the pituitary and hypothalamus are the two major glands that really control all the physiological activities of the body. Unlike the brain the hypothalamus is not protected by the blood brain barrier, hence it detects any changes that take place in the blood stream. Any sensory information from the brain is routed through the hypothalamus and thus it connects neural and blood borne information and coordinates both sets of information to give out appropriate response. The sequence of secretions in the hypothalamus: hypothalamus → anterior pituitary → endocrine glands enables a weak signal to be amplified several folds as can be seen in Fig. 7.13 which shows how 0.1 µg of corticotropin-releasing hormone (CRH) can stimulate the deposition of 5600 µg of glycogen in the liver.

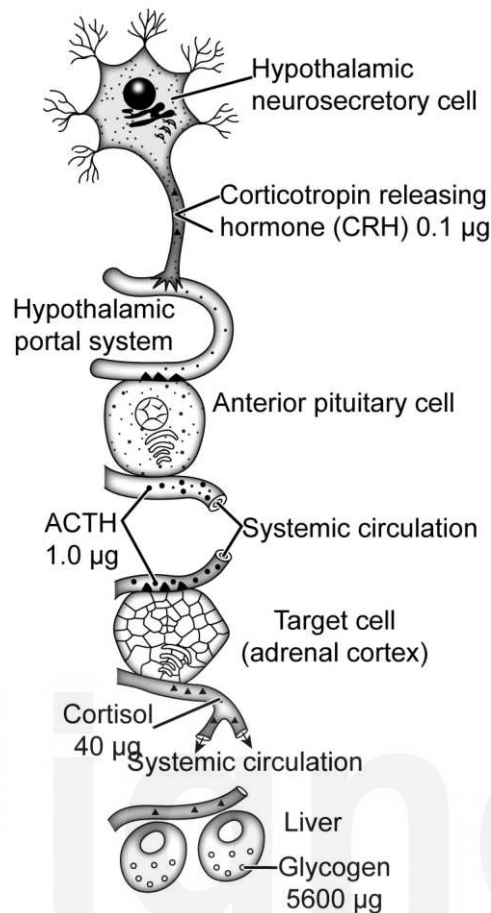


Fig.7.14: Amplification in the Adrenocorticotrophic-Endocrine System.

The posterior lobe of the pituitary (neurohypophysis) stores and releases oxytocin and antidiuretic hormone (see Table 7.2). These two neurohormones are synthesized in the neurosecretory cells that form the supraoptic and paraventricular nuclei in the anterior part of the hypothalamus. The axons of these secretory cells extend into the posterior pituitary gland and release the hormones directly into the capillaries there.

7.5.2 Regulation of Hormone Secretion

The secretion of hormones occurs normally at a basal (minimum) level that is required by the body to regulate the composition of body fluids or its rate of metabolism as well as other bodily functions. This basal level is increased or reduced by signals acting on the endocrine tissue. Endocrine tissue may secrete in response to external or internal stimuli without modulation or the secretion may be part of a feedback loop in which the secretion is affected by the consequences of the secretion itself. In most cases hormone production is directly or indirectly controlled by the nervous system.

The secretion of hormones is generally under negative feedback control. In negative feedback systems, a stimulus causes the release of a substance and once when the substance reaches a level of concentration, it sends a signal to stop further release of the substance. So the further secretion of the hormone is inhibited by the concentration of the hormone itself or by the response of the target tissue. In this way, the concentration level of hormones in blood is maintained within a narrow range.

There are three mechanisms that stimulate the endocrine glands to synthesize and secrete hormones which are as follows: **humoral (body fluids) stimuli** (sing: **stimulus**), **hormonal stimuli** and **neural stimuli**.

Humoral stimuli (or stimulus) refer to the control of hormone secretion in response to changes in the extracellular fluids such as blood or ion concentration in the blood. For example, an increase in the level of glucose in the blood would send a signal to the pancreatic cells to secrete insulin in the blood and when the glucose levels decrease a signal is sent to pancreatic cells to stop producing insulin and start production of glucagon (Fig.7. 14a). Let us understand this by another example. A drop in the calcium level in the blood signals the parathyroid to release parathyroid hormone, which initiates the release of calcium from the bones, decreases excretion of calcium by the kidneys and increases absorption of calcium in the gut. This leads to the restoration of normal calcium levels in the blood, which in turn signals the parathyroid to stop the secretion of the hormone (Fig.7. 14 b). These are examples of short feedback loops and similar simple feedback loops control the secretion from the posterior pituitary.

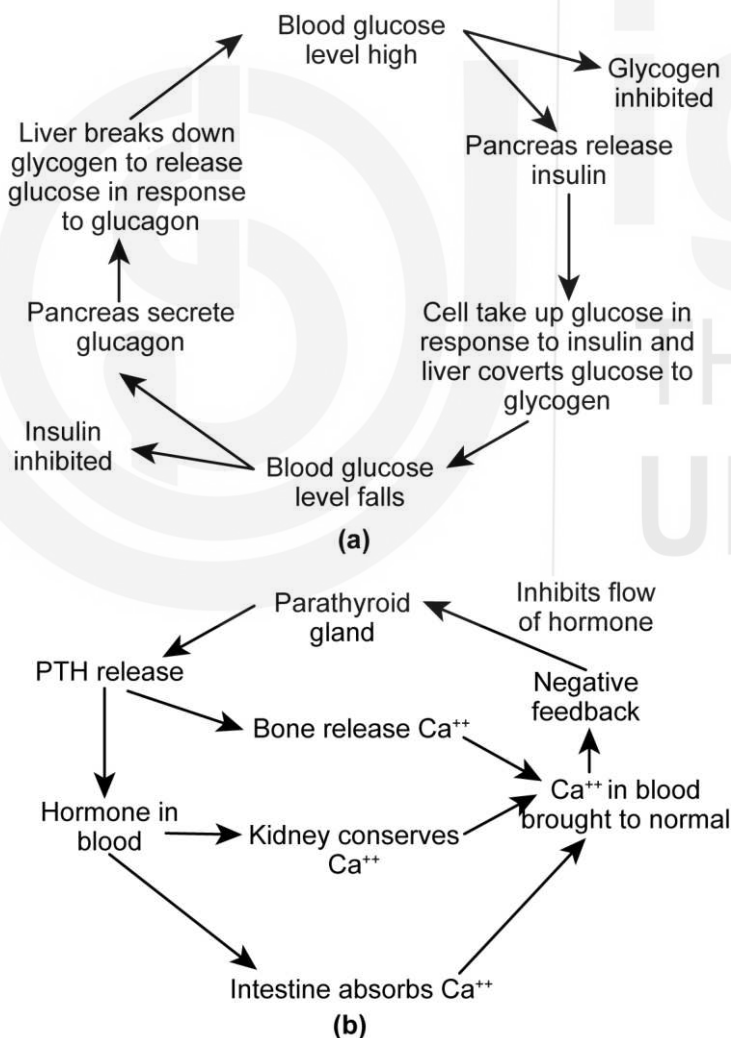


Fig.7.15: Negative feedback control of (a) blood glucose levels (b) parathyroid hormone secretion.

Hormonal stimuli refer to the release of hormone in response to another hormone and there can be control at two or more levels, forming long negative feedback loops. An example of **hormonal stimuli** is seen in the control of

secretions from the anterior pituitary. For example the hypothalamus produces hormones that control the secretion of hormones from the anterior pituitary gland which further controls the secretion of hormones from other endocrine glands. In Figure 7.15 you can see that the control of thyroid hormones is under negative feedback control. Thyrotropin releasing hormone (TRH) from the hypothalamus stimulates the anterior pituitary gland to release thyroid stimulating hormone (TSH) which stimulates the thyroid gland to secrete T3 and T4. When the concentration of these two hormones rises beyond a certain level in the blood, then both the hypothalamus and the pituitary gland are inhibited from producing their respective stimulatory hormones.

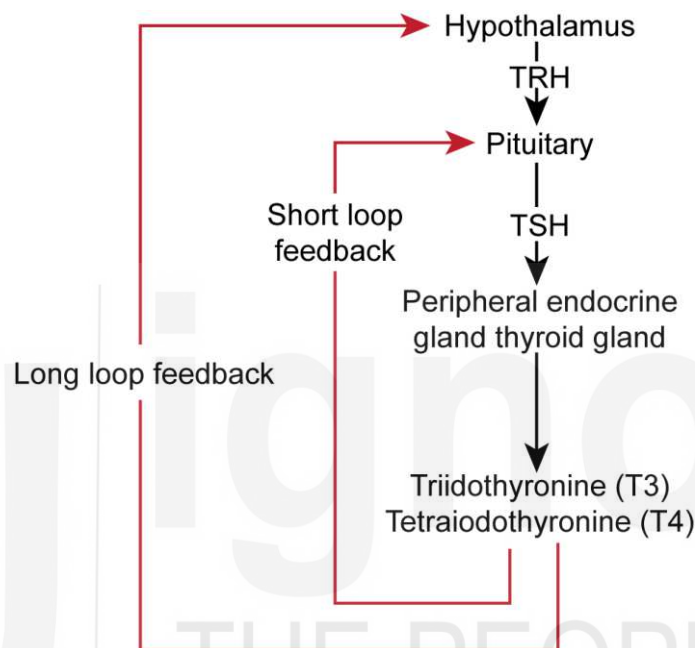


Fig.7.16: An example of hormonal stimuli depicted by a line diagram, showing the “Long-loop feedback control of hormone secretion” from the anterior pituitary. Black arrows show the stimulation of secretions and red arrows show the inhibition of secretions.

In situations where a rapid buildup of hormone concentration is required, the endocrine secretion is under positive feedback as seen in the secretion of reproductive hormones. This means that the initial secretion of hormone leads to further secretion and a peak concentration of the hormone is reached rapidly. Ultimately this process has to be controlled by negative feedback so that basal level of hormone secretion is restored.

Neural stimuli refer to cases where nervous system directly stimulates the endocrine glands to release hormones. The short term stress response hormones epinephrine and norepinephrine are released when the nerve endings of the sympathetic nervous system directly stimulate the adrenal medulla.

SAQ 6

- a) Given below are some statements that are not entirely incorrect but need to be modified to be more precise. Make corrections where possible.
 - i) The secretions from the anterior pituitary are under the control of releasing factors or hormones secreted by the brain.

- ii) The cells of the anterior pituitary are connected to the hypothalamus by neurons.
 - iii) The secretion of thyroxine is regulated by the pituitary gland.
 - iv) Positive feedback is a mechanism to regulate the secretion of corticosteroids from the adrenal cortex.
 - v) Rapid hormonal release is primarily controlled by negative feedback system.
- b) Which mechanism of hormone stimulation would be affected if the signaling to hypothalamus secretions is blocked off?
-

7.6 PHEROMONES

In the previous sections you have studied that both neurotransmitters and hormones are chemical messengers in the body's communication system. While these chemicals carry messages inside the body, certain chemicals known as **pheromones** carry information outside the body to other members of the same species.

A pheromone therefore is a chemical substance released by an animal into its surroundings which influences the behavior or development of individuals of the same species. Pheromones have been identified in every part of the animal kingdom, including mammals, and are seen to be involved in a wide range of functions including attraction of the sexes, mate choice, trail following, announcing and marking territory, directing other members of the species towards a food source or resting sites etc., and interactions between parents and offspring, depending on the species. Much research work has been done in insects and alarm pheromones have been found in termites and bees. The termite soldiers liberate alarm pheromones thus communicating with and attracting the more aggressive workers to participate in attacking the intrusive individuals. Aggregate pheromones direct both sexes to aggregate which helps in feeding, protection and reproduction etc.

Most pheromones, including the female sex pheromones of most moths and some mammalian pheromones, are not single compounds. Instead they tend to be a species-specific multi-component combination of molecules. For example, in the **house mouse, sulfated oestrogens and a particular fraction of female urine form a multi-component mouse pheromone**, produced by oestrous females, which promotes mating. Most pheromones are detected by the sense of smell. Pheromone molecules can be volatile (easily evaporated at normal temperatures) or involatile (not volatile), soluble or insoluble, large or small, depending on whether they are carried to the receiver in air or water or, for example, deposited on the nose of the receiver. Pheromones can be short or long range, or act on contact. In honey bees the queen bee produces a chemical that is known as **queen bee substance** that inhibits the development of another queen in the same hive.

Mammals in particular use pheromones in urine, faeces, or from secretions of special scent glands to mark traits and territories. When a male dog urinates on a tree, it is telling other dogs that this tree is part of his territory. Other large male cats such as lions, tigers do the same in the forest. Pheromones also accelerate reproductive maturity in a number of species and permit members of one sex to know which members of the opposite sex are in breeding condition.

The term "pheromone" itself came about in 1959 with the discovery and identification by Adolf Butenandt of a powerful pheromone secreted by female silk moths called "bombykol pheromone." The bombykol sex pheromone is observed to be effective over kilometers of distance. The males are able to recognize the species specific pheromones by means of receptors on their antennae even though there might be other species of moth releasing their own pheromones in the same space. The pheromones used to mark territories or attract mates produce immediate effects on the nervous system, physiology and behavior of the receiving animal.

There are pheromones that act more slowly and have longer lasting effects. For example, if a newly fertilized female mouse is caged with a strange male mouse, the odor of that male will terminate the pregnancy. The pheromone responsible for this phenomenon comes from the urine of the male. It is received by the olfactory receptors of the female and triggers activity in the hypothalamus which directs the pituitary to release inhibiting hormone that reduces the output of steroid hormones from the ovaries. The uterus does not receive adequate hormones for implantation of the foetus and so the pregnancy aborts.

Since humans are mammals it is thought that pheromones have a role to play in behavior. However, despite decades of research, the role of pheromones in humans is still controversial. Scientific research regarding it is still in the early stages and is inconclusive.

7.7 SUMMARY

In this unit you have studied that:

- Communications between cells in the animal kingdom can be of several types. When the secretion from cells is carried by the bloodstream to distant target tissue in the body it is known as endocrine. These endocrine messenger molecules are termed as hormones that act on target cells to regulate development, growth, energy metabolism, reproduction, and many behaviors.
- There are three basic types of hormones: lipid-derived, amino acid-derived, and peptide. Lipid-derived hormones are structurally similar to cholesterol and include steroid hormones such as estradiol and testosterone. Amino acid-derived hormones are relatively small molecules and include the adrenal hormones epinephrine and norepinephrine. Peptide hormones are polypeptide chains or proteins.

and include the pituitary hormones, antidiuretic hormone (vasopressin), and oxytocin.

- All hormones except steroid are secreted by process of exocytosis; steroids can diffuse through the membrane. Duration of hormone action depends on its longevity and rate of breakdown in the liver or excretion from the body via the kidneys. Since receptors for hormones are very sensitive and specific, hormones are required in very minute quantities.
- Receptors for steroid hormones and for thyroid hormones lie in the cytoplasm as the hormones can diffuse through the membrane into the cytoplasm and bind to their respective receptor forming the “receptor hormone complex”. This receptor hormone complex can be carried to the nucleus where it attaches to its specific site on the DNA and induces transcription activity. Receptors to peptide hormones are plasma membrane bound. The hormone is called a first messenger and the cellular component is called a second messenger. G-proteins activate the second messenger (cyclic AMP), triggering the cellular response. Response to hormone binding is amplified as the signaling pathway progresses. Cellular responses to hormones include the production of proteins and enzymes and altered membrane permeability. The number of receptors on a target cell can increase or decrease in response to hormone activity.
- Specialised neurosecretory cells secrete neurohormones into the blood directly which transports them to the target cells. Because of this neuro-endocrine connection the nervous system to a large extent controls the activity of the endocrine system.
- The hypothalamus – pituitary gland connection is an important source of physiological regulation. The hypothalamus is part of the brain and pituitary or master gland is divided into two lobes. The anterior lobe synthesizes and secretes mainly tropic hormones that regulate the function of the major endocrine glands of the body. The posterior lobe contains axon endings of neurosecretory cells located in the hypothalamus that release hormones produced in the hypothalamus. The hypothalamus also regulates the secretions of the anterior pituitary by means of releasing and release inhibiting hormones or factors.
- In vertebrates, the arrangement of neurohormones ensure that their action on the endocrine cells of the pituitary gland to releases hormones for stimulating other endocrine glands, greatly amplifies the original signal. It also forms mostly negative feedback loops that finally regulate the entire hormonal system and maintains homeostasis.
- Pheromones are another system of chemical signaling found widely in the Animal Kingdom. These chemical signals carry information outside the body and are species specific, eliciting a response only from individuals of the same species. They influence development or behavior. Pheromones affect the olfactory receptors which transmit the signal to specific neural circuits to decode the pheromone signal

- Communication whether neural or hormonal basically utilize chemical signals that interact with specific target organs. The two differences are that neural signals are fast and short lived and can affect single cells while hormonal signals are slower, long lasting and diffuse.

7.8 TERMINAL QUESTIONS

1. What are the factors that determine:
 - i) which target tissue responds to a particular hormone and
 - ii) duration of response?
2. Compare the action of steroid and peptide hormones with respect to:
 - i) structure
 - ii) receptor
 - iii) mechanism of action.
3. List the hormones secreted by each of the following endocrine glands and give their actions briefly.
 - i) Posterior pituitary
 - ii) Anterior lobe of pituitary
 - iii) Adrenal medulla
 - iv) β - cells of pancreas
4.
 - a) If a new compound is used that binds to membrane receptors by blocking them which hormones action will be blocked as a result?
 - b) If cAMP formation is inhibited in the cell then what step in the hormone action will be affected?
 - c) How can hormones mediate changes in the cell's function?
 - d) What is the role of calcium ion as a second messenger?
5. Pheromones are also part of the chemical signaling systems of the animal. In which way are they different from hormone action?
6. How does the hypothalamus regulate all the endocrine activity in mammals?

7.9 ANSWERS

Self-Assessment Questions

1.
 - a) Signals affect locally placed cells
 - b) Signals target cells locally or at a distance via blood
 - c) Signals released from neurons and act on distant target cells via blood

- d) Signals affect the target cell over a large distance outside the body
- 2.
- a) Calcitonin for reducing Ca^{2+} in the blood and PTH for releasing Ca^{2+} from the body's stores.
 - b) Testosterone is responsible for secondary sexual character in males.
 - c) Insulin for uptake of glucose from blood and glucagon for releasing glucose from glycogen.
 - d) Increases metabolism and heart rate and promotes growth.
 - e) Erythropoietin, mainly from kidneys
- 3.
- a) The precursor for steroid hormone is pregnenolone. it is synthesized in the membrane of mitochondria. While protein hormones are the result of the translation of the : mRNA to pre hormone in the rough endoplasmic reticulum to prohormone in Golgi which is (prohormone) cleaved to give hormone in cell or in the plasma.
 - b) Steroid hormones being derived from cholesterol are not soluble in plasma and other body fluids and so need to be transported in blood by being bound to plasma carrier proteins. Furthermore, being lipophilic they are able to cross any membrane and so may enter the surrounding cells instead of reaching their target cells thus they need to be bound to a carrier protein to be able to reach their target. Also binding of steroid hormones to plasma carrier proteins allows their slow release.
- 4.
- a) ii), iii) and i)
 - b) the changes in the cell as a result of the binding of hormone to the receptor
 - c) Phosphodiesterase
- 5.
- i) True
 - ii) False - Steroid hormones do not have protein receptors on the cell membrane but are able to diffuse through the membrane and bind to their intracellular receptors and nuclear receptors in order to mediate changes in the cell's functions.
 - c) False - Type I receptors for steroid hormones are bound to heat shock proteins and Type II receptors are free and bind to nuclear receptors Type I intracellular receptors for steroid hormones are free intracellular receptors.
 - d) True
- 6.
- a) i) The secretions from the anterior pituitary are under the control of releasing factors or hormones secreted by the **hypothalamus**.

- ii) The cells of the anterior pituitary are connected to the regulatory secretions of hypothalamus via a portal system.
 - iii) The secretion of thyroxine from the thyroid is regulated by the TSH secreted by anterior pituitary.
 - iv) Negative feedback is a mechanism to regulate the secretion of corticosteroids from the adrenal cortex.
 - v) Rapid hormonal release is primarily controlled by positive feedback system
- b) The negative feedback loop would be disrupted if no stimulus reaches the hypothalamus disturbing the secretion from the pituitary lobes. The hormonal stimulation mechanism from pituitary gland would be continuous in turn affecting other endocrine glands of the body that are stimulated to release their hormones by the anterior pituitary.

Terminal Questions

1. The target tissue that has the appropriate and specific receptors for a particular hormone. The duration of response depends on the half life of the hormone in the blood, that is how much hormone and for how long it is available to bind to the receptors in the target cells.
2. Refer to Section 7.4.
3. Refer to Table 7.1 and 7.2.
4.
 - a) Peptide and protein hormones as they cannot enter the cell but need membrane receptor to activate second messengers to bring about the change in the target tissue.
 - b) Activation of protein kinases.
 - c) By binding to receptors that either activate or inactive enzymes or suppress enzyme activity; make new products, increase or decrease membrane permeability, increase or suppress gene activity thereby, causing mRNAs to be altered resulting in synthesis of new proteins.
 - d) Refer to Subsection 7.4.1.
5. Hormones are chemical signals that are carried inside the body to elicit a response in their target cells, while pheromones are chemical signals that are deposited in air or as liquids outside the body to affect the behavior of individuals of the same species. Pheromones act on olfactory receptors which carry the information to the brain which directs appropriate behavior.
6. Hint; by regulating the activity of the master gland pituitary. Refer to subsection 7.5.1

UNIT 8

REPRODUCTION |

Structure

- | | |
|--|--|
| 8.1 Introduction | 8.5 Mammalian Male Reproductive Physiology : Humans |
| Objectives | |
| 8.2 Mechanisms of Reproduction | Structure of Testes |
| Asexual Reproduction | Hormones of Human Testis |
| Sexual Reproduction in Animals | Hormonal Regulation of Testis |
| 8.3 Sex Determination in Sexually Reproducing Animals | 8.6 Mammalian Female Reproductive Physiology : Human |
| Genotypic or Chromosomal Sex Determination | Oogenesis |
| Non-Genotypic Sex Determination | Female Hormones |
| | Hormonal Regulation of Ovary |
| 8.4 Reproductive Systems in Sexually Reproducing Animals | 8.7 Reproductive Cycles |
| Invertebrates | 8.8 Summary |
| Reproductive Systems of Vertebrates | 8.9 Terminal Questions |
| | 8.10 Answers |

8.1 INTRODUCTION

Reproduction is the fundamental biological process of all life forms and the mainstay for the continuance of life and the survival of species. This is because if species of an organism develop, grow and live their normal life span, without reproducing then the evolutionary changes in their populations and the continuity and survival of their future generations both of which are a result of reproduction would come to an end leading to their extinction. Reproduction thus, ensures that the older generations of organisms of a

species are constantly replaced by younger generations which are similar but somewhat variable thus, ensuring the survival of the species. Successful reproduction in fact is the ultimate objective of all living organisms.

In the earlier units of this course (BZYCT-135 Animal Physiology and Biochemistry), you have studied the various physiological processes that are essential for the survival of animals. In this unit you shall study about the physiology of animal reproduction, various reproductive mechanisms, the process of gametogenesis, the role of hormones of reproduction, breeding cycles and regulation of reproduction. Asexual mode of reproduction in animals has also been dealt with briefly in the present unit.

Objectives

After studying this unit you should be able to :

- ❖ explain the necessity for reproduction in animals;
- ❖ describe the reproductive mechanisms in animals;
- ❖ discuss and compare the reproductive physiology in male and females;
- ❖ outline the breeding cycles in animals; and
- ❖ explain the mechanisms that regulate reproduction.

8.2 MECHANISMS OF REPRODUCTION

Reproduction is a biological process by which organisms produce their offsprings. Organisms reproduce in two ways by: i) asexual reproduction or ii) sexual reproduction. Let us now study about these two types of reproduction.

8.2.1 Asexual Reproduction

Asexual or **agamic reproduction** (reproduction without fertilization) takes place by mitotic division or mitosis. In this type of reproduction offsprings are produced by only one parent by process of mitotic cell division. As a result the offsprings produced by this process inherit all their genes from the single parent and so are genotypically identical copies of their single parent and of each other. This is because genetic mixing does not occur in these organisms during reproduction. In asexually reproducing organisms special reproductive organs or gametes are absent. Asexually reproducing organisms have successfully persisted in large numbers on earth for 3.5 million years. Their involvement in important events of life such as food chain, clearly demonstrates that these organisms are successful and very important. Major methods of asexual reproduction are: (i) fission (ii) budding (iii) fragmentation, and (iv) parthenogenesis. In this section we shall study about these methods in brief.

- i) **Fission** : In this method the organisms divide mitotically into two or more equal sized offsprings also called daughter cells. This method of asexual division of the organism into two or more equal sized daughter cells is known as **binary fission**. It occurs in prokaryotes and some animals like

protists (Fig.8.1). Some protists also exhibit sexual reproduction.

Multiple fission occurs in sporozoan protists. In multiple fission the nucleus of the parent cell divides by mitosis into many nuclei, each of which gets surrounded by the cytoplasm of the parent cell, producing new individuals. Each new individual or daughter organism which is produced contains cytoplasmic organelles and the genetic material of the single parent individual, and each grows to the size of its parent. Some organelles like mitochondria divide at the time of division, while others like flagella and contractile vacuoles are formed afresh by the daughter organisms..

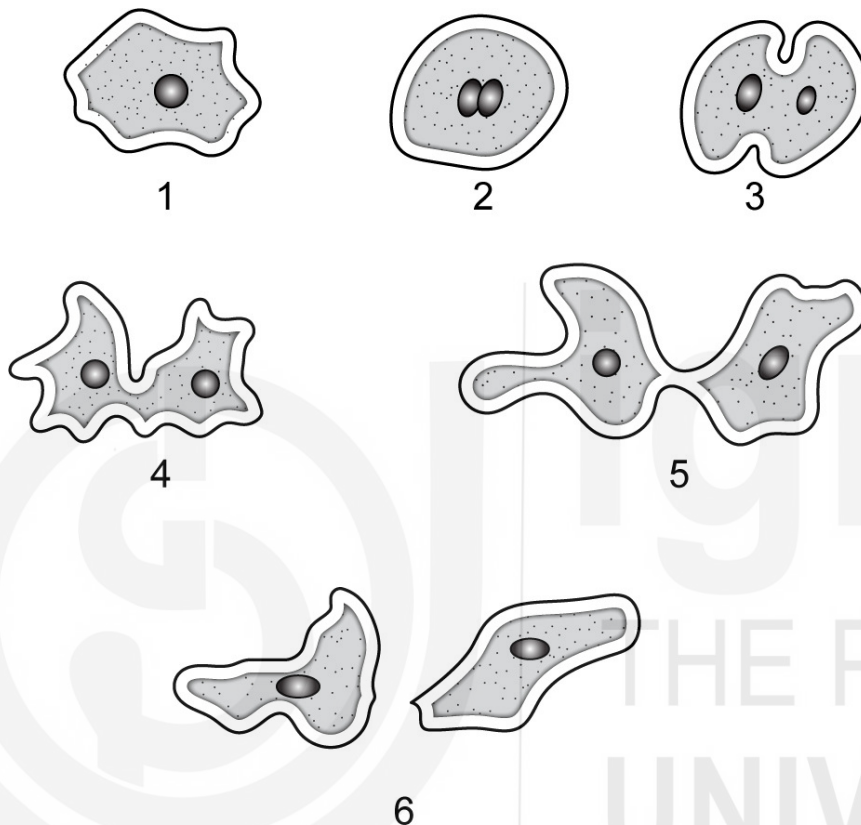


Fig 8.1: Fission in the amoeba.

- ii) **Budding:** In this method of reproduction an organism develops by mitotic division an outgrowth or bulge called bud which contains the identical genetic and cytoplasmic material of the parent organism. The bud detaches from the parent organism to become a new individual. In each **hydra**, there may be one or more buds. Budding takes place in some protists, coelenterates, platyhelminthes and several groups of annelids. Fig.8.2 shows hydra generating offsprings by budding.
- iii) **Fragmentation:** In fragmentation an organism breaks into two or more pieces, each of which grows into a new individual. This method of reproduction is common in animals with a high capacity for regeneration. Sponges, hydroid coelenterates, planarians and annelids reproduce by fragmentation. For example, if a sponge is macerated by pressing it through fine gauge and separating the cells and if the cells are brought back together the cells forms groups and grow into new individuals. Very small fragments of free-living flatworms will regenerate into new individuals under favourable conditions.

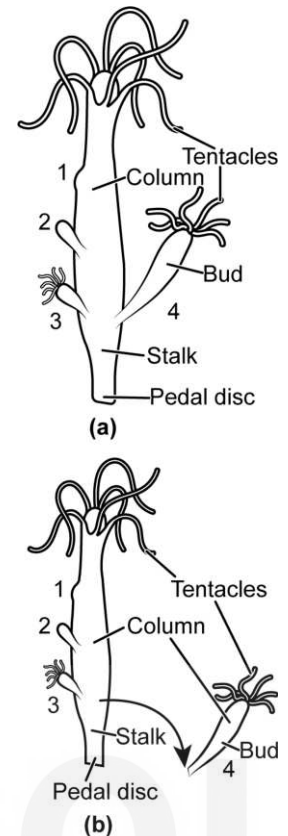


Fig.8.2: a) Hydra parent hydra with developing buds in various stages of development : (1) newly forming bud at the side of the parent hydra; (2) development and growth of bud; (3) developed bud with mouth and tentacles;(b) fully formed miniature hydra detaches from parent and becomes independent.

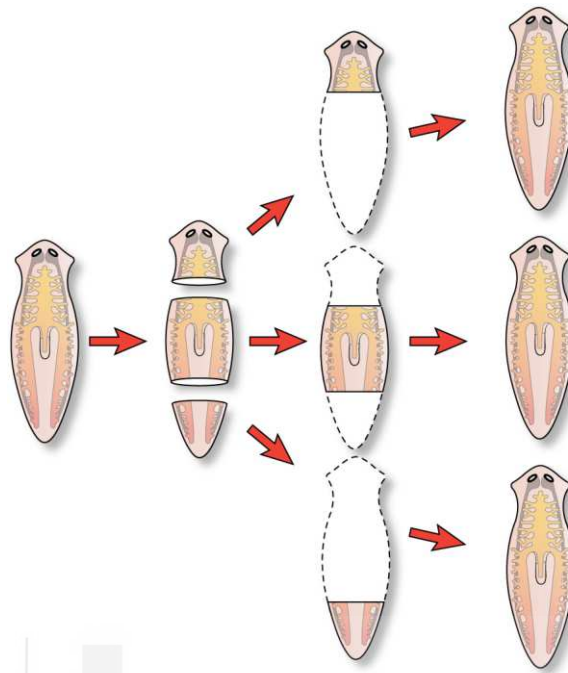


Fig 8.3: Fragmentation in Planaria (only the first figure should be redrawn the second is redundant).



Fig 8.4: The first parthenogenetic birth was observed and documented in May 2006, in a female lizard species of a Komodo dragon named Flora, housed in the Chester Zoo, London. Zookeepers observed that though Flora had never come in contact with a male Komodo dragon it laid 25 eggs, including 11 that were viable. A paternity test confirmed that all the genetic material in the eggs had come from Flora and it was confirmed that Flora had reproduced parthenogenetically.

- iv) **Parthenogenesis** : Parthenogenesis is also called agamogenesis and is a unique form of reproduction where embryonic development occurs in unfertilized eggs without the participation of a gamete from the opposite sex. It is a spontaneous activation of a mature egg, followed by normal egg divisions and subsequent embryonic development. Parthenogenesis has been defined as 'the production of an embryo from a female gamete without any genetic contribution from a male gamete and with or without eventual development into an adult'. Parthenogenesis is considered distinct from asexual forms of reproduction, such as fission and budding and fragmentation, as it involves the female gametes.

Parthenogenic species may be: i) obligate (that is, incapable of sexual reproduction) or ii) facultative (that is, capable of switching between parthenogenesis and sexual reproduction depending upon environmental conditions and availability of food). Most parthenogenetic animals reproduce sexually at some point in their life history and so are facultative. Facultative parthenogenesis may be seasonal and may also be influenced by environmental factors such as temperature or food supply or some chemicals.

Facultative parthenogenesis may occur at irregular intervals or may be cyclical.

Many facultative parthenogenetic invertebrates have a cyclical alternation of asexual with bisexual reproduction influenced by season. An example is the crustacean *Daphnia* that lives in freshwater throughout the world. In any particular year *Daphnia* reproduces exclusively by parthenogenesis producing diploid female offspring that continue to grow in a brood pouch. The eggs are released when the mother moults and sheds her exoskeleton. In late summer or early fall, some of the females start producing male offspring through

parthenogenesis. Then the males produce haploid sperms and fertilize the haploid eggs produced by the females. The offspring produced through this sexual reproduction again go into the asexual mode of reproduction in spring. So far more than 2,000 species of organisms are known to reproduce parthenogenitically. Parthenogenesis occurs commonly among the lower invertebrate animals (particularly rotifers, arthropods such as aphids, ants, wasps, and bees, spider, mites etc.) and rarely occurs among vertebrates. However though not very common among vertebrates it does occur in some species of sharks (egs: hammer head, zebra shark), Amazon molly fish (*Poecilia formosa*) and amphibian species such as the common water frog (*Pelophylax kl. esculentus*), silvery salamander (*Ambystoma platineum*), mole salamander (*Ambystoma talpoideum*) Among reptiles facultative parthenogenesis is seen in Komodo dragon (*Varanus komodoensis*) (Fig. 8.4) while obligate parthenogenesis occurs in whiptail lizards (Refer to Box 8.1) such as New Mexico whiptail (*Cnemidophorus neomexicanus*) and species of *Aspidoscelis*. Parthenogenesis occurs even in birds and is seen in Chinese painted quail (*Coturnix chinensis*) which reproduces by facultative parthenogenesis. At present about 90 species of vertebrates have been discovered to be strictly unisexual in which reproduction is by obligate parthenogenesis.

Parthenogenesis also plays an important role in social organization in colonies of certain bees, wasps, and ants. In honeybees and some wasps unfertilized eggs develop into haploid males and fertilized eggs give rise to diploid females. In these insects, large numbers of males (drones) are produced parthenogenitically, whereas sterile female workers and reproductive females (queens) are produced sexually.

Box.8.1

Most lizard populations are evenly divided between females and males. Deviations from this pattern have been noted in obligate parthenogenetic species which are unisexual and in which the young are produced from unfertilized eggs. Parthenogenetic lizards appear to live in areas that are ecologically marginal for representatives of their genera. Scientists as early as 1960 were aware that a number of whiptail lizards in Mexico and the southwestern United States were made up entirely of females. The most notable of these species, the New Mexico whiptail lizard, is known to be able to produce healthy, well-bred offspring without the help of male fertilization. New Mexico whiptails have helped scientists to unlock the secret as to how it's possible for a species that produces exclusively asexually or parthenogenitically to thrive successively. The **molecular biologist** Peter Baumann who has co-authored a study on the lizards that was published in the journal *Nature* back in 2010 has explained the success of the parthenogenetic species of whiptails. According to him parthenogenetic species are generally genetically isolated because they only inherit the DNA of one parent and are liable to be susceptible to a disease or physical mutation if any genetic weaknesses occurs in their population since the genetic weaknesses cannot be "overridden" or shielded by the healthy genes from a second parent. The shallower the gene pool, the more likely it is to produce sick or mutated offspring. However, the all-female whiptail lizard species for dealing with this issue, have evolved to start the reproductive process with twice as many chromosomes as their sexually-producing lizard relatives.



New Mexico whip tail parthenogenetic species (*Cnemidophorus neomexicanus*) seen in the centre is flanked on either side by whiptails that reproduce sexually (Alistair J. Cullum)

Cloning is a process of generating a new individual which is genetically identical to its parent. The DNA of both the organisms is exactly same. Since there is no fertilization or

Animals that reproduce parthenogenitically have substantially less genetic variability than do animals with chromosome sets from two parents. This condition may be an advantage for animals that are well adapted to a relatively stable environment. However, in meeting the challenges of a changing environment, parthenogenetic animals may have less flexibility, which may explain why this form of reproduction is relatively uncommon.

SAQ 1

Explain the difference between the four ways of asexual reproduction.

8.2.2 Sexual Reproduction in Animals

In the previous subsection and the previous Course BZYCT-133 you have already studied about asexual reproduction where recombination of genes occurs. You have also learnt that sexual reproduction occurs in a large number of animal species and takes place due to the involvement of two genetically different male and female gametes produced by the process of gametogenesis. The male gonad called testis produce male gametes (spermatozoon or sperms) and the female gonad called ovary produce the gametes ova by the process of spermatogenesis and oogenesis respectively. The production of gametes (sperm and ova) is collectively termed gametogenesis. A sperm combines with the ovum producing a zygote. The genetic material of the zygote differs from the sperm and egg which united to form it and so it has a new genotype compared to the parents.

Sexual reproduction in Hermaphrodites

Nearly all vertebrates and many invertebrates as you are aware have separate sexes and such a condition is called dioecious and this type of reproduction is called biparental reproduction. However, some animals such as most flatworms, some hydroids, annelids, crustaceans and some fishes have both male and female organs in the same individual. Such a condition is called hermaphroditism. In contrast to the dioecious state of separate sexes, hermaphrodites are monoecious, that is both male and female organs are present in the same organism and it may be able to self-fertilise the gametes it generates. However, Most of the hermaphrodites avoid self-fertilization and instead members of the species exchange gametes with each other. For

example, although the individual of an earthworm species may contain both male and female organs, its eggs as a rule are fertilised by the male organs of a different individual earthworm and vice versa (Fig8.5). Hermaphrodites also prevent self-fertilisation by developing their eggs and sperms at different times.

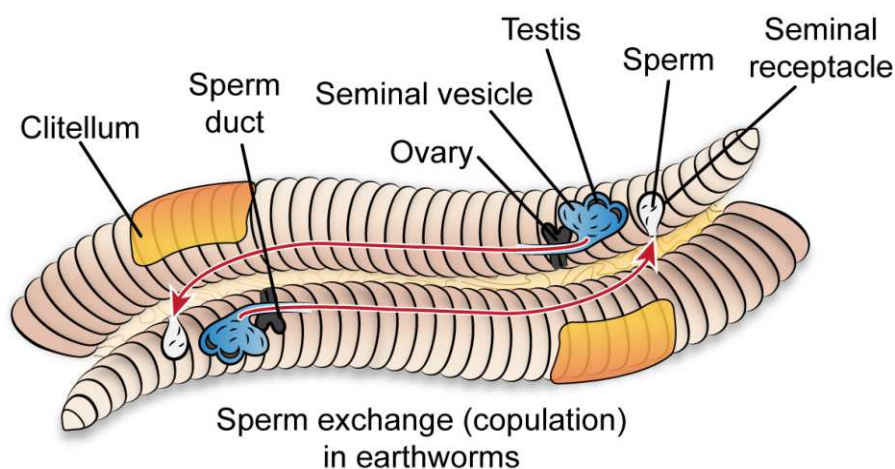


Fig: 8.5: Position of copulation and fertilization in mating earthworms.

Biparental Sexual Reproduction

Biparental sexual reproduction and male-female distinction is more clearly evident in metazoan species of animals in which male and female individuals are distinct and can be differentiated on the basis of their reproductive system and the type of the gametes they produce. The process of meiosis during formation of gametes is essential for sexual reproduction. The germ cells during formation of gametes undergo meiotic division in which the chromosomes replicate once and the cell divides twice (Refer again to Unit 12 in Volume 2 of BZYCT-133) due to which each germ cell gives rise to four haploid daughter cells or gametes. During bisexual fertilization, two haploid gametes namely a sperm (male gamete) generated from the male parent and an ovum (female gamete) generated from the female parent combine to form the diploid zygote in which the chromosomal number of species is restored. Although the zygote produced has the same numbers of chromosomes as present in each parent, however, it is genetically different from both of them due to genetic variability of the gametes. Genetic variability arises during gamete formation as a result of two events. One event occurs while the germ cell undergoes the first meiotic division. The other event responsible for genetic variability in gametes occurs during crossing over in prophase 1 stage of meiosis. In this event genetic recombination occurs among homologous chromosomes whereby one maternal chromosome and its corresponding paternal chromosome pair up and exchange genetic material. Thus, it is in this way that sexual reproduction introduces new gene combinations in a population. A combination of parental characters creates variations and favourable variations allow better adaptations that ensure the perpetuation of the species.

Biparental sexual reproduction is found in most of the multicellular organisms. Even single celled protists reproduce sexually during certain periods of life (Refer to BZYCT-133 Course-Animal Diversity-I). Sexual reproduction in protists may or may not involve male and female gametes. Sometimes two

mature sexual parents merely join together to exchange nuclear material or merge their cytoplasm. It is not possible to distinguish sexes in them.

Generally the gametes produced by the male and female of a particular species differ from each other in structure, size and behaviour, for which reason such gametes are known as heterogametes. Ova (egg), which are produced by the female are large, non-motile and produced in relatively small numbers while the spermatozoon (sperm) produced by the male are small, motile, and generated in enormous numbers. The union of gametes is known as syngamy or fertilization. During the fertilisation process a sperm penetrates an egg and donates its nucleus to the egg. Sexual reproduction is found in all the multicellular organisms. Let us now see how sex determination takes place in animals

Table 8.1: Advantages and Disadvantages of Asexual and Sexual reproduction.

ASEXUAL REPRODUCTION	SEXUAL REPRODUCTION
Advantages	Advantages
1. The asexually reproducing animals do not require to spend unnecessary time and energy in locating a mate, copulating and nurturing their offsprings. 2. Asexual reproduction is very beneficial for sessile organisms or organisms with low population densities. 3. One advantage of asexual reproduction is that a constant combination of genes matches a stable, unchanging environment in which the animal lives.	1. Increased diversity because of new combinations of genes due to fertilization enables sexually reproducing animal populations to adapt to new disease and changing environment conditions. If a sexually reproducing population is threatened with disease or drastically changing environment at least some members of the population will be able to resist, adapt and survive the disease or changing environment due to their genetically diverse gene pool.
Disadvantages	Disadvantages.
1. Asexual reproducing species tend to evolve very slowly, because all offspring produced by of any one of the individual are alike, providing less genetic diversity for evolutionary selection. 2. Since genetic diversity does not occur so even a single environmental event may destroy an entire species.	1. The essential requirement to locate a mate for reproduction is difficult to accomplish in sessile organisms or organisms with low population densities. 2. Time and energy is wasted in locating a mate, attracting it, copulating and nourishing the offsprings. 3. Exposure to predation during the mating may occur. 4. Exposure due to disease from the mate may occur

8.3 SEX DETERMINATION IN SEXUALLY REPRODUCING ANIMALS

The biological process that decides whether an individual in a species will be a male or a female is known as sex determination. In animals, the process of sex determination directs and controls all the activities involved in the differentiation of the genital system into male or female type and may be: i) genotypic, or ii) non-genotypic.

8.3.1 Genotypic or Chromosomal Sex Determination

In genotypic sex determination, the genes that will determine the sex of the animal are already present in the newly formed zygote after fertilization. At a certain period during development these genes will cause the release of sex hormones that will accordingly direct the development of the observable primary sexual features. Sex determination in this case depends upon the sex chromosomes inherited from the parents. You will recall that the genotype of cells of multicellular organisms consists of two types of chromosomes:

autosomes and **sex chromosomes** (in human, for example, there are twenty two pairs of autosomes and one pair of sex chromosomes the X and Y chromosomes). In mammals, most frogs, some fishes and dipterous insects there are two types of sex chromosomes, X and Y. The Y chromosome is the male determining sex chromosome. A zygote bearing XY pair of chromosomes gives rise to a male and it is called **heterozygote**. A zygote with XX pair of chromosomes develops into a female, and it is called **homozygote**. Since a mammalian male is **heterogametic**, containing XY chromosomes, therefore, half of spermatozoa bear X chromosomes and the other half Y chromosomes. A mammalian female is **homogametic** containing XX chromosomes, therefore ova contain only X chromosomes. The union of the spermatozoon bearing X chromosome with an egg gives rise to a female and union of the spermatozoon bearing Y chromosome with the egg will be a male.

In birds, the female is the heterogametic sex having WZ pair of chromosomes. The small chromosome, equaling to the Y in mammals, is designated in this case as W, and the X chromosome is designated as Z. Half of the eggs in birds carry W chromosome and the other half carry Z chromosome. All the sperms carry a Z chromosome. The homozygous (ZZ) condition produces males, and the heterozygous (ZW) produces females. This type of mechanism operates not only in birds, but in most reptiles, salamanders, some fishes and insects. XX-XY type of sex determination is called mammalian type of sex determination and ZZ-ZW type is called avian type of sex determination.

FORMATION AND DIFFERENTIATION OF VERTEBRATE GONADS

A critical element of successful sexual reproduction is the generation of sexually dimorphic adult reproductive organs, the testis and ovary, which produce functional gametes. The examination of different vertebrate species shows that the adult gonad is remarkably similar in its morphology across different phylogenetic classes. The male and female reproductive tracts originate from the same embryonic or foetal tissues. The vertebrate gonads

and internal and external genitalia begin as bipotential or indifferent tissues developing from

a pair of longitudinal thickenings of the coelomic epithelium and the underlying mesenchyme (unspecialized tissue) on either side of, the dorsal mesentery (a double layer of peritoneum that encloses the intestines and attaches them to the posterior abdominal wall). As the embryo develops further, these gonadal ridges of indifferent tissue become transformed into a structure that consists of a medulla (inner region) and cortex (outer region). If the gonad is to become a testis, only the medullary component differentiates. If the gonad is to become an ovary, only the cortex differentiates. Thus, in XX embryos the ovary will originate from the cortex and the medulla will decline. In the XY embryo the medulla will develop into the testes and the cortex regress. This is known as primary sex determination, after which, the production of hormones by the testis or ovary influences the differentiation of male and female secondary sex characteristics including the internal sex ducts, the external genitalia, and other sexually dimorphic features, such as pigmentation and body size.

PHYSIOLOGICAL ASPECT OF SEX DETERMINATION : EXAMPLE HUMANS.

Let us now study the physiological or hormonal processes in genotypic sex determination that occurs in vertebrates by with the help of human beings as an example. During the first two months of human gestation, the two sexes develop identically. The gonadal stage is the period during which indifferent gonads develop into either ovaries or testes. The phenotypic stage is induced in response to gonadal differentiation and causes the internal genital tract and external genitalia to develop into characteristic male or female structures.

As development proceeds in the human embryo which is genetically male (46, XY), a “male-determining gene” present on the Y chromosome called SRY (sex-determining region Y) organizes the developing gonad into a testis instead of an ovary (see Fig 8.6) It is now an established fact that the sex determination of the male is imposed on the foetus by the testicular hormones testosterone and Müllerian inhibiting substance (MIS) , respectively, which are responsible for the masculinisation of the mesonephral ducts, (Müllerian ducts), urogenital sinus and external genitalia as well as for regression of the Mullerian ducts. In the absence or inactivity of these hormones, the development of the foetus is kept at an indifferent stage; thus, it becomes phenotypically female. By the eighth week of gestation, Leydig cells of the testes begin to produce testosterone and the testes can influence sexual differentiation of the genital ducts and external genitalia. Formation of the external genitalia is completed by the 12th week.

In female embryos with a 46, XX sex chromosome complement, the primitive sex cords dissociate into irregular cell clusters. These clusters, which contain groups of primitive germ cells, occupy the medullary part of the ovary. Later, they disappear and are replaced by a vascular stroma that forms the ovarian medulla. These cords split into isolated cell clusters, each surrounds one or more primitive germ cells. Germ cells subsequently develop into oogonia, while the surrounding epithelial cells, descendants of the surface epithelium, form follicular cells. The various stages of sex determination are summarized in Figure 8.6.

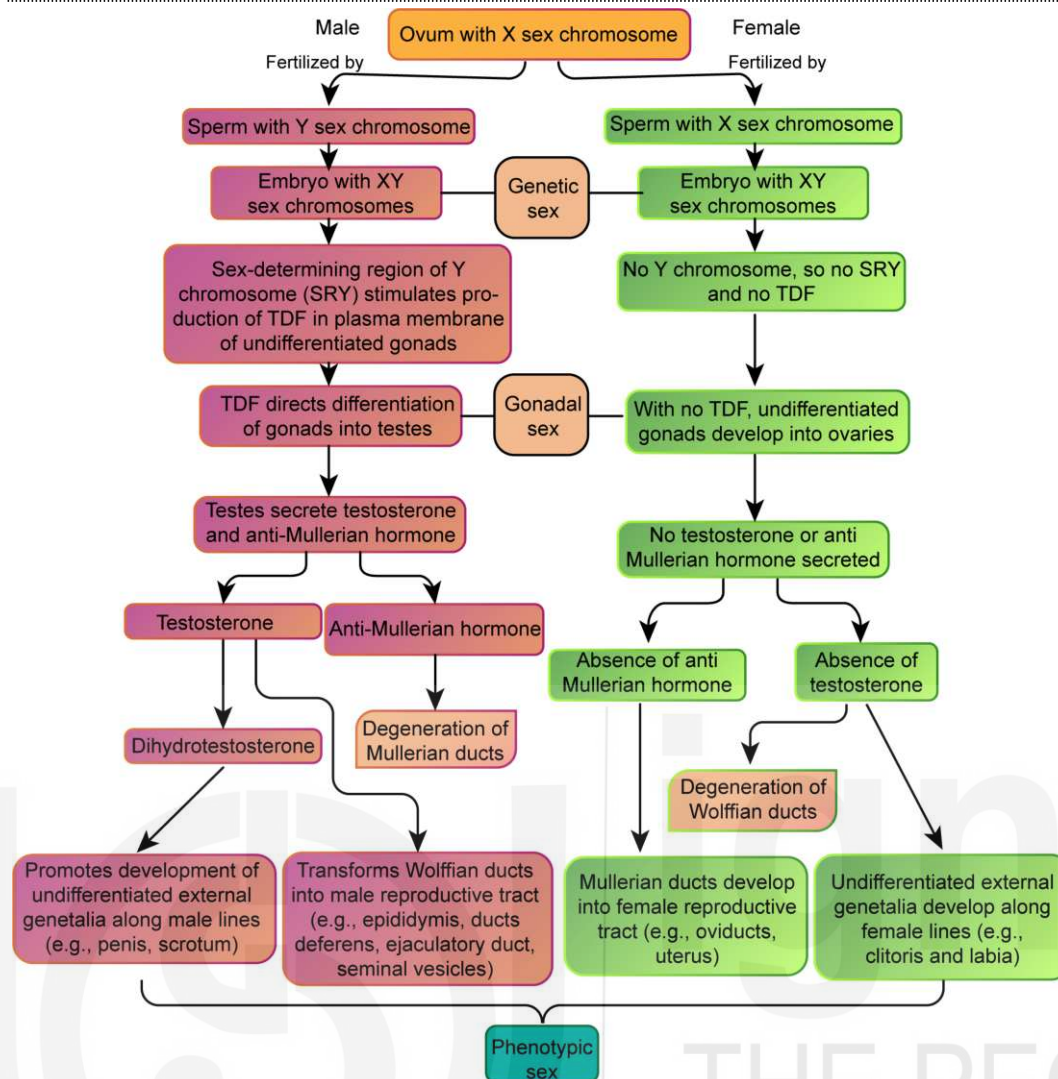


Fig 8.6: Steps in Sex determination and differentiation in humans in male and female.

8.3.2 Non-Genotypic Sex Determination

You have learnt that sex determination is strictly due to sex chromosomes in mammals, birds, amphibians, most reptiles, and probably most fishes. However, some fishes and reptiles lack sex chromosomes altogether and in these groups, gender is determined by nongenetic factors such as internal and external environmental factors, particularly temperature or behavior. In such cases, the release of the sex hormones during the development of the zygote of the animal is influenced by environmental factors. In non-genotypic type of sex determination, genetic control operates during the life cycle of the organism. In these animals, sex determination is not final and permanent, and sex reversal can occur at any time during their life span.

In a number of animal species in which the non-genotypic type of sex determination operates, temperature plays a major role in determining or reversing the sexual constitution of the individuals. Among vertebrates, in all crocodilians, certain turtles, some lizards, and many fishes, sex determination is temperature dependent. In these animals, a specific incubation temperature of the nest determines the sex of the offspring at a vulnerable period, probably indirectly activating and/or suppressing genes that direct development of the animals' sex organs. A variation of less than 2 degrees in

temperature can result in sex reversal. In alligator for example, eggs, incubated at low temperature all become females while those incubated at higher temperature all become males. Thus, sensory stimuli from the animal's social environment determine whether it will be male or female.

SAQ 2

What is the role of meiosis in creating genetic variability in the organism?

8.4 REPRODUCTIVE SYSTEMS IN SEXUALLY REPRODUCING ANIMALS

The basic components of reproductive systems of sexually reproducing animals as you will recall from studying Courses BZYCT-131 and BZYCT-133 are similar in invertebrates and vertebrates, although differences in reproductive habits and methods of fertilization have produced many variations. Sexual systems of animals consist of two main components: (1) primary organs, which are the gonads that produce sperm and eggs and sex hormones; and (2) accessory organs, which assist the gonads in formation and delivery of gametes, and may also serve to support the embryo. They are of great variety, and include gonoducts (sperm ducts and oviducts), accessory organs for transferring spermatozoa into the female, storage organs for spermatozoa or yolk, packaging systems for eggs, and nutritional organs such as yolk glands and placenta.

8.4.1 Invertebrates

In those sexually reproducing invertebrates in which fertilization is external the reproductive systems may consist only of centers that produce gametes by gametogenesis. These gametes are then released into the water for enabling fertilization. For example, polychaete annelids have no permanent reproductive organs and in them gametes are generated by the proliferation of cells lining the body cavity. When mature the gametes are released through coelomic or nephridial ducts or, in some species, may exit through ruptures in the body wall.

Internal fertilization is not always correlated with viviparity or the presence of Intromittent (copulatory) organs. In species with internal fertilization, females may or may not cooperate with males. In the first case, females expose the genital pore to males and facilitate intromission of the male's copulatory organ. In the second case, a male chases a female while trying to insert the copulatory organ into the female's genital pore.

Most invertebrates from flatworms to insects that utilize internal fertilization to transfer sperm from male to female have structures that facilitate such transfer in the invertebrates.

In the males (Fig.8.7) sperms are produced in the testes and transported via a sperm duct to a storage area called the seminal vesicle. Prior to mating, some invertebrates (e.g., cephalopods, scorpions, leeches, and some insects)

incorporate a large number of sperms into packets termed spermatophores. Spermatophores provide a protective casing for sperm and facilitate the transfer of large numbers of sperm with minimal loss. Some spermatophores are even motile and act as independent sperm carriers. Sperm or the spermatophores are then passed into an ejaculatory duct to a copulatory organ (e.g., penis, cirrus, and gonopore). The copulatory organ is used as an intromittent structure to introduce sperm into the female's system. Various accessory glands (e.g., seminal vesicle) may be present in males that produce seminal fluid or spermatophores.

In the female, ova (eggs) are produced in a pair ovaries formed from a series of egg tubes (ovarioles). (Fig.8.8), Mature ova pass through oviducts to a common genital chamber and then to a short copulatory bursa (vagina). In most insects, the male transfers sperms by inserting the penis directly into the female's genital bursa (vagina). These sperms migrate, and become stored in a seminal receptacle. Often a single mating provides sufficient sperms to last the reproductive life of a female. Fertilization occurs when sperms from the seminal receptacle move up the oviduct and encounter the ova which they fertilize them. Accessory glands (e.g., those that produce egg capsules or shells) may also be present in females.

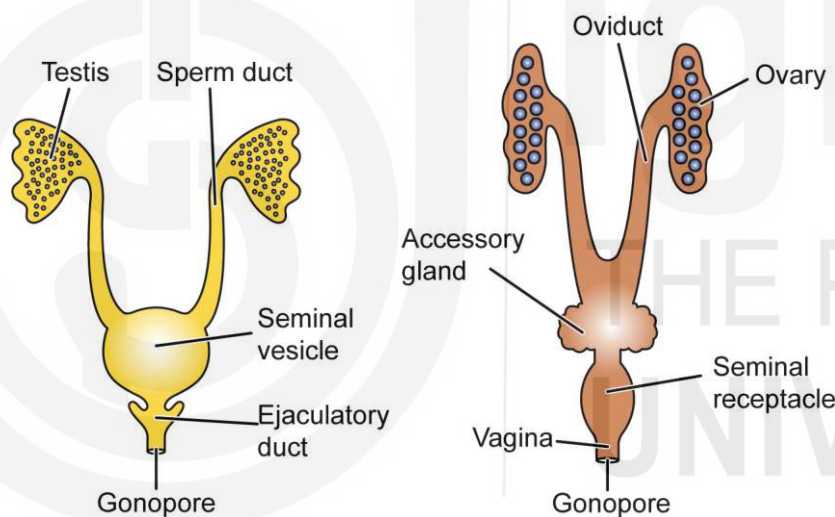


Fig 8.7 and 8.8: Diagrammatic representation of reproductive system of sexually reproducing invertebrate animals in which fertilization is internal:8.7) Male reproductive system in which sperms from the paired testes of males pass through sperm tubes (vas deferens) to an ejaculatory duct present in the penis; and 8.8: Female reproductive system in which, eggs from the ovaries pass through oviducts to the genital bursa. At mating the sperms enclosed in a membranous sac (spermatophore) formed by the secretions of the accessory gland are deposited in the genital bursa of the female. These spermatophores then migrate to the seminal receptacle of the female where they are stored. The female controls the release of a few sperm to fertilize her eggs at the moment they are laid, using the needlelike ovipositor to deposit the eggs in the soil. (why not make them one figure with a and b??)

8.4.2 Reproductive Systems of Vertebrates

You have already studied the morphology of the reproductive systems of various vertebrate groups in the previous courses BZYCT-131 (Animal Diversity) and BZYCT-133(Comparative Anatomy and Developmental Biology of Vertebrates) and know that in some aquatic and all the terrestrial

vertebrates in which fertilization is internal or external there are separate and distinct male and female individuals. The primary male gonads or testes, produce only sperm cells by means of **spermatogenesis** and the primary female gonads-the ovaries produce ovum by the process of **oogenesis**. Furthermore, various accessory reproductive structures in addition to the gonads are present in the sexually reproducing vertebrates. The accessory reproductive organs as you will recall consist of ducts and glands specialized for storage and for conveyance of the gametes and later for conveyance of fertilized eggs or young ones to be born. The functional status of these organs is conditioned by the respective gonadal hormones.

I have removed this entire section as it has been dealt with in animal diversity and functional anatomy both using similar diagrams of male and female systems both these courses are compulsory so only ref can be given no need to keep repeating the diagrams and information here as well.

8.5 MAMMALIAN MALE REPRODUCTIVE PHYSIOLOGY : HUMANS

In several mammalian males, including humans, the male gonads called testes or **testicles** are paired and are located behind the penis in an integumentary pouch called the scrotal sac or scrotum which is **located** outside the pelvic region of the body. The location of the testes outside the body is an adaptation for allowing them to stay cooler than the body temperature. However; in non-mammalian vertebrates the testes are present inside the body cavity. The two main function of testes in all vertebrate species is : i) proliferation of spermatozoa, and ii) synthesis and secretion of hormones.

8.5.1 Structure of Testes

In the previous course BZYCT-133 you have already studied that each testis in human (mammalian) is divided into compartments by connective-tissue septa, or walls (Fig.8.9 a). The seminiferous tubules are grouped into lobules in each compartment. The arrangement permits the packing of an extensive amount of germinal epithelium into a small space. Each compartment as you will recall consists of a series of elongated tightly coiled follicles called seminiferous tubules (Fig.8.9 a). The seminiferous tubules are lined internally by a germinal layer from which the spermatozoa proliferate. The interspaces between the seminiferous tubules are occupied by connective tissues, blood vessels and interstitial cells of Leydig. Each seminiferous tubule is limited by a thin basement membrane. If we study the cross-section of a seminiferous tubule in an adult mammalian testis then we will observe sperms at different levels of development (Fig.8.9 b). The early stages of the developing sperms are, located just inside the basement membrane, and the progressively, maturing stages of the sperms (from spermatogonia to spermatozoa (sperms), from the basement membrane towards the lumen of the seminiferous tubules are also observable. The lumen, or tubule cavity, contains the tails of many sperm (the heads of which are embedded in Sertoli cells), free sperm, and fluid that is probably resorbed. The mature sperms are released into the

lumen. You should bear in mind that in the mammalian testes including humans in any single zone along a seminiferous tubule, all sperms are at the same stage of maturation; adjacent zones contain different generations of sperm, and a period of sperm formation and discharge is followed by an interval of inactivity.

In immature males and in adult males between breeding seasons, the seminiferous tubules are inconspicuous and the epithelium is inactive; in some species, however, spermatogenesis, or production of sperm, proceeds at a variable pace throughout the year.

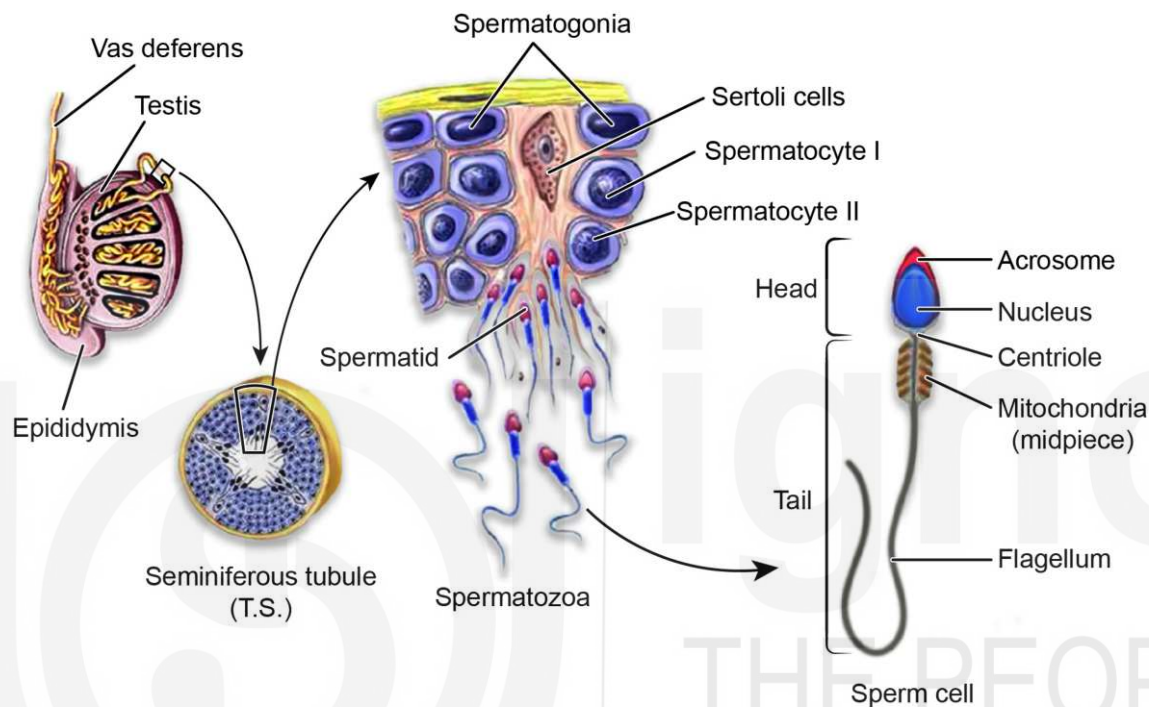


Fig. 8.9: Section of mammalian testis showing a) cross section of a seminiferous tubule; b) sperms at various stages of development in the seminiferous tubule; c) a mature mammalian sperm

The seminiferous tubules of the testes also contain somatic cells called Sertoli's cells, which are a type of sustentacular cell. Sustentacular cells are those which are primarily associated with structural support and are also present in other tissues of the body.

The Sertoli cell plays an essential role in embryonic determination of male somatic sex and in spermatogenesis during adult life. The first appearance of foetal Sertoli cells in the primitive gonad defines the initial stage in the development of the embryonic testis. The testes cells as you will recall from earlier express the *sry* gene, that determines the male sex of the gonad. The foetal Sertoli cells are the only source for secretion of anti-Müllerian hormone that are responsible for inhibiting the development of internal female genitalia. These testes cells and the foetal Sertoli cells together with another type of somatic testicular cell, the peritubular cell, are essential for the formation of the testis cords which are the prospective seminiferous tubules. The immature Sertoli cell differs extensively from the mature cell with respect to both morphology and biochemical activity. During testes development the Sertoli cell supplies a clone of developing germ cells with nutrients and growth

factors. Sertoli cells continue to proliferate and differentiate until the beginning of puberty, when they stop dividing and start nursing the germ cells. At this point of development, the future capacity of the testis for sperm production gets determined. As puberty approaches, the Sertoli cells become elongated and tight junctions are established between them. Sertoli cells then begin to produce seminiferous fluid, which results in the transformation of the testis cords into seminiferous tubules, possessing a lumen. (have deleted the table as what is the point of it in this course)

In the seminiferous tubules of sexually mature males the fully differentiated Sertoli cells appear large in size and irregularly columnar in shape and lie within the seminiferous epithelium. Their bases lie against the basement membrane of each tubule, and their tips point toward the cavity. They extend from the basement membrane towards the lumen of the tubule and provide the supporting framework in which the germ cells are embedded. Sertoli cells provide nourishment to the sperms. Additional functions of Sertoli cells are the secretion of testicular fluid into the lumen of the seminiferous tubules and the phagocytosis (engulfing) of the remains of degenerated germ cells. Tight junctions between the basal portions of adjacent Sertoli cells are present and function as a blood–testis barrier. This blood–testis barrier (Fig. 8.10) however, thus does not separate the blood from testicular tissue, but rather constitutes a delicate boundary between diploid and haploid germ cells. This barrier protects the developing haploid spermatozoa which contain sperm specific antigens from attack by the male body's immune system. This is because the specific antigens present on the sperms are not found in the rest of the somatic cells and the body's immune system would destroy them regarding them as foreign.

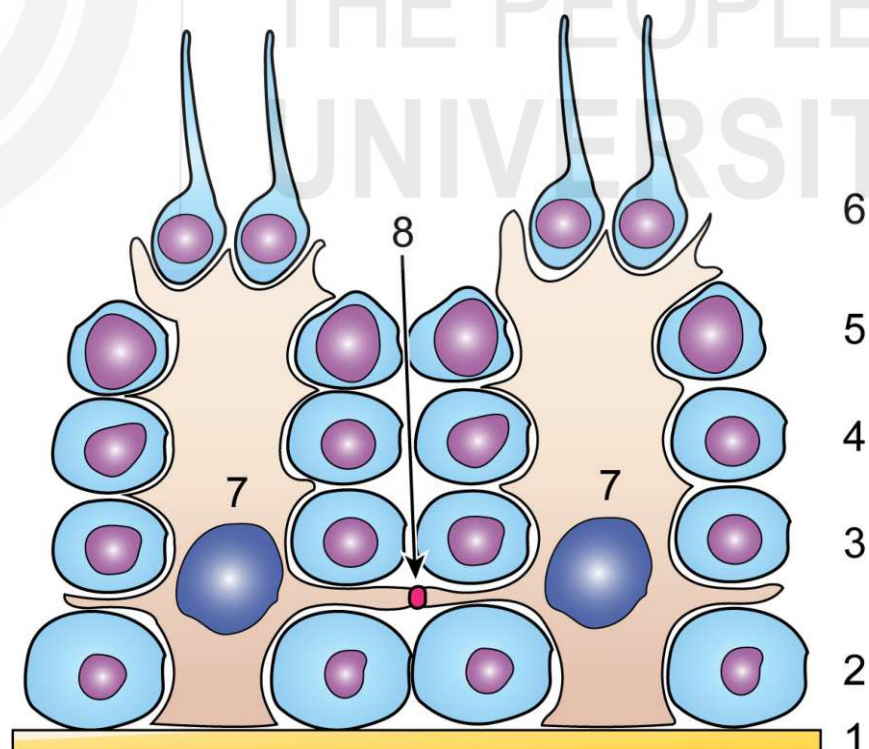


Fig 8.10: Germinal epithelium of the testicle. 1 basal lamina, 2 spermatogonia, 3 spermatocyte 1st order, 4 spermatocyte 2nd order, 5 spermatid, 6 mature spermatid, 7 Sertoli cell, 8 occlusive junctions forming blood testes barrier.

In addition the blood–testis barrier prevents the leakage of certain molecules between Sertoli cells and allows these cells to control the chemical composition of testicular fluid within the seminiferous tubules, resulting in a unique microenvironment in the tubules. Sertoli cells secrete various proteins, including androgen-binding protein, as well as hormones such as inhibin and anti-Müllerian hormone. Sertoli cells also produce enzymes that convert testosterone into estrogen and to 5 α -dihydrotestosterone (DHT). The development of male gametes is closely dependent on Sertoli cells and the rate of production of a man's sperm is related to the number of Sertoli cells present in his testes. Sertoli cell number is determined at puberty; no new Sertoli cells are produced in adult men. In some species, including male humans the sperm heads remain embedded in the Sertoli cells for relatively long periods. The release of spermatozoa from the Sertoli cells as you will recall from earlier units is termed as **spermiation**, a process that is analogous to **ovulation** in the female.

Leydig cells, also known as **interstitial cells of Leydig**, are found adjacent to the seminiferous tubules in the testicle. The mammalian Leydig cells are polyhedral in shape, and have a large prominent nucleus, an eosinophilic cytoplasm and numerous lipid-filled vesicles. Leydig cells are responsible for biosynthesis and release of a class of hormones called androgens (19-carbon steroids). They secrete testosterone, androstenedione and dehydroepiandrosterone (DHEA), when stimulated by the luteinizing hormone (LH) which is released from the anterior pituitary. Consequently Leydig cells, regulate the secondary sex characteristics of males which include testicular descent, development of prostate, scrotum and penis, and differentiation of the Wolffian duct, which leads to the formation of epididymis, vasa deferentia and seminal vesicles. Foetal Leydig cells are found in the interstitium of the testis shortly after sex determination, from the 8th to the 20th week of gestation. These foetal Leydig cells produce enough testosterone for masculinisation of a male foetus and are replaced by adult Leydig cells a few days after birth. After the quiescent phase between birth and puberty another adult LC population appears and persists until old age. Their testosterone production is the key hormonal stimulus of the male phenotype. Foetal and adult Leydig cells show different gene expression profiles.

SAQ 3

Name the following and write one main function of each.

- a) Male gonad
- b) Female gonad

8.5.2 Hormones of Human Testis

In the above subsection you have studied about testis and sperm production by the testis. We shall now learn about the hormones synthesized by the testis. Our focus in this section will be on the hormones synthesized by the

testis in human male which will be considered as the representative example of a mammalian amniotic vertebrate.

Recall from the earlier part of the section that Leydig cells and the Sertoli cells are steroid hormone synthesizing cellular sites in the testis. Leydig cells are the major source of **testosterone** and **androstenedione**, the main circulating androgens of testicular origin (Fig 8.11). Recall from the previous unit 7 that all steroid hormones are derived from cholesterol. The basic structure of all the steroid hormones is the steroid ring. The mechanism of action of androgens, which are testosterone and androstenedione, is similar to that of the other steroid hormones.

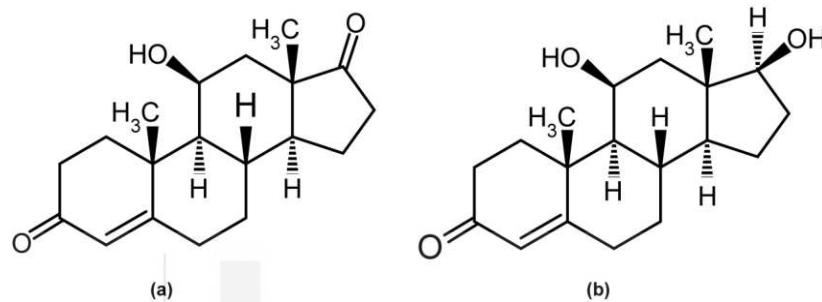


Fig.8.11: a) Androstenedione; and b) Testosterone.

Recall that androgens are essential for the development of **secondary sex characters** of the male and for the functional competence of the accessory reproductive glands and the ducts. The more pronounced metabolic action of these steroids is the promotion of protein anabolism. Androgens decrease the urinary loss of nitrogen without increasing non-protein nitrogen of the blood, and produce at least a temporary increase in body weight. Since androgens increase protein matrix of bone, they have been used in the clinical treatment of certain skeletal defects. They also promote muscle growth.

In human males, androgens are involved in the control of hair patterns, voice changes, skeletal configurations, and regulation of the sebaceous-gland activity. Androgens also exert effects upon the germinal epithelium of the testis tubules and thus influence sperm production. Testosterone, which is synthesized in the Leydig cell, diffuses into the tubule, where it is the principal stimulus for germ cell differentiation.

The accessory system of male ducts and glands are morphologically and physiologically dependent upon the production of androgens. In the experimental adult animals deprived of androgens these organs involute until they approximate the same structure as juvenile animals. Administration of androgens completely restores all of these organs to the normal conditions.

Androstenedione is an intermediate in the biosynthesis of testosterone and has a weak functional activity of androgen.

8.5.3 Hormonal Regulation of Testis

Testicular activity is under the control of the gonadotropins, luteinizing hormone (LH) and follicle-stimulating hormone (FSH), which are synthesized in the anterior pituitary gland (Fig. 8.12). LH and FSH are released into the circulation and activate their receptors expressed on Leydig cells and Sertoli

cells, respectively. FSH is required for the differentiation of spermatogonium into spermatozoa, and LH (luteinizing hormone, also known as **interstitial cells stimulating hormone -ICSH** in males) to stimulate the Leydig cells for the production of androgens. The increased levels of androgens in the blood suppress the synthesis and secretion of gonadotropins in the pituitary. Testicular tissue involutes (decreases in size) in experimental animals deprived of pituitary hormones. Sertoli cells, apart from providing nourishment to the developing sperm, secrete certain substances that help in regulatory process. They secrete inhibin a glycoprotein hormone that depresses the production of FSH (follicle stimulating hormone) and GnRH (gonadotropin releasing hormone). In this way these cells also provide negative feedback control of spermatogenesis.

Androgen binding protein is secreted by these cells in the lumen so that concentration of androgens is elevated in the seminiferous tubule thus, aiding the stimulation of spermatogenesis.

You have studied earlier that the time required for the spermatogonia to differentiate into spermatozoa is a biologic constant, varying with the species and strain, which cannot be altered by hormones and other factors. On the other hand, the number of spermatozoa produced is dependent upon pituitary gonadotropins, androgens, nutritional factors, temperature, light, etc.

Pituitary hormone effects:

LH and FSH stimulate spermatogenesis and testosterone by the testes.

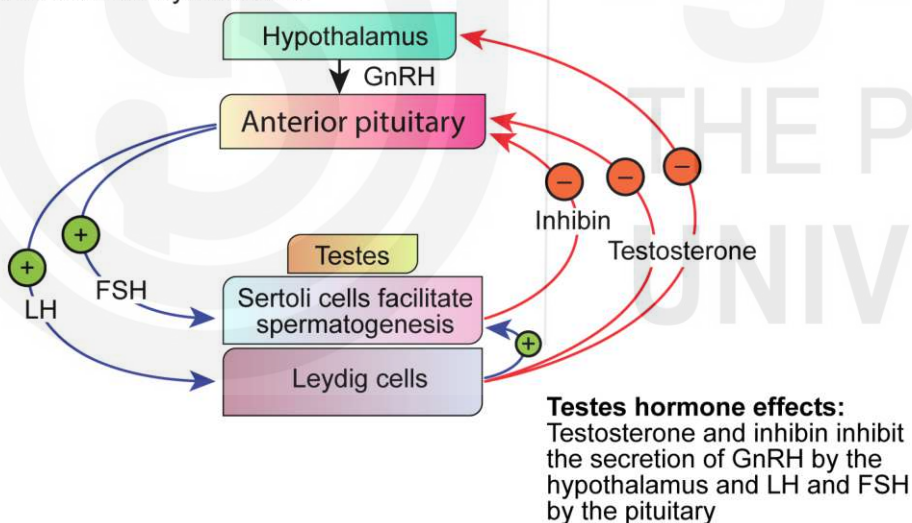


Fig. 8.12: Hormones control sperm production by negative feedback (the diagram is from <https://opentextbc.ca/biology/chapter/24-4-hormonal-control-of-human-reproduction/> get it redrawn)

SAQ 4

Write the function of following in male reproductive system.

- Seminiferous tubules
- Leydig cells
- Epididymis
- Androgen

8.6 MAMMALIAN FEMALE REPRODUCTIVE PHYSIOLOGY: HUMAN

The mammalian ovary is not only the female gonad, containing the supply of germ cells to produce the next generation, but also the female reproductive gland, controlling many aspects of female development and physiology by secreting the female hormones. Ovaries in mammals are flattened structures lying on each side in the pelvic cavity. These are attached to the peritoneum by mesovaria and ovarian ligaments. Mesovarium is a part of broad ligament, a thickened fold of mesentry that supports and stabilizes ovaries at their position. The free surface of the organ is covered by a single layer of **germinal epithelium**. The ovary is roughly divisible into two structural components: **cortex** and **medulla**. In the mature ovary the cortex contains **follicles** and **corpora lutea** in their different stages of differentiation and degradation, whereas, medulla contains large blood vessels. Apart from these structures ovary contains **interstitial cells** which fill all the space not occupied by follicles, corpora lutea and blood vessels (Fig 8.13).

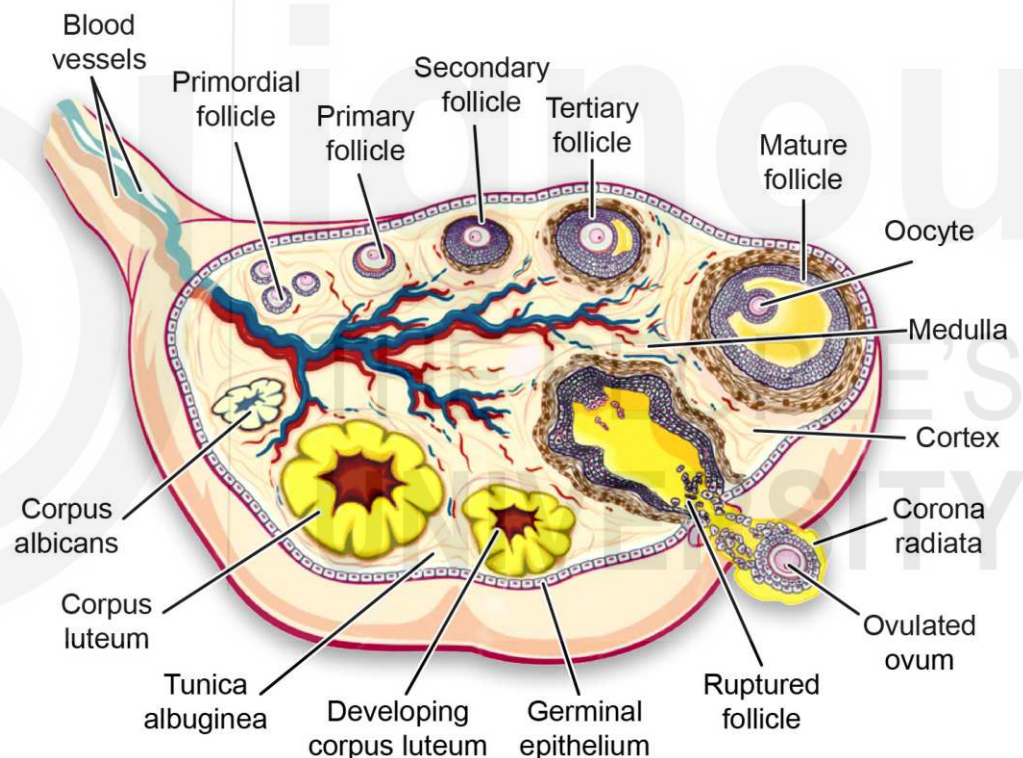


Fig.8.13: Diagrammatic representation of mammalian ovary showing the development of an ovum and the development of corpus luteum. The interstitial cell mass is not prominent in primates! am also enclosing another fig of the ovary in a separate doc so change them and see which ever will not produce copyright issues the enlargement of follicular cells can be deleted

Ovarian follicles are the gamete containing structures, surrounded by layers of follicular cells and derived from the cells of germinal epithelium. A follicle undergoes stages of differentiation to become a mature follicle known as antral follicle or the **Graafian follicle** (see Fig.8.13). After expulsion of the egg at ovulation, a follicle differentiates into a **corpus luteum**, a temporary endocrine structure in the ovary. The ovary also contains some follicles which due to unavailability of hormones fail to develop into a Graafian follicle and

undergo degeneration. The degenerating follicles are known as the **atretic follicles**. In an ovary one can find atretic follicles and corpora lutea in different stages of retrogression.

If you compare Fig. 8.13 with Fig. 8.14 you can see that the mammalian ovary contains follicles in different stages of development, i.e. there may be primary follicles, secondary follicles, tertiary i.e., preantral follicles and mature i.e., Graafian follicle. Whereas the ovary of non-mammalian vertebrates contains follicles mostly in the same stages of differentiation, present in groups enclosed by a membrane. Such a group of follicles is called a **cyst**. In non-mammalian vertebrates ovarian follicles grow synchronously therefore one can find follicles of the same stage of development. The other major difference between the mammalian ovary and the non-mammalian ovary is the presence of yolk. The mammalian follicles contain negligible quantities of yolk, whereas the follicles of the non-mammalian vertebrates are laden with yolk (Fig. 8.14).

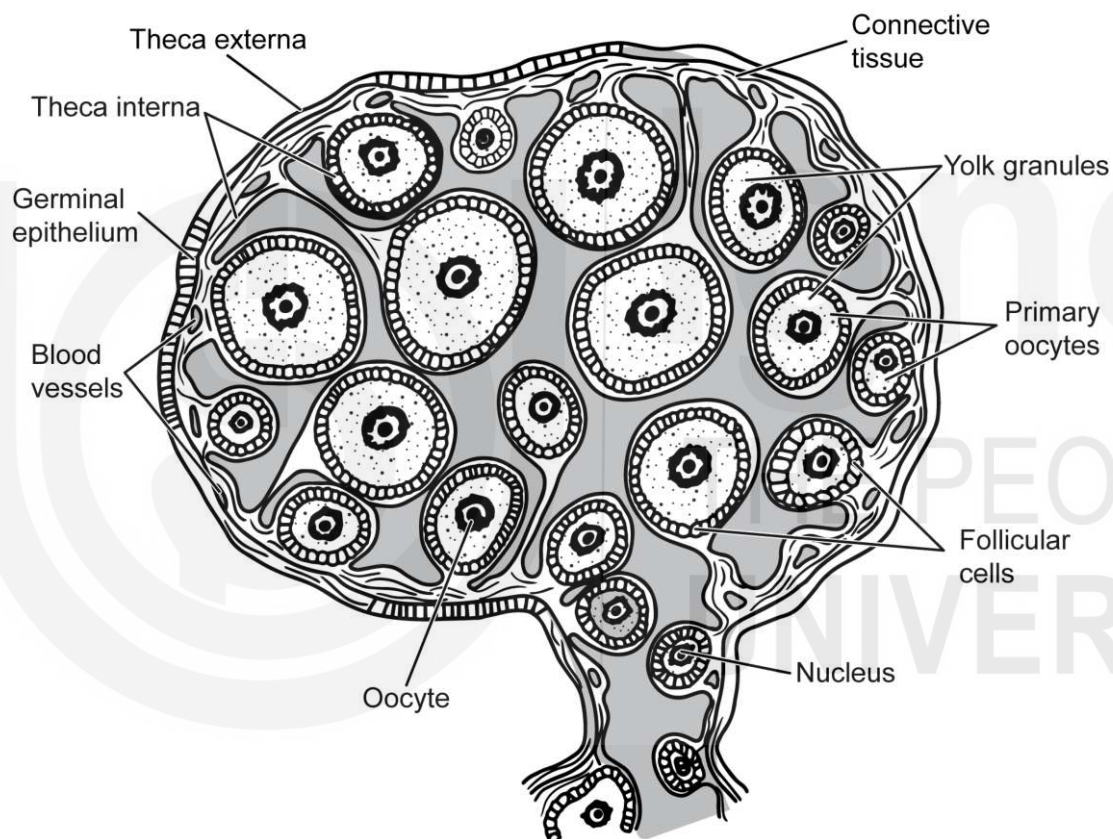


Fig.8.14: T.S. ovary of frog in a diagrammatic representation All other good photos were for a price and will create copyright issues

The ovary of vertebrates performs the following functions:

- i) production of eggs,
- ii) synthesis and secretion of hormones needed for the chemical coordination of reproduction,
- iii) elaboration of nutrient material (yolk) for the early stages of embryonic development, and
- iv) maintenance of pregnancy; via secretion of hormones during development of the young in viviparous animals.

8.6.1 Oogenesis

You already know that the production of egg cell or female gametes is a process known as oogenesis. The stem cells or the primordial germ cells for the female gametes are diploid and known as **oogonia** (singular oogonium) which undergo a period of vigorous multiplication while the female is still in the embryonic stage and differentiate into cells called oocytes (these are still diploid). Because this process occurs during embryonic development, this means that a female mammal is born with every single egg she will be able to produce during her lifetime already present in an immature form in her ovaries. This situation is very different from males, whose spermatogonia do not begin producing spermatocytes (the male cells equivalent to oocytes) until puberty. The first meiotic division of oocytes begins in the female just prior to her birth or just after birth depending on the species and is arrested at late prophase I stage. At this stage the oocyte is known as **primary oocyte** (see Figs. 8.13 & 8.14). In human ovary the primary oocytes are held in late prophase I stage at the time of birth till the time of ovulation at the onset of puberty. At this time under the influence of gonadotropic hormones from the hypothalamus that cause the pituitary to release FSH and LH, groups of primary oocytes resume their meiotic activity and divide to form a large cell containing most of the cytoplasm which becomes the **secondary oocyte** and a small cell with very little cytoplasm and the nucleus. This small cell is known as the **first polar body**. The haploid secondary oocyte begins the second meiotic division but remains arrested in metaphase-II stage until it is penetrated by a sperm during fertilization. Thus oogenesis produces only one ovum, because cytoplasm of primary oocyte gets unevenly distributed resulting in one secondary oocyte and three polar bodies. Secondary oocyte does not extrude a second polar body until the oocyte has been penetrated by a sperm. The germ cell becomes a mature ovum after second polar body is released (Fig. 8.15).

As you can see in Fig 8.13 the primary oocyte is surrounded by a single layer of supporting cells known as follicular cells. A homogenous membrane, **zona pellucida** appears between the primary oocyte and the follicular cells. The primary oocyte is now called the **primary follicle**. The number of follicle cells increases rapidly forming layers. They are later differentiated into **theca** and **granulosa**. At this stage of the thickened follicular wall the oocyte is called **secondary follicle**. Under the influence of pituitary gonadotropins fluid-filled spaces called **antrum** appear in the granulosa and the follicle that has grown in size becomes a **Graafian follicle** containing a mature ovum.

At any given time during the reproductive life, a small group of follicles is maturing. However, after progressing to a certain stage, most oocytes and their follicles die. To survive, the follicle must be exposed to gonadotropic hormones at the right time. Thus, for the oocyte to mature, the follicle needs to be at a certain stage of development when exposed to the rise in gonadotropins and the resulting secretion of ovarian hormones. In the following sub-section let us learn about hormones synthesized by ovary their functions and regulation.

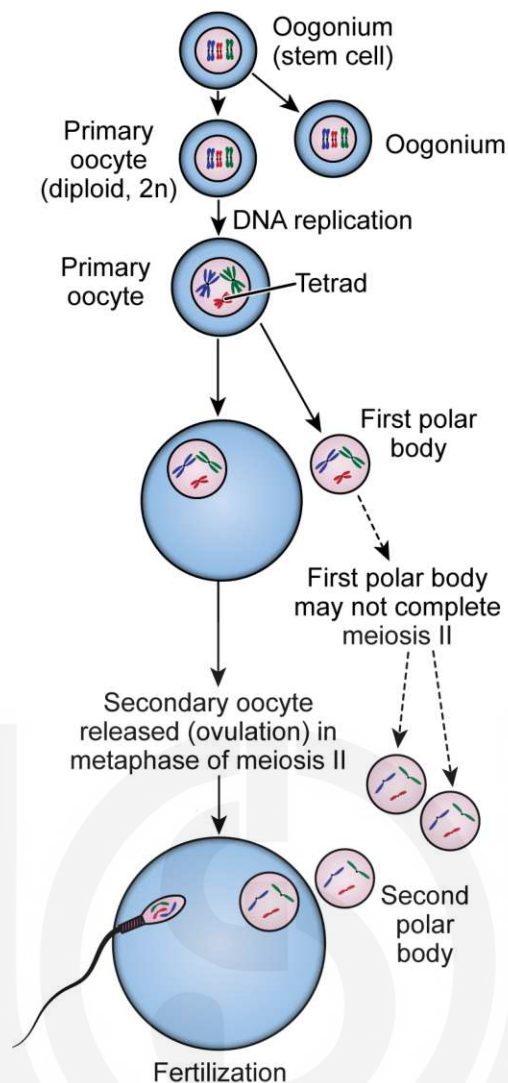


Fig.8.15: Steps of cellular division during oogenesis. get this redrawn

Mitosis of oogonium

Unlike spermatogonia, the oogonia of female reproductive stem cells, complete their mitotic division before birth

Meiosis I

Between the third and seventh months of fetal development, the daughter cells, or primary oocytes, prepare to undergo meiosis. They proceed as far as the prophase of meiosis I, but then the process comes to a halt.

The primary oocytes remain in a state of suspended development until puberty, when rising levels of FSH trigger the start of the ovarian cycle. Each month after the ovarian cycle begins, some of the primary oocytes are stimulated to undergo further development. Meiosis I is then completed, yielding a first polar body and a secondary oocyte.

Meiosis II

Each month after the ovarian cycle begins, usually one secondary oocyte leaves the ovary suspended in metaphase of meiosis II.

At the time of fertilization, a second polar body forms and the fertilized secondary oocyte is then called a mature ovum. (A cell in any of the preceding steps in oogenesis is sometimes called an immature ovum).

8.6.2 Female Hormones

Apart from production of mature eggs, the other major function of the ovary is elaboration of hormones that regulate the reproductive tract and secondary sexual characters, control the mating reaction and affect other metabolic processes.

The ovary secretes steroid hormones such as **estrogens**, **progestogens**, **androgens** and a polypeptide hormone called **relaxin**. The mature follicle is an important source of estrogen. Estrogen is synthesized from the androgens secreted by the theca interna cells that are converted to estrogens in the granulosa cells. The corpus luteum elaborates estrogenic and progestational steroids as well as relaxin.

Now let us learn about the structure and function of these hormones.

The Estrogens

- The predominant natural estrogens of the human female are 17 β -estradiol, estrone and estriol (Fig.8.16). All have similar effects on their target tissue. Estradiol is the most abundant and has the most

pronounced effect on the target tissue. Estrogens contain eighteen carbon atoms (C-18) as seen in Figure.8.11. As you now know all steroid hormones are derived from cholesterol and have steroid ring structure. Estradiol is synthesized from androstenedione which is first converted to testosterone which in turn is converted to estradiol by the action of the enzyme aromatase.

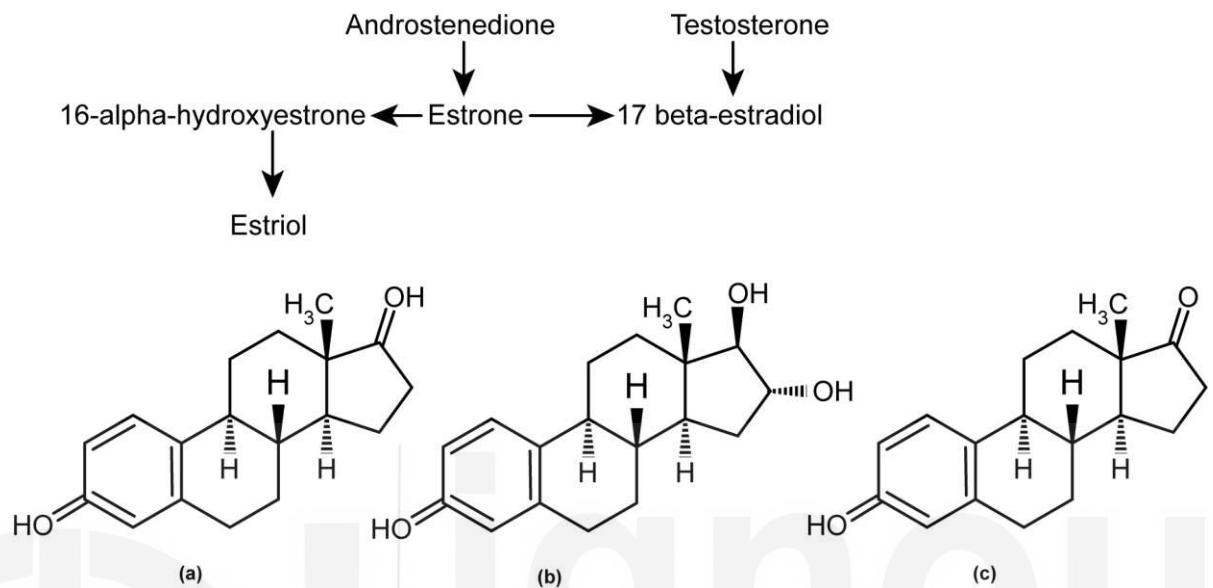


Fig.8.16: a) Estradiol, b) estrone and c) estriol.

The estrogens act directly or in cooperation with other hormones to produce a great variety of effects on specific target organs and on the chemistry of the body as a whole. We shall now discuss some of the actions of estrogens.

- The most general effect of the estrogens is to promote tissue growth which is more pronounced in the accessory sex tissues. Estrogens stimulate cell division in the deeper parts of the skin and cause a more rapid replacement of the outer cornified layers of skin. There is evidence that high levels of estrogens (under pathological conditions) may be potentially dangerous as they may encourage the formation of cancer in certain individuals.
- Estrogens are required for the maintenance of vaginal lining and uterine growth. Administration of estrogens to the estrogen-deprived animals causes rapid growth of the vaginal and the uterine tissue.
- Estrogens are essential for the anatomic preparation of the mammary glands for milk secretion. In some species it affects mammary development in combination with progesterone. But in some species, estrogens alone or progesterone alone produce the effect.
- In mammals **sexual receptivity** or **heat** coincides with a period during which the ovaries are secreting large amounts of estrogens. Full mating behavior generally depends upon both estrogen and progesterone.

You know from Unit 7 that steroid hormones enter the cells and become associated with cytoplasmic receptor protein. The hormone-receptor complex enters the nucleus and initiates transcription and RNA synthesis. Estrogens being steroid hormones, stimulate synthesis of mRNA, proteins and DNA.

The Progestogens

The progestogens are C-21 steroids having the basic structure of the **pregnane** nucleus and include pregnenolone, progesterone and 17-hydroxyprogesterone (Fig.8.17). Pregnenolone is of primary importance in the ovary because of its key position as a precursor of all steroid hormones. Progesterone is the principal secretory product of corpus luteum. It is responsible for cell differentiation and induction of secretory activity in the endometrium of the estrogen-primed uterus. Progesterone is essential for implantation of the fertilized ovum and maintenance of pregnancy.

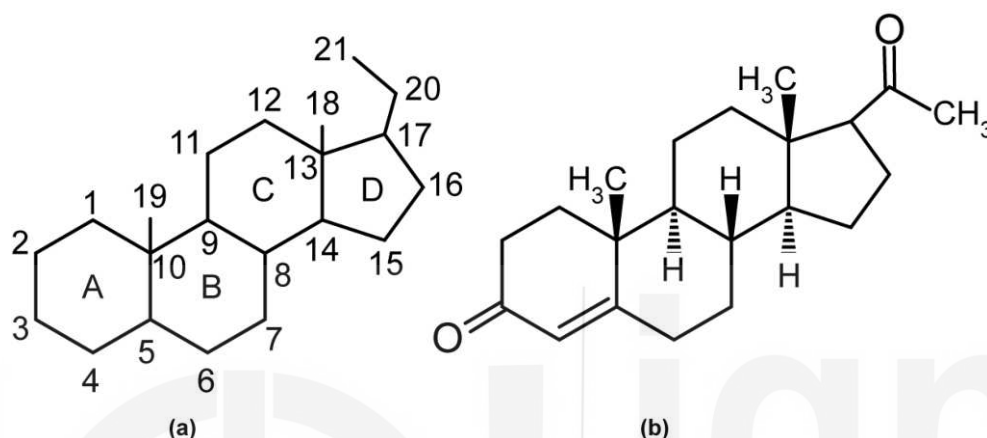


Fig.8.17: a) Prenane nucleus; b) Naturally occurring progesterone.(get progesterone redrawn)

The cellular sites of its synthesis are the granulosa lutein cells of the corpus luteum. Placenta also secretes progesterone. Progestogens have varied actions upon female reproductive organs under normal physiological conditions. They often act synergistically with estrogens though they are capable of inhibiting the actions of each other.

Ovarian Androgens

As you have studied in previous section, androgens are masculinising compounds that are produced chiefly by the testis under normal conditions. They also arise from the adrenal cortex, thecal cells of ovaries and placenta. These are C-19 compounds, derived from the basic structure **androstane** (Fig.8.18). Since testosterone is an intermediate in the biosynthesis of estrogens, this hormone is produced by the ovaries. The ovarian androgens exhibit the same biological activity as that of testicular androgens.

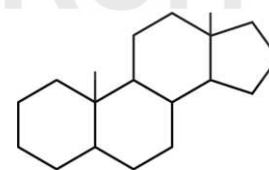


Fig.8.18: Androstane.

Pathological ovaries may release tremendous amount of androgens, but the amount of androgens secreted by the normal ovaries is not significant.

Relaxin

This is a water soluble peptide hormone present in the ovaries, placentae and uteri of various mammalian species during pregnancy. In women, relaxin is secreted into the circulation by the corpus luteum in the ovary. During pregnancy it is also released from the placenta. Relaxin helps in the enlargement of birth canal by softening and widening of uterine cervix and relaxation of pelvic ligaments.

8.6.3 Hormonal Regulation of Ovary

The ovary is most profoundly regulated by the pituitary gonadotropins, namely **follicle stimulating hormone (FSH)** and **luteinising hormone (LH)**. The growth and development of ovarian follicles of mammals depend upon FSH, but LH is required for final maturation. LH acts upon FSH-primed follicles and stimulates estrogen secretion. Corpora lutea secrete progesterone. Its maintenance and secretion is under the influence of **prolactin**, a hormone of the pituitary also known as **luteotropic hormone**.

Prolactin is not a luteotropic hormone in the majority of mammals. In some species of mammals it causes regression of testes and ovaries.

Large amounts of estrogens, given to animals, inhibit the gonads by altering the release of pituitary gonadotropins. There is a **negative feedback** mechanism regulating the ovarian activity. The increased levels of gonadotropins stimulate the synthesis of estrogens by the ovary and the increased levels of estrogens in the blood suppress the gonadotropin secretion, which in turn inhibit the estrogen synthesis and the related activities. Figure 8.19 explains the regulation of human ovarian activity.

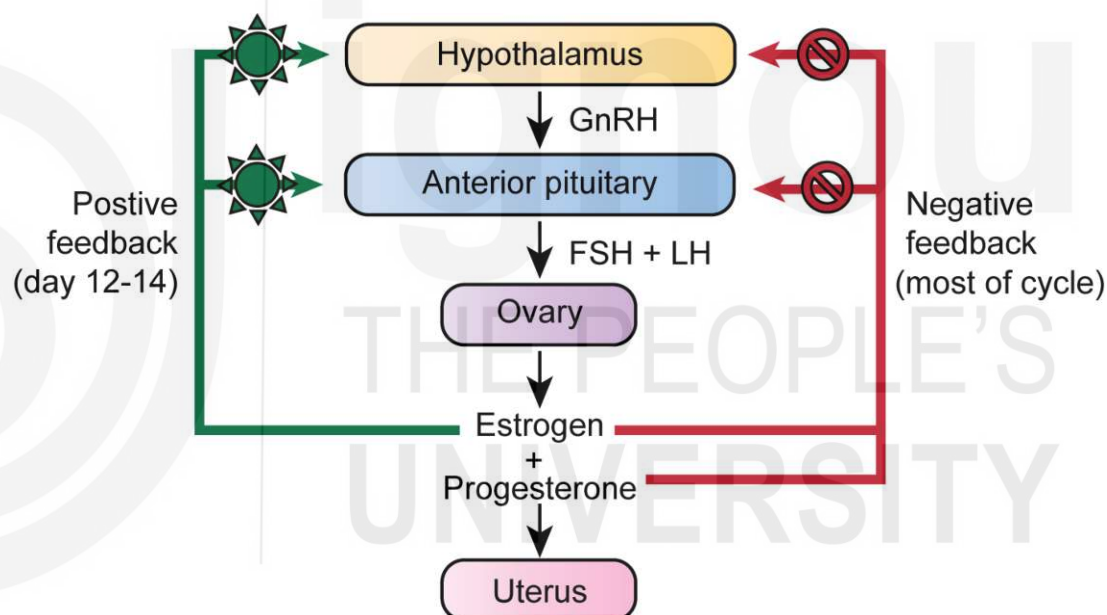


Fig.8.19: Hormonal regulation of human ovary.

SAQ 5

Write the term used for the following.

- Female reproductive stem cell.
- Mature follicle containing fluid filled spaces.
- A polypeptide hormone synthesized by ovary.
- C-21 steroid hormones having basic structure of pregnane nucleus.
- Luteotropic hormone of pituitary.
- The process of yolk synthesis.

8.7 REPRODUCTIVE CYCLES

In the earlier sections you have learnt about structure and function of the reproductive organs. In this section we shall learn about the reproductive cycles in vertebrates and mammals in particular. You must remember that gamete production is not a continuous phenomenon. It is recurring and cyclical. In most of the animals maturation of the gametes takes place during the seasons which are most favorable for the development and growth of the young.

Animals are categorized as biannual breeders, annual breeders, biennial breeders etc., based on the frequency of gamete maturation followed by breeding activity. Most of the non-mammalian vertebrates exhibit annual reproductive cycle. The gonads of such animals mature once in a year and hence they reproduce once in a year. Studies have shown that it is the ovary which exhibits gamete differentiation in phases whereas spermatogenesis is a continuous process.

In non-mammalian vertebrates the ovarian cycle consists of the following phase:

- (i) Prebreeding phase (ii) Breeding phase and (iii) Postbreeding phase.

During prebreeding phase growth and differentiation of the ovarian follicles takes place. The follicles start accumulating yolk and at the end of this phase the follicles are ready for ovulation and fertilization. Ovulation, mating and fertilization occur during breeding phase. This phase is followed by the post breeding phase in which ovary contains the spent follicles, or postovulatory follicles (the follicles from which the ovum is expelled during ovulation), some follicles which failed to ovulate, and atretic follicles. Degeneration and disintegration of postovulatory and atretic follicles also take place during postbreeding phase.

Hormones from the pituitary and the gonads regulate the reproductive cycles. Apart from the endogenous mechanisms, external stimuli also affect the gonadal activity.

Mammals exhibit two types of ovarian cycles: i) Estrous cycle, exhibited by non-primates such as rats, cats, dogs, pigs, and ii) Menstrual cycle, found in the primates (monkeys, chimpanzees and humans). We will study the Menstrual cycle in humans in this unit.

Menstrual Cycle

Menstrual cycles are characteristic of primates and do not occur in other vertebrate groups. The length of the cycle is highly variable among primates, though 28 days is generally regarded as typical for human female. Both estrous and menstrual cycles are regulated by the same interactions of pituitary and ovarian hormones, and the effects of the ovarian hormones on the reproductive tract are comparable in most respects. Major differences between the two types of cycles are; i) the presence of a **menstrual phase** in primates, and ii) the spreading of sexual receptivity throughout the cycle in primates, rather than the limitation of it to a definite period as found in nonprimates.

In conjunction with changes in the ovary as you can see in Figure 8.8 and Figure 8.17, the lining of the uterus undergoes dramatic thickening and regression. Ultimately the lining is shed and expelled from the vagina as menstruation or expulsion of uterine lining. By convention, this is regarded as the beginning of the primate cycle (day 0) lasting four to seven days. The cycle itself has two distinct phases: i) the **follicular phase** generally lasting for 14 days in which a follicle matures and releases its secondary oocyte into the oviduct (ovulation); ii) **luteal phase** which also lasts on average for 14 days. During this phase the corpus luteum is formed from the ruptured follicle and subsequently degenerates.

We have said earlier in the sections that hormones are responsible for the changes that occur in the ovary and uterus during the reproductive cycles. Recall that LH and FSH are produced in the anterior pituitary in response to the release of gonadotropin release hormone (GnRH) and progesterone is produced along with estrogens from the follicular cells in the ovaries. Let us look at Figure 8.20 to understand the interaction of hormones that are responsible for the menstrual cycle.

- i) Let us start at day one of the cycle when the uterus begins to shed its endometrial lining during menstruation. In the ovary a follicle is stimulated by FSH to mature.
- ii) As the follicle grows it produces more and more estradiol which stimulates mitosis and increase in cell number in the uterine lining. At this time the follicular cells also produce some progesterone. While the estradiol level is still low, it suppresses the secretion of LH by negative feedback inhibition.
- iii) Once the follicle has grown enough to produce larger amounts of estradiol, it starts to exert a positive feedback loop. As you can see in the figure the positive feedback produces a spike in both LH and estradiol. The high estrogen content of the blood causes the pituitary to diminish its production of FSH and increase the output of LH.
- iv) The LH surge triggers ovulation when the balance between FSH and LH has swung sufficiently in favor of LH and the follicular phase of the cycle ends here.
- v) As the corpus luteum develops from the ruptured follicle, it secretes large amounts of progesterone and small amounts of estradiol in response to LH.
- vi) This large surge of progesterone stimulates the uterine lining to become thick and spongy with a well developed blood supply. In this way the uterus becomes ready to accept the blastocyst if fertilization occurs
- vii) If fertilization does not occur in the corpus luteum degenerates approximately 12 days after ovulation. This causes the uterine lining to degenerate.
- viii) As a result falling levels of progesterone its inhibitory effect on the hypothalamus and pituitary are lifted, LH and FSH levels rise and a new cycle begins.

- ix) If fertilization does occur then corpus luteum does not degenerate and progesterone and estradiol levels remain high to support pregnancy. Secretory competence of the corpus luteum diminishes slowly after the fourth month of pregnancy, although it remains structurally intact until the end of pregnancy. The **placenta**, rather than the ovary, is the principal source of progesterone and estrogen during the latter half of pregnancy. Removal of the ovaries after mid pregnancy neither terminates pregnancy nor diminishes the levels of the two types of steroid hormones in the circulation
- x) There are cyclic variations in the body temperature of the human female that correlate with menstrual changes. A distinct rise in basal body temperature occurs at ovulation and remains high until the onset of the next menstrual period. The changing titers of hormones during the menstrual cycle apparently account for the temperature fluctuations.

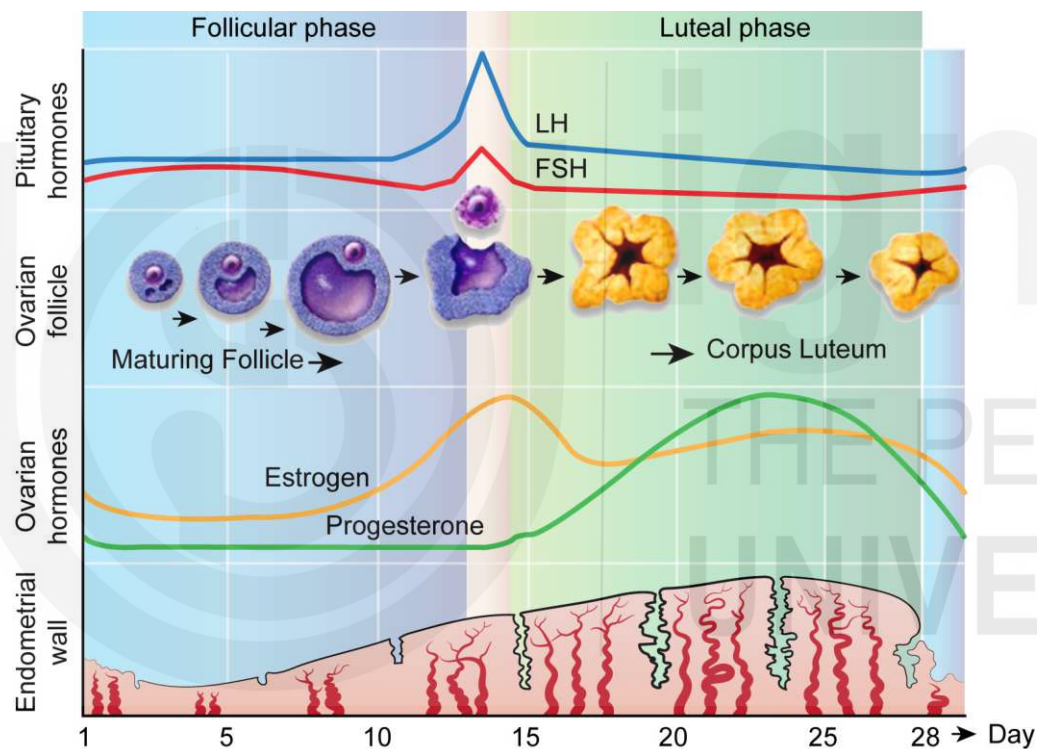


Fig.8.20: Diagram exhibiting changes in endometrium, the ovaries and the circulating ovarian hormones during menstrual cycle.

SAQ 6

List the two types of reproductive cycles in vertebrates and their phases.
(4 dotted lines for student's answer)

Box 8.2

Contraceptive Pill

Millions of women in the world are using oral steroid contraceptives. These contraceptives usually consist of a synthetic estrogen combined with synthetic progesterone in the form of pills that are taken once each day for three weeks after the

last day of menstrual period. This procedure causes an immediate increase in blood levels of ovarian steroids (from the pill), which is maintained for the normal duration of a monthly cycle. As a result of negative feedback inhibition of gonadotropin secretion, ovulation never occurs. The entire cycle is like a false luteal phase, with high levels of progesterone, estrogen and low levels of gonadotropins.

Since the contraceptive pills contain ovarian steroid hormones, the endometrium proliferates and becomes secretory just as it does during a normal cycle. In order to prevent an abnormal growth of the endometrium, women stop taking the pill after three weeks. This causes estrogen and progesterone levels to fall, and permits menstruation to occur. The contraceptive pills is an extremely effective method of birth control, but it does have potentially serious side effects – including an increased incidence of thromboembolism, cardiovascular disorders, and endometrial and breast cancer. It has been pointed out, however, that the mortality risk of contraceptive pills is still much lower than the risk of death from the complications of pregnancy – or from automobile accidents.

8.8 SUMMARY

In this unit you have studied that:

- Organisms reproduce by asexual and sexual methods. Fission, budding, fragmentation and parthenogenesis are the asexual methods of reproduction. In sexual reproduction there is involvement of two parents of different sexes, male and female.
- The gonads of the male (testes) produce male gametes, the sperm, and the female gonads (ovary) produce the egg. Gametes are formed by meiotic division occurring in the gonads. Genetic recombination occurring during prophase1 stage of meiotic1 division creates variability in the offspring. Additionally, parental chromosomal pairs are randomly assorted to form haploid gametes, which is another source of variability.
- Most of the animals are dioecious, i.e. having separate sexes, but some animals have both the sexes in the same animal, a condition called hermaphroditism.
- Sex of an individual is determined at fertilization depending upon the genetic constitution for example, a zygote bearing XX chromosomes differentiates into a genetic female and XY into a genetic male. The genetic determination also gets modified or reversed by some internal and external environmental factors.
- Testis produces spermatozoa, and synthesises and secretes steroid hormones. Its activity is also regulated by pituitary gonadotropins and its own hormones (androgens) by negative feedback mechanism. Formation of sperms from spermatogonium is called spermatogenesis.
- Ovary produces eggs, elaborates hormones and yolk. The ovarian activity is regulated by pituitary gonadotropins, and by its own hormones (estrogens) by negative feedback mechanism. Formation of ovum from oogonium is called oogenesis.
- The accessory reproductive organs consist of ducts and glands specialized for storage and conveyance of the gametes. The female

accessory reproductive organs are the oviducts, the uterus, the vagina and the external genitalia. The male accessory reproductive organs are multiple ductuli efferentes, paired epididymis, vasa deferentia, seminal vesicles, ejaculatory ducts, cowpers' glands, prostate gland, the urethra and the penis.

- Gamete production is not a continuous phenomenon. It is recurring and cyclic, takes place during the seasons which are most favorable for the development and growth of the young.
- Most of non-mammalian vertebrates exhibit annual reproductive cycle in which maturation of the gametes and breeding activity takes place only once in a year. Gametogenic activity in the males is usually continuous. The mammalian females exhibit two types of ovarian cycles:
- The estrous cycle, exhibited by nonprimate mammals and the menstrual cycle, exhibited by primates. The chief difference between the two cycles are (i) the presence of a menstrual phase (bleeding) in primates and (ii) the spreading of sexual receptivity throughout the cycle in the menstrual cycle, rather than limited to a definite period found in estrous cycle.

8.9 TERMINAL QUESTIONS

1. Differentiate between sexual and asexual reproduction.
2. Explain what causes sex differences in humans and birds?
3. Draw a labeled diagram of section through mammalian seminiferous tubule.
4. With the help of a flow diagram explain the function of female hormones in humans. How is it regulated?
5. Make a table to summarize the endocrine regulation of menstrual cycle.

8.10 ANSWERS

Self-Assessment Questions

1.
 - a) Fission produces equal sized off spring by mitotic cell division.
 - b) In budding ofspring are produced as an outgrowth from the parent.
 - c) In fragmentation small fragments of the parent organism develop into offspring.
 - d) Parthenogenesis is development of offspring from unfertilized egg.
2. Meiosis creates variability by genetic recombination during meiotic¹ division and random assortment of parental chromosomes during gamete generation.
3.
 - a) Testis produces spermatozoa.

- b) Ovary produces ovum.
- 4.
 - a) Production of spermatozoa.
 - b) Synthesis of steroid hormone.
 - c) Storage of spermatozoa.
 - d) Maintenance of functions of male reproductive organs.
- 5.
 - a) Oogonium
 - b) Graafian follicle
 - c) Relaxin
 - d) Progestogens
 - e) Prolactin
 - f) Vitellogenesis
- 6. Estrous cycle-estrus, metestrus, diestrus and proestrus phase Menstrual cycle-menstrual, proliferative (follicular), ovulatory and progestational (luteal) phases.

Terminal Questions

Please refer to following sections and subsections for the answers to the terminal question and reply in your own language giving examples from your reference studies where ever applicable:

- 1. Refer to Section 8.2.
- 2. Refer to Section 8.2.
- 3. Refer to Section 8.3.
- 4. Refer to Subsection 8.4.3.
- 5. Refer to Section 8.5.