CHAPTER-1 GENERAL THEMES IN PHYSIOLOGY

TOPIC 1 THE SPECTRUM OF STUDY OF PHYSIOLOGY

Physiology—Definition

Animal Physiology deals with the study of functions of the tissues, organs and organ systems of animals.

The ultimate goal of the study of physiology is to understand the mechanisms that operate in animals at all levels, in physical and chemical terms.

Physiological Mechanisms Obey Laws of Physics and Chemistry:

The knowledge of Physiology is firmly rooted in the laws and concepts of physics and chemistry. Following are the examples of some physical and chemical laws and concepts that relate to various physiological processes:

- Ohm's Law—applies to blood flow and pressure; ionic current; capacitance of membranes.
- Boyle's Law and the Ideal Gas Law—apply to respiration.
- Law of Gravity—applies to blood flow.
- Concepts of kinetic and potential energy—apply to muscle contraction; chest movements during inhalation and exhalation.
- Concepts of Inertia, momentum, velocity and drag—apply to animal locomotion.

These are just a few examples. Many more physical and chemical laws and concepts are used to explain various physiological phenomena.

Curiosity underlies the learning of Physiology

Underlying all studies of animal physiology is the curiosity (desire to know) about how animals and their systems work. e.g.

- How can a Hummingbird's heart beat 20 times a second during hovering flight?
- How do insects see in the ultraviolet spectrum?
- How do kangaroo rats survive in the desert with no access to drinking water?

Such questions fuel the curiosity of animal physiologists and there is no bound to this curiosity. The more we know, the more we realize how little we know about physiological systems of animals.

From Animal Physiology to Human Physiology

Study of animal physiology has provided an insight into the physiological processes of humans. The human species shares the same fundamental biological processes with all other animal species and has a linked evolutionary history.

To illustrate this relationship let's give few examples:

- The heart beat in the human body results from the same physiological mechanisms that underlie heart function in fishes, frogs, snakes, birds, or apes.
- Similarly, the molecular events that produce an electrical nerve impulse in the human brain are fundamentally the same as those that produce an impulse in the nerves of a squid, crab or rat.

For these reasons, the study of animal physiology has made innumerable contributions to understanding human physiology. In fact, most of what we have learned about the functions of human cells, tissues, and organs was known first through the study of various species of vertebrate and invertebrate animals.

While animal physiology lays the foundation of human physiology, the human physiology is the foundation of scientific medical practice. Understanding of the functioning and malfunctioning of living tissues provides the foundation for developing effective, scientifically sound treatment for human diseases.

In the modern times, animal physiology has contributed through new techniques for generating unique animal models for specific human diseases (e.g., diabetic mice, congenitally fat rats, zebra fish embryos with heart defects). These models allow a wide range of experiments that provide the insights into the underlying physiological processes of such diseases and defects.

TOPIC 2 CENTRAL THEMES IN ANIMAL PHYSIOLOGY

Our major goals of study of animal physiology are to:

- explore the physiological processes that are basic to all animal groups
- show how they have been shaped by selective forces during evolution

Comparing and contrasting how different organisms have adapted to survive similar environmental challenges provides useful insights about the patterns of physiological evolution and the adaptive value of physiological processes.

Central themes in animal physiology:

As we study animal physiology and physiological adaptations, we notice several basic themes, repeatedly emerging.

We shall briefly discuss five major themes here, i.e.

(i) Structure-function relationships
(ii) Adaptation, Acclimatization and Acclimation
(iii) Principle of homeostasis
(iv) Feedback control systems
(v) Conformity and Regulation

TOPIC-3 STRUCTURE-FUNCTION RELATIONSHIPS

One of the central principles of animal physiology is that “function is based on structure”.

In other words, in living organisms, structural design is matched to functional demands.

In very simple manner we can say that the way something is arranged enables it to play its role and fulfill its job, within an organism.

Such structure-function relationships arise through evolution and natural selection.

Example:

Let’s illustrate this with a comprehensive example:

- A frog leaps for a prey. It contracts the powerful skeletal muscles attached to the bones of its limbs.
- As the prey is swallowed, it reaches the stomach where the smooth muscles grind and mix the food contents.
- After digestion, the nutrients are absorbed into the blood. The blood flows due to the beating of cardiac muscles of the heart.

Throughout this process in frog’s body, three structurally distinct forms of muscles carry out three distinct functions.

Thus our basic point is elaborated:

- The skeletal muscles are evolved and adapted for movement of the bones.
- The smooth muscles of digestive tract are adapted for such contractions that help grinding and mixing the food materials.
- Cardiac muscles are specialized to pump and circulate blood throughout the body.

Structure-Function Relationships are demonstrated at all levels of biological organization:

The structure-function relationships are not restricted only to the muscles but are found in every tissue of an animal’s body.

And more correctly speaking, these relationships are demonstrated at all levels of biological organization down to the molecular and atomic levels.

Example:

To illustrate this, let’s have a look at the figure.

This figure illustrates the structure-function relationships of muscle tissue at all levels of biological organization. Biological function at each level of organization depends on the structure of that level and more microscopic levels below it.

Beginning with the whole animal, this principle can be traced down from muscles through cells to molecular levels.

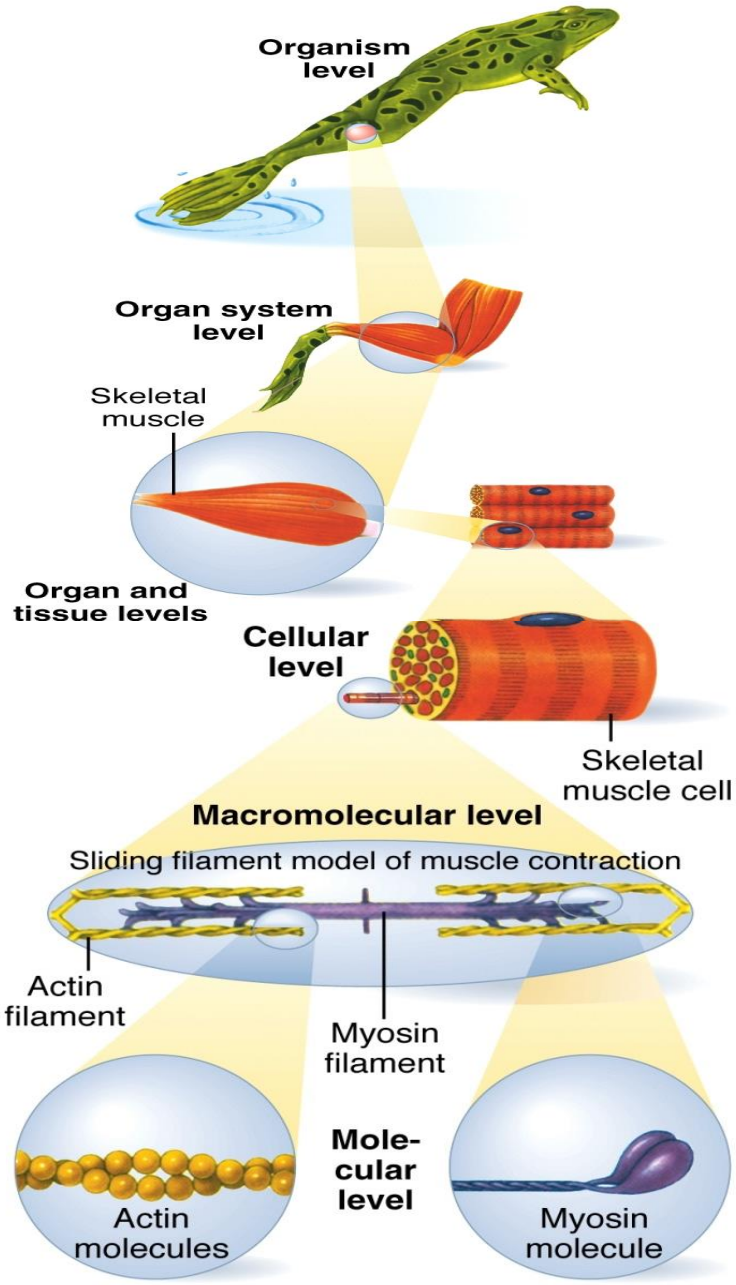
SYSTEM LEVEL: Groups of skeletal muscles form a system that helps to move frog's limbs.

CELLULAR LEVEL: Skeletal muscles themselves are composed of muscle cells.

MOLECULAR LEVEL: The muscle cells are formed from thousands of macromolecular assemblages known as sarcomeres. These sarcomeres form the basic unit of muscle contraction. The sarcomeres are formed from a pair of contractile proteins—actin and myosin.

Conclusion:

We can precisely say that the principle that function depends on structure holds true across the whole range of physiological processes.



TOPIC-4 ADAPTATION, ACCLIMATIZATION AND ACCLIMATION

Adaptation: Adaptation is an evolutionary process that occurs extremely slowly in a species over thousands of generations as a result of which the physiology of the members of that species becomes very well matched to the environment in which it lives.

This phenomenon ensures the survival of the species.

Adaptations are generally not reversible.

Acclimatization: Acclimatization is a physiological, biochemical, or anatomic change within an individual animal that results from the animal's chronic exposure to new, naturally occurring environmental conditions.

Acclimation: Acclimation refers to the same process as acclimatization, but the changes are induced experimentally in the laboratory or field by the investigator.

Acclimatization and acclimation are acquired characters that are restricted to only one or few members of a species. The adaptations acquired are not inheritable, so have no evolutionary significance. Generally, both acclimation and acclimatization are reversible.

Examples:

(a) Acclimatization:

Let's consider an animal that voluntarily migrates from a valley to a high mountain i.e. a voluntary change happens in its natural environment in which oxygen partial pressure is low.

Effects:

- The lung ventilation rate will increase initially to acquire adequate oxygen.
- However, within few days, lung ventilation will begin to drop back towards normal rates as the other physiological mechanisms that facilitate gas exchange at high altitude begin to operate.
- This individual animal is said to have acclimatized to the new high-altitude conditions.

(b) Acclimation:

Now consider another condition in which an animal physiologist places that same animal in a hypobaric chamber (that is at low atmospheric pressure) simulating high-altitude conditions.

Effects:

The animal breathing rate will react in the same way as during acclimatization but we shall call that it has acclimated to the experimental conditions.

(c) Adaptation:

In contrast to these short-term responses let's consider the bar-headed goose, which is able to fly above the peaks of Mount Everest.

This species of goose has become adapted to high altitude due to natural selection that has operated for thousands of years on the species.

TOPIC-5 PRINCIPLE OF HOMEOSTASIS

Walter Cannon coined the term homeostasis in 1929 to describe the tendency of organisms to maintain relative internal stability despite of significant external environmental changes.

Fluctuations in Environmental parameters are challenging for animals

Although many animals seem to live comfortably in their environment, most habitats are actually quite hostile to animal cells. For example:

- For many aquatic animals, the surrounding freshwater is more dilute while seawater is more salty than their own body fluids. This causes problems of water influx or water loss for the animals.
- Many terrestrial and aquatic animals may live in environments that are too hot or too cold when compared to their own body temperatures. So they face the problem of over heating or heat loss.
- Moreover most environments exhibit fluctuations in their physical and chemical properties.

Need for homeostatic mechanisms

Such environmental fluctuations around an animal are disruptive to the functions of cells, tissues and organs. So, physiological regulatory systems to maintain relatively stable conditions within an animal's tissues and cells become a necessity.

Homeostasis—definition:

During evolution, each species has assumed a specific set of internal environment with an ability to resist environmental changes by making adjustments to keep its internal fluctuations in a narrow range. This ability to protect internal environment from the harms of fluctuations in external environment is termed as homeostasis.

Homeostasis does not mean to keep a fixed internal environment as the changes maintained within a specific range are necessary for normal body functions.

Example:

- Water availability may fluctuate tremendously in the external environment, from abundant supply to almost dry conditions.
- The quantity of water in the body i.e. internal environment may vary, but in a narrow range, in response to either abundant supply and dry condition.
- It means that the homeostatic control systems would not let the body flooded with water in abundant supply and also not let it to dehydrate in dry conditions.

Other Examples:

- Homeostasis maintains the temperature of healthy human body near 37^{o}C, inspite of environmental temperature variations.
- The pH of blood and interstitial fluid is maintained at 7.4 with a fluctuation range of only 0.1 pH unit.

- The concentration of glucose in the bloodstream is regulated near the range of 90 mg per 100 ml of blood even if one is fasting or full stomach.
- Similar homeostatic regulations apply to osmotic pressure, oxygen level and various ion concentrations.

Mechanism of Homeostasis:

The internal factors which are influenced by external environment are called variables e.g. body temperature, water concentration, pH etc.

Various control systems have been acquired for homeostatic regulations of these variables.

The ideal or normal value of the variable is known as the set point that is stored in the memory.

These living control systems operate just like the physical control systems i.e. they have three components: Receptor, Control centre and effectors.

Example:

Let's take a familiar example of a temperature control system that operates in air conditioners and water heating geysers.

- In both these systems, there is a sensor (thermometer) that monitors temperature change from a set point and signals to the control center to take action by switching on heating or cooling units in response to drop or raise in the temperature compared to the set point. The overall result is the maintenance of temperature within a narrow range of set point.
- Similar to this automatic mechanical control of temperature, the endothermic animals also have a set point in temperature that is monitored by thermoreceptors which detect temperature changes and send signals to the thermostatic control center which is the hypothalamus. The hypothalamus sends appropriate messages to the effector organs e.g. sweat glands or muscles for heat generation or cooling actions. Thus temperature is controlled and regulated within a narrow range of the set point.

TOPIC-6 FEEDBACK CONTROL SYSTEMS

Definition:

Many biological processes have the ability of self-regulation by a mechanism which is called feedback mechanism. The basic principle of feedback in living systems is that the output or product of a process itself regulates the process.

Significance:

The feedback regulatory processes maintain homeostasis in the cells and the body of multicellular organism as a whole.

Mechanism:

The feedback controls respond to the sensory information about a particular variable e.g., temperature, salinity or pH that requires regulation. This regulation requires continuous sampling of controlled variables and respective corrective actions.

Types of feedback systems:

Two types of regulatory feedback systems are present:

1. Negative feedback systems
2. Positive feedback systems

1. Negative feedback systems:

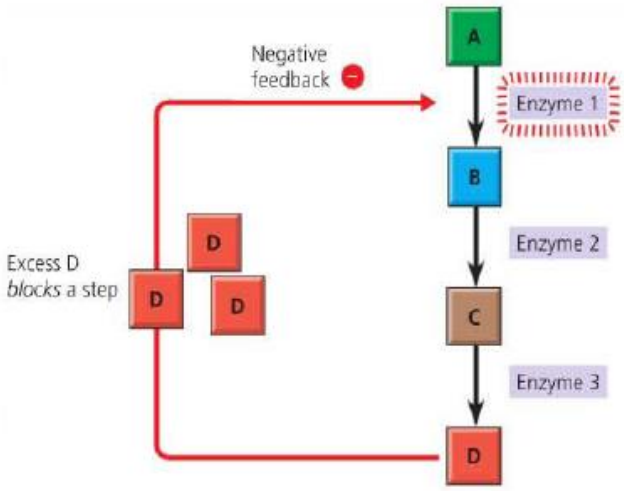
In life, the most common form of regulation encountered is the negative feedback, in which accumulation of an end product works to stop or slow down that process.

Example-1

The breakdown of sugar in the cells generates chemical energy in the form of ATP. When a cell makes more ATP than it can use, the excess ATP "feeds back" and inhibits an enzyme near the beginning of the pathway. This results in temporary stoppage of ATP production.

The figure illustrates the negative feedback:

The three-step chemical pathway shown here converts substance A to substance D. A specific enzyme catalyzes each chemical reaction. Accumulation of the final product (D) inhibits the first enzyme in the sequence, thus slowing down production of more D.



Example-2

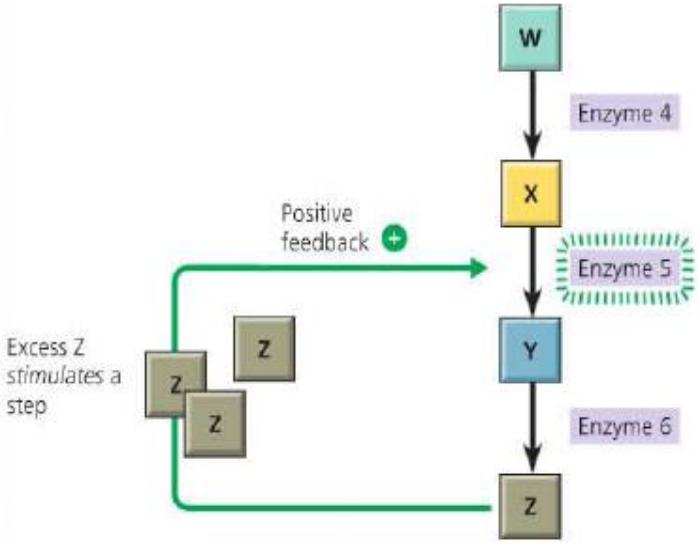
The control of blood sugar (glucose) by insulin is another good example of a negative feedback mechanism.

When blood sugar rises, receptors in the body sense a change. In turn, the control center (pancreas) secretes insulin into the blood effectively lowering blood sugar levels. Once blood sugar levels reach homeostasis, the pancreas stops releasing insulin.

2. Positive feedback systems:

There are many biological processes that are regulated by positive feedback, although they are less commonly found. In positive feedback systems, an end product speeds up its production by enhancing the effect of original stimulus.

The figure explains the positive feedback system in a biochemical pathway. A product stimulates an enzyme in the reaction sequence, increasing the rate of production of the product.



Example-1

Clotting of blood in response to an injury is an example of positive feedback. When a blood vessel is damaged, platelets begin to aggregate at the site of injury. Positive feedback occurs as the chemicals released by platelets attract more platelets towards them. So, the platelets continue to pile up and release chemicals until a clot is formed that seals the wound.

Example-2

Another good example of a positive feedback system is seen during child birth.

During labor, the hormone oxytocin is released that intensifies and speeds up contractions of the uterus. The increase in contractions causes more oxytocin to be released and the cycle goes on until the baby is born.

TOPIC-7 CONFORMITY AND REGULATION

When an animal is confronted with changes in its environment e.g., salinity, oxygen availability or temperature, it shows one of the two broad categories of responses that are conformity or regulation.

Conformity and Conformers:

An animal is said to be a conformer for a particular environmental variable if it allows its internal conditions to conform to the external changes.

Such animals are unable to maintain homeostasis for internal conditions like body fluid salinity or tissue oxygenation or temperature.

The degree to which conformers survive the changing parameters depends upon the tolerance of their body tissues to external changes.

Examples:

Osmoconformers: These animals do not actively adjust their internal osmotic state. The animal body fluids are kept isotonic to the external environment.

Echinoderms like the starfish are osmoconformers, whose internal body fluids come to equilibrium with their environment, showing an increase in body fluid salinity when placed in high-salt water and a decrease in body fluid salinity when placed in low salt water.

Oxyconformers: The oxygen consumption of oxyconformers like annelid worms rises and falls depending on the availability or unavailability of oxygen.

Thermoconformers: They conform to the temperature of the environment in which they live. As the environment warms or cools, so do the cells of the animal. Such animals are known as poikilotherms.

Regulation and Regulators:

An animal is said to be a regulator if it uses internal control mechanisms to regulate internal conditions in the face of broad range of fluctuation in a particular external environmental variable.

Regulators use biochemical, physiological, behavioral and other mechanisms to regulate their internal environment and maintain homeostasis.

Examples:

Osmoregulators: The animals which can maintain body fluid concentrations that differ noticeably from the outside environment. They can maintain the ion concentrations of body fluids above environmental levels when placed in dilute water and below environmental levels when placed in concentrated water. The osmoregulatory strategy of these animals is to discharge excess water in hypotonic environments while conserving water in hypertonic conditions.

Oxyregulators: Many crustaceans, most mollusks and almost all vertebrates are oxyregulators. They maintain their oxygen consumption at near-steady levels even when environmental oxygen concentration falls. However, if the available oxygen becomes so limited that oxygen consumption cannot be maintained, the animal reverts to oxygen conformity.

Thermoregulators: Thermoregulators regulate the temperature of their body in the wake of changing environmental temperature, keeping their body at a temperature that is independent of that of the environment. Such animals are the homeotherms.

Conformers as well as Regulators

An animal may not be a regulator or conformer for all the variables of the environment. An animal may regulate some internal conditions while conform to many others.

MEMBRANE PHYSIOLOGY

TOPIC-8 MEMBRANE PERMEABILITY

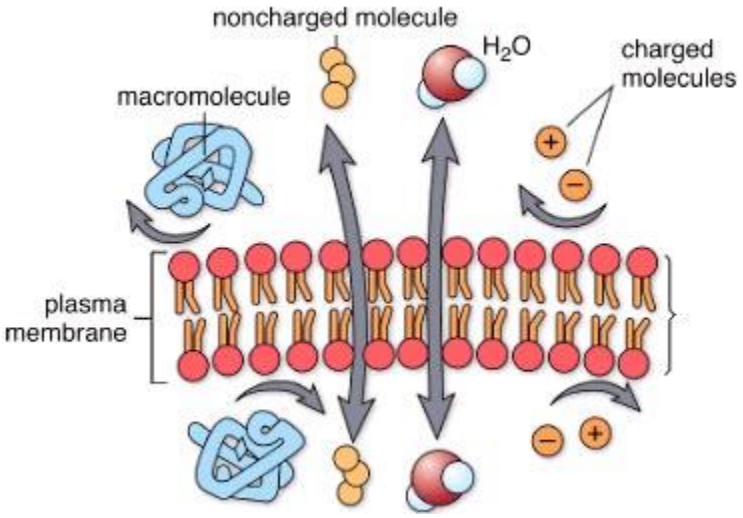
- The structural features of plasma membrane confer it with the property of selective permeability.
- Due to selective permeability, plasma membrane can regulate the movement of substances across it.
- Permeability is fundamental to the functioning of living cell and to the maintenance of intracellular physiological conditions.

Membrane permeability varies greatly for the type and size of the molecules such as:

Lipid-soluble substances:

As the membrane has a rather continuous lipid bilayer, the non-polar, lipid-soluble substances can cross the plasma membrane passively by dissolving in the molecules of lipid bilayer.

The rate at which such substances penetrate depends on their solubility in lipids and the size of the molecules. Smaller and more soluble substances penetrate at faster rates and vice versa.



Polar substances and ions:

Polar, water soluble substances and ions have difficulty in passing through membranes because of the hydrophobic interior of the lipid bilayer that makes membranes highly nondiffusible to most polar and charged molecules.

Macromolecules:

Large particles and macromolecules, like proteins, cannot cross plasma membrane due to their size.

As the movement of such substances is necessary for the functioning of the cells, various structural and functional mechanisms have evolved for the transport of such substances through the membrane. These mechanisms include passive as well as active transport mechanisms.

PASSIVE PERMEABILITY AND PERMEABILITY CONSTANT OF THE MEMBRANE:

The permeability of the membrane to a substance is the rate at which that substance passively penetrates the membrane.

If we assume that a continuous concentration gradient exists for a diffusible substance across the membrane, then:

$$\frac{dQ_s}{dt} = P(C_I - C_{II})$$

Where:

- dQ_s/dt is the amount of substance "s" crossing a unit area of membrane per unit time
- C_I and C_{II} are the respective concentrations of the substance on the two sides of the membrane
- P is the permeability constant of the substance. Permeability constants for different substances vary greatly. For example, the permeability of red blood cells to different solutes ranges from 10^{-12} cm/sec to 10^{-2} cm/sec.

This equation applies only to the molecules that are not being actively transported or influenced by any forces other than simple diffusion. This excludes electrolytes, since they are electrically charged when dissociated, and consequently their flux depends not only on the concentration gradient, but also on the electrical gradient.

<u>Permeability can be altered:</u>

The permeability of some membranes to certain substances can be altered greatly by hormones and other molecules that react with receptor sites on the membrane and thereby influence channel size or carrier mechanisms.

Antidiuretic hormone, for example, can increase the water permeability of the renal collecting duct in mammals by as much as 10 times. Similarly, neurotransmitters, acting on specialized integral membrane proteins in nerve and muscle cells, induce large increases in permeability to ions such as Na^+, K^+, Ca^{2+}, or Cl^-.

TOPIC-9 DIFFUSION AND MEMBRANE FLUX

Diffusion:

Molecules have thermal energy due to which they are in continuous motion which is called thermal motion. One result of thermal motion is the diffusion which is defined as:

"the random thermal motion of suspended or dissolved molecules resulting in their dispersion from regions of higher concentration to regions of lower concentration".

Much of the traffic across cell membranes occurs by diffusion. When a substance is more concentrated on one side of a membrane than on the other, there is a tendency for the substance to diffuse across the membrane down its concentration gradient. However the membrane must be permeable to that substance.

Example:

One important example of diffusion is the uptake of oxygen by a cell. Dissolved oxygen diffuses into the cell across the plasma membrane. As the oxygen enters the cell, cellular respiration consumes it rapidly, so a concentration gradient of oxygen is established between the intra-cellular and extracellular environments. This gradient favors the diffusion of oxygen to continue into the cell.

The diffusion of a substance across a biological membrane is a passive transport because the cell does not have to expend energy to make it happen. The concentration gradient itself represents potential energy and drives diffusion. Moreover, each substance diffuses down its own concentration gradient, unaffected by the concentration differences of other substances.

However, as the membranes are selectively permeable and therefore have different effects on the rates of diffusion of various molecules.

Fick Diffusion Equation:

The rate of diffusion of a solute is defined by the Fick Diffusion Equation:

Where:

$$\frac{dQ_s}{dt} = D_s A \frac{dC_s}{dx}$$

- dQ_s/dt is the rate of diffusion i.e. quantity of substance "s" diffusing per unit time.
- D_s is the diffusion coefficient of "s"
- A is the cross sectional area through which "s" is diffusing.
- dC_s/dx is the concentration gradient of "s" i.e. the change in concentration (dC_s) with distance (dx).

Here:

- The gradient factor dC_s/dx is clearly very important, because it determines the rate at which "s" will diffuse down the gradient.

- D_s varies with the nature and molecular weight of substance and of the solvent, which is water in most physiological situations.

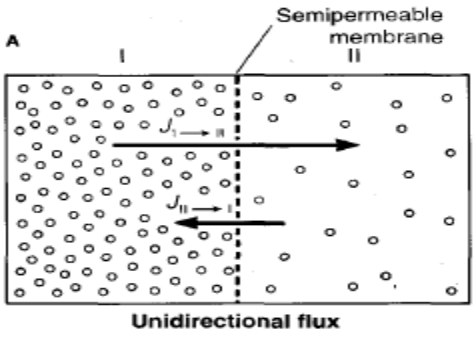
Membrane Flux

The amount of solute that passes through a unit area of membrane every second in one direction is known as the flux. It is represented by "J". So,

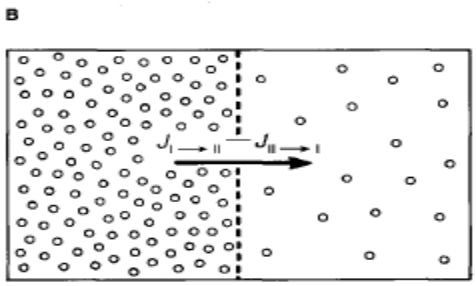
$$J = \frac{dQ_s}{dt}$$

If a solute occurs on both sides of a membrane through which it can diffuse, it will exhibit a unidirectional flux in each direction.

The flux in one direction (say, from cell exterior to cell interior) is considered independent of the flux in the opposite direction. Thus, if the influx and efflux are equal, the net flux is zero. If the unidirectional flux is greater in one direction, there is a net flux, which is the difference between the two unidirectional fluxes.



Unidirectional flux

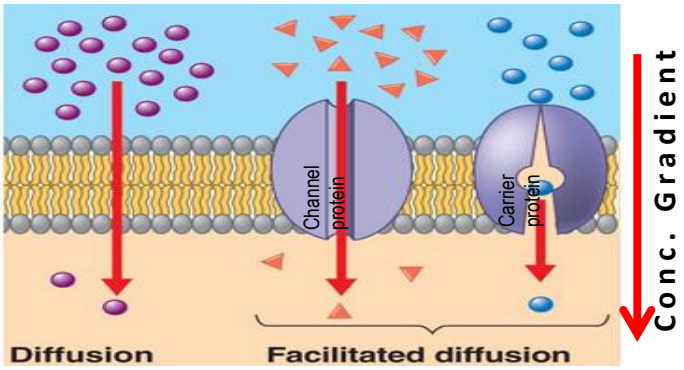


Net flux

TOPIC-10 DIFFUSION THROUGH MEMBRANE CHANNELS AND CARRIER PROTEINS: THE FACILITATED DIFFUSION

Facilitated diffusion:

Many polar molecules and ions, which cannot diffuse freely through the lipid bilayer are able to diffuse passively with the help of transport proteins that are present in the membrane. This phenomenon is called facilitated diffusion. Facilitated transport is a passive process that does not require energy in the form of ATP.



Transport proteins are very specific. They transport some substances but not others.

Types of transport proteins:

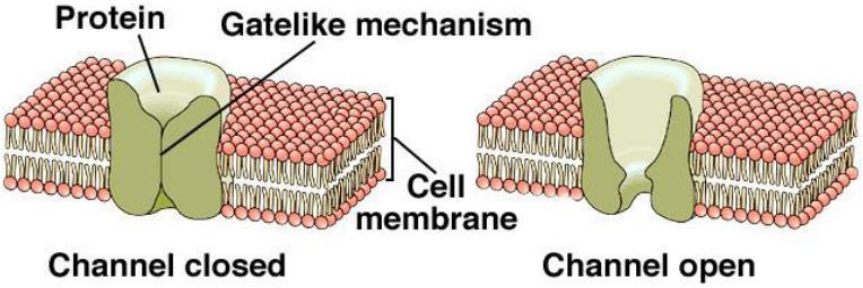
The two types of transport proteins are:

- Channel proteins
- Carrier proteins

1. Channel Proteins:

Special channel proteins have evolved that extend across the cell membrane. Channel proteins have water-filled pores in them which allow a specific molecule or ion to pass through and cross the membrane. These pores are called membrane channels.

The opening and closing of membrane channels is regulated. So polar molecules can only cross the membrane when these pores are open.



Membrane channels presumably have diameters of less than 1.0 nm. Principles of diffusion i.e. concentration gradient apply to the movement through these channels.

Examples of facilitated diffusion through Channel Proteins:

a) The water channel proteins—Aquaporins:

Although water molecules are small enough to cross through the phospholipid bilayer, the rate of water movement by this route is relatively slow because of the polarity of the water molecules.

Membranes have water channel proteins known as Aquaporins which facilitate diffusion of water molecules.

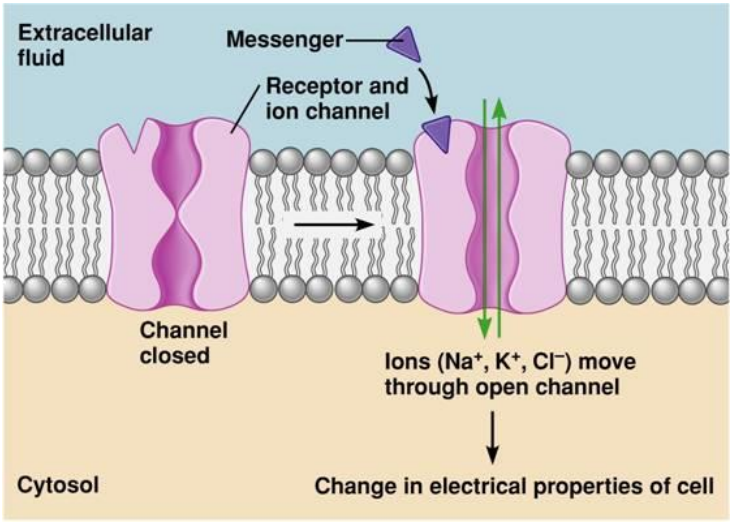
These channel proteins provide hydrophilic passageways through which water molecules and small ions (e.g. Na^+, K^+, Ca^{2+}, and Cl^-) in dissolved form flow very quickly from one side of the membrane to the other.

b) Ion Channels:

Another group of channel proteins are ion channels, many of which function as gated channels, which open or close in response to a stimulus.

The stimulus may be electrical or chemical. The chemical stimulus is a substance other than the one that is to be transported.

For example, in nerve cells, certain neurotransmitter molecules act as stimulus for the opening of sodium gated ion channels that allow sodium ions into the cell. Later, an electrical stimulus activates the ion channel protein, and potassium ions rush out of the cell.



c) Specialized membrane channels:

Many small, uncharged polar molecules, such as CO_2, NO, and CO, are also supposed to diffuse through specialized membrane channels.

2. Carrier proteins:

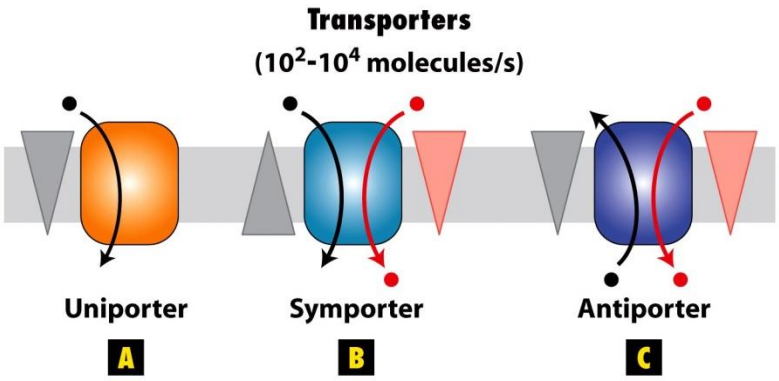
Membranes are somewhat permeable to many polar molecules such as sugars, amino acids, nucleotides and certain cell metabolites that would cross lipid bilayers by diffusion only very slowly.

The movement of such molecules is enhanced by the action of membrane transport proteins called carrier proteins. Carrier proteins are very selective about which species of molecules they facilitate.

Types of Carrier proteins:

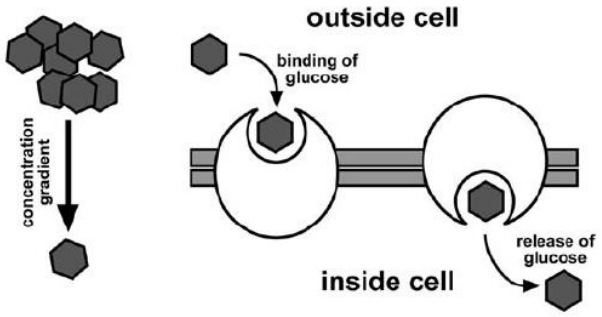
Carrier proteins exist in many forms in all types of membranes.

- Carrier proteins that transport a single solute from one side of the membrane to the other are called uniporters.
- Those that transfer one solute and simultaneously or sequentially transfer a second solute are called coupled transporters.
    - C oupled transporters that transfer two solutes in the same direction are called symporters.
    - Coupled transporters that transfer solutes in opposite directions are called antiporters.



Mechanism of transport through carrier proteins

A carrier protein has a solute binding site and has the capacity to alternate between two conformations, so that the solute binding site is sequentially translocated from one side of the bilayer to the other. This happens due to slight change in the shape of protein molecule. These changes in shape may be triggered by the binding and releasing of the transported molecule.



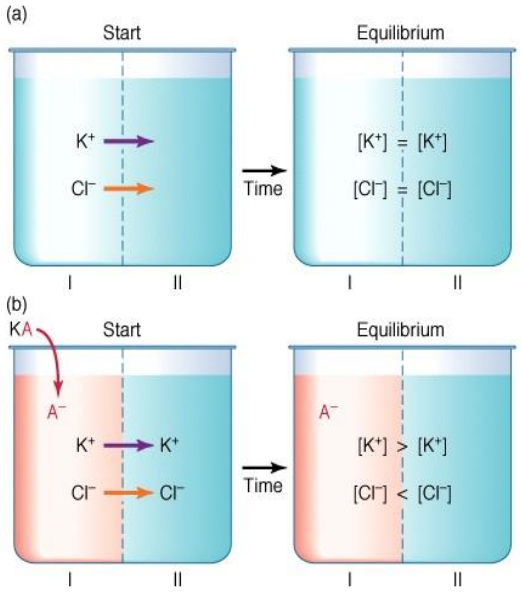
TOPIC-11 DONNAN EQUILIBRIUM

In 1911 Frederick Donnan discovered the phenomenon of unequal distribution of ions across the two sides of a differentially permeable membrane. This phenomenon is known as Donnan equilibrium and can be defined as:

"If diffusible solutes are separated by a membrane that is freely permeable to water and electrolytes but totally impermeable to one species of ion, the diffusible solutes become unequally distributed between the two compartments".

To understand a Donnan equilibrium, let's take an example:

- We start with pure water in two compartments, separated by a membrane.
- Now let's add some KCl to one of them.
- The dissolved salt will ionize and its ions K^+ and Cl^- will diffuse through the membrane until the system is in equilibrium i.e. the concentrations of K^+ and Cl^- will become equal on both sides of the membrane.
- Now let's add a potassium salt "KA" having a macromolecular nondiffusible anion "A" to the solution in compartment-I. It will produce K^+ and A^- ions. K^+ is diffusible, but A^- is not, so it will remain confined to compartment-I.
- The K^+ and Cl^- , which were in equilibrium, quickly become redistributed until a new equilibrium is established by movement of some K^+ and some Cl^- from compartment-I to compartment-II.
- The presence of nondiffusible anion A^- in compartment-I will result in an unequal distribution of ions in both compartments. So, at equilibrium, the K^+ will be more concentrated in the compartment-I in which the A^- is confined, whereas the Cl^- will become less concentrated in that compartment.
- So the Donnan equilibrium is characterized by a reciprocal distribution of the anions and cations. This happens because the gradients are not only chemical but are also electrical. There must be electroneutrality within both compartments; i.e. in each compartment the total number of positive charges must equal the total number of negative charges.



Donnan effect—An implication of Donnan Equilibrium:

Donnan equilibrium implies that if there is a nondiffusible solute in one of the solutions separated by semi-permeable membrane, the concentrations of solutions on both sides do not equalize. The concentration of the solution with nondiffusible solute remains high even at equilibrium. This is known as Donnan effect.

The Donnan effect can be correlated to living cells which contain nondiffusible anionic colloids, made up of proteins and organic phosphates which cannot cross the cell membrane. As a result of this, there is a

high concentration of non-diffusible anions across the cell membrane, thus creating the Donnan Equilibrium. This means that there are more ions inside the cell than outside.

Effects of Donnan Equilibrium

The flow of molecules and ions between a cell and its environment is regulated by the Donnan effect.

1. **Movement of water into the cell**
   At Donnan equilibrium, the osmotically unequal distribution of solute particles makes water move into the cell. This increases the hydrostatic pressure of the cell.

2. **Development of electrical potential**
   The unequal distribution of ions across the cell membrane results in the development of an electrical potential between the two sides of the membrane.

TOPIC-12 ION DISTRIBUTION ACROSS THE PLASMA MEMBRANE

The plasma membrane maintains different concentrations of ions inside and outside the cell.

Examples:

K^+ ions:

- The potassium ions are 10-30 times more concentrated in the cytosol than the extracellular fluid.
- This is because cell membranes are more permeable to K^+.
- This makes K^+ the most concentrated inorganic ions in the cytosol.

Na^+ and Cl^- ions

- The internal concentrations of free Na^+ and Cl^- are typically less (approximately one-tenth or less) than the external concentrations.
- The lower concentration of Na^+ is due to lower permeability of the cell membrane to Na^+. However the permeability is not low enough to prevent Na^+ from leaking steadily into the cell.
- Membrane permeability to chloride ions varies. In some cells it is similar to that of K^+ while in others it is lower.

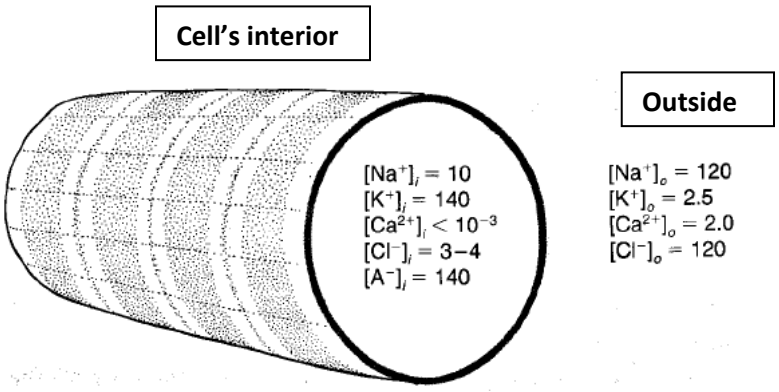
Ca^{2+} ions

- The intracellular concentration of Ca^{2+} is maintained several orders of magnitude below the extracellular concentration. This difference in Ca^{2+} concentration is due to two factors:
    - active transport of Ca^{2+} out across the cell membrane
    - sequestering of this ion into the mitochondria and endoplasmic reticulum
- As a result, the concentration of Ca^{2+} in the cytosol is generally well below 10^{-6} M.

Donnan Equilibrium and unequal ion distribution:

The differential permeability of the membrane to different ion species can be explained with Donnan equilibrium.

The nondiffusible peptide and protein molecules have many carboxyl and other anionic groups. These anionic groups produce net negative charge inside the cell which must be balanced by positively charged counter-ions such as Na^+, K^+, Mg^{2+}, and Ca^{2+}. As non-diffusible anions produce Donnan effect i.e. unequal distribution of ions across the membrane, a multitude of such anions cause unequal distribution of almost all ions as we can see in the figure.



TOPIC-13 ACTIVE TRANSPORT AND Na^+/K^+ PUMP

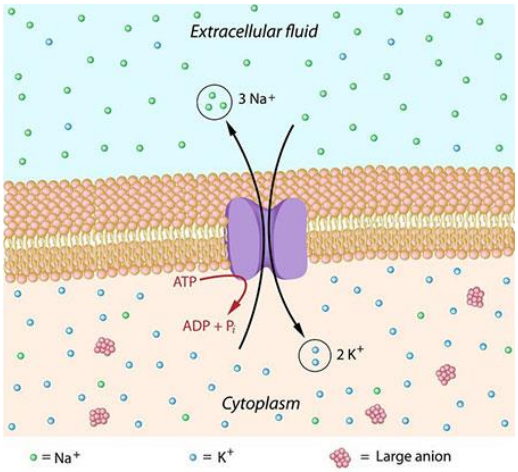
The distribution of ions across cell membranes, through passive mechanisms, is at true equilibrium only in dead cells.

All living cells continuously spend chemical energy to maintain the transmembrane concentrations of solutes far away from equilibrium. This requires uphill movement of solutes against the concentration gradients. Energy is typically supplied in the form of ATP. As this process requires expenditure of energy, it is called as active transport.

The active transport of solutes is carried out by specialized carrier proteins which can move solutes across the plasma membrane against their concentration gradients.

The mechanisms that involve carrier proteins to actively transport substances against a gradient are collectively called membrane pumps.

The Na^+/K^+ Pump as a Model of Active Transport:



Many of the features of active transport are demonstrated in the system that maintains steep concentration gradients for Na^+ and K^+ in the cell, known as Na^+/K^+ Pump.

- The concentration of K^+ is about 10-20 times higher inside cells than outside, while the opposite is true for Na^+.
- These concentration differences are maintained by a Na^+/K^+ pump found in the plasma membrane of virtually all animal cells.
- This pump is a carrier protein known as Na^+/K^+ ATPase which is an antiport that couples the transfer of Na^+ and K^+ in opposite directions.
- The transfer process involves obligatory exchange of three Na^+ ions from inside with two K^+ ions from outside the cell at the expense of one ATP molecule.
- This unequal stoichiometry of Na^+/K^+ pump makes it an electrogenic pump because of net transport of charge across the membrane, that contributes to membrane potential.

Important features of active transport and Na^+/K^+ Pump:

We shall discuss active transport by taking Na^+/K^+ Pump as a Model.

1. ***Active transport takes place against substantial concentration gradients.***

2. ***The active transport systems exhibit a high degree of selectivity.***

3. ***ATP is required as the source of chemical energy.*** Metabolic poisons that stop the production of ATP bring active transport to a halt.

4. ***Energy for active transport is released by the hydrolysis of ATP by enzymes (ATPases) present in the membrane.*** ATPases are the enzymes that catalyze the hydrolysis of ATP into ADP and

inorganic phosphate. Associated with the Na^+/K^+ pump are Na^+ and K^+ activated ATPases, while Calcium-activated ATPases are associated with calcium-pumping membranes.

5. ***Certain membrane pumps exchange one kind of molecule or ion from one side of the membrane for another kind* of *molecular or ion from the other side.*** The Na^+/K^+ antiport features active outward transport of Na^+ with simultaneous inward transport of K^+ by the sodium-potassium pump. This process involves the obligatory exchange of two potassium ions from outside the cell for three sodium ions from inside the cell.

6. ***Some pumps perform electrical work by producing a net flux of charge.*** For example, the Na^+/K^+ exchange pump produces a net outward movement of one positive charge per cycle in the form of three Na^+ ions exchanged for only two K^+ ions. Ionic pumps that produce net charge movement are said to be rheogenic because they produce a transmembrane electric current. If the current produces a measurable effect on the voltage across the membrane, the pump is also said to be electrogenic. The sodium-potassium pump is the major electrogenic pump of animal cells.

7. ***Active transport follows Michaelis-Menten kinetics and exhibits competitive inhibition by analog molecules.*** Both behaviors are characteristic of enzymatic reactions.

The Na^+ pumping activity of ATPase can be blocked by the inhibitor Ouabain, resulting in an increase of intracellular sodium.

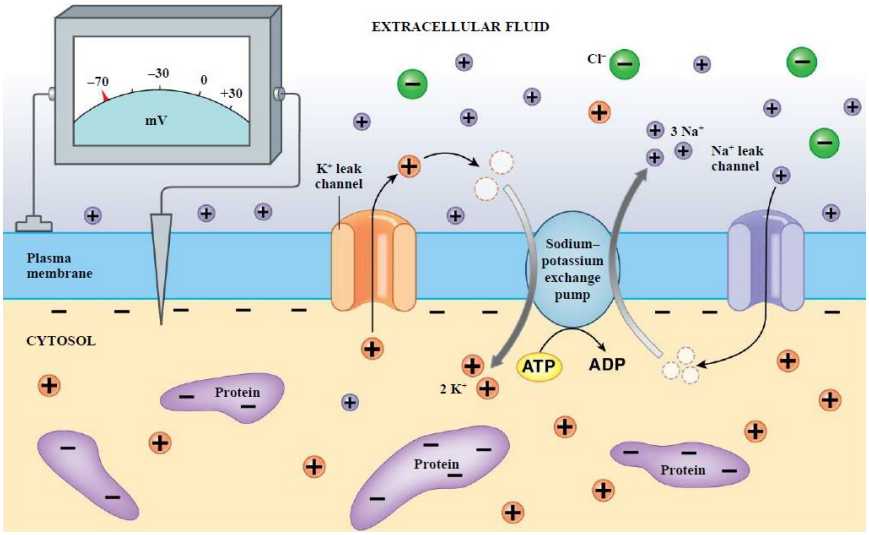
TOPIC-14 MEMBRANE POTENTIAL AND MEMBRANE EXCITATION

Membrane potentials:

All electrical phenomena in the cells and particularly neurons depend on transmembrane potential difference, generally called as membrane potential, V_m. This potential difference is electrochemical in nature. This potential difference is the basis of generation of signals which are used by neurons in communication and muscles in contraction.

Membrane potential arises from two features found in all eukaryotic cells:

1. the concentrations of several ions inside the cell are different from their concentrations in the fluids outside the cell. These concentration gradients are maintained at the expense of metabolic energy.
2. the ion channels in the membrane are selectively permeable to different ionic species.



Membrane potential: ranges

By convention, the membrane potential is always taken as the intracellular potential relative to the extracellular potential and is expressed in millivolts (mV).

The membrane potential varies with physiological states of the cell and ranges between -30 to -100 millivolts (mV) in different types of cells.

The minus sign indicates that the cytoplasm inside of the cell is negatively charged relative to the extracellular fluid. This is because of an unequal distribution of anions and cations on opposite sides of the membrane.

Electric field across the membrane:

The entire potential difference is localized across the surface membrane and the regions immediately adjacent to the interior and exterior surfaces of the membrane.

This potential difference constitutes an electrical gradient that acts as an energy source to move ions across the membrane.

The electric field (E) is measured as the voltage (V) in volts divided by the distance (d) in meters. So,

$$E = V/d$$

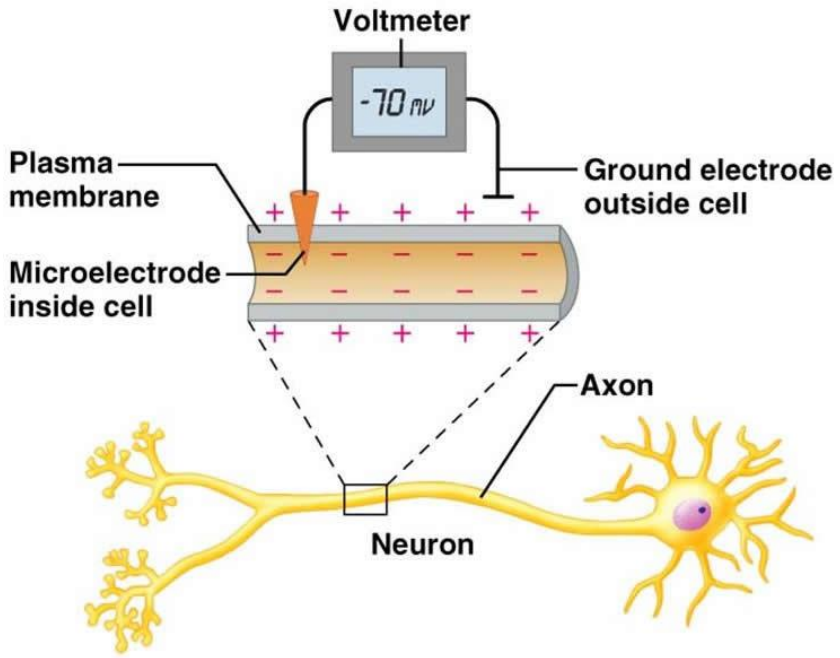
Considering the distance (d) in terms of the thickness of the membrane, which is approximately 5 nm, we can conclude that the actual electric field across cell membranes is very large.

Voltage Clamp Method: Detection and measurement of membrane potentials

Electric currents are generated in living tissues due to a net flux of charged particles across the membrane.

Such currents can be detected directly by the Voltage Clamp method. In this method two electrodes are used. One electrode is placed in the cytosol and the other is placed in the extracellular medium. The two electrodes detect the voltage, or potential difference, between the cytosol and the extracellular fluid.

Classical instrument used for the recordings of membrane potentials was an oscilloscope. Now advanced digital equipments have been invented that are operated through computers and display data during experiments.



Membrane excitation

Although a stable voltage (or potential difference) exists across the plasma membrane of all animal cells, only the membranes in electrically excitable cells (e.g., neurons, muscles, and sensory cells) can respond to changes in the potential difference by generating action potentials.

When a stimulus (i.e. an ionic current) is received on the surface membrane of an excitable cell, it decreases the potential difference across the membrane i.e. the potential difference becomes less negative. This is known as depolarization. Depolarizing causes the opening of voltage-gated Na^+ channels in the membrane. This results in an influx of sodium ions into the cell that triggers an action potential.

The opening of voltage-gated Na^+ channels in response to depolarization, and the resulting flow of Na^+ ions into the cell, is known as membrane excitation.

TOPIC-15 ROLE OF ION CHANNELS IN ELECTRICAL RESPONSES

Many proteins in the plasma membrane form the ion channels that function in the passive and active electrical responses of excitable cells.

Resting K^+ selective channels:

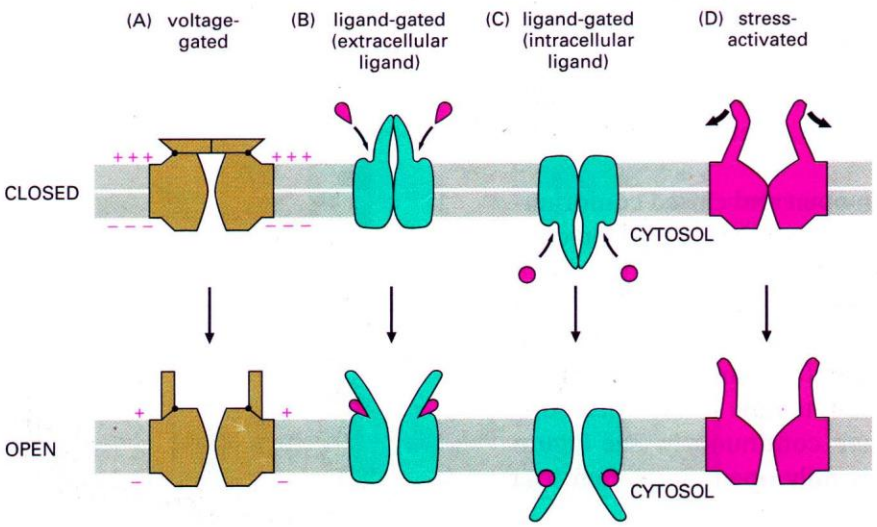
- The resting K^+ selective channels are uniformly distributed over the entire membrane of excitable cells and always remain open.
- They are largely responsible for maintaining the resting potential, V_{rest}, across the cell membrane.
- These channels are also responsible for the passive change in membrane potential (V_m) that occurs in response to hyperpolarization or depolarization.

Voltage-gated ion selective channels:

- Numerous voltage-gated ion selective channels are responsible for nearly all active electrical signals in the living tissues.
- These are the ion channels that make the cell membranes excitable and are mainly localized to particular areas of excitable cells e.g. the axonal membrane of neurons.
- The active changes in membrane potential (V_m) that occur in excitable cells in response to depolarization of the membrane depend on the opening or closing (i.e. gating) of voltage-gated ion-selective channels.
- These gated channels control the flow of ionic currents that are generated due to the electrochemical gradients of different ionic species.
- Most membrane channels exhibit some degree of ion selectivity. They allow only one or a few species of ions to pass through them much more readily than any other ions.
- The voltage gated ion selective channels are named for the ionic species that normally moves through them. The main voltage-gated ion channels include voltage-gated Na^+ channels, voltage-gated Ca^{2+} channels, voltage-gated K^+ channels and Ca^{2+} activated K^+ channels.
- The voltage-gated Na^+ channels are fast-acting channels. They are activated by depolarization and produce rising phase of action potential.
- The voltage-gated Ca^{2+} channels are activated by depolarization but more slowly than Na^+ channels. They allow Ca^{2+} ions to enter the cell, where they act as second messenger.
- Voltage-gated K^+ channels are also known as “delayed rectifiers”. They allow potassium ions to flow out of the cell and rapidly repolarize the membrane to terminate an action potential.
- The Ca^{2+} activated K^+ channels are activated by depolarization and elevated cytoplasmic concentration of Ca^{2+} ions. They remain open as long as cytoplasmic calcium ion concentration remains high.

Ligand-gated ion channels

- The ligand-gated ion channels are activated when specific ligand molecules bind to receptor proteins present in the cell surface membrane.
- The ligands that activate these channels are the second messenger molecules and neurotransmitters.
- Ligand binding causes a conformational change in the channel protein that leads to the opening of the channel gate and resulting in ion flux across the plasma membrane.



Stimulus-activated ion channels:

Some ion channels are activated by specific stimulus energies. These are found in sensory receptor cells.

For example:

- Specific ion channels in photoreceptors are stimulated by light.
- Some ion channels in taste buds and olfactory neurons are activated by chemicals.
- Certain ion channels in mechanoreceptors are activated by mechanical strain.

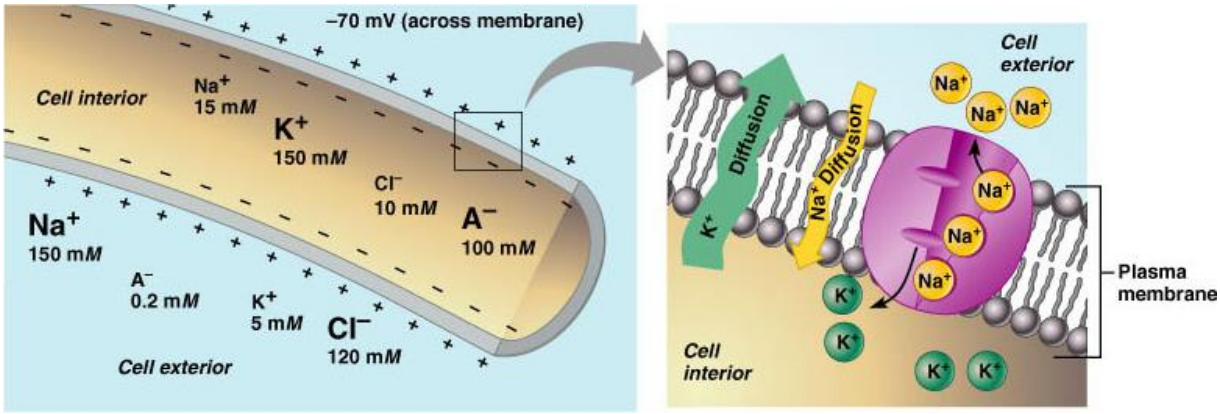
TOPIC-16 RESTING MEMBRANE POTENTIAL

Every cell that is in a non-excited or "resting" state has a potential difference, V_{rest}, across its membrane. The values of V_{rest} vary in different types of cells. Generally the reference value of resting membrane potential in neurons is taken as -70mV, when no impulse is being conducted.

Most of the biological membranes are permeable to more than one ion. All these diffusible ions influence the potential across a membrane in proportion to the permeability of the membrane to each of the ionic species present.

The major ions that are responsible for the resting membrane potential are K^+, Na^+ and Cl^-.

The nondiffusible ion species (e.g. large organic ions inside the cells) have no effect on membrane potential, because non-permeating ions cannot carry charge from one side of the membrane to the other.



Calculating the effect of single ion species on membrane potential—Nernst Equation:

If a membrane is permeable to only one species of ions, the distribution of that ion will dictate the transmembrane potential. This can be predicted by using the Nernst equation for that ionic species.

The Nernst equation describes the equilibrium potential of a diffusible ion in terms of absolute temperature, the valence of the ion and the ratio of concentration of ion on both sides of the membrane:

$$E_x = \frac{RT}{zF} \ln \frac{[X]_I}{[X]_{II}}$$

In which:

- E_x is the equilibrium potential for ion X.
- z is the valence of ion X
- $[X]_I$ and $[X]_{II}$ are the concentrations of ion X on sides I and II of the membrane.

Calculating the effect of multiple ions on membrane potential–Goldman's Equation:

The value of resting membrane potential (V_{rest}) is possible to predict by calculating the effect of multiple ions with the help of Goldsman equation.

$$E_{ions} = \frac{RT}{F} \ln \frac{P_K[K^+]_o + P_{Na}[Na^+]_o + P_{Cl}[Cl^-]_i}{P_K[K^+]_i + P_{Na}[Na^+]_i + P_{Cl}[Cl^-]_o}$$

in which:

- E_{ions} is the equilibrium potential of the ions
- R is the gas constant
- T is the absolute (Kelvin) temperature
- F is the Faraday constant (96,500 coulombs/gram equivalent charge)
- P_K, P_{Na}, and P_{Cl}, are the permeability constants for the major ion species.
- $[K^+]_i$ and $[K^+]_o$ indicate the concentrations outside and inside the cell, respectively.

These relationships described by the Nernst and Goldman's equations apply equally well to all excitable cells i.e. neurons and muscle cells. This emphasizes the fact that the important functional elements among excitable cells remained conserved during the course of evolution.

Role of ion channels in maintaining resting membrane potential:

Resting potentials of muscle, nerve and most other cells have been found to be far more sensitive to changes in the $[K^+]_o$ than they are to changes in the concentrations of other cations.

This is due to the relatively high permeability of cell membranes to K^+ as compared to other cations.

The high permeability of K^+ is due to a set of K^+ selective channels that remain open in the resting membrane.

Large changes in $[Na^+]_o$ have little effect on the resting potential, because the resting membrane is relatively nondiffusible to Na^+ as sodium channels are closed in resting membrane.

Role of Active Transport in producing resting membrane potential:

In addition to the ion gradients, another factor that contributes to establish resting membrane potential is the active transport because it moves particular ions across the cell membrane against their concentration gradients and hence results in their asymmetrical distribution.

TOPIC-17 ACTION POTENTIALS

Action potentials are the type of signals that neurons use to send information over long distances.

Definition:

Actions potentials are large but brief changes in V_m that are propagated along axons. These changes propagate without decrement i.e. once an AP is initiated in a neuron, the signal travels along the cell membrane, producing the same amount of change in V_m at every point.

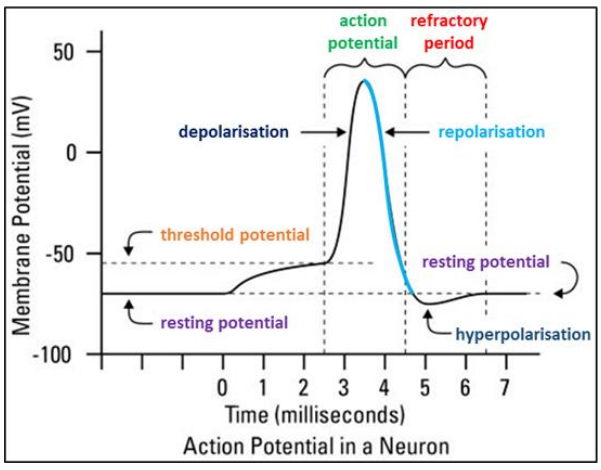
Importance of action potentials:

- APs in the nervous system are responsible for every sensation, every memory, every thought—indeed every impulse to act in the environment.
- The action potentials carry information over long distances in nerve and muscle tissues.
- They also control:
    - effector responses
    - activation of electrically gated ion channels
    - muscle contraction
    - exocytosis

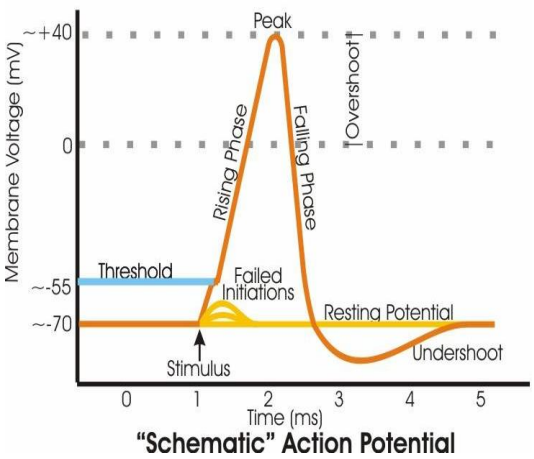
Phases of Action Potential:

The course of the action potential can be divided into five phases:

- Stimulation
- Rising phase (Depolarization)
- Peak phase
- Falling phase (Repolarization)
- Undershoot (afterhyperpolarization)



Action Potential in a Neuron

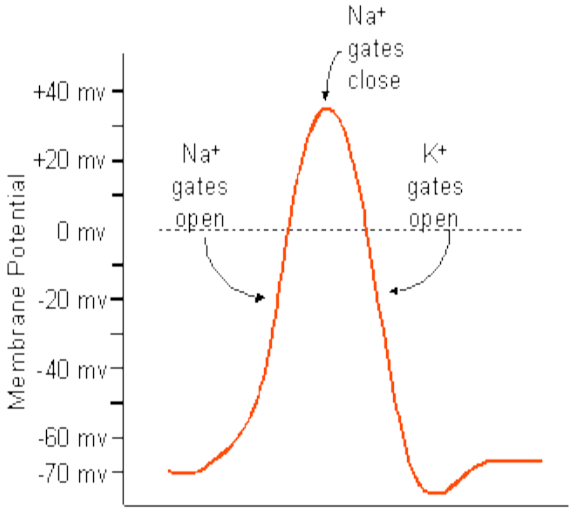


"Schematic" Action Potential

Stimulation

A typical action potential begins at the axon hillock when an effective stimulus (threshold or suprathreshold) that increases the V_m is applied. It causes some voltage-gated Na^+ channels to open and sodium ions start to diffuse in through these channels along their electrochemical gradient. Being positively charged, sodium ions begin a reversal in the potential difference across the membrane. This causes a local depolarization of the membrane.

A depolarization of about -55mV is threshold, for most mammalian neurons, that triggers an action potential.



Rising phase (Depolarization)

As sodium ions enter and the membrane potential becomes less negative, more sodium channels open, causing an even greater influx of sodium ions due to positive feedback. As potassium channels are still closed, the sodium current dominates and the membrane potential becomes positive inside, towards the sodium equilibrium potential (E_{Na}).

The peak phase

The positive feedback of the rising phase slows and comes to a halt as the sodium ion channels become maximally open.

At this point the membrane potential reaches a maximum, close to the sodium equilibrium potential E_{Na} ~ +55mV. This phase is called the peak phase. At this stage further depolarization stops.

The very brief period when V_m is inside-positive is called the overshoot

Falling phase—Repolarization

The raised membrane potential has two major effects that produce the falling phase of the action potential:

- Most of the voltage-gated Na^+ channels start closing, preventing further influx of sodium ions.
- The voltage-gated potassium channels begin to open permitting K^+ outflow, driven by the potassium concentration gradient.

These changes in sodium and potassium permeability cause V_m to drop quickly towards E_K (~-58 mV). This causes the reversal of the membrane potential to negative-inside and repolarization of the neuron.

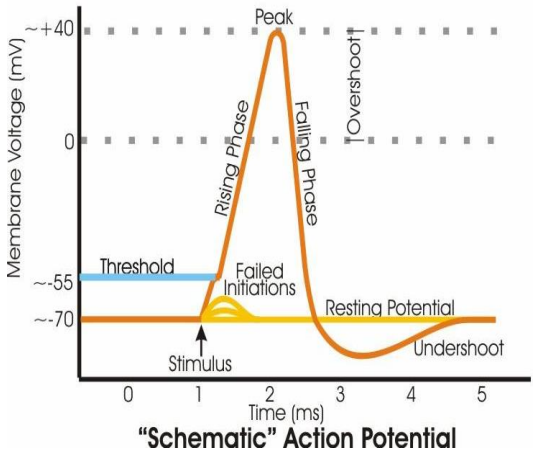
Undershoot or afterhyperpolarization

- The membrane repolarization due to the exit of potassium ions initiates the closing of voltage-gated potassium channels.
- Closing of these channels is both voltage and time dependent.

- Usually, voltage-gated potassium channels do not close immediately in response to a change in membrane potential, that is why they are known as delayed rectifiers.
- As a result, potassium continues to flow out of the cell even after the membrane has fully repolarized.
- Thus the membrane potential dips below the normal resting membrane potential of the cell for a brief moment i.e. membrane becomes hyperpolarized. This brief hyperpolarization is termed as undershoot or afterhyperpolarization.
- It persists until the membrane potassium permeability returns to its usual value.

TOPIC-18 GENERAL PROPERTIES OF ACTION POTENTIALS

1. Action potentials are also called as spikes and nerve impulses. APs are generated by the plasma membranes of neurons and muscle cells, as well as by some receptor and secretory cells.
   Action potentials differ in different types of cells due to different channel properties.
2. **Threshold potential**
   A stimulus generates short pulses of depolarizing current across the membrane of a nerve cell. These pulses produce passive depolarization until the current delivered is strong enough to depolarize the membrane to its threshold potential, whereupon an AP is triggered.
   The minimum strength of stimulus that can produce action potential is called a threshold stimulus.
   Most neurons have threshold potentials between -30 mV and -50 mV.
3. **Sub-threshold stimulus**
   If the depolarization is just too small to reach threshold, there may be an abortive, nonpropagated excitation called "a local response", which is simply the beginning of an AP that died out before it could be triggered.
   Such a stimulus that is too weak to produce an action potential is called a Subthreshold stimulus.



"Schematic" Action Potential

4. **Action potentials are "All-or-None" events**
   On application of a stimulus, an excitable membrane either responds with a maximal or full-fledged action potential that spreads along the nerve fiber, or it does not respond with an action potential at all. This property is called the all-or-none law.

   It refers to the fact that there is no "in-between" action potential.

   This is similar to firing a gun. Either the trigger is not pulled sufficiently to fire the gun (subthreshold stimulus) OR it is pulled hard enough to fire the gun (threshold is reached). Squeezing the trigger harder does not produce a greater explosion, just as pulling the trigger halfway does not cause the gun to fire halfway.
5. **APs are regenerative**
   Once the threshold potential is reached, the AP becomes regenerative; that is, the event becomes self-perpetuating, and V_m continues to change with no further stimulus required.
6. Action potentials propagate along nerve fibers without any reduction in amplitude. The speed of propagation is also constant.
7. As long as threshold is surpassed, the shape, magnitude, and time course of all APs produced by a particular cell type are essentially identical. Any additional increases in stimulus strength do not lead to increases in the magnitude.
8. **Time duration of APs**
   In mammalian neurons, APs typically last only a millisecond or so.
   In many invertebrate species, APs can last as long as 10-or even 100-milliseconds.
   In other types of excitable cells in vertebrate animals (e .g. heart muscle cells), each AP can last as long as half a second.

9. The number of ions that are moved inside or outside the membrane during different phases of action potential is relatively small. It means that only a small number of ions diffusing across the membrane cause the membrane to depolarize or repolarize.
   For example, in a squid giant axon, the number of Na^+ that cross the membrane during depolarization represents an increase of only 0.00003% of the total intracellular Na^+ concentration.

TOPIC-19 GENERAL PROPERTIES OF ACTION POTENTIALS (continued)

10. **Refractory period**

    Each action potential is followed by a refractory period.

    The time during which a subsequent action potential is impossible or difficult to fire is called the refractory period.

    Absolute refractory period

    A membrane that has just fired an action potential cannot fire another one immediately, since the ion channels have not returned to the deactivated state. The period during which no new action potential can be fired is called the absolute refractory period.

    Relative refractory period

    At longer times, after some but not all of the ion channels have recovered, the axon can be stimulated to produce another action potential, but with a higher threshold, requiring a much stronger depolarization. The period during which action potentials are unusually difficult to evoke is called the relative refractory period.

    Significance of refractory period

    - The Refractoriness, or diminished excitability, during and immediately after the Action potential permits the propagation of discrete impulses and prevents fusion or summation of impulses.
    - This intermittent, i.e. Not continuous conduction of nerve impulses is one of the reasons why a nerve fibre can respond to continuous stimulation for hours without getting tired. Thus, it decreases fatigue in a nerve fibre.
    - Only a certain number of Action Potentials can be produced in a nerve fibre because the interval between any 2 action potentials cannot be shorter than the Absolute Refractory Period. This prevents fatigue of the nerve fibers and sets an upper limit on the maximum numbers of AP that can be produced in a nerve fibre in a given period of time.
    - The refractory period ensures the one-way propagation of the action potential down the axon away from the initial site of activation.

11. **Accommodation**

    If a neuron is stimulated by a series of subthreshold depolarizations, a time-dependent decrease in excitability occurs (i.e., the threshold potential increases).

    For example, if the membrane is depolarized gradually with a current of steadily increasing intensity, a greater depolarization is required to elicit an AP than when the stimulus has an abrupt onset. The slower the rate of increase in the intensity of the stimulating current, the greater the increase in threshold potential.

    This characteristic of excitable membranes is called accommodation. It results from time-dependent changes in the sensitivity of membrane channels to depolarization.

12. **Adaptation**

    When neurons are stimulated continuously by a current of constant intensity, some neurons adapt rapidly and stop generating more APs after one or two initial action potentials at the beginning of the stimulus period.

    These neurons are said to have a phasic response.

    Some neurons accommodate more slowly and therefore fire repetitively, but gradually decreasing frequency, in response to a prolonged constant-current stimulus. These neurons are said to have a tonic response.

    This difference among neurons plays a key role in how sensory neurons transmit information.

    The reduction in the frequency of action potentials that is typically seen in a neuron during a sustained stimulus is termed as adaptation.

TOPIC-20 IONIC BASIS OF ACTION POTENTIAL

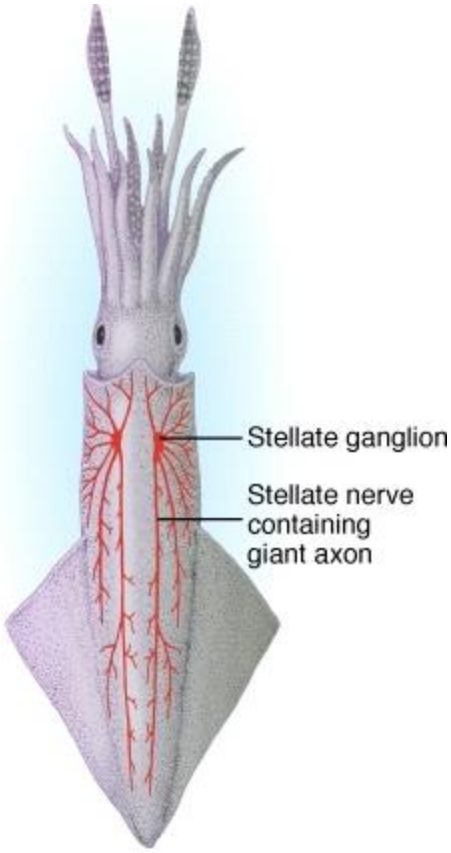
An action potential results from ion movements through the voltage-gated sodium and potassium channels. Membrane depolarization opens both types of channels, but they respond independently and sequentially.

The production of an action potential depends on:

- The unequal concentration of ionic species generates an electrochemical gradient across the membrane that provides a source of potential energy.
- The plasma membrane of a resting neuron contains many open potassium channels but only a few open sodium channels. However, when neurons are active, membrane permeability and membrane potential change. The changes occur because neurons also contain voltage-gated ion channels that open or close in response to stimuli. This gating of ion channels forms the basis of nearly all electrical signaling in the nervous system. The opening or closing of ion channels alters the membrane's permeability to particular ions, allowing ionic currents, driven by electrochemical gradients, to flow through the channels which in turn alter the membrane potential.
- Two types of voltage-gated ion channels, Na^+ and K^+ channels are involved in producing action potentials. These two channel types are quite different from the Na^+/K^+ pump and passive channels involved with resting membrane potential. The Na^+ and K^+ channels responsible for the action potential have different properties from one another, and their interdependent activity is responsible for essentially all features of the action potential.

TOPIC-21 VOLTAGE-GATED ION CHANNELS — LOCALIZATION AND CHARACTERIZATION:

Discovery of voltage-gated ion channels — Hodgkin and Huxley's experiments:



Much of what we know about how action potentials are generated rests on experiments carried out by A. L. Hodgkin and A. F. Huxley in the 1940s and 1950s on giant axons found in squids.

These experiments revealed that the membrane conductance of sodium and potassium ions i.e. (g_{Na} and g_K) change during an action potential.

To explain these observations, Hodgkin and Huxley hypothesized that these changes in conductance permitted ions to move across the membrane and the resulting ionic currents caused the AP.

Based on their elegant experiments, they predicted the presence of membrane channels in neurons that must characterize the macroscopic properties of the APs. However, they could not reveal the precise nature of these voltage-gated conductance channels, the basis for their selectivity, or how they are activated.

Molecular nature of ion channels:

In the years to follow, two important advances contributed significantly to our understanding of membrane channels.

- First, techniques (such as patch-clamping technique) were developed for measuring ionic currents across small regions of the cell membrane, even from one single ion channel.
- Second, the techniques of protein chemistry and molecular biology made it possible to identify the membrane proteins that constitute the channels.

We now have a clear and consistent view of the molecular, protein nature of ion channels. And we now know how these channels help to change the conductance of a membrane to particular ionic species.

Localization and characterization of voltage-dependent channels—Role of Neurotoxins:

- Localization and characterization of voltage-dependent channels has been facilitated by several naturally occurring neurotoxins that bind to specific channels.
- One particularly potent and useful toxin is tetrodotoxin (TTX) obtained from the Japanese puffer fish.
- TTX selectively blocks fast-acting, voltage-gated Na^+ channels.
- When radioactively labeled TTX molecules are added to the extracellular fluid, they bind to Na^+ channels.

- Examination of neurons labeled by this technique has allowed the density of bound molecules, and hence of Na^+ channels, to be estimated.

More recently, antibodies to the channel proteins have been developed, allowing the molecules to be labeled and viewed directly.

TOPIC-22 VOLTAGE-GATED SODIUM (Na^+) CHANNELS

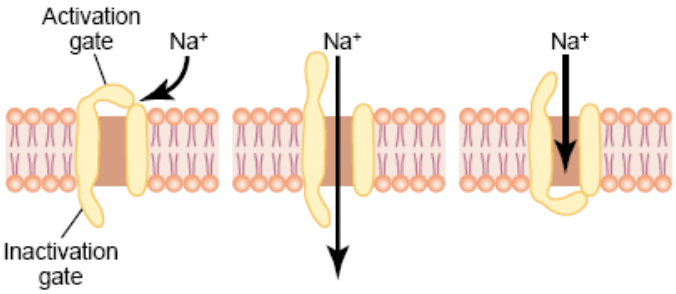
These channels are highly sensitive to voltage changes, so they are called as fast-acting Sodium channels.

They are activated when a stimulus causes depolarization of membrane. Their opening results in inward flow of Na^+ ions that produce rising phase of action potential.

The sodium channels consist of protein molecules that are inserted in the lipid bilayer of the plasma membrane.

The channel has two gates:

- one on the outside called activation gate
- other on the inside called inactivation gate.



Density of Na^+ channels in axons:

The Na^+ channels are not very densely packed in the axonal membranes of neurons.

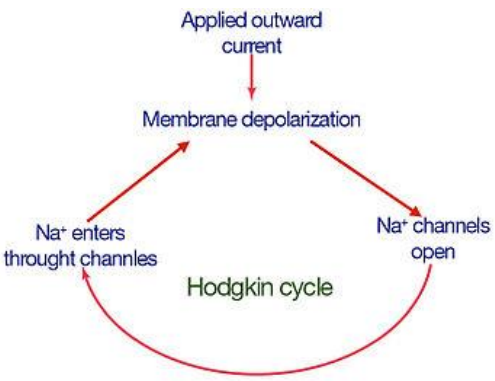
Membranes have about 500 Na^+ channels per μm^2, occupying only 1/100 (1%) of the total surface area.

Each channel can pass up to 10^7 (10 million) Na^+ ions per second, providing enough I_{Na} (sodium current) to account for the macroscopic currents that have been measured in various neurons.

Opening and closing of Na^+ channels—the Hodgkin cycle: **[Whole topic re-write from ppts]**

The number of Na^+ channels open at any instant depends on V_m as well as on time i.e. the phase of action potential.

Thus changes in the conductance of sodium ions (g_{Na}) occur as a function of V_m and time and reflect the behavior of thousands of Na^+ channels, each one opening and closing during depolarization in accord with certain principles.



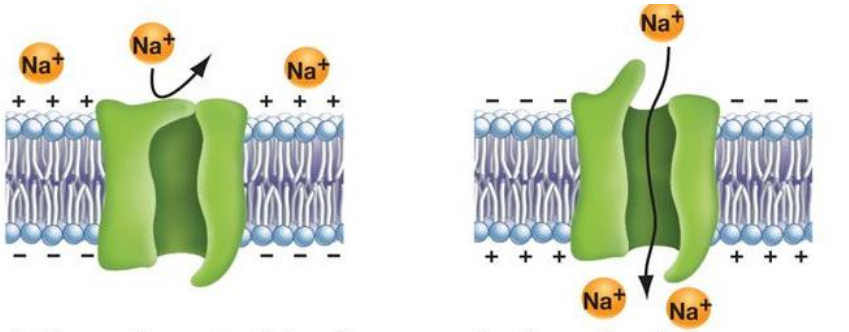
During an AP, Na^+ channels respond to an initial depolarization by opening, allowing Na^+ to enter the cell, which further depolarize the membrane. This depolarization causes more channels to open, allowing still more Na^+ to enter the cell and triggering an explosive,

regenerative event. This relationship between membrane potential and sodium conductance is termed as the **Hodgkin cycle** and represents a type of positive-feedback system.

Mechanism of opening and closing of Na^+ channels:

- Depolarization causes changes in membrane potential.
- Changes in V_m regulate the opening and closing of channels.
- This happens because the channel proteins bear a net charge, so, a change in V_m produces an emf on the charge.
- The emf causes the charge to move in space.
- Movement of charge causes conformational change in the protein molecule.
- This results in opening of the channel and sodium conductance (g_{Na}) increases through the channel.

This movement of charge also corresponds to a small gating current (I_g) that is associated with the opening and closing of channels.



At the resting potential, voltage-gated Na^+ channels are closed.

Conformational changes open voltage-gated channels when the membrane is depolarized.

Selectivity of Na^+ channels:

The selection of ions by channels depends on the size and charge of the permeating ions. The cation-selective Na^+ and K^+ channels have negative charges located at their outer ends, so they attract cations and repel anions.

A channel's selectivity is indicated by its relative permeability for various ion species.

For example the permeability of the Na^+ channel for Na^+ ion is 1.00, while its permeability for Li^+ is 0.93 and for K^+ ions it is only 0.09.

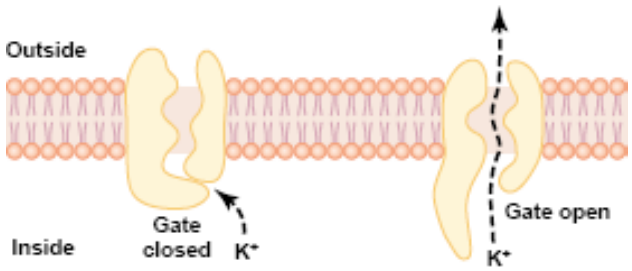
TOPIC-23 VOLTAGE-GATED POTASSIUM (K^+) CHANNELS

Size:

The voltage-gated potassium channels are slightly smaller than the sodium channels. The channel size is 0.3 by 0.3 nanometer as compared to sodium channel size of 0.3 by 0.5 nanometer.

Channel Gates:

The channel gates are on the intracellular ends of the potassium channels, so the opening of these channel gates results in the outflow of K^+ ions.



Opening of K^+ Channels:

These channels remain closed in a resting neuron. They open during the action potential when the inside of the cell membrane becomes positively charged by depolarization of the membrane.

Delayed Rectifiers:

Voltage-gated K^+ channels respond more slowly to voltage changes as compared to the voltage-gated Na^+ channels. That is why these K^+ channels are also known as “delayed rectifiers”.

Effect on Membrane Potential:

The membrane conductance for potassium ions (g_K) begins to increase when AP is near its peak, and remains high in the falling phase. This results in a net outward flow of K^+ ions.

The outward flow of K^+ ions through the voltage-gated K^+ channels brings the membrane potential closer to equilibrium potential for potassium i.e. E_K which is -90 mV at 37°C.

As the membrane potential approaches E_K, the separation of charge i.e. polarization, increases. This increase in the magnitude of membrane potential is called hyperpolarization that terminates an action potential.

Fundamentally, the voltage-gated K^+ channels do not inactivate, as do voltage-gated Na^+ channels. Instead, their conductance to ions g_K decreases according to the V_m.

The role of voltage-gated K^+ channels is not to generate Action potentials, but they are involved in the acceleration of membrane repolarization. So the presence of more activated voltage-gated K^+ channels shortens the duration of action potentials. It helps the neurons to generate Action potentials at a higher frequency. The neurons which generate action potentials of longer duration have lower number of these channels while some myelinated mammalian neurons lack them entirely.

TOPIC-24 VOLTAGE-GATED CALCIUM (Ca^{2+}) CHANNELS

Voltage-gated Ca^{2+} channels occur in virtually all cell types. They have a selective permeability to Ca^{2+} ions.

The molecular structure of these channels is strikingly similar to voltage-gated Na^{+} channels.

Activation of particular voltage-dependent calcium channels allows Ca^{2+} to rush into the cell.

Slow Activation of Ca^{2+} Channels:

Ca^{2+} channels are normally closed at resting membrane potential.

They are activated with depolarization but more slowly than Na^{+} channels, requiring 10 to 20 times as long for activation as the sodium channels.

Therefore, they are called slow channels, in contrast to the sodium channels, which are called fast channels.

Role of Ca^{2+} Channel Activation:

In neurons and skeletal muscle fibres, Ca^{2+} channels carry a part of the inward regenerative depolarizing current along with Na^{+} current.

In these cells, the I_{Ca} is not strong enough to produce an all-or-none AP without help from I_{Na}.

Ca^{2+} Channels in Smooth Muscles:

In some types of smooth muscles, the fast sodium channels are hardly present, so that the action potentials are caused almost entirely by activation of slow calcium channels.

In such smooth muscle cells, the membrane has far more voltage-gated calcium channels.

Action Potentials due to Ca^{2+} Channels

The action potentials generated due to calcium flow occur in the same self-regenerative way as occur for the sodium channels in nerve and skeletal muscle fibers.

However, the calcium channels open more slowly than the sodium channels, and they also remain open much longer. This accounts for the prolonged action potentials of these smooth muscle fibers.

<u>Role of Ca^{2+} ions:</u>

The Ca^{2+} ions that enter the cell through the Ca^{2+} channels have two functions:

- propagating an electrical signal
- acting as an intracellular messenger that triggers subsequent intracellular events e.g.
    - the release of neurotransmitters from the presynaptic terminals
    - contribute to contraction of muscles

CHAPTER-3 NERVE PHYSIOLOGY

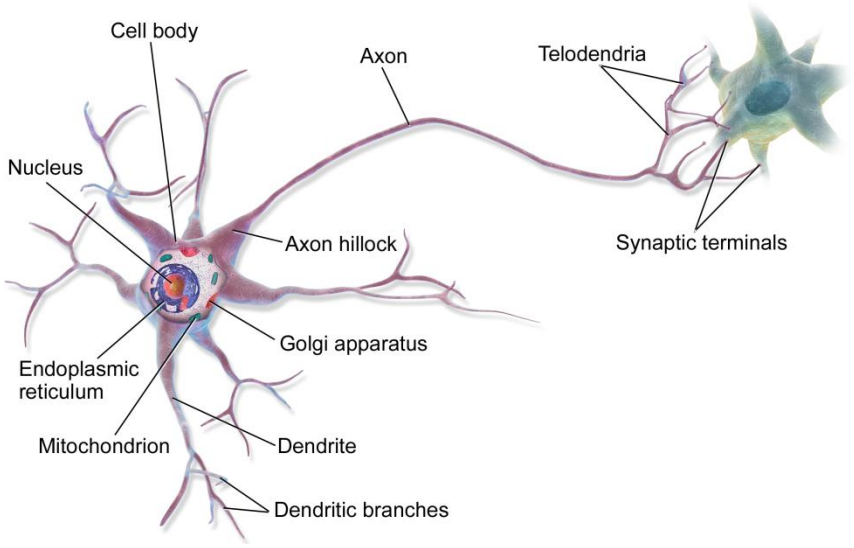
TOPIC-25 STRUCTURAL FEATURES OF NEURON

- Neurons are the structural and functional units of nervous system.
- Neurons vary considerably in shape and size.

Basic Components of Neuron

All neurons have three basic components:

1. A cell body or soma
2. Dendrites
3. Axon



STRUCTURE OF A TYPICAL NEURON
https://www.medicalsciencenavigator.com/wp-content/uploads/2014/01/Blausen_0657_MultipolarNeuron.png

1. Cell body or soma:

Shape and Size:

The cell bodies of different neurons vary in size and shape. They are found in fusiform, stellate, oval, rounded or pyramidal shapes and range in size from 5 µm to 135 µm.

Functions of the cell body

- It is the main nutritional part of the nerve cell.
- It is responsible for the biosynthesis of materials necessary for growth and metabolic maintenance of the cell.

Structural components of soma:

The cell body contains the nucleus and all cell organelles along with Nissl's bodies and neurofibrils.

Nissl's bodies

Nissl's bodies consist of a group of ribosomes and rough endoplasmic reticulum. They are associated with protein synthesis.

Neurofibrils

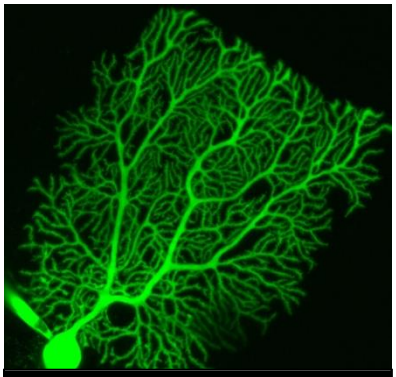
Neurofibrils are delicate threads running from cytoplasm of the nerve cell body into the axon and the dendrites. They are formed by clumping of neurotubules and neurofilaments.

Their functions are:

- transport substances from the cell body to the distal cell processes.
- give support and shape to the neuron.

2. Dendrites

- A typical neuron has numerous dendrites that extend from the cell body.
- These are short, thin and highly branched, cytoplasmic processes that receive signals from other neurons and conduct impulses towards the cell body.
- The dendrites of certain brain cells (e.g. Purkinje cells of human cerebellum) branch profusely, giving cell a tree-like appearance (hence the name derived from Greek word "Dendron" meaning tree
- The neurons with an extensive and complex dendritic tree typically receive many inputs.



A Purkinje cell
http://www.riken.jp/~/media/riken/research/riken research/figures/hi_4309.jpg

3. Axon

- An axon is a long and thick process that arises from the cell body and has a constant diameter.
- The lengths of the axons vary from few millimeters to more than a meter.
- The longest axons are seen in whales, where the axon of a single spinal motor neuron may extend many meters from the base of the spine to the muscles in the tail fin.

Axon—Functions

- The axons are specialized to conduct signals away from the cell body.
- They have evolved mechanisms that allow them to carry information for long distances with high fidelity and without loss.

Structural components of axons:

The axon contains a jelly-like semi-fluid substance called Axoplasm, surrounded by the plasma membrane which is called Axolemma.

Axon has mitochondria and ER but lacks Nissl's granules. So exons are not involved in protein synthesis.

Axon terminals:

- Each axon may divide into numerous branches at its termination. These branches of axon are called axon terminals.
- Each axon terminal has small extensions called telodendria with enlarged ends called terminal knobs. These knobs have granules or vesicles that contain neurotransmitters.
- The axon terminals allow transmission of signals to many other neurons, glands or muscle fibers simultaneously.

Axon hillock:

- The region of an axon where it joins the cell body is cone-shaped and is called the axon hillock.
- This is the region where the signals that travel down the axon are generated.

Myelin sheath:

- Specialized neuroglial cells, known as Schwann cells are located at regular intervals along the axons of many neurons.
- These Schwann cells secrete a fatty layer known as myelin sheath, over the axons.
- The myelin sheath is not continuous, but there are non-myelinated points in between, which are called Nodes of Ranvier.

Saltatory impulse

In myelinated neurons, impulses jump over node to node. Such impulses are known as saltatory impulses. This pattern in insulated axons increases the speed of nerve impulse.

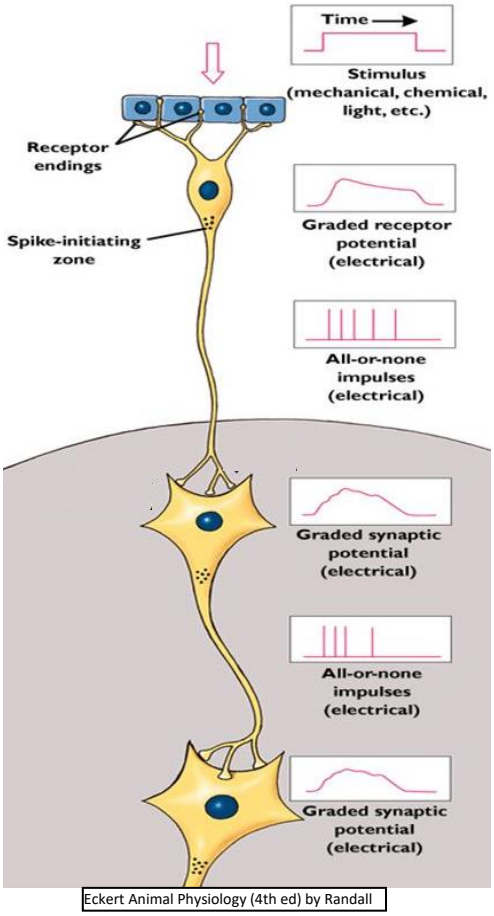
TOPIC-26 Transmission of Signals in the Nervous System

Methods of Signal Transmission:

The neuronal signals are transmitted from one neuron to the other in two forms:

- Graded, electro-tonically conducted potentials
- Action potentials

These two basic forms of transmission alternate as the information received at receptor site is passed along one neuron and transmitted on to another neuron.



Eckert Animal Physiology (4th ed) by Randall

Coding of Signals:

In the process of transmission of signals in the nervous system, a signal is coded alternately in graded potentials and in all-or-none action potentials.

Graded potentials are produced at sensory and postsynaptic membranes where short distance conduction is required.

On the other hand, all-or-none nerve impulses are generated for long-distance conduction along the axons.

Signal transmission also involves the inter-conversion between electrical and chemical methods of signal conduction as it travels through the synapses.

Signal Transmission in Nervous System: Example

Let us take an example of the transmission of a signal generated by a stimulus that is received by a sensory neuron present in a receptor organ.

Reception of Signals: Graded Receptor Potential:

When a stimulus is received at the receptor endings of a sensory neuron, it results in change in the membrane potential V_m in proportion to its strength. This potential change at the receptor site is known as receptor potential. This potential varies in a continuous fashion, so it is known as graded receptor potential.

The time course and amplitude of a receptor potential are closely related to the time course and intensity of the stimulus. So, the receptor potential is an electrical neuronal analog of the stimulus.

Spreading the signals: Passive Electro-tonic Transmission:

Depolarization due to Receptor potential spreads away from the receptor site passively through electrotonic transmission.

However, it decays over a relatively short distance.

The decay happens because the receptor part of the neuronal membrane lacks voltage-gated ion channels. So, all-or-none APs cannot be produced and signals cannot be propagated regeneratively in this part of sensory neuron.

Distant Transmission: Regenerative Action Potentials:

Passive transmission is not effective for carrying signals to terminal parts of the neuron.

For long distance transmission, the sensory signals must be transformed into APs, which can conduct signals without decrement for long distances.

The membrane at the spike initiating zone i.e. axon hillock of a sensory neuron contains the voltage gated ion channels that permit APs to start.

So, if the passively propagated depolarization of a receptor potential reaches the spike-initiating zone, the signal is transformed into action potential and can be carried without decrement along the axon of sensory neuron, which may span many meters.

Synaptic Transmission:

As the signal reaches axon terminals, it is transformed from electrically encoded signals to chemical signals (neurotransmitter molecules).

This chemical signal is transmitted across the synapses to next neuron.

Graded Postsynaptic Potentials:

The neurotransmitters cause change in the membrane potential of the postsynaptic neuron.

The change in the membrane potential of the postsynaptic neuron happens as the chemical signal is reconverted into an electrical signal.

The membrane potential generated in the postsynaptic neuron is called the postsynaptic potential (psp). The psp is a graded signal, reflecting the properties of the original stimulus.

This graded postsynaptic potential brings the spike-initiating zone of the postsynaptic neuron to threshold, triggering one or more all-or-none APs in this neuron.

Following this course of transmission, signals travel to the CNS.

TOPIC-27 Transmission of Signals in a Single Neuron

Signal Reception and Integration:

A nerve cell receives input signals through its dendrites and the membrane of its soma.

The soma integrates messages from all inputs and determines whether the signal should be transmitted to the next neuron passively or actively through action potential.

Spread of Information through a Neuron:

The information received by a neuron is in the form of a stimulus-generated local depolarization. The depolarization spreads through the neuron, away from its point of origin, by two basic mechanisms:

- Passive electrotonic conduction—in nonspiking, local-circuit neurons
- Active regenerative APs—in neurons with functional voltage-gated ion channels

Nonspiking, Local circuit Neurons

Many small neurons lack the voltage-gated ion channels and have only the resting K^+ ion channels. They are incapable of producing APs and are referred to as nonspiking neurons or local-circuit neurons. Their conductance depends only on the passive electrical properties of the membrane i.e. capacitance and resistance, also known as the cable properties.

Cable properties:

The passive electrical properties make axons comparable to electric wires, thus are known as cable properties.

The cable properties affect the speed and distance of transmission of electrical signals through the axon.

One important implication of these properties is that any current flowing longitudinally along an axon decays with distance. This decay happens because of resistance of cytoplasm and cell membrane to the flow of electrical signals. Moreover, there is no insulation surrounding the axonal membrane. So the current (that is in the form of K^+ ions flow) decreases as it can leak out of the cell across the plasma membrane at every point as it travels down longitudinally.

Passive Electrotonic Conduction of Signals in Local-circuit neurons:

Local-circuit neurons are only few millimeters in length, so the graded signals can be transmitted through passive, electrotonic conduction to the axon terminals without the aid of APs.

The amplitude of the signals in these neurons is attenuated as they spread through the cell, but the signals are still large enough at the terminals to modulate the release of a neurotransmitter.

Neurons Conducting APs

The neurons with functional voltage-gated ion channels in the axonal membranes have active electrical properties. They carry electrical signals without decrement through regenerative action potentials.

Usually the neurons with relatively longer axons generate action potentials and transmit signals to long distances.

TOPIC-28 Propagation of Action Potentials

Property of Regeneration:

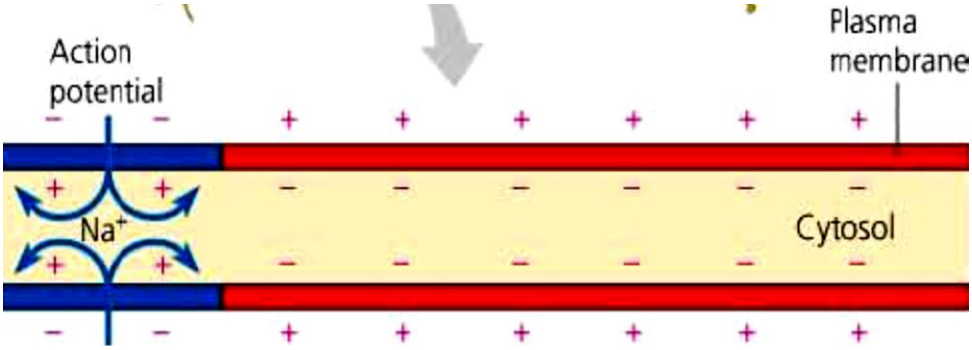
The action potentials contain the information of stimulus in electrical form. To carry this information to the central parts of the nervous system is the basic requirement of communication system. So the propagation of APs along the axons of neurons must happen. As an action potential occurs over a region of few millimeters only, the events of action potential must regenerate i.e. occur over and over again along the length of an axon.

To accomplish this, the action potential has the property of regenerating itself as it travels down from the cell body along the length of axon to the synaptic terminals. Due to this property, action potential functions as a mode of long-distance signal transmission.

Mechanism of Propagation:

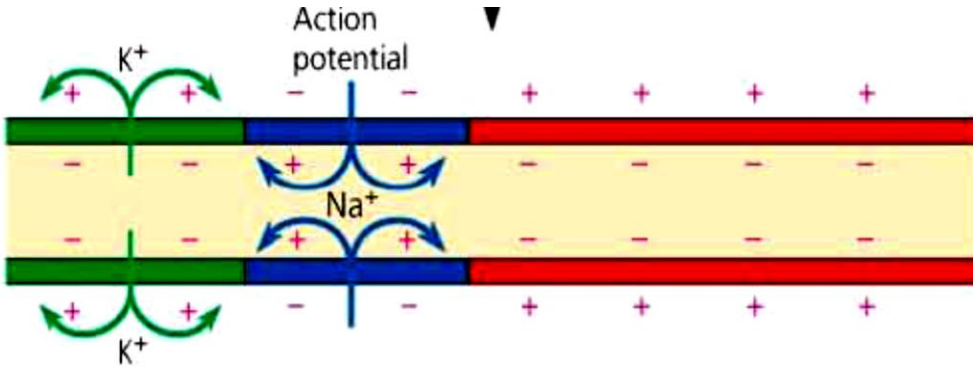
In this process, the action potential elicited at any one point on an excitable membrane, spreads excitation to the adjacent portions of the membrane, resulting in its propagation along the membrane.

The site where an action potential is initiated (usually the axon hillock), an inflow of Na^+ current starts. This initiates the rising phase of action potential.

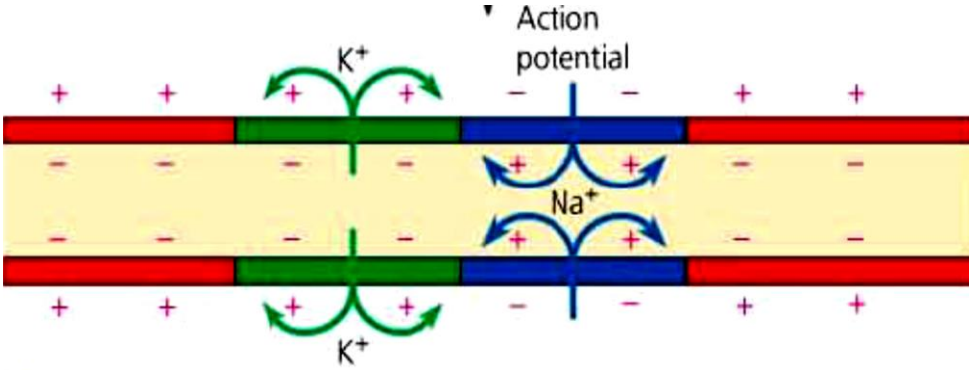


The sodium current in one region, also affects about one to three millimeters of the adjacent neighboring area of axonal membrane. This causes excitation and depolarization in this region too.

As the depolarization reaches threshold level, it acts as a stimulus for this region and an action potential is also initiated there.



Immediately behind the traveling zone of depolarization due to Na^+ inflow is a zone of repolarization due to K^+ outflow.



The depolarization-repolarization process is repeated in the next region of the membrane. In this way, local currents of ions across the plasma membrane cause the action potential to be propagated along the length of the axon.

AP Propagation is Unidirectional:

In the repolarized zone, the sodium channels become inactivated. Consequently, the inward current that depolarizes the axon membrane ahead of the action potential cannot produce another action potential behind it.

This prevents action potentials from traveling back toward the cell body. Thus, an action potential that starts at the axon hillock moves in only one direction—towards the synaptic terminals.

Propagation without Decrement

At each position along the axon, the process is identical. That is, the shape and magnitude of the action potential remain constant. It ensures propagation of initial excitation without decrement.

TOPIC-29 Speed of Propagation

Speed of Propagation of APs vs Electric Current:

- Although action potential is an electrical current, it is not due to the flow of electrons.
- The electric current produced during an action potential is actually carried by ions flowing through pores of proteins present in the membrane.
- This kind of signal travels much more slowly than electricity, which is carried by electrons flowing longitudinally through a conducting wire.
- Therefore, the speed of conduction of AP is several orders of magnitude slower than the speed of current that flows through the copper wires ($2.8x10^8$ m/s).

Speed of Propagation in Axons

- In invertebrates the speed of conduction varies from several centimeters per second in very narrow axons to about 30 m/sec in the giant axons of some arthropods and molluscs.
- The vertebrate axons have narrow diameters but can still conduct action potentials at high speed due to the presence of a myelin sheath.
- In the large axons of vertebrates, APs can travel as fast as 120 m/s while in small diameter, non-myelinated fibers it may be as low as 0.25 m/s.

Length Constant affects the speed of propagation

- The velocity of impulse propagation varies with the length constant.
- The length constant increases with axon diameter and presence of a myelin sheath.
- Wider axons conduct action potentials more rapidly than narrow ones because resistance to electrical current flow is inversely proportional to the cross-sectional area.

Length Constant: Evolutionary Trends

- Among animals, the conduction velocity of APs has increased with evolutionary increase in the length constant of axons.
- One of the ways in which the length constant has been increased (typified by the giant axons of squid, arthropods, annelids, and teleosts) is by an increase in axonal diameter, which reduces the internal longitudinal resistance.
- In the vertebrates, a single nerve can consist of tens of thousands of axons, and another mechanism, myelination, evolved to increase the length constant.

TOPIC-30 Axon Myelination and Saltatory Conduction

Myelin Sheath

- Myelin sheath is a thick and multi-layered membranous structure that surrounds many vertebrate axons.
- It is mainly composed of a fatty substance sphingomyelin.

Deposition of Myelin Sheath

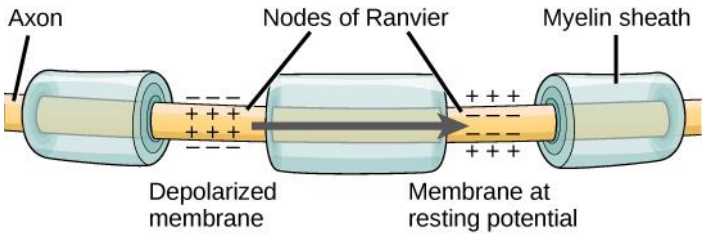
Myelin sheath is deposited around the axon during the course of development.

Two types of specialized glial cells deposit myelin sheath. These are:

- Oligodendrocytes in the CNS
- Schwann cells in the PNS

Nodes of Ranvier

- Myelin sheath is not continuous but after every 1 to 3 millimeters along the length, there are gaps having a small uninsulated area that is 2 to 10 micrometers in length. These gaps are known as Nodes of Ranvier.
- Voltage-gated sodium channels are restricted to these nodes. The extracellular fluid is in contact with the axon membrane only at the nodes. So, ion exchange can occur through these nodes between the extracellular and intracellular fluids.
- The segments of axon that lie under the myelin wrapping are called internodes.



Functions of Myelin Sheath

1. Electrical insulation
2. Increase the speed of conduction
3. Space efficiency
4. Saltatory conduction

Electrical Insulation

- The sheath mainly contains lipid substance sphingomyelin, which is a poor conductor of electrical current.
- Thus it provides electrical insulation for the axon, decreasing ion flow through the membrane about 5000-fold.
  In this way it acts as an analogue to the plastic insulation that covers many electrical wires.

Increase the Speed of Conduction

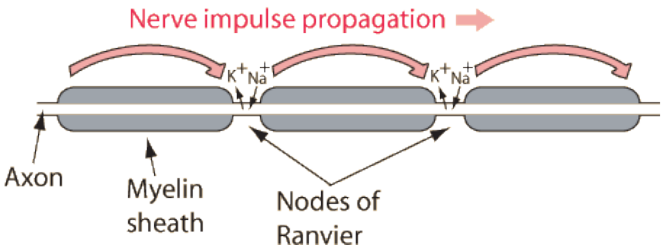
- The insulation provided by the myelin sheath increases the transmembrane resistance to ion flow and decreases the membrane capacitance.
- Both factors enhance the efficiency of longitudinal spread of current, resulting in rapid transmission of nerve impulse.
- In non-myelinated fibers the speed of nerve impulse is increased by increasing the axon's diameter.
- Myelination renders the thin axons higher conduction speed than very thick non-myelinated axons. For example, a myelinated axon that has a diameter of only 20 µm has a conduction speed faster than that of a squid giant axon having 40 times greater diameter.

Space Efficiency

- The great advantage of myelination is its space efficiency.
- Thousands of myelinated axons can be packed into the space occupied by just one giant axon.

Saltatory Conduction in Myelinated Fibers

- In myelinated fibers, ions cannot flow through the internodes that are covered by thick myelin sheaths.
- As a result, action potentials are not generated in the regions between the nodes.
- Ions can flow with ease only through the nodes of Ranvier. So the inward Na^+ current produced at a node during the rising phase of the action potential travels all the way to the next node, where it depolarizes the membrane and regenerates the action potential.
- In this way, action potential appears to jump along the axon from node to node. This mechanism of conduction is called saltatory conduction.



Significance of Saltatory Conduction

- It increases the velocity of nerve transmission 5 to 50 fold.
- It conserves energy because it reduces the loss of ions up to 100 times.

TOPIC 31 Synapses and Their Types: Electrical Synapses

Synapses

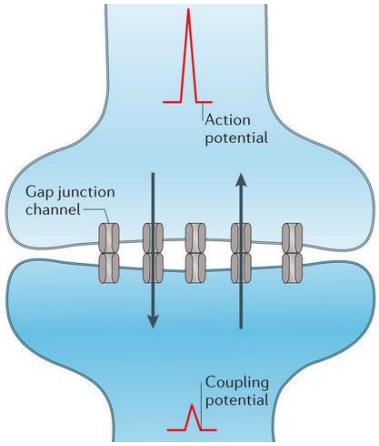
The junctions between axon terminals of one neuron and the dendrites of another neuron are known as synapses. At these junctions, transmission of signals takes place from one neuron to another.

Types of Synapses

There are two types of synapses:

- Electrical synapses
- Chemical synapses

Electrical Synapses



At electrical synapses, the plasma membranes of the pre- and postsynaptic cells are in close apposition.

They are electrically coupled by particular proteins called gap junctions present within the membranes. Electrical current can flow directly from one cell into the other through these gap junctions.

Electrical synapses transfer information between cells much rapidly as compared to the chemical synapses which transmit signals at much slower pace. However, electrical synapses are relatively rare and most signaling between neurons takes place at chemical synapses.

Signal Transmission through Electrical Synapses

The transfer of information across electrical synapses occurs purely by electrical means and does not involve any chemical transmitter. It involves the passive spread of local circuit current that depolarizes and excites the region ahead. This way of transmission is very much like signal transmission along a single axon.

Limited efficacy of electrical synapses

The electrical signal in the presynaptic cell produces a similar, but somewhat attenuated, signal in the postsynaptic cell. Due to this attenuation a single presynaptic action potential might be unable to provide enough local circuit current across an electrical synapse to elicit an action potential in the postsynaptic cell. This reduces the efficacy of electrical synapses and is considered as the basic reason why electrical synapses are less common than chemical synapses.

Advantage of electrical synapses

Electrical synapses conduct signals much more rapidly than do chemical synapses. This gives them definite advantages where rapid signal transmission is important.

The rapidity of electrical synapses makes them particularly effective in the synchronization of electrical activity within a group of cells.

It is also effective for rapidly transmitting information across a series of cell-cell junctions. For example, in the myocardium of the vertebrate heart, in which signals are passed between muscle cells.

Occurrence of electrical synapses

Electrical transmission has been discovered between cells in the vertebrate central nervous system and in the vertebrate retina, between smooth muscle fibers, between cardiac muscle fibers, between receptor cells, and between some axons of PNS.

TOPIC 32 Synapses and Their Types: Chemical Synapses

The chemical synapses

The chemical synapses are involved in chemical synaptic transmission involving neurotransmitters. This mode of synaptic transmission is more common as compared to the electrical synaptic transmission.

Types of chemical synapses

- Fast chemical synapses
- Slow chemical synapses

Fast Chemical Synapses

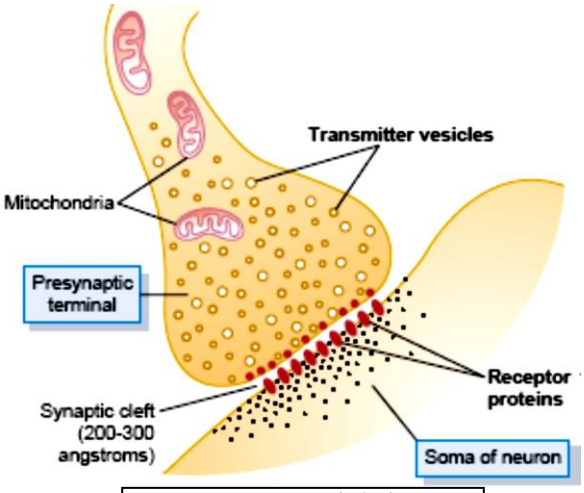
Fast chemical synapses are found in the central nervous system and at the neuromuscular junctions. Although this transmission is called "fast" it is in fact considerably slower than transmission across electrical synapses.

Neurotransmitters at Fast Chemical Synapses

- The neurotransmitters involved in fast chemical synapses are typically small molecules (e.g. Acetylcholine).
- Neurotransmitters are stored in synaptic vesicles that are small, clear vesicles in the axon terminals.

Release of Neurotransmitters

- At a fast chemical synapse, action potentials in the presynaptic neuron cause the release of neurotransmitter molecules at the axon terminals.
- Neurotransmitters are released by exocytosis into the synaptic cleft through specialized sites on the membrane.
- The synaptic cleft is a narrow, fluid-filled space, about 20 nm wide that separates the membranes of pre- and postsynaptic neurons.



Textbook of Medical Physiology (11th ed) by Guyton

Mode of Action of Neurotransmitters

- Neurotransmitter molecules bind to specific protein receptors which are ligand-gated ion channels in the postsynaptic membrane.
- This binding results in the opening of the channels that allows an ionic current to flow into the postsynaptic cell.
- The postsynaptic current causes a change in the membrane potential of the postsynaptic cell.
- If the change in membrane potential exceeds the threshold, an AP is initiated.

Slow Chemical Synapses

Transmission through slow chemical synapses takes place by a different postsynaptic mechanism.

The onset of postsynaptic response is slower (hundreds of milliseconds), but it can last much longer (from seconds to hours).

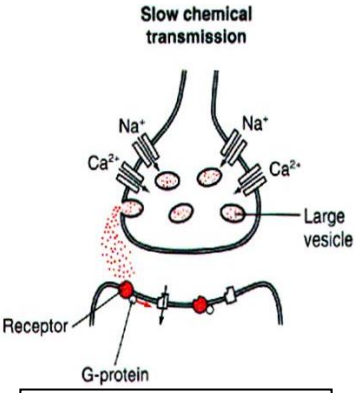
Neurotransmitters at Slow Chemical Synapses:

The neurotransmitters involved in slow synaptic transmission are:

- typically large molecules.
- synthesized from one or more amino acids.
- of two types:
  - **Biogenic amines:** are synthesized from a single amino acid
  - **Neuropeptides:** Consist of several amino acid residues.

Packaging and Release of Neurotransmitters:

- Vesicles in the slow system are larger.
- They are usually synthesized in the cell body, after which they are transported to the nerve terminals.
- Vesicles may release the transmitter molecules at many sites in the presynaptic terminal that lack morphological specialization. These sites are located away from the sites of release of fast neurotransmitters.



Eckert Animal Physiology (4th ed) by Randall

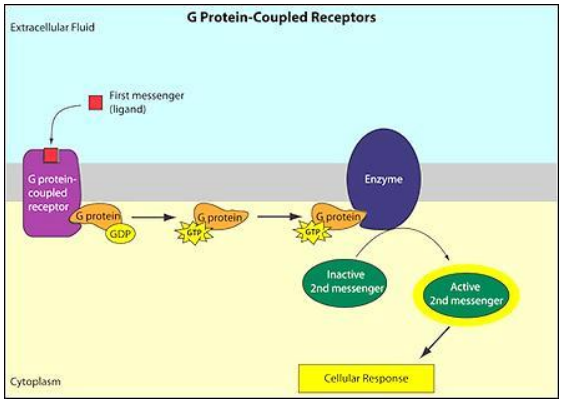
Mode of Action of slow Neurotransmitters

Slow response transmitters don't act through ligand-gated channels.

They act through G protein-linked receptors.

When a neurotransmitter binds to its receptor, the neurotransmitter-receptor complex activates a G protein.

The G protein, in turn, activates a signal transduction pathway through a second messenger e.g. cAMP.



http://signaltransductionpathway.weebly.com/uploads/3/0/8/6/30865779/612632978.jpg?446

The second messengers modify the functions of channels and other intracellular processes.

A Neuron May Produce Both Types of Transmission

Physiological and anatomical evidence indicates that single presynaptic neuron may participate in both kinds of neurotransmission and a single neurotransmitter may affect postsynaptic neurons both by means of ligand-gated channels and by means of G-protein-coupled receptors.

TOPIC-33 Mechanism of Release of Neurotransmitters

Mechanisms of release:

The release of neurotransmitter into the synaptic cleft is controlled by mechanisms that are common to both fast and slow synaptic transmission.

Two basic patterns of release of neurotransmitter are found in neurons. These are:

- Release with Action Potential
- Nonspiking release

Release of Neurotransmitter due to Action Potential

Most neurons release neurotransmitters when an action potential reaches their axon terminals.

Mechanism:

- As an AP arrives at the axon terminals, it activates voltage-gated Ca^{2+} channels, allowing Ca^{2+} to enter the terminal.
- The calcium ions bind with special protein molecules present on the inner surface of the membrane at special release sites.
- This binding causes the release sites to open through the membrane allowing the vesicles to release their transmitter into the synaptic cleft.
- An action potential and influx of Ca^{2+} into the terminal is essential for transmitter release; therefore, when the influx of Ca^{2+} drops at the end of AP, the release of neurotransmitter is also stopped.

Quantal Release of Neurotransmitters

The neurotransmitters are generally released in tiny packets called quanta. Each quantum may consist of about 2000 to 10,000 molecules of transmitter molecules that are packed in membrane bound vesicles in the presynaptic endings.

Depolarization-Release Coupling

The probability of quantal release dramatically increases when the presynaptic membrane is depolarized due to action potential. Moreover, the amount of transmitter released varies directly with depolarization of the presynaptic terminal: more depolarization causes more transmitter molecules to be released.

Nonspiking Release

Some neurons release neurotransmitter from their terminals even in the absence of APs, which is called nonspiking release.

In these neurons information transfer is accomplished by electrotonically conducted graded potentials.

The amount of transmitter that is released into the synaptic cleft by these cells also depends on the membrane potential. When the cells are more strongly depolarized, they release more transmitter; when they are less strongly depolarized, less transmitter is released.

TOPIC-34 Excitatory and Inhibitory Postsynaptic Potentials

Excitatory Postsynaptic Potentials

An excitatory postsynaptic potential (EPSP) is a synaptic potential that makes the postsynaptic neuron more likely to fire an action potential.

It results from the flow of positively charged Na^+ or Ca^{2+} ions into the postsynaptic cell. It happens when specific ligand-gated ion channels open due to the binding of certain neurotransmitters during fast chemical transmission.

The flow of ions that causes an EPSP is known as excitatory postsynaptic current. However the current flowing through a single ion channel is too small to generate a measureable potential difference in the post synaptic cell. Therefore, ionic currents flowing through many channels (about 40 to 80) are summed up by a process called summation to produce an EPSP.

Larger EPSPs result in greater membrane depolarization and thus increase the likelihood that the postsynaptic cell reaches the threshold for firing an action potential.

The neurotransmitter most often associated with EPSPs in CNS is Glutamate while Acetylcholine is the most common excitatory neurotransmitter at the neuromuscular junctions.

Inhibitory Postsynaptic Potentials

An inhibitory postsynaptic potential (IPSP) is a kind of synaptic potential that makes a postsynaptic neuron less likely to generate an action potential.

Inhibitory postsynaptic potentials (IPSPs) usually result from the flow of negative ions into the cell or positive ions out of the cell.

Inhibitory synaptic currents are typically carried by channels that are permeable either to K^+ or to Cl^-.

IPSPs can take place at all chemical synapses that release inhibitory neurotransmitters e.g. GABA and Glycine. These neurotransmitters bind to the postsynaptic receptors that induce a change in the permeability of the postsynaptic neuronal membrane to particular ions, causing either Cl^- inflow or K^+ outflow.

Such ionic currents cause the postsynaptic membrane potential to become more negative than the resting membrane potential. As a result the post synaptic membrane becomes hyperpolarized.

In order for an action potential to be generated, depolarization of the postsynaptic membrane needs to occur, where the membrane potential becomes more positive than resting membrane potential.

Therefore, hyperpolarization of the postsynaptic membrane makes action potential less likely to occur in the postsynaptic neuron.

Channel properties are more important than the neurotransmitter:

It is noteworthy that there is nothing inherently excitatory or inhibitory about any particular transmitter substance. Rather the properties of the channels that are opened by the transmitter and the identities of the ions that flow through those channels, determine how a transmitter affects the postsynaptic cell.

For example, ACh is an excitatory transmitter at the vertebrate neuromuscular junction, where it opens channels that allow Na^+ to flow in and K^+ to flow out of the postsynaptic membrane.

In contrast, ACh is inhibitory at the terminals of parasympathetic neurons in the vertebrate heart, where it affects K^+ selective channels only that prolong hyperpolarization and thereby inhibiting the generation of action potentials.

TOPIC-35 Neurotransmitters: Diversity and Classification

Diversity

By the mid-1960s, only three neurotransmitters had been identified. These were acetylcholine, norepinephrine and γ-aminobutyric acid (GABA). Today, more than 100 neurotransmitters have been identified that vary in size and molecular weight and belong to various chemical categories.

Classification Based on Chemical Structure

Based on their chemical structure, neurotransmitters can be sorted into two groups:

1. **Small, low molecular weight Neurotransmitters.**
   They include:
   - **Acetylcholine**
   - **Amino acids**
     Include GABA, Glycine, Glutamate, Aspartate
   - **Biogenic amines**
     Include Norepinephrine, Epinephrine, Dopamine, Serotonin and Histamine.
   - **Gases**
   - e.g. Nitric oxide (NO) and Carbon monoxide (CO)

2. **Large, high molecular weight Neurotransmitters**
   They are derived from amino acids and include:
   - **Neuropeptides**
     They are larger molecules that are constructed of amino acids. More than 40 neuropeptide transmitters have been identified in the mammalian central nervous system. These include many hypothalamic and pituitary peptide hormones, Substance-P, endorphins, enkephalins and many other amino acid derivatives.

Classification Based on Mode of Action:

1. **Fast, Direct Neurotransmitters**
   These transmitters act directly on ion channel proteins and change the conductance of postsynaptic membrane for various ions.
   These include acetylcholine, amino acids (glutamate, aspartate, glycine and γ-Aminobutyric acid).
2. **Slow, Indirect Neurotransmitters**
   These transmitters work through an indirect biochemical pathway within the postsynaptic cell that involves G protiens. They change the state of a second messenger that results in changes in conductance of ion channel proteins.
   They include biogenic amines and neuropeptides.
   Many of these neurotransmitters may also act as neuromodulators. Neuromodulators can affect neighboring neurons and modify their behavior at once.

TOPIC-36 Fast, Direct Neurotransmitters

Fast, direct neurotransmitters may be excitatory or inhibitory.

The neurotransmitters that participate in fast excitatory synaptic transmission are acetylcholine, glutamate and aspartate.

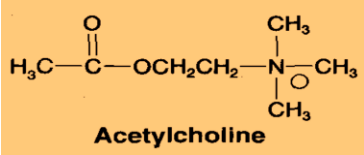
The neurotransmitters γ-Aminobutyric acid (GABA) and glycine are involved in fast inhibitory synaptic transmission.

Fast Excitatory Transmitters

The excitatory transmitters act by opening the ion channels in the postsynaptic cell membrane.

Acetylcholine

- The most familiar fast acting neurotransmitter substance is the Acetylcholine.
- In most instances, acetylcholine has an excitatory effect.
- It also acts as inhibitory transmitter in some instances e.g. at the peripheral parasympathetic nerve endings where it is involved in the inhibition of the heart by the vagus nerves.



Acetylcholine

Cholinergic Neurons

Neurons that release Acetylcholine are said to be cholinergic. They are widely distributed throughout the animal kingdom. These neurons include:

- vertebrate motor neurons
- preganglionic neurons of the vertebrate autonomic nervous system
- postganglionic neurons of the parasympathetic division of the autonomic nervous system
- many neurons of the vertebrate central nervous system
- a number of invertebrate neurons e.g. cells of the molluscan central nervous system, motor neurons of annelid worms, and sensory neurons of arthropods.

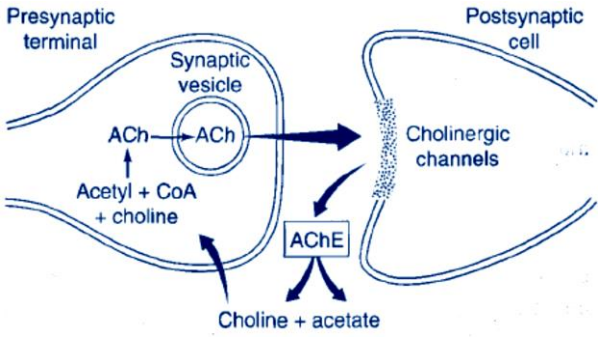
Mode of Action of Acetylcholine

- When acetylcholine (ACh) is released into the synaptic cleft, it binds to the ligand-gated ACh-specific receptors in the postsynaptic membrane.
- The binding causes Na^+ and K^+ ion channels to open briefly that produce an EPSP.

Role of Acetylcholinesterase (AChE)

- The enzyme AChE is abundantly present in the synaptic cleft.
- Transmission is terminated at cholinergic synapses when Acetylcholine is hydrolyzed to choline and acetate by AChE.

- The choline that remains in the cleft is actively reabsorbed by the presynaptic membrane and recycled by condensation with acetyl coenzyme A (acetyl CoA) to form new molecules of Acetylcholine.



Inhibition of AChE

- Some substances block the activity of AChE and produce dramatically dangerous effects.
- These substances include the nerve gases and many insecticides.
- When AChE is blocked, acetylcholine piles up in the synaptic cleft and causes disruption in the function of nervous and neuromuscular systems. Death can follow.

Acetylcholine Agonists

- Molecules that mimic the action of a neurotransmitter are said to be agonists.
- For example, carbachol, Nicotine and Muscarine mimic acetylcholine and can activate cholinergic synapses.

Acetylcholine Antagonists

- The molecules that block the action of a neurotransmitter are called antagonists.
- Such molecules have structural features in common with a transmitter.
- For example, D-tubocurarine, the active agent in the South American blow-dart poison curare, blocks transmission at many cholinergic synapses.

Glutamate (glutamic acid)

- It is released at excitatory synapses in the vertebrate central nervous system and is the most common excitatory neurotransmitter in the brain.
- In insects and crustaceans it is released at fast excitatory neuromuscular junctions.

Aspartate (Aspartic acid)

- It is an excitatory neurotransmitter, primarily localized to the ventral spinal cord.
- Aspartate is produced in the mitochondria and transported into the cytoplasm, and packaged into synaptic vesicles.
- It forms excitatory/inhibitory pair with glycine in the ventral spinal cord.

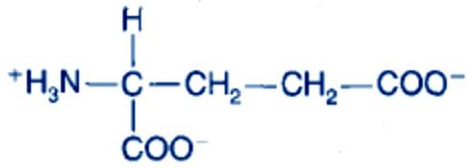
Fast Inhibitory Transmitters

Glycine

Glycine is secreted mainly at inhibitory synapses in the spinal cord and always acts as an inhibitory transmitter.

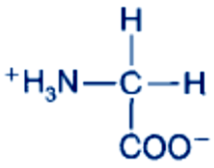
γ -Aminobutyric acid

- It plays a very important role as an inhibitory transmitter in the vertebrate central nervous system.
- It forms an excitatory/ inhibitory pair with glutamate in the brain.
- It is also released at the inhibitory motor synapses in crustaceans and annelids.
- It produces inhibitory postsynaptic potentials by increasing the permeability of the postsynaptic membrane to Cl^-.



Glutamate

γ-Aminobutyric acid (GABA)



Glycine

TOPIC-37 Slow, Indirect Neurotransmitters

These neurotransmitters include two major classes:

- Biogenic amines
- Neuropeptides

Biogenic Amines

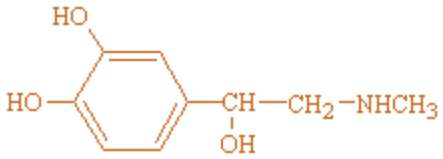
The biogenic amines act through second messengers to produce slow synaptic transmission.

This class of neurotransmitters includes:

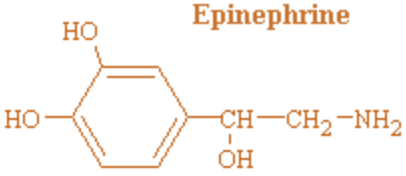
- Catecholamines (Norepinephrine, Epinephrine and Dopamine)
- Serotonin (an indolamine)
- Histamine (an imidazole)

Norepinephrine and Epinephrine

- Neurons that use epinephrine or norepinephrine as transmitters are called adrenergic neurons.
- Norepinephrine is the primary excitatory transmitter released by postganglionic cells of the vertebrate sympathetic system.
- Epinephrine is excitatory at some synapses while at others, it is inhibitory. Its effect depends on the properties of the postsynaptic membrane.
- Both of these are also released by the chromaffin cells of the vertebrate adrenal medulla.
- Epinephrine and norepinephrine are structurally very similar and have similar pharmacological actions.



Epinephrine



Norepinephrine

Synthesis and inactivation of Norepinephrine

- Norepinephrine is synthesized from the amino acid phenylalanine.
- It is inactivated in two ways:
  1. It is taken up into the cytoplasm of the presynaptic neuron, where some of it is repackaged into synaptic vesicles for release and some of it is inactivated by monoamine oxidase.
  2. It is also deactivated by methylation within the synaptic cleft.

Biogenic Amine Analogues

Several psychoactive drugs (e.g. Mescaline, amphetamines and cocaine) have molecular structures that are similar to the biogenic amines. This allows them to act at synapses that use these transmitters.

Mescaline: It acts as a psychoactive drug that induces hallucinations by interfering with its analog norepinephrine at synapses in the central nervous system.

Amphetamines: They exert their effect by interacting with adrenergic neurotransmission. They mimic norepinephrine and act as potent CNS stimulant.

Cocaine: It also mimics norepinephrine and interferes with the inactivation of norepinephrine.

Neuropeptides

Neuropeptides include more than 40 peptide molecules that are produced and released in the vertebrate central nervous system.

Many of these molecules, or their analogs, have also been found in the nervous systems of invertebrates.

A number of these neuropeptides are produced in many tissues, not just in neurons. Thus, a single molecular species may be released from intestinal endocrine cells, from autonomic neurons, from various sensory neurons, and in various parts of the central nervous system.

Examples include many hypothalamic and pituitary peptide hormones, gastrointestinal hormones glucagon, gastrin and cholecystokinin, Substance-P, endorphins, enkephalins and many other amino acid derivatives.

Neuropeptide Release:

A single neuropeptide species may be liberated as a transmitter from some neurons and as a neurosecretory substance from other neurons and as a hormone from non-neuronal tissue.

Transmitters are released into the confined space of a synaptic cleft. Neurosecretory peptides are liberated into the circulation and are carried by the blood to their targets neural tissues. Hormones are released into the blood and target non-neural tissues.

Effectiveness of Neuropeptides:

Neuropeptides are more potent transmitters than small neurotransmitters for three reasons:

1. They bind to receptors at much lower concentrations than do other neurotransmitters (about 10^{-9} M versus 10^{-5} M for typical neurotransmitters
2. They act through second messenger pathways that can provide significant amplification. Thus, even a small amount can produce a large effect.
3. The mechanisms that terminate their actions are slower, so they remain available to their receptors for a longer time.

TOPIC-38 Neuropeptides: Endorphins and Enkephalins

Pharmacological Actions

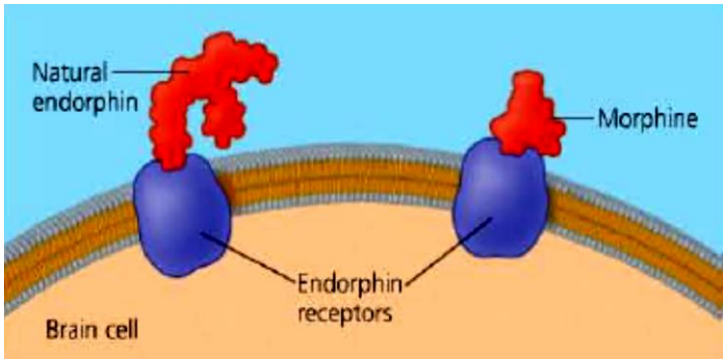
The neuropeptides endorphins and enkephalins are two groups of naturally occurring signaling molecules that are produced within the central nervous system.

They act as analgesics that reduce the perception of pain and induce euphoria during times of physical or emotional stress. They also decrease urine output and depress respiration.

Endorphin Receptors (Opioid Receptors)

The surface membranes of many CNS neurons contain endorphin receptors. These receptors normally bind the enkephalins and endorphins.

The narcotic opiate drugs e.g. opium, morphine and heroin have structures similar to endorphins and mimic them. So these opiates can bind to endorphin receptors in the brain and produce similar effects on pain perception and emotional state. That is why these receptors are also called opioid receptors.



Endogenous Opioids

The levels of endorphin and enkephalin molecules have been found to rise in the brain in response to activities generally perceived as pleasurable e.g. eating or listening to pleasant music.

Because of their properties and because these neuropeptides bind to the same receptors in the nervous system to which opiates such as opium and its derivatives bind, they are called endogenous opioids.

Basis of Analgesic Action

The analgesic properties of the endorphins and enkephalins depend on the ability of these neuropeptides to block the release of transmitter from certain nerve endings that are involved in the perception of pain.

Basis of Opioid Addiction

When opioid molecules bind to the receptors, they elicit such intense feelings of pleasure that people learned to use opiate narcotics to stimulate the receptors.

There is, however, a physiological problem associated with this intense pleasure i.e. repeated doses of the exogenous opiates provoke compensatory changes in neuronal metabolism.

So the removal of the opiate shifts the nervous system into a state that is perceived as extreme discomfort until the opiate is re-administered.

This metabolically induced dependence is termed addiction.

Naloxone and opioid receptors

Naloxone is a drug which acts as a competitive blocker of the opioid receptors and antagonizes (opposes) the narcotic effect of opiates. It binds tightly to the opiate receptor without activating the receptor, so it blocks the opiates to act on their target cells.

These antagonistic properties of naloxone have proved to be a useful tool in studies of opioid receptors and the responses mediated by these receptors.

TOPIC-39 Receptors in Fast, Direct Neurotransmission

Postsynaptic Cell Receptors

The membranes of postsynaptic cells have specific protein receptors to which the neurotransmitter molecules bind and elicit a response directly.

The properties of these receptors and their specificity for certain neurotransmitter determine the type of responses.

Fast, direct neurotransmitters act by changing the permeability of the postsynaptic membrane to certain ions. Permeability changes occur due to the opening or closing of ion channels.

When a synaptic channel opens, a minute ionic current passes through the channel. Many such single-channel currents sum up to form the macroscopic synaptic current that produces postsynaptic potentials.

Examples:

Acetylcholine Receptors and Channels (AChRs)

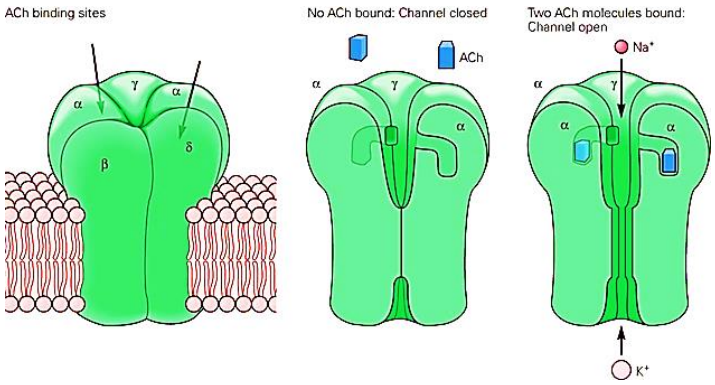
- Most of the knowledge about fast channels has been obtained through the studies of acetylcholine receptors and channels at the vertebrate neuromuscular junction.
- Acetylcholine receptors are of two types: Nicotinic AChRs and Muscarinic AChRs.
- Both receptors consist of two different types of channel proteins that are activated by acetylcholine. They are differentiated and named on the basis of their activation by muscarine and nicotine.

Nicotinic AChRs (nAChRs)

- The nicotinic AChR were the first ligand-gated ion channels to be purified chemically and studied electrically.
- These acetylcholine activated receptors are also activated by nicotine but not with muscarine.
- Nicotinic receptors are found at the synapses in the autonomic ganglia of both the sympathetic and parasympathetic systems. They are also present at many non-autonomic nerve endings, like the neuromuscular junctions.

Structure of nAChRs

Each nicotinic AChR consists of five subunits that associate and form a channel at the center.



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There are two identical α subunits. The other three subunits are β, γ, and σ. The receptor sites are on each of the two α-subunits. When both sites are occupied by the ligand molecules i.e. ACh or its agonists carbachol and nicotine, the channel becomes activated and opens allowing Na^+ and K^+ to flow through it.

Muscarinic AChRs (mAChRs)

Muscarinic receptors are found on all effector cells that are stimulated by the postganglionic cholinergic neurons of either the parasympathetic nervous system or the sympathetic nervous system.

In addition to acetylcholine, they are activated when muscarine, a poison from toadstools, binds to them. Muscarine does not activate the nicotinic AChRs.

Nature of Muscarinic AChRs

The mAChRs are not ion channel proteins. Instead, they belong to the family of G protein-coupled receptors that activate other ionic channels via a second messenger cascade. So they follow the slow, indirect transmission mechanism instead of fast, direct neurotransmission.

Other ligand-gated channels

In addition to AChRs, many other types of ligand-gated channels are also found in neurons which mediate rapid postsynaptic responses. For example the receptors for glycine and GABA.

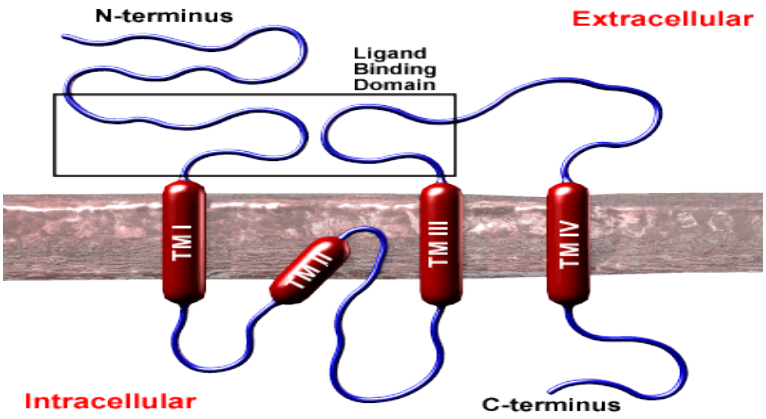
Each type of receptor is expressed in a unique and characteristic pattern within the mammalian brain.

All these different channel proteins have remarkable homologies in their structures. These receptors have a common pentameric structure, and each is composed of two to four different kinds of subunits, out of which only one type binds the ligand.

Glutamate Receptors

Glutamate receptors belong to a separate family having only a slight resemblance to AChRs.

At present, three types of fast-acting glutamate receptors have been identified.



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Currently, there is intense interest in this receptor family because glutamate is the most common excitatory neurotransmitter in the mammalian central nervous system. Moreover, glutamate receptors participate in modifications of synaptic strength, which may underlie learning and memory.

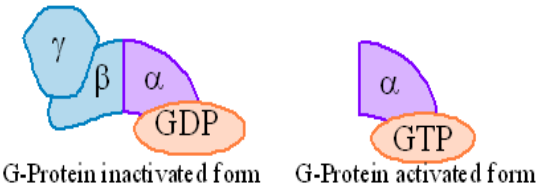
TOPIC-40 Receptors in Slow, Indirect Neurotransmission

G Protein-Linked Receptors

- Neurotransmitters that produce slow postsynaptic response bind to the receptors that are linked to G proteins.
- Most such receptors act by activating the G protein that regulates the activity of associated effector proteins by using GTP as energy source.
- There are more than 100 receptors that act through G proteins.

G Proteins

The G proteins family consists of about 20 different proteins that are composed of three subunits, α, β and γ.



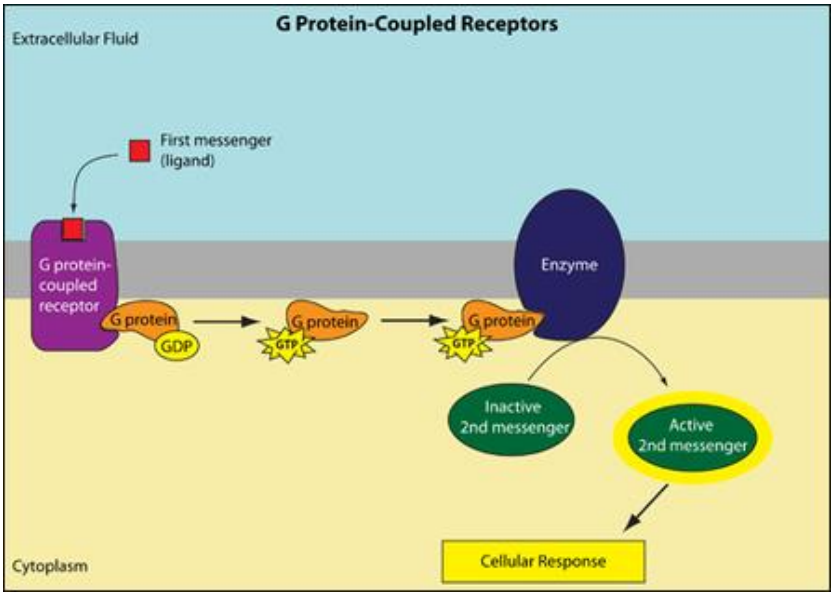
The α subunit of inactive molecule binds to a GDP. When active, GDP is converted to GTP.

The Receptor Molecules

The neurotransmitter receptor molecules span the membrane, binding the neurotransmitter on the extracellular face and catalyzing G-protein activation on the cytoplasmic face.

Effects of G Protein Activation:

- Activated G protein regulates the activity of effector proteins.
- Effector proteins are ion channels or enzymes or both. They control the active concentration of intracellular second messengers.
- Second messengers are responsible for cellular response.



Example

A well-studied example of indirect neurotransmission is the regulation of ion channels by acetylcholine in the atrial cells of heart.

Here acetylcholine acts on muscarinic receptors that activate a G-protein.

The G protein activates and results in the opening of K^+ channels. This leads to the prolonged hyperpolarization of atrial cells.

This causes a decrease in cardiac activity that is necessary in the regulation of cardiac cycle.

TOPIC-41 Neuromodulation

Definition

Neuromodulation is a physiological process by which the neurotransmitters released by a small group of neurons diffuse through large areas of the central nervous system, and interact and modulate the effect of many neurons simultaneously.

This is in contrast to classical synaptic transmission, in which one presynaptic neuron directly influences a single postsynaptic neuron.

Neuromodulators

The neurotransmitters that are involved in altering the cellular properties and efficacy of synaptic transmission of multiple postsynaptic neurons are called neuromodulators. They act through G-protein linked receptors involving ion movements through voltage-gated ion channels. The generation of response is relatively slow, like slow synaptic transmission and lasts longer (from seconds to minutes).

Major neuromodulators in the central nervous system include dopamine, serotonin, acetylcholine, histamine, and norepinephrine. Moreover endorphins, enkephalins and substance-P are also neuromodulators.

Basis of Neuromodulatory Action:

A neuromodulator is released as a neurotransmitter. But it is not reabsorbed by the pre-synaptic neuron or broken down into its metabolites. So it stays for a significant interval of time in the cerebrospinal fluid (CSF), influencing or "modulating" the activity of several neurons in the brain or spinal cord.

Mechanism of Action of Neuromudulators:

- Neuromodulators do not cause the formation of EPSP or IPSP.
- They bring about long term changes that slightly modify, depress or enhance the action of neurotransmitter at the synapse.
- They may act as autocrine or paracrine agents.
- As an autocrine agent, they bind to presynaptic cell (that produced them) to affect the amount of neurotransmitter released when an action potential occurs in that neuron.
- As a paracrine agent, they bind to the receptors on one or more postsynaptic cells to affect the release of neurotransmitter.

Effects of neuromodulation:

The phenomenon of neuromodulation plays critical roles in the development of complex behavioral patterns e.g. happiness, revenge, reward, greed and exploration. Neuromodulation is also involved in the processes of thinking, cognition, planning, learning and memory.

Many behavioral problems are also based on neuromodulation e.g. mood swings, sleep disturbances, feelings of stress, anxiety, depression and anger.

Pharmacological applications of neuromodulation

The phenomenon of neuromodulation has vast pharmacological applications for the treatment of challenging and complex nervous systems diseases including ADHD, narcolepsy, epilepsy, depression, dementia, Alzheimer's disease and Parkinson's disease.

TOPIC-42 Neural Integration

Definition

Neurons in the brain receive thousands of synaptic inputs from other neurons. These neurons add up these inputs before the generation of an output through a process that is called neuronal integration.

The neural integration occurs through two summation processes:

- Temporal summation
- Spatial summation

Temporal summation

When two EPSPs occur at a single synapse in such rapid succession that the postsynaptic neuron's membrane potential has not returned to the resting potential before the arrival of the second EPSP, the EPSPs are added together. This is known as temporal summation.

Explanation

When a presynaptic terminal fires, the released transmitter produces an EPSP in the postsynaptic neuron by opening membrane channels for almost a millisecond. But the changed postsynaptic potential lasts up to 15 milliseconds. So during rapid firing rate by the presynaptic terminal, the channels are opened again adding to the postsynaptic potential that increases to a greater level.

Spatial Summation

EPSPs produced nearly simultaneously by different synapses on the same postsynaptic neuron can also add together. This effect is known as spatial summation.

Explanation

Excitation of a single presynaptic terminal on the surface of a neuron almost never excites the neuron. The reason for this is that the transmitter substance released by a single terminal can cause an EPSP of about 0.5 to 1 millivolt. However, an EPSP of 10 to 20 millivolts is normally required to reach threshold for excitation.

To provide this amount of EPSP, many presynaptic terminals are usually stimulated at the same time. Their effects can summate even if they are spread spatially on the soma and cause the excitation to occur. This effect of summing simultaneous postsynaptic potentials by activating multiple terminals on widely spaced areas of the neuronal membrane is called spatial summation.

Significance of Summation

Due to summation, the postsynaptic potential becomes much higher. This ensures that an output AP is produced that can generate a response.

Lesson-08

RECEPTOR PHYSIOLOGY

Topic-043 Sensory Stimuli, Sensory Organs and Receptor Cells

Components of a Sensory System

Sensory stimuli, sensory organs and receptor cells are the three components of a sensory system.

Sensory Stimuli

- A sensory stimulus is a detectable change in the internal or external environment that causes a neuro-physiological response.
- Stimuli are the sensory inputs that are gathered constantly from the environment and keep the animal aware of its external or internal environment.

Nature of Stimuli

All stimuli represent some form of energy which may be mechanical (e.g. sound, vibration, gravitation, pressure) or chemical (e.g. odorants, tastants, allergens) or it may be photon energy of light.

Threshold Level of Stimulus

In order for a stimulus to be detected, its level must exceed the threshold.

Subthreshold stimuli are not detected by the receptors.

If the intensity of a stimulus reaches threshold, the information is transmitted to the central nervous system (CNS).

Sensory Organs

- The specialized organs or structures where sensory receptor cells are concentrated and is specialized for receiving a particular type of stimulus.
- Sensory organs provide the channels of communication that gather sensory information from external environment more accurately than the isolated receptor cells and can transmit it into the nervous system.
- Sensory organs are positioned at many locations both on the surface and inside of the body. Most sensory organs are concentrated at the anterior end of the animal.
- The major sensory organs of human body are eyes, ears, nose, tongue and skin.

Receptor cells

- Sensory organs have receptor cells which are specialized to respond to particular kinds of stimuli.
- They receive information through stimuli from outside the body as well as from inside the body and generate a sensory signal and transmit this signal to the nervous system.

Location of Receptor cells

Some receptor cells are concentrated in particular sensory organs (e.g. the olfactory, visual, gustatory and sound receptors are found in nose, eyes, tongue and ear respectively).

Many receptor cells are found in the skin and also in the deeper parts of the body e.g. heat, cold, pressure and pain receptors.

Topic-044 Sensations and Quality of Stimulus

Sensations

- Sensations are the subjective phenomena closely associated with the perception of stimulus.
- Sensations arise when sensory receptor cells, receiving a stimulus, transmit signals through the nervous system to particular parts of the brain that interprets or perceives these signals. The subjective description of these neuronal perceptions is termed as sensation.
- Interpretation of sensations is based on experience and learning i.e. previous exposure and its interpretation stored in the memory.

Examples

Examples of sensations are the feelings of pain, color, taste (e.g. sweet) noise, melody, bad or good odor etc.

Quality of Stimulus

Stimuli possess features that distinguish them from one another. The features that characterize stimuli are called stimulus qualities.

Sensations depend on the quality of the stimulus.

For example, pitch is a quality of sound which may be perceived as noise or music. Similarly, quality of light is described by its colors e.g. red or blue.

Sensations are Subjective

Human perception of sensations for a particular kind of stimulus is subjective i.e. the described qualities are not really inherent in the stimuli themselves.

- If sugar is placed on the tongues of many people, all are likely to report that it as "sweet."
- Similarly, light with a wavelength of 650-700 nm is described as "red".

In both cases, these perceptions are not inherent in the stimuli themselves.

Sensations depend on Neuronal Processing

Subjective sensations about a particular stimulus depend entirely on the neuronal processing of the stimulus. They also depend on the properties of receptor cells that send different types of signals for different stimuli to the nervous system which processes information to produce recognizable sensations.

Topic-045 Sensory Modalities and Receptor Types

Sensory Modalities

Sensory modalities are the types of sensory information that we can distinguish. In familiar terms they are known as "senses".

They may be external or internal depending on the source of stimulus.

Human Sensory Modalities

The human sensory modalities include five major senses perceived through five sense organs having specific receptors for external stimuli:

- Sense of vision perceived through eyes having photoreceptors
- Sense of hearing perceived through ears having mechanoreceptors
- Sense of touch perceived through skin having Meissner's corpuscles
- Sense of taste perceived through taste buds in tongue having gustatory receptors
- Sense of smell perceived through nasal cavity having olfactory receptors

Sensory modalities that perceive internal stimuli are responded through interoceptive receptors. They constitute internal sensory systems and respond to signals from within the body.

Interoceptive Receptors

These include:

- Receptors of vestibular system that monitor the orientation of the body. They are present in the semicircular canal in inner ear.
- Thermoreceptors that keep track of thermal state of the body. They are found scattered on the skin.
- Chemoreceptors that keep track of chemical state of the body. Various types of these receptors are distributed in specific parts of the body.
- Proprioceptors that monitor the position of muscles and joints and are located in the movable joints.
- Nociceptors perceive the sensation of pain and are distributed evenly in the skin and deeper body parts.
- Pacinian corpuscles that are situated deep in the body and receive pressure stimulus. In the limbs, they receive vibrations.

Importance of Interoceptive Receptors

- The interoceptive receptors communicate information to the brain by pathways that often are not brought into consciousness.

Although we are not consciously aware of the signals of interoceptive receptors, these internal receptor systems play crucial roles in providing information to the brain about the state of the body and its position in space.

Imagine how complicated walking would be if we had to pay conscious attention to the position of every muscle and joint taking part in the process.

Sensory Modalities in Nonhuman Animals

Many nonhuman animals also possess other sensory modalities that are unavailable to human beings.

Examples:

- **Distance thermoreception:** Pit organs are found in some snakes (e.g. pit vipers and rattle snakes) and can detect heat energy (infrared radiation) emitted from mammalian bodies. They use this sense to identify their prey due to temperature difference.
- **Electroreception** Detection of very low frequency electric signals. This sense is found in some electric fishes which use it to communicate with one another in murky waters.
- **Magnoreception:** Some animals appear to sense Earth's magnetic field with magnoreceptors. Magnoreceptors are found in many migratory birds which use it as a navigational guide..

Topic-046 Properties of Receptor Cells

General properties common to all sensory receptor cells include:

1. Selectivity
2. Transduction
3. Sensitivity
4. Transmission

Selectivity of Receptor Cells

- Each kind of receptor cell is highly selective for a specific kind of stimulus energy.
- Sensory receptor cells are selective because their membranes have receptor proteins having affinity for a specific stimulating agent.

Examples of Selectivity:

- **Photoreceptors:**
  External energy, such as light, may strike any part of the body; but only the eyes contain sensory cells that can receive and respond to the stimulus of light and transduce photons into neuronal energy.
- **Mechanoreceptors:**
  The membranes of mechanoreceptors contain molecules that respond to slight distortions in the cell membrane.

Capacity to Transduce Energy Forms

- Receptor cells have the capacity to transduce the energy of a physical or chemical stimulus into the electrical energy of nerve impulse.
- In the process of transduction, receptor cells often amplify the received signal.

Sensitivity of Receptor Cells

- Receptors are extremely sensitive to their stimuli.
- They can even receive very weak stimuli that are very near the theoretical lowest limits of the stimulus energy.

Examples of Receptor Sensitivity

- Photoreceptors can be activated by a single photon.
- Mechanoreceptor hair cells can respond to displacements equal to the diameter of a hydrogen atom.
- Odor receptors can detect only a few molecules of the odorant substance.

Transmission of signals

After receiving and processing the signal in the cell, the final step in all receptor cells is the transmission of signals to the cells of nervous system.

Receptor cells are innervated with nerve endings or are closely associated with neurons so that they are able to transmit the signal to the nervous system directly.

Topic-047 Sensory Transduction

Definition

Sensory receptor cells convert the physical or chemical energy of stimulus into electrical signals i.e nerve impulse. This conversion is called sensory transduction.

Mechanism of Sensory Transduction

All sensory transduction systems operate through similar cellular mechanisms and contain related molecules to transduce signals in four steps:

- Detection of stimulus
- Amplification of stimulus
- Encoding of signal
- Transmission of signal

Detection of Stimulus:

- The initial event in all sensory transduction systems is the detection of stimulus.
- Only the stimuli that have a minimum level of energy i.e. threshold are detected.
- **Threshold of detection:** The smallest amount of stimulus energy that will produce a response in a receptor 50% of the time is called the threshold of detection.

Amplification of Stimulus

- In some sensory systems, amplification of stimulus is carried out within the receptor cells, if stimulus energy received at the receptor site is low.
- Amplification is mediated by a number of intracellular mechanisms that involve a cascade of chemical reactions in the cell.
- It results in amplification of the signal by many orders of magnitude.

Encoding of Signal

- Intracellular processing in the receptor cell converts the physical or chemical stimulus into the form of ionic current.
- These ionic currents are the encoded form of original stimulus, containing all its attributes.

Transmission of Signal

- The encoded signal is transmitted to the nervous system by generating action potentials or by electrotonic conduction.

Encoding Multiple Stimulus Qualities

- Responses within a single receptor neuron encode information about a single quality of the stimulus. But they cannot directly report all the qualities of a stimulus. For example, a single photo-receptor can report the intensity of light but cannot report its color.
- Sensory organs contain a variety of receptor cells that respond differentially to different qualities of a stimulus.
- For example, some photoreceptors respond to red light, while others respond to blue light.
- So, the receptor cells grouped into organs convey significantly more information about the stimulus. For example, its absolute intensity, its spatial distribution, and other qualities such as the wavelength of light or the frequency of a sound.

Topic-048 Range Fractionation

Definition

In a sense organ, sensory receptors are arranged in an order of increasing sensitivity to different range of intensities of the stimulus. This hierarchical arrangement of receptors is known as range fractionation.

Range Fractionation and Stimulus Intensities

Each individual receptor, in a sense organ, covers only a fraction of the total dynamic range of the stimulus.

Receptors work together in an orderly way to provide discrimination of stimulus intensities.

Recruitment Phenomenon

One important implication of range fractionation is the recruitment phenomenon.

- The most sensitive receptors in the population produce a response at stimulus intensities that are just above the threshold. Above that intensity, the most sensitive receptors become saturated.
- If the stimulus energy is increased a little, the less sensitive receptors in the population will join in and respond.
- With still greater stimulus intensities, another, formerly inactive lower-sensitivity population of receptors will join in.
- In this way, as the stimulus intensity is increased, receptors that are less and less sensitive will become active, until the least sensitive sensory fibers will finally be recruited, and all receptors will respond maximally.
- At that point, the system will be saturated and therefore unable to detect further increases in intensity.

This phenomenon of activation of receptors in a graded fashion is called recruitment.

Importance of Range Fractionation

- It results in increasing the active range of multineuronal sensory system than the range of any individual single receptor.
- It also increases the overall precision of the sense organ.
- It enables the sensory processing centers of the CNS to discriminate stimulus intensities over a range much greater than that of any single sensory receptor.
- The extended dynamic range of the entire system is possible because individual receptors of a sensory system cover different parts of the full spectrum of sensitivity.

Example:

Eyes have rod cells which are high sensitivity photoreceptors while cone cells have low sensitivity.

At low light intensity, i.e. dimmer light, only rod cells are recruited and we can see dimly, as black/white image.

As the brightness increases, cone cells start to recruit and we are able to see colors. Very bright light gives us perception of truly colored image.

After the highest intensity limit, increasing intensity does not increase clarity of the image because the system becomes saturated.

Topic-049 Sensory Adaptation

The decrease in perceived intensity, when the intensity of the stimulus has not itself changed, is known as sensory adaptation. The phenomenon is due to reduction in the frequency of sensory response during a sustained stimulus.

Adaptation is shown by all sensory components of nervous system: neurons, receptor cells, accessory tissues and central nervous system.

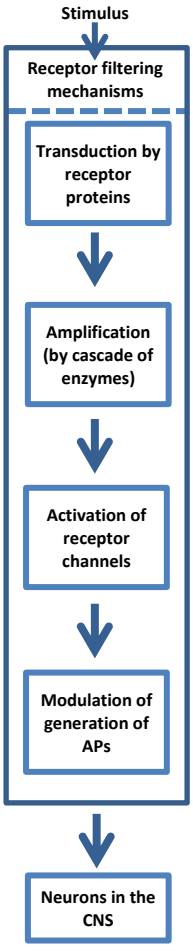
Significance

Adaptation allows detection of new sensory stimuli in the presence of ongoing stimulation, and it thus makes the sensory system much more useful.

Example:

Wearing clothing stimulates touch receptors at all points where our garments touch the skin. But we typically adapt to the touch input from our garments. So we can easily detect any new touch stimuli that impinge on our skin, even at locations covered by our clothing.

Other common examples of adaptation under our everyday observation are with the stimuli of smell, hot or cold water and dim or bright intensity of light.



Mechanisms of adaptation

Adaptation in receptor cells takes place through many mechanisms at various stages of sensory transduction pathway.

1. The mechanical properties of the receptor cell may act as a filter that can pass transient, rather than sustained, stimuli. This mechanism is common among mechanoreceptors.

2 The transducer molecules themselves may "run down" during a constant stimulus. For example, a significant percentage of visual pigment molecules can become bleached when exposed to continuous light and must be regenerated metabolically before they can again respond to illumination.

3 The enzyme cascade activated by a transducer molecule may be inhibited by the accumulation of a product or an intermediate substance.

4 The electrical properties of the receptor cell may change in the course of sustained stimulation. In some receptors, activation of receptor channels diminishes because intracellular free Ca^{2+} increases during sustained stimulation. Accumulation of intracellular free Ca^{2+} can also activate Ca-dependent K^{+} channels, producing a shift in membrane potential back

toward the resting potential.

5 The membrane of the spike-initiating zone may become less excitable during sustained stimuli.

6 Sensory adaptation can also occur in the cells of CNS that stop responding to continuous flow of signals.

Topic-050 Chemoreceptors: Taste and Smell Receptors

Chemoreceptors are receptor cells that are specialized for acquiring information about the chemical environment and transmitting it to other neurons.

Chemoreceptors can be divided into two categories:

- Gustatory (taste) receptors
- Olfactory (smell) receptors

These receptors operate quite differently from one another.

Gustatory (taste) receptors

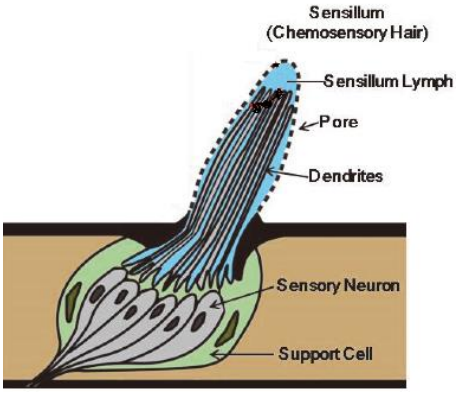
The gustatory (taste) receptors respond to dissolved molecules that come in direct contact with the receptive structure.

Taste receptors in insects

The organs of taste in insects are sensory sensilla that are located on the feet and mouthparts.

Every sensillum contains several receptor cells, each of which is sensitive to a different chemical stimulus e.g., water, cations, anions, or carbohydrates.

The receptor cells of sensilla appear to be hair-like due to longer dendrites. The dendrites are sent to the cuticle. The cuticle around dendrites has minute pores that allow stimulant molecules to contact the dendrites.



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The stimulus is converted into electrical signal by the soma of sensory cells.

Taste receptors in vertebrates

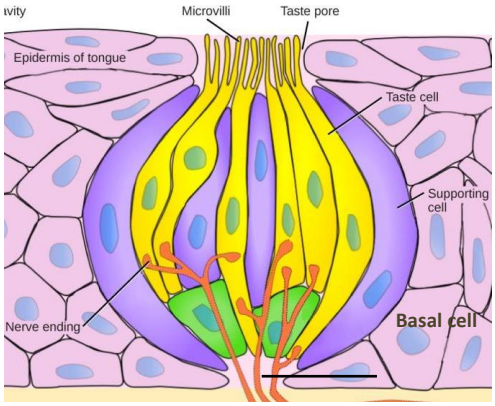
- Many aquatic vertebrates have taste receptors on different locations of the body.

  For example some fishes have modified pectoral fins that have taste receptors at the tips of the fin rays that are used to locate food in the muddy bottom.

- In terrestrial vertebrates, taste receptors are located at the anterior region of digestive tract e.g. on the tongue and epiglottis, in the back of the mouth, in the pharynx and upper esophagus.

Taste buds

- The gustatory organs of vertebrates are called taste buds.
- The taste bud is composed of about 50 modified epithelial cells including supporting cells (sustentacular cells), basal cells and taste receptor cells.
- The basal cells are progenitor cells that give rise to new taste receptors. They regularly generate new sensory taste receptor cells which have an active life of only 10 days.



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Taste Receptor Cells

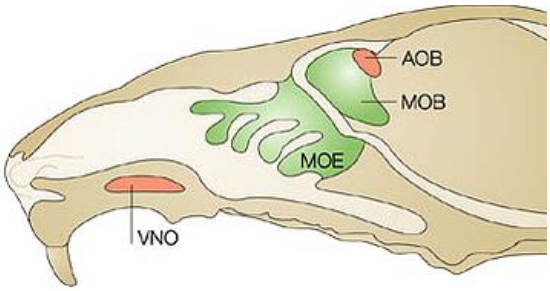
- The outer tips of the taste cells are arranged around a minute taste pore.
- From the tip of each taste cell, several microvilli, or taste hairs, protrude outward into the taste pore to approach the cavity of the mouth.
- These microvilli provide the receptor surface for taste.
- Interwoven around the bodies of the taste cells is a branching terminal network of taste nerve fibers that are stimulated by the taste receptor cells.

Olfactory (Smell) Receptors

The olfactory (smell) receptors respond to airborne molecules that stimulate the receptor from distance.

They detect odorants and pheromones.

- In insects, olfactory sensilla are present on their antennae.
- In vertebrates, the olfactory receptors are present in the nasal cavity.



Olfactory system has two anatomically distinct organs:

- Main Olfactory Epithelium (MOE) that is responsible for the detection of odorants
- Vomeronasal Organ (VNO) that detects pheromones.

Topic-051 Mechanism of Taste Reception

Sense of Taste

The sense of taste can be grouped into five primary sensations of taste: sweet, salty, sour, bitter and umami.

All perceived tastes depend on various combinations of these fundamental sensations.

Taste Receptors

Each individual taste cell expresses a single receptor type and transmits action potentials to the brain representing only one of the five tastes.

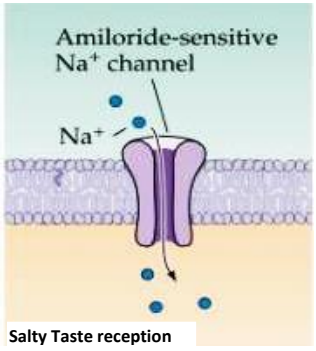
In humans, there are more than 30 different receptors for bitter taste, each able to recognize multiple bitter tastants. However there is only one type receptor each for sweet and umami tastes.

The receptors of sweet, umami, and bitter tastes are G protein-coupled receptors, while the receptors for salty and sour tastes are ion channels.

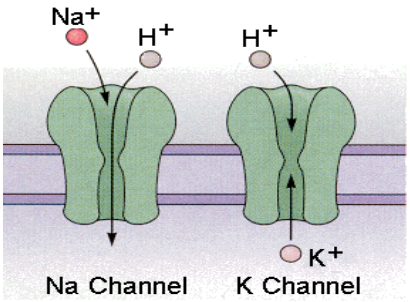
Mechanisms of Taste Reception

Salty Taste Reception

- Salty stimuli such as NaCl, readily dissociate in water into Na^+ and Cl^- ions.
- The Na^+ ions enter receptors through Na^+ channels in the membrane to directly depolarize the receptor cell membrane.
- These Na^+ channels are distinctive because they can be blocked by the drug amiloride unlike the voltage-gated Na^+ channels that mediate most APs.



Salty Taste reception

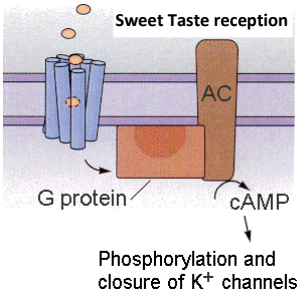


Sour Taste reception

Sour Taste Reception

- Sour stimuli are characterized by excess H^+ ions.
- They act either through the Na^+ channels or by blocking the K^+ channels.
- In either case, the membrane is depolarized.

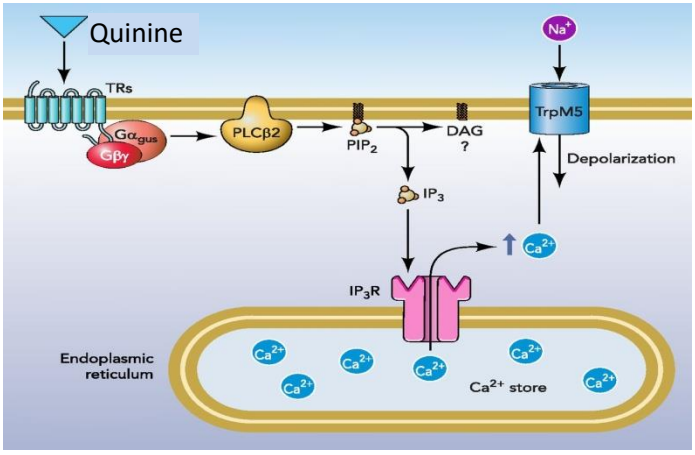
Sweet Taste Reception



Many sweet compounds and the amino acid alanine (Ala) bind to receptors and activate a G protein. The activated G protein activates adenylate cyclase that forms cAMP. Increased conc. of cAMP closes the K^+ channels in the basolateral membrane, depolarizing the receptor.

Bitter Taste Reception

Some bitter substances, such as quinine, bind to the receptor and activate a G protein that is coupled with phospholipase C. Phospholipase C converts Phosphatidylinositol bisphosphate to inositol triphosphate ($InsP_3$). Increased intracellular inositol triphosphate ($InsP_3$) causes the release of Ca^{2+} from the intracellular stores. Increased Ca^{2+} conc. causes the cell to depolarize.



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Umami Taste Reception

The receptors for umami (savory or delicious) taste were discovered in the taste buds in year 2000. This taste is produced by the amino acid glutamate and its salt monosodium glutamate. This taste is manifested by meat and aged cheese.

The receptor for MSG is a G-protein coupled receptor that results in a cellular cascade causing the release of Ca2+ ions and depolarization.

Release of Neurotransmitters

In all cases, depolarization in the receptor cell eventually results in the release of neurotransmitters which propagate the signal in nervous system.

Transmission of Taste Signals

Taste receptors generate APs, but they have no axons, so they cannot themselves carry information to the central nervous system.

Instead, they synapse with, and modulate activity in, neurons whose axons run in the facial, glossopharyngeal, and vagus nerves (seventh, ninth, and tenth cranial nerves).

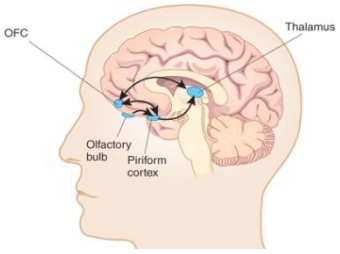
Labeled Line Coding

Each receptor subtype for five kinds of taste sensations is connected to a particular set of axons.

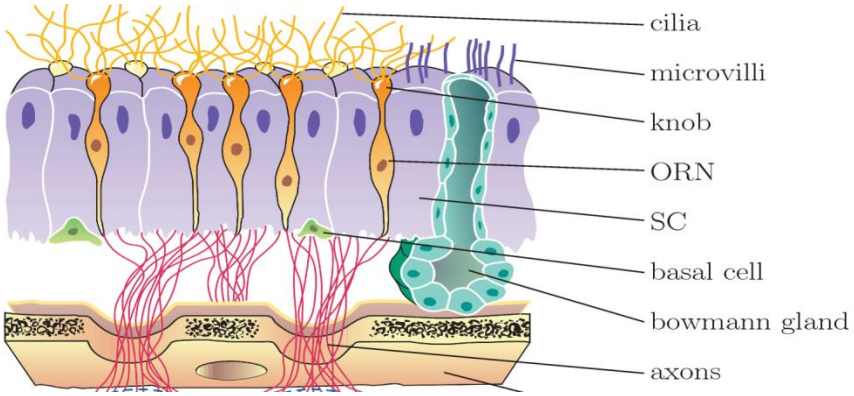
In that arrangement, for example, information about "sweetness" would be carried by some specific subset of axons. Such a pattern is called labeled line coding.

Topic-052 Mechanism of Olfactory Reception

Olfactory Receptors



- The olfactory receptors of vertebrates are located inside the nasal cavity.
- The sensory receptor cells involved in olfaction are actually neurons.
- These neurons have long axons. All these axons are packed together in the olfactory nerve. Nerve impulses are sent directly to the olfactory bulb of the brain, along the axons.
- Each receptor neuron has a long thin dendrite that terminates in a small knob at the surface.
- The knob has 4 to 25 olfactory hairs (also called olfactory cilia) that are about 200 μm long. These cilia are covered by a protein solution called mucus.



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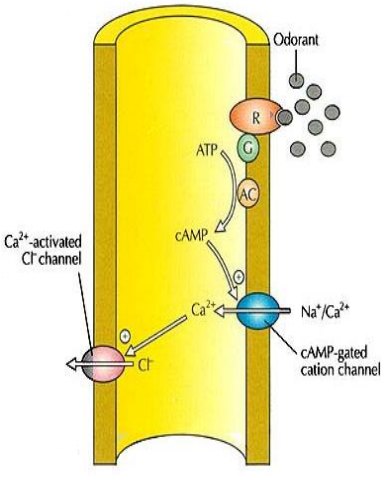
Olfactory Transduction

- The portion of each olfactory cell that responds to the olfactory chemical stimuli is the olfactory cilia.
- The odorant substance first diffuses into the mucus that covers the cilia.
- Then it binds with receptor protein in the membrane of each cilium.
- This protein is coupled to a G-protein.
- The G-protein activates adenylyl cyclase that, in turn, converts ATP into cAMP.
- This cAMP opens channels in the plasma membrane that are permeable to both Na^+ and Ca^{2+}.
- Ca^{2+} inflow also triggers opening of Cl^- channels allowing Cl^- ion outflow.



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- The flow of these ions causes depolarization that results in the excitation of the olfactory neuron and generation of action potential.
- The action potentials are transmitted to the central nervous system through the olfactory nerve.

This mechanism of transduction ensures amplification of excitatory effect of even the weakest odorant, thereby increasing the sensitivity of the olfactory receptors.

Basis of Differentiating Smells

The receptor protein in the olfactory cilia actually belongs to a very large family of proteins that are expressed only in olfactory epithelial cells. All these proteins have small variation in their structure, giving rise to large number of subtypes. Each subtype is associated with a different odorant. This forms the basis of ability to distinguish a wide variety of smells.

Topic-053 Mechanoreception

Mechanoreception

Mechanoreception is the sensory detection of physical stimuli that have mechanical energy such as stretch, touch, pressure, sound and gravity (equilibrium).

These stimuli cause physical changes (deformation, displacement, bending or stretching) in the receptive structures of mechanoreceptors.

Mechanoreceptors

Mechanoreceptors typically consist of ion channels that are linked to external cell structures (such as sensory hairs) as well as internal cell structures (such as the cytoskeleton).

Mechanoreceptors can be extremely sensitive, responding to mechanical displacements of as little as 0.1 nm.

Mechanism of Mechanoreception

Bending or stretching of the external structure generates tension that alters the permeability of the ion channels. This change in ion permeability alters the membrane potential, resulting in a depolarization or hyperpolarization.

Mechanoreceptor Structure

The simplest mechanoreceptors consist of morphologically undifferentiated nerve endings found in the connective tissue of skin.

More complex mechanoreceptors have accessory structures that transfer mechanical energy to the receptive membrane.

Mechanoreceptors for Touch, Vibration and Pressure

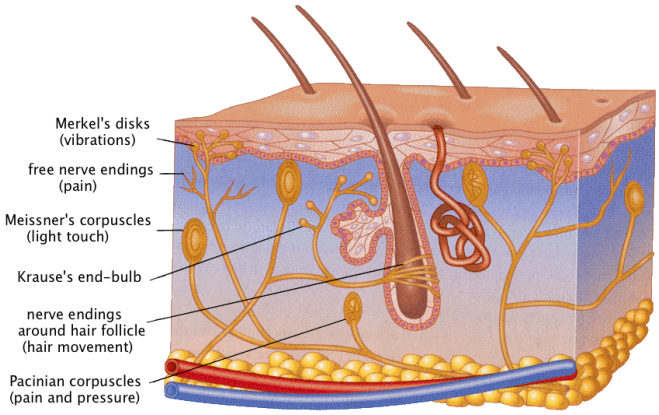
Multiple receptors for these senses are embedded in the skin. These include:

Hair end organs: Situated at the base of hairs and receive gentle touch stimulus due to displacement of hairs.

Meissner's Corpuscles: are the touch receptors. They have encapsulated nerve endings which lie in papillae which extend into the ridges of fingertips.

Pacinian corpuscles: are situated quite deep in the skin. They have encapsulated nerve endings and receive deep pressure stimulus.

Merkel's Disks: are associated with the reception of vibration.



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Stretch Mechanoreceptors

- The stretch receptors of various kinds are found in muscles of arthropods and vertebrates. Most common of these are proprioceptors that detect muscle movements.
- They consist of mechanically sensitive sensory endings (dendrites of sensory neurons) which are associated with specialized muscle fibers.
- When the muscle is stretched, dendrites receive this stimulus and action potentials are triggered in the sensory neuron and transmitted to the spinal cord.

Sound and Equilibrium Receptors

- Hearing and the perception of body equilibrium are related in most animals.
- For both senses, mechanoreceptor cells produce receptor potentials when settling particles or moving fluid cause deflection of cell surface structures.
- The receptors for sound and equilibrium are found in the vertebrate middle and inner ear and in the vestibular system.

Topic-054 Hair Cells

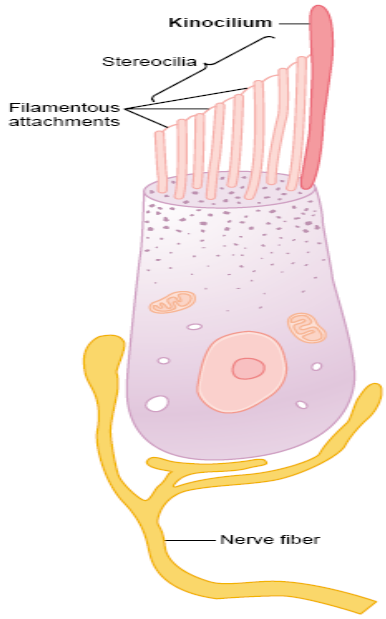
The hair cells of vertebrates are extraordinarily sensitive mechanoreceptors found in several sensory organs and are responsible for transducing mechanical stimuli into electrical signals.

Lateral-line System is Based on Hair Cells

The lateral-line system of fish and amphibians that is involved in detection of motion in the surrounding water is based on hair cells.

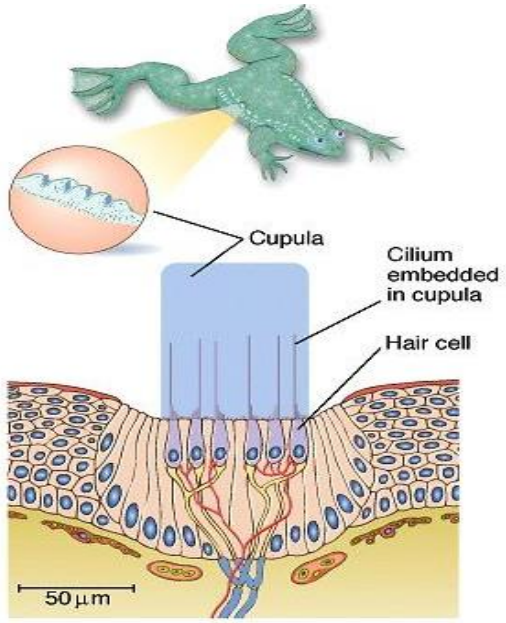
Ear and Vestibular System is Based on Hair Cells

The vertebrate organs of hearing and the organs of equilibrium are also based on hair cells.



A Hair cell

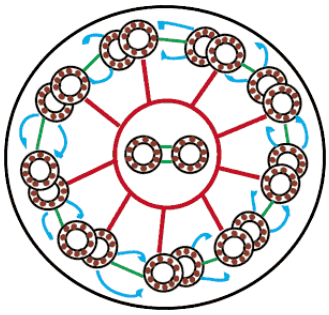
Textbook of Medical Physiology (11th ed) by Guyton



Hair Cells in Lateral-line System

Eckert Animal Physiology (4th ed) by Randall

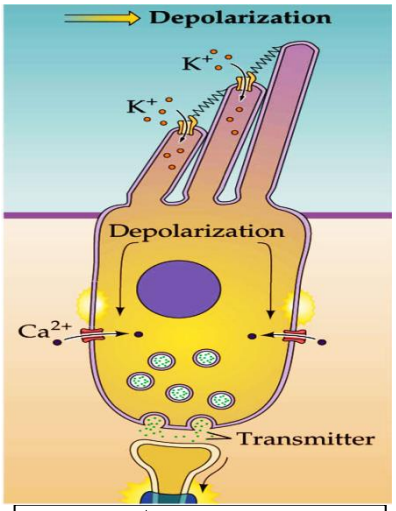
Hair Cell Cilia



- Hair cells are named for the many cilia that project from the apical end of each cell.
- These cilia fall into two classes: kinocilium and stereocilia.
- Each hair cell typically has a single kinocilium. The kinocilium has a "9 + 2" arrangement of internal microtubules that are similar to that of other motile cilia.
- The stereocilia are structurally and developmentally distinct from the kinocilium.
- They are not formed of microtubules.
- They are formed of fine longitudinal actin filaments.
- Each hair cell has 20-300 nonmotile stereocilia.

- The stereocilia of a hair cell are arranged in order of increasing length from one side of the cell to the other.

Working Mechanism of Hair Cells



Neuroscience, 3rd ed (2004) by Purves & Dale

- The stimulus (pressure or force) moves bundles of stereocilia that produces an electrical signal.
- When the cilia bend toward the tallest cilium, a hair cell depolarizes.
- When they bend in the opposite direction, the cell hyperpolarizes.
- Hair cells do not produce APs.
- Instead, they form chemical synapses onto afferent neurons and release neurotransmitter in a graded fashion.
- The afferent neurons then carry information into the central nervous system.

Topic-55 Organs of Equilibrium

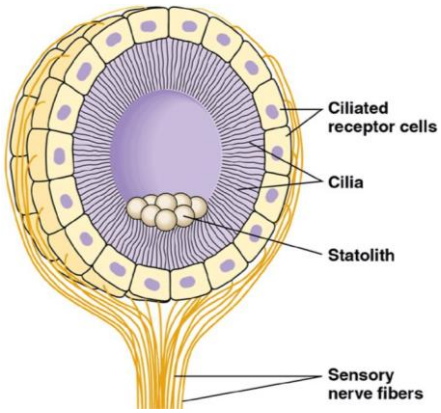
The organs of equilibrium detect an animal's position with respect to gravity or its acceleration.

Statocyst: Invertebrate Organ of Equilibrium

The simplest organ of equilibrium, found in invertebrates is the statocyst.

A statocyst consists of a fluid filled cavity lined with ciliated mechanoreceptor cells and has a solid particle statolith inside it.

Forms of this type of organ are found in most invertebrate groups except the insects.



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Working Mechanism of Statocyst

When the position of animal changes, statolith strikes on the sensory mechanoreceptor cells of the statocyst.

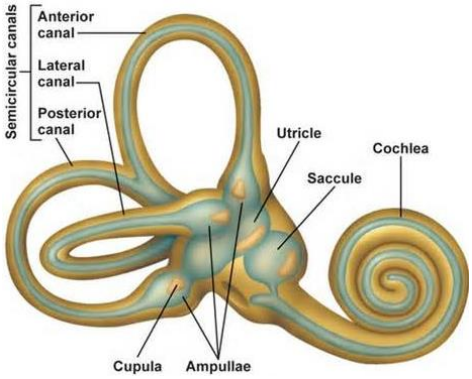
The stimulated receptor cells generate signals that travel to the central nervous system and set up reflex movements of the appendages that bring the body in equilibrium.

Vertebrate Organ of Equilibrium

The vertebrate organ of equilibrium is the vestibular apparatus. It is located in the inner ear.

This apparatus consists of:

- The saccule
- The utricle
- Three semicircular canals lying orthogonally in three mutually perpendicular planes.



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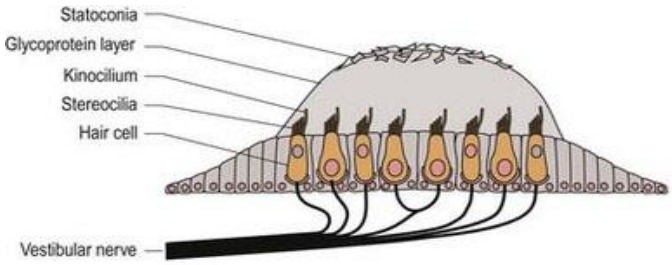
Saccule and Utricle

The inside surfaces of utricle and saccule have a small sensory area which is called macula.



Each macula is covered by a gelatinous layer in which many small calcium carbonate crystals called otoliths (statoconia) are embedded.

In each macula thousands of hair cells are present whose cilia project into the gelatinous layer.

The cilia of these cells bend and generate signals due to the movement of otoliths in the direction of gravity.

The signals are transmitted from the hair cell through the vestibular nerve to the CNS.

Role of Saccule and Utricle

Saccule and utricle maintain the static equilibrium of the head.

The macula of the utricle lies in the horizontal plane on the inferior surface.

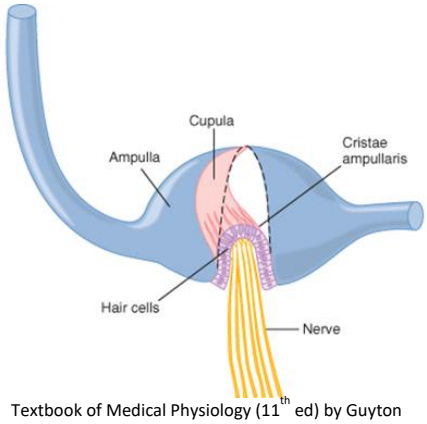
It plays an important role in determining orientation of the head when the head is upright.

The macula of the saccule is located in the vertical plane.

It determines head orientation when the person is lying down.

Semicircular Canals

- The three semicircular canals are lying orthogonally in three mutually perpendicular planes.
- Each semicircular duct has an enlargement at one of its ends called the ampulla.
- The ducts and ampulla are filled with a fluid called endolymph. Endolymph differs from most extracellular fluids because it is high in K^+ (about 150 mM) and low in Na^+ (about 1 mM).
- In each ampulla, there is a small ampullary crest at which a loose gelatinous tissue mass cupula is present.



Textbook of Medical Physiology (11th ed) by Guyton

- Hair cells are located on the ampullary crest. The cilia of these hair cells project into the cupula.

Role of Semicircular Canals

- Hair cells in the three semicircular canals detect acceleration of the head.
- The orthogonal arrangement of the three canals allows them to detect any movement of the head in three-dimensional space.
- Any rotational movement of the head results in flow of endolymph through one of the ducts.
- When fluid strikes the cupula, it moves.
- Movement of cupula results in the displacement of cilia of the hair cells at its base.
- Displacement of cilia results in the change of membrane potential of the hair cells, which are excited and generate an action potential.

Topic-56 The Mammalian Ear

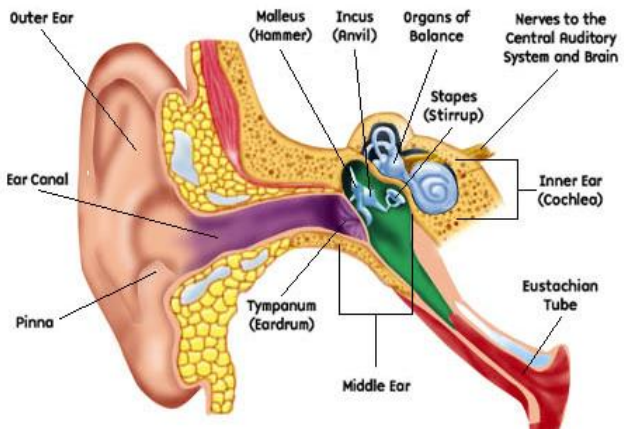
The ear is the organ of hearing that detects sound within a particular frequency range.

The detection range of human ear for different frequencies of sound lies between 20 to 20000 hertz

Functional Anatomy of Mammalian Ear

The ear has three major divisions:

- External ear
- Middle ear
- Inner ear



The three parts of ear are designed to conduct sound waves through three principally different media i.e., air, bone and fluid.

The conducted waves are converted into electrical signals through a series of complex steps.

External Ear

External ear includes:

- The pinna (auricle)
- Tragus
- External auditory meatus (auditory canal)
- Tympanic membrane (eardrum or tympanum)

These structures act as a funnel to collect sound waves from the environment and concentrate them onto a specialized surface, the eardrum or tympanic membrane.

The pinna and tragus act as an acoustic antenna which facilitate the collection of sound waves.

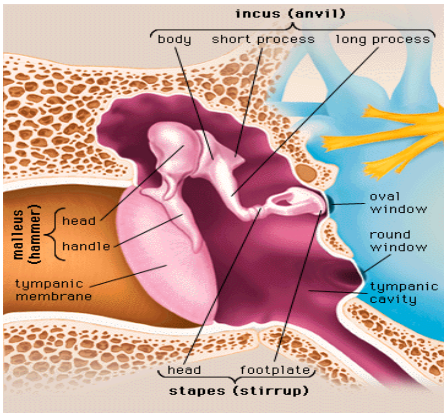
The ear canal acts as a resonator that amplifies sound in particular frequency ranges.

The tympanic membrane is a thin, double-layered, epithelial partition between the external and middle ear. The collected and amplified sound strikes the tympanic membrane; as a result, it vibrates.

Middle Ear

The middle ear is a narrow air-filled cavity that connects the outer ear canal to the inner ear.

It has a series of three small bones known as the auditory ossicles. These ossicles are the malleus, incus, and stapes.



The middle ear ossicles: malleus, incus and stapes

These ossicles are connected in a series; at one end malleus is attached to the tympanic membrane and at the other end stapes is attached to the oval window of cochlea.

Middle ear ossicles perform two functions:

1. Receive sound waves in the form of vibrations from the tympanic membrane and transmit them onto the oval window of cochlea.
2. Provide amplification of sound waves (more than 20 fold) due to their geometrical organization and surface area difference between tympanic membrane (0.6 cm^2) and oval window (0.032 cm^2).

Inner Ear

- The inner ear is a complex structure that is buried deep within the temporal bone of skull.
- It is concerned with dual function of hearing as well as maintaining balance of the body.
- It consists of a bony labyrinth which is filled with perilymph and has an oval and a round window.
- Oval window is attached to the middle ear ossicle stapes, which pulls the window back and forth, transmitting the sound vibrations to the inner ear.
- In the bony labyrinth lies the membranous labyrinth which has membranous channels and compartments filled with endolymph. It consists of three parts:
  - Three semicircular canals
  - Vestibule (sacculus and utricles)
  - Cochlea
- The semicircular canals and vestibule are concerned with maintaining balance while cochlea is the sensory structure concerned with hearing.

Topic-57 Cochlea

Cochlea

The cochlea is the sensory part specialized for hearing. It is a coiled structure located in the inner ear. Its purpose is to take the vibrations of the middle ear bones and transform them into nerve impulse that goes to the brain.

Structure of Cochlea

The cochlea is divided along its length into three fluid-filled compartments:

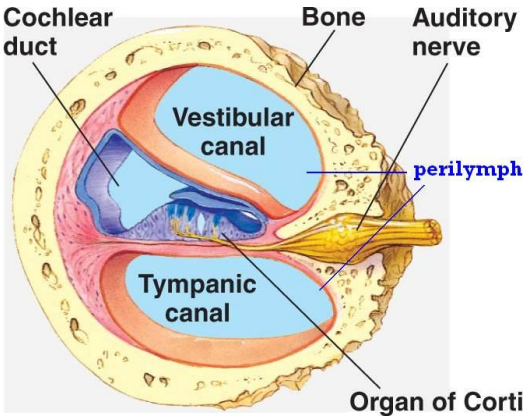
1. Upper, scala vestibuli (vestibular duct) filled with perilymph.
2. Middle triangular passageway, scala media (cochlear duct), filled with endolymph.
3. Lower, scala tympani (tympanic duct), filled with perilymph

The partition between scala vestibuli and scala media is the Reissner's membrane (vestibular membrane).

The partition between scala media and scala tympani is the basilar membrane.

The oval window is at the base of the cochlea in the scala vestibuli.

The round window is at the base of the cochlea in the scala tympani.



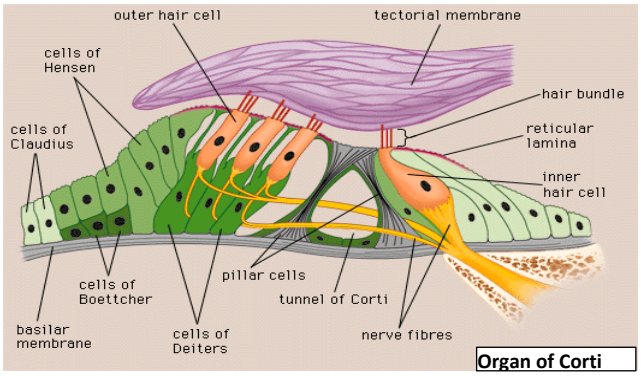
Organ of Corti

The cochlear duct contains the sensory organ of hearing, the Organ of Corti that contains the hair cells and transduces auditory stimuli into sensory signals.

It is the organ due to which human ear can detect and distinguish among different sound frequencies.

It is composed of:

- Hair cells
- Support cells
- A specialized basilar membrane
- Auditory nerve endings
- Tectorial membrane



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Hair Cells in Organ of Corti

Two types of hair cells are present in the organ of Corti:

- Inner hair cells (IHC)
- Outer hair cells (OHC)

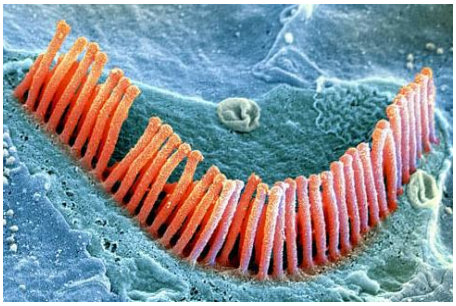
Both types are quite different in their functional anatomy.

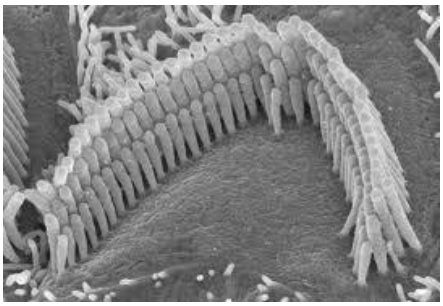
Inner hair cells (IHC)

- There are about 3,500 IHCs arranged in a straight line or wide 'U'.
- They are the true sensory cells, sending impulses via the auditory nerve.

Outer hair cells (OHC)

- There are about 12,000-25,000 OHCs in mammals.
- They are arranged in three or four rows forming a characteristic 'W' shape.
- The outer hair cells have both sensory and motor elements that contribute to hearing sensitivity and frequency selectivity.





Basilar membrane

- Basilar membrane forms the floor of the cochlear duct and bears the organ of Corti.
- It is involved in the detection of sound according to its frequency range.

Tectorial membrane

- Tectorial membrane is a fibrous sheet with fine gelatinous layer lying on the apical surface of organ of Corti.
- The stereocilia of the hair cells are embedded in the gelatinous layer of the tectorial membrane.
- When the basilar membrane is displaced, the tectorial membrane moves across the tops of the hair cells. it exerts a shearing force (i.e., a force perpendicular to the axis of the cilia) that bends the stereocilia of the hair cells. The hair cells generate nerve impulse that is transmitted to the sensory axons of the auditory nerve.

Topic-58 Sound Transduction by Cochlear Hair Cells

Reception of Sound at Cochlea

The sound vibrations are received by cochlea at the oval window through the stapes of middle ear.

These vibrations cause displacement of basilar membrane that, in turn, causes the movement of tectorial membrane across the tips of the hair cells in the organ of Corti present in the cochlear duct.

Movement of tectorial membrane exerts a shearing force at the tips of stereocilia of hair cells that bend laterally (towards the tallest stereocilium).

Mechanoelectrical Transduction

The lateral bending of stereocilia causes the transduction event to happen.

The mechanical deflection of stereocilia influences the conformational state of transduction ion channels in their tips, causing these channels to open.

The threshold of cochlear hair cells is a deflection of only 0.1-1.0 nm.

When the ion channels open, K^+ ions enter the cell from the endolymph in cochlear duct.

This inward K^+ current depolarizes (excites) the hair cells, producing the hair cell receptor potential.

Release of Neurotransmitter

Hair cell excitation due to inward K^+ current also causes the opening of voltage-gated calcium channels.

The resultant Ca^{2+} influx causes transmitter (mainly glutamate) release from the basal end of the cell onto the auditory nerve endings, stimulating them to send an electrical signal along the cochlear nerve.

Repolarization of Hair Cells

K^+ entry via the transduction channels causes the opening of voltage gated Ca^{2+} channels as well as the K^+ channels located in the membrane of the soma of hair cell at the basal end.

The opening of these K^+ channels causes K^+ efflux that results in repolarization.

The efflux occurs because the perilymph surrounding the basal end is low in K^+ relative to the depolarized cytosol.

Repolarization of the hair cell via K^+ efflux is also facilitated by Ca^{2+} ions, which, in addition to modulating the release of neurotransmitter, also open the Ca^{2+}-dependent K^+ channels, which provide another avenue for K^+ efflux into the perilymph.

Unusual Depolarization with K^+ Ions

The inward K^+ current causing depolarization of hair cells is somewhat unusual as Na^+ current is generally involved in depolarization of receptors.

This is due to the unusual adaptation of the cochlear hair cell that uses K^+ ions for both to depolarize and repolarize the cell.

This adaptation has arisen because the basal and apical surfaces of the hair cell are exposed to different extracellular ionic environments.

The apical end (having the stereocilia) protrudes into the scala media (cochlear duct) that is filled with endolymph which is K^+-rich, Na^+-poor fluid.

The basal end of the hair cell body is exposed to perilymph (typmpanic duct) which resembles other extracellular fluids in that it is K^+- poor and Na^+-rich.

The differences in endolymph and perilymph composition result in endocochlear potential. Due to these differences, the compartment containing endolymph (cochlear duct) is about +80 mV more positive than the perilymph compartment (tympanic duct).

Considering the hair cell having a resting potential of -60 mV, the inside of the hair cell is about 45 mV more negative than the perilymph on its basal end and 140 mV more negative than the endolymph at its stereociliary end.

This large electrical gradient across the stereocilia drives K^+ through open transduction channels into the hair cell, even though these cells already have a high internal K^+ concentration.

This large potential difference also serves a tremendous ionic force to drive the mechanoelectrical transduction process of the hair cells

Moreover, this steep gradient, especially at the tip of the cell, is thought to sensitize the cell to the slightest sound.

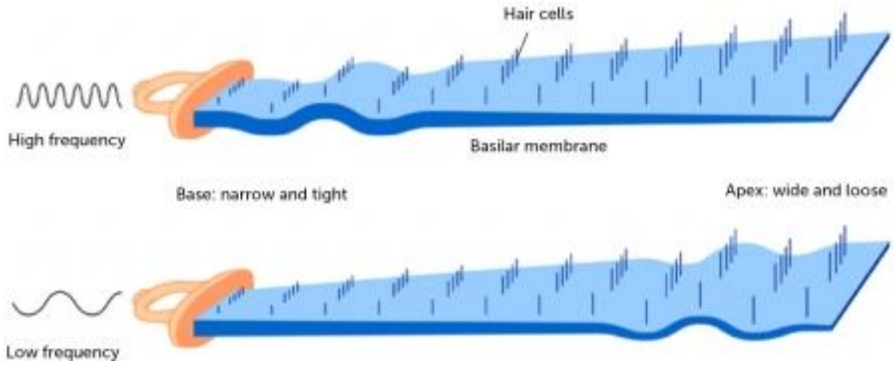
Topic-59 Frequency Analysis by Cochlea

Tonotopic Sensitivity of Cochlea

The cochlea is tonotopically (frequency-wise) tuned organ.

The tonotopic sensitivity of cochlea is due to two reasons:

1. Variations in the width and stiffness of basilar membrane which is relatively narrow (~ 0.1 mm wide) and stiff at the base and wider and more flexible at the apex of cochlea (~0.5 mm wide).
   As a result, different frequencies of sound cause different portions of the basilar membrane to vibrate, stimulating particular hair cells and sensory neurons.
2. Placement of hair cells tuned to particular frequencies at particular positions in narrow bands on the basilar membrane.
   Each hair cell in the cochlea is tuned to a particular band of sound frequency as a result of both mechanical and channel properties.
   Each cell has a resonance frequency that is determined by the length of the stereocilia in the hair bundle.
   Cells with long hairs are most sensitive to low frequency sounds, whereas cells with short hairs are tuned to high-frequency sounds.



Frequency Analysis by Cochlea

The sound vibrations encounter the basal membrane of the cochlea through its stiff basal end that is closest to the middle ear cavity.

The base vibrates immediately in response to pressure changes.

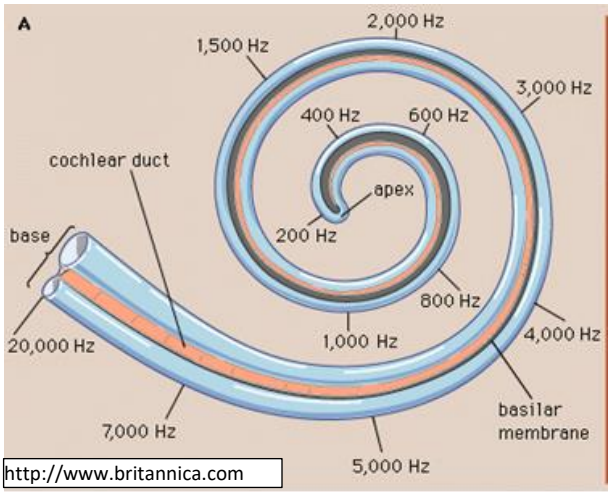
These vibrations travel along the basilar membrane from the base toward its apex causing displacement of the membrane.

However, the region of maximal displacement of the basilar membrane varies with sound frequency.

The properties of the membrane nearest the oval window (base) are such that it resonates optimally (under goes the largest deformation) with high frequency tones while the more distant regions of the membrane (near the apex) vibrate maximally in response to low frequency sounds.

Thus the frequencies of incoming sound waves are sorted out along the basilar membrane and each frequency has its characteristic place.

Very low frequencies (< 200 Hz) are compressed on to a relatively limited section at the apical end of the membrane.



Topic-60 Electroreception

All organisms produce weak electric fields due to the activity of their nerves and muscles.

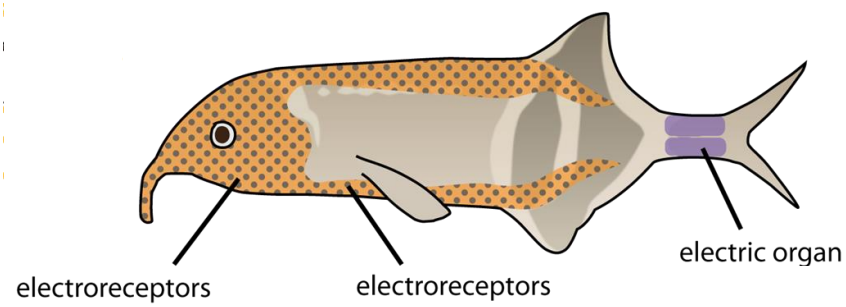
Electroreception is defined as the ability to detect electric fields generated by the animal itself or by other animals in the aquatic environment.

Electroreception is an important sense in aquatic environments and has been found in many fishes, some amphibians and a monotreme mammal duckbilled platypus.

Electroreceptors

The electroreceptor cells of fishes and amphibians are spread in the head and trunk regions. They are linked to the lateral line system.

The electroreceptors of platypus are present on its bill. They detect electric fields generated by the muscles of crustaceans, frogs, small fish, and other prey.



Mechanism of Electroreception

The current in water enters the sensory pores in the epidermis of the skin.

At the base of each pore, there is an electroreceptor cell.

Each electroreceptor is actually a modified hair cell that has lost its cilia.

The electroreceptor has synaptic connection with axons of the eighth cranial nerve that innervates the lateral-line system.

This sensory information is processed in the greatly enlarged cerebellum of the fish, enabling it to detect and locate objects in its immediate environment

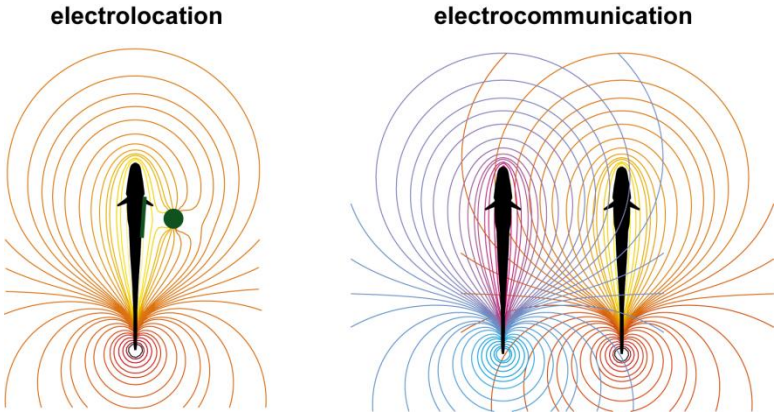
Significance of Electroreception

The ability to detect electric fields helps a fish to find mates, capture prey, avoid predators and for orienting towards or away from certain objects.

Some sharks are especially adept at locating their prey by sensing the electric currents emanating from the active muscles of an animal.

This is an especially valuable sense in deep, turbulent, or murky waters where vision is of little use.

Some fishes also use electric fields produced by the members of their own species for communicating with one another (electrocommunication).



Some fishes possess specialized electric organs at one end of body that generate weak electrical fields. The electrical pulses produced by these organs re-enter the fish through epithelial pores in the lateral-line system, thereby generating an electric field around the fish body. The electroreceptors in lateral line system detect distortion of electric field caused by any intruding object or animal. This helps these fishes to find prey and avoid predators (Electrolocation).

Topic-61 Thermoreception

Thermoreception is the sense by which an organism perceives hot or cold temperatures.

Thermoreceptors are located in the skin, upper surface of the tongue and anterior hypothalamus.

Skin thermoreceptors detect changes in environmental temperature while thermoreceptors in anterior hypothalamus detect changes in body core temperature.

Thermoreceptors are phasic-type receptors i.e. they respond very rapidly to minute changes in temperature but adapt and quit firing quickly, if the stimulus persists.

Warmth and Cold Receptors

There are two kinds of thermoreceptors in the external skin and upper surface of the tongue:

- Cold receptors
- Warmth receptors

Cold Receptors

The cold thermoreceptors are 3.5 times more common in skin than heat receptors.

They consist of free nerve endings of neurons that have thin myelinated Aδ fibers having faster conduction velocity (19m/s).

They increase their firing rate when the skin is cooled below body temperature.

Warmth Receptors

Warmth Receptors increase their firing rate in response to temperatures above body temperature.

They consist of free nerve endings of neurons that have unmyelinated C fibers with low conduction speed (0.8m/s).

Both these receptors are quite sensitive which enable human beings to detect a change in skin temperature of as little as 0.01°C.

TRP Proteins in Thermoreceptors

The membranes of thermoreceptors have ion channel proteins belonging to the family of transient receptor potential (TRP) proteins.

There are many subfamilies within the TRP family of ion channels, which form many different types of receptors. The TRP's involved in thermoreception are TRPA, TRPM and TRPV.

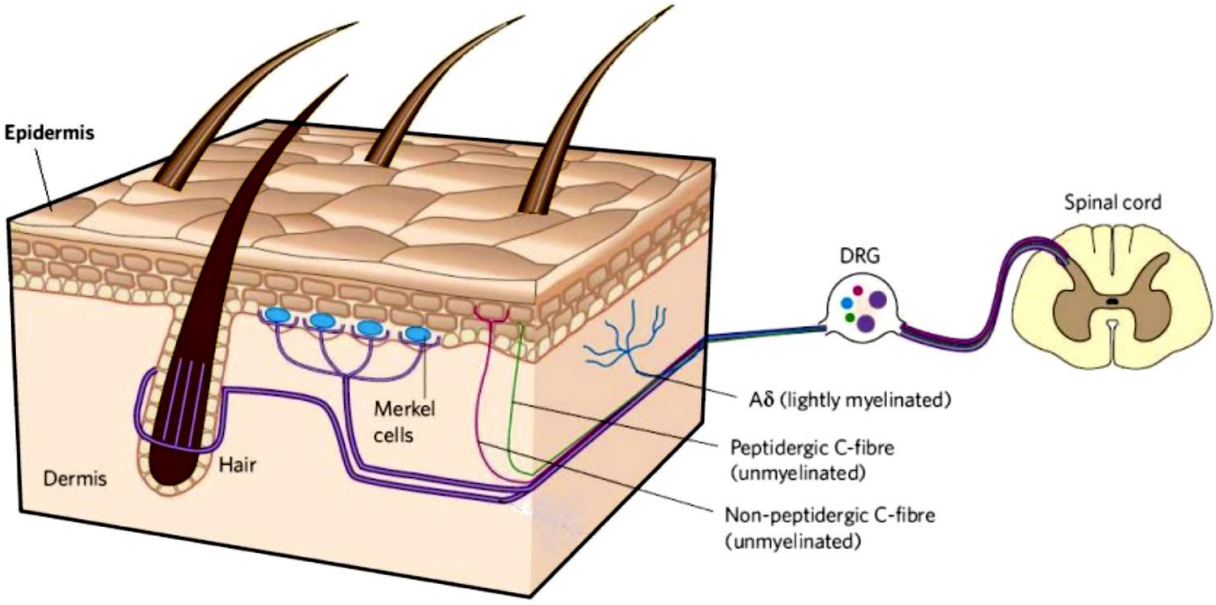
The transduction of temperature in cold receptors is mediated by the TRPA and TRPM while TRPV are involved in warmth reception.

TRP ion channels allow an influx of many cations which tends to be dominated by Ca^{2+}. The increase in ion concentration depolarizes the membrane, and causes action potentials to fire

Neural Pathway of Temperature Sensation

Both warm and cool stimuli transduce information along the same neural pathway.

Cell bodies of neurons of cutaneous thermoreceptors reside in the dorsal root ganglion (DRG) or the trigeminal ganglion on the dorsal horn of the spinal cord. The neurons of dorsal horn of the spinal cord communicate via synapses to the thalamus and then to the hypothalamus. The hypothalamus then elicits action potentials to induce the proper thermoregulatory responses.



Topic-62 Photoreception: Basics

Photoreception consists of transducing photons of light into electrical signals that can be interpreted by the nervous system.

Photoreceptors:

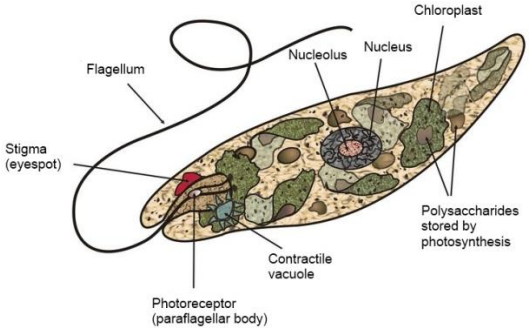
Photoreceptors possess light-sensitive pigments which are carotenoids retinal and 3-dehydroretinal associated with opsin proteins to form rhodopsins.

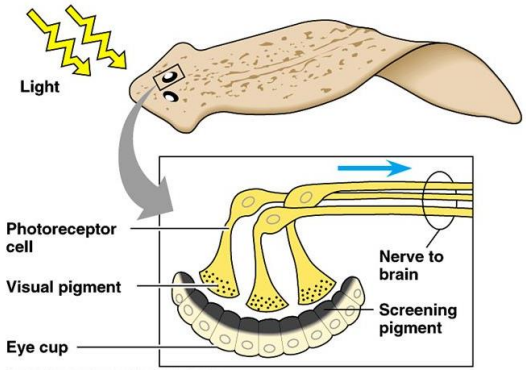
These pigments absorb photons of light energy and then produce a generator potential.

Photoreceptive Structures

The complexity and arrangement of photoreceptors within various animals vary.

The simplest photoreceptive structures are the Eyespots or Stigma found in some protozoa e.g. euglena. Stigma is a bright red colored structure having carotenoid pigments. It gives a sense of light and dark and helps in phototaxis.





Cnidarians and flatworms have multicellular photoreceptive structures call eyecups or Ocelli. They consist of a cuplike depression containing photoreceptor cells. They cannot form image and only provide the animal a sense of direction.

Eyes

In higher invertebrates and all vertebrates, the photoreceptive organs are the image-forming eyes that give an animal more precise information about the surrounding objects.

Eyes of invertebrates (cephalopods) have lens and retina but lack cornea and form a blurred image.

The eyes of vertebrates have also developed cornea which enables them to gather more light which is focused onto the retina and form a sharp images.

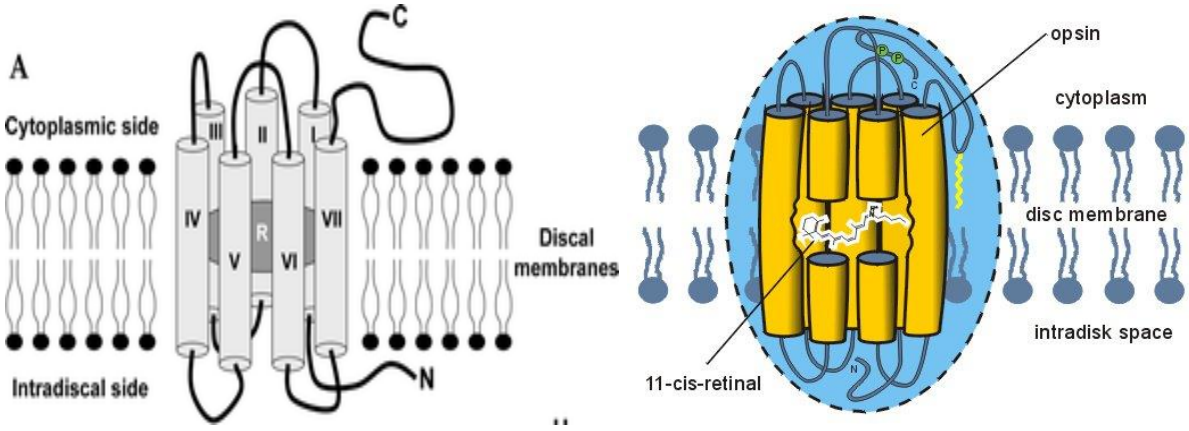
Pigments in Visual Transduction

Although the physical structure of eyes varies greatly among species, visual transduction is based upon a very highly conserved set of protein molecules.

These visual molecules are the proteins known as opsins and are found in the cell membranes of all photoreceptor cells.

They provide an optical pathway to capture photons within the photoreceptors.

Each opsin molecule consists of seven transmembrane domains.



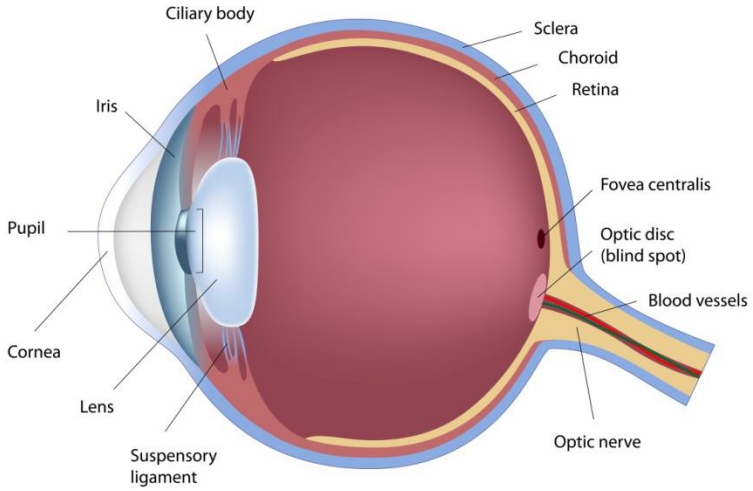
Opsins are coupled to light-absorbing photopigment Retinal to form a functional pigment molecule rhodopsin.

The photopigments are the molecules which are structurally altered by the absorption of photons.

When a photon is captured, it produces a transient structural change that activates a cascade of associated molecules, ultimately changing the functional state of ion channels in the receptor cell membrane and generation of receptor potential.

Topic-63 The Vertebrate Eye: Structural Physiology

Structural features of the eye



The eyes of higher vertebrates are structurally and functionally similar.

The functional parts of the eye involved in focusing and image formation are cornea, a biconvex lens, pupil and retina.

Role of Cornea

- Light enters the eye through cornea which is the clear outer surface of the eye.
- It focuses the light rays onto the lens inside.
- In fact, most of the refraction that occurs in the eye (about 85% of the total) takes place at the air-cornea interface.

Role of Pupil

Size of the pupil can be increased or decreased according to the intensity of light.

The diameter of the pupil is decreased by the contraction of circular smooth muscle fibers in the iris. This decreases the entry of high intensity light into the eye.

Pupil is dilated in dim light by the contraction of radially oriented muscle fibers. This allows an increased amount of light to enter the eye.

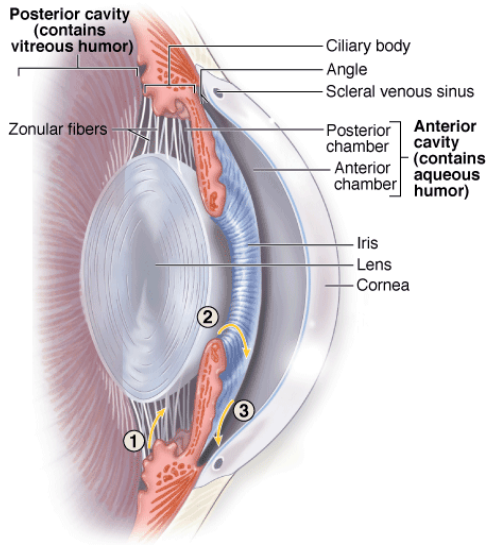
Role of Lens

- The lens causes the light rays to bend and refract onto the retina.
- Fishes focus images on the retina by moving the lens forward or backward.

- In higher vertebrates, image is focused by changing the curvature and thickness of the lens. The curvature and thickness of the lens is controlled by the suspensory ligaments (fibers of Zonula) and ciliary muscles.

Role of Fibers of Zonula

- The shape of the lens is changed by the fibers of the zonula that held the lens in place.
- These fibers can exert an outwardly directed tension on the perimeter of the lens.



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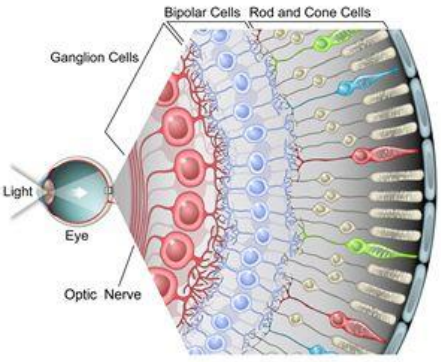
Role of Ciliary muscles

- Ciliary muscles are attached with the fibers of zonula.
- Their contraction and relaxation adjusts the amount of tension exerted on the lens.
- When the ciliary muscles contract, the lens is flattened by elastic tension exerted by the fibers of the zonula, which pull the perimeter of the lens outward. In this state, objects far from the eye are focused on the retina, but objects close by would be fuzzy.
- When the ciliary muscles relax, lens becomes more rounded. This focuses the objects close to the eye.

Role of Retina



Retina is the sensory layer of the eye.

Here, photoreceptor cells—rods and cones—are present which transduce the photon energy of light into the nerve impulse.

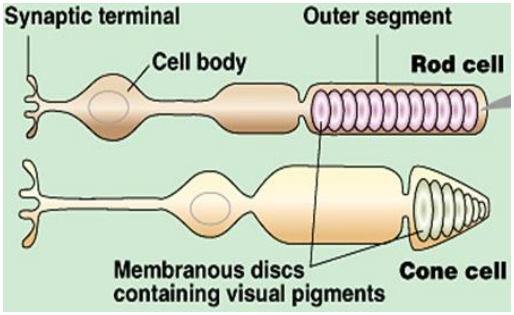
From retina, the impulses are carried by the optic nerve to the brain.

Topic-64 Visual Receptor Cells of Vertebrates

Visual Receptor Cells: Rods and Cones

The photoreceptor cells that capture the energy of light and transduce it into neuronal signals are located in the retina of the vertebrate eye.

The visual receptor cells of vertebrates fall into two classes, rods and cones.



Light Reception by Rods and Cones

Rods are more sensitive to light, so they provide night vision. However, they cannot distinguish colors, so provide achromatic vision (black and white) only.

Cones are less sensitive and contribute very little to night vision. They function best in bright light and provide high resolution with color vision.

There are three types of cones. Each has a different sensitivity across the visible spectrum, providing an optimal response to red, green, or blue light.

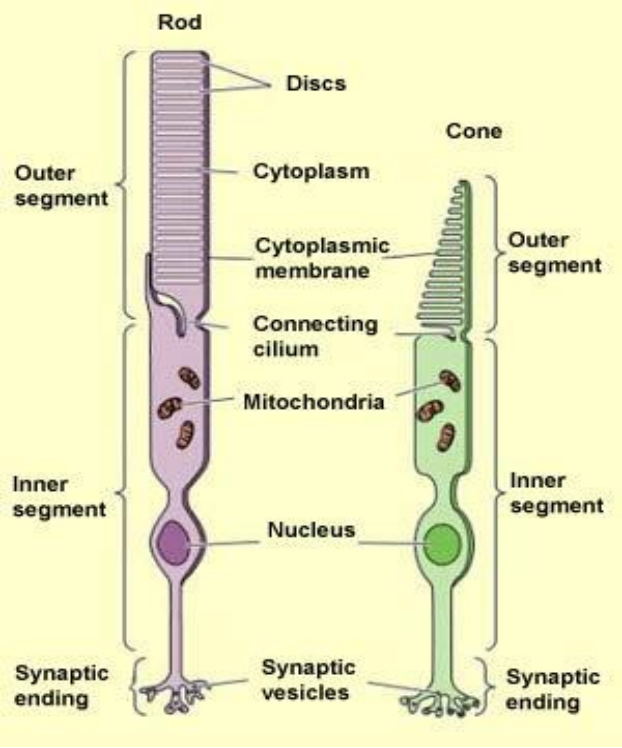
Number of Rods and Cones

- The relative numbers of rod and cones in the retina varies among different animals and correlates with the extent to which an animal is active at night.
- Most fishes, amphibians, reptiles and birds have strong color vision.
- Humans and other primates have well developed color vision, but most nocturnal mammals have reduced capacity to see colors.
- The nocturnal mammals have a high proportion of rods in the retina that gives them keen night vision.
- The human retina contains about 125 million rods and about 6 million cones.

Distribution of Rods and Cones

Fovea centralis: The center of the visual field in many mammalian retinas is called fovea centralis. It is about 1 mm^2 central part of retina and has a very high density of cones (about 150,000 cones per mm^2) but no rods. It provides very detailed information about the visual field, a characteristic called high visual acuity.

The ratio of rods to cones increases with distance from the fovea, with the peripheral regions having only rods.



Structure of Rods and Cones

The general cell structure of rods and cones has certain basic similarities. Generally, the rods are narrower and longer than the cones. However they vary in their photopigments

The major functional segments of either a rod or a cone are:

the outer segment

the inner segment

Synaptic body

The Outer Segment

The light-sensitive photochemical is found in the outer segment.

In rods, this is rhodopsin while in cones it is one of three color photopsins.

The outer segments of rods and cones have large numbers of discs. These discs are formed by the infolding of cell membrane.

There are as many as 1000 discs in each rod or cone.

In cones the lumen of each lamella is open to the cell exterior while in rods, lamellae pinch off completely from the surface membrane so as to form flattened disks stacked together.

Both rhodopsin and the color pigments are incorporated into the membranes of the discs in the form of transmembrane proteins.

Because the photopigments lies in the disk membranes of the rod outer segment but not in the surface membrane, the primary step in photochemical transduction takes place in the disk membranes, rather than in the surface membrane.

The Inner Segment

The vertebrate receptor cells contain a rudimentary cilium that connects the outer segment to the inner segment.

The inner segment contains the cytoplasm with organelles and nucleus.

The Synaptic Body

At the end of inner segment, there is a synaptic body or synaptic terminal that connects the rod or cone with neuronal cells.

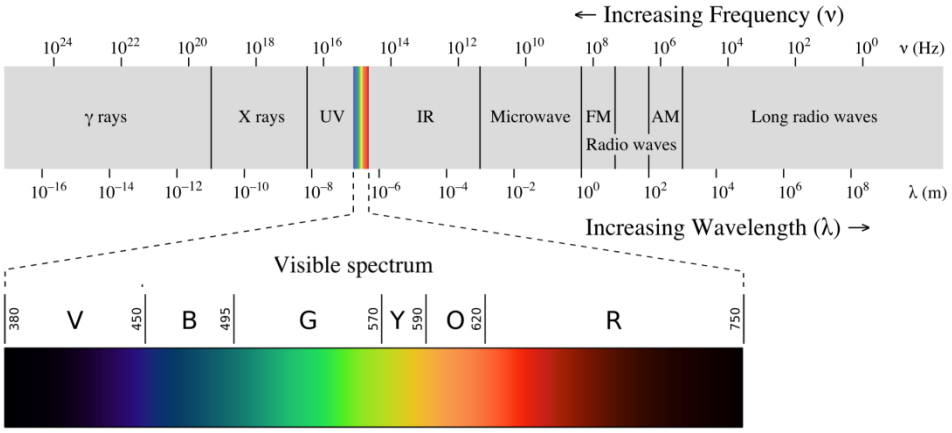
Topic-65 Visual Pigments and Their Photochemistry-I

Visible Light

All visual receptor cells can detect only a part of the spectrum of electromagnetic radiation. This part of radiation is called the visible light.

Various wavelengths within the spectrum of visible light are perceived as different colors.

The visible spectrum for human eyes lies between the wavelengths of 400-740 nm.



Pigments are Necessary for Vision

This visible spectrum of an animal depends on the presence of visual pigments that absorb these wavelengths of light and transduce the electromagnetic energy into chemical energy.

If an animal has pigments that can absorb light falling in the range of ultraviolet spectrum, it can also detect that light e.g. insects can see the UV light.

Most vertebrates lack the capacity to see in the ultraviolet spectrum because vertebrate life evolved in water, which heavily filters electromagnetic radiation. The range of the spectrum to which vertebrate photopigments are sensitive matches the spectrum of light that is admitted through water.

Light Absorbing Capacity of Pigments

The organic pigments absorb light selectively due to the presence of alternating single and double bonds in a carbon chain or ring.

When a quantum of radiation is absorbed by a photopigment molecule, it raises the energy state of the molecule by increasing the orbital diameter of the electrons associated with a conjugated double bond.

Visual Pigments

Both rods and cones contain pigments that decompose on exposure to light and, in the process, excite the nerve fibers leading from the eye.

The light-sensitive pigment in the rods is called rhodopsin while the light-sensitive pigments in the cones are called cone pigments or color pigments, have compositions only slightly different from that of rhodopsin.

Chemistry of Rhodopsin

Rhodopsin is found in the outer segments of rods in vertebrates and in the photoreceptors of many invertebrates.

Rhodopsin molecules are packed densely into receptor membranes (there may be as many as 5×10^{12} molecules per square centimeter).

A rhodopsin molecule consists of two major components: Opsin protein and a light-absorbing molecule that may be retinal or 3-dehydroretinal.

Retinal is the aldehyde of a carotenoid vitamin A_1 (Retinol). 3-dehydroretinal is the aldehyde of vitamin A2 (3-dehydroretinol).

In addition to these major components, rhodopsin includes a six-sugar polysaccharide chain and a variable number (as many as 30 or more) of phospholipid molecules.

The opsin bound with phospholipids and the polysaccharide chain, is found as an integral part of the photoreceptor membrane.

Carotenoid molecules (Retinal and 3-dehydroretinal) move back and forth between the photoreceptor membrane and the pigmented epithelial discs at the back of the retina during bleaching and regeneration of the visual pigment.

Topic-65 Visual Pigments and Their Photochemistry-II

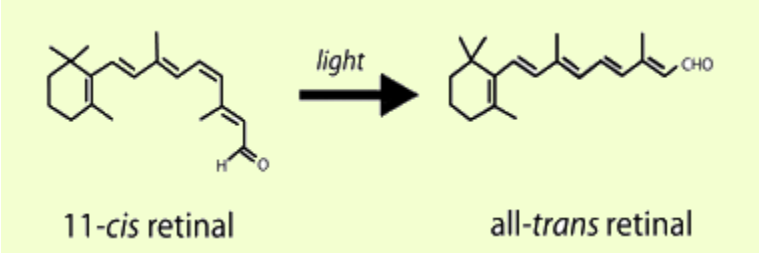
Isomerization of Rohodopsin

The retinal molecule assumes two sterically distinct states in the retina.

In the absence of light, retinal is in the 11-cis configuration and is linked to opsin covalently by a Schiff's base bond ($R_2C=NR$).

In the presence of light, the 11-cis retinal isomerizes into the all-trans configuration.

This cis-trans isomerization is light's only direct effect on the visual pigment.

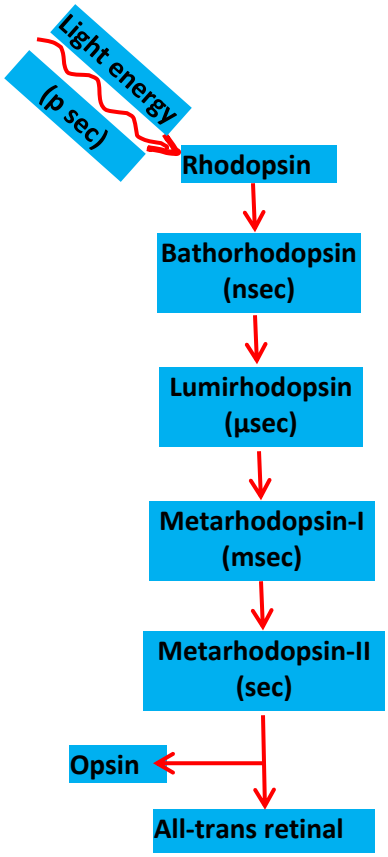


Activation of Rhodopsin

This change in configuration destabilizes rhodopsin molecule which starts to decompose.

This state of decomposition is the activated state of rhodopsin that results in a series of biochemical activity in the receptor membrane resulting in transduction of light energy captured by rhodopsin into electrical form.

Light activation of rhodopsin also causes the color of rhodopsin to change from purple to yellow, so it is called "bleaching."



Decomposition of Rhodopsin

When light hits the photopigment rhodopsin, the immediate product is bathorhodopsin, which is a partially split combination of the all-trans retinal and opsin.

Bathorhodopsin is extremely unstable and decays in nanoseconds to lumirhodopsin which then decays in microseconds to metarhodopsin I, which in about a millisecond transforms to metarhodopsin II, and finally, much more slowly (in seconds), into the completely split products opsin and all-trans retinal.

Role of Metarhodopsin II in Visual Transduction

It is the metarhodopsin II that is called activated rhodopsin. It excites electrical changes in the rods which generate graded receptor potential and transmit the visual impulse into the nervous system

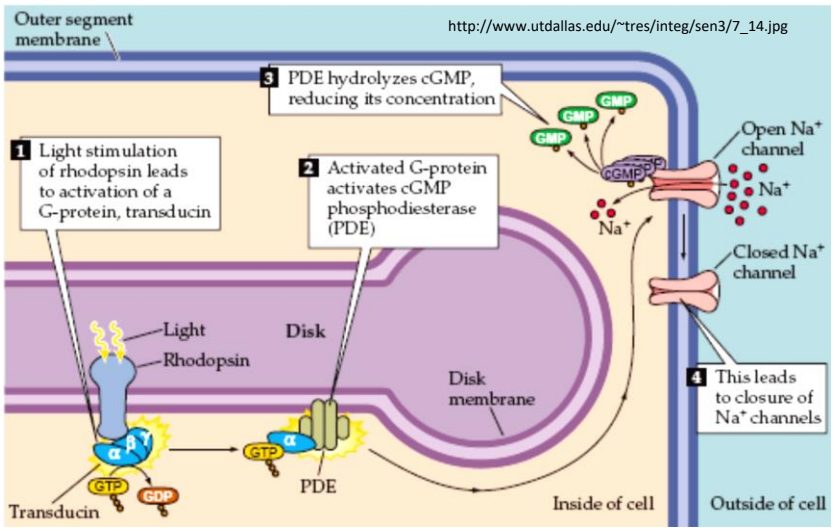
Metarhodopsin II activates a G protein transducin that is associated with the membrane.

The activated transducin activates the enzyme phosphodiesterase, which hydrolyzes cGMP to 5'-GMP.

The membrane of the rod outer segment contains a class of channels that are permeable to three cations: Na^+, Mg^{2+} and Ca^{2+}. When the level of cGMP drops, the conductance through these channels drops.

As the inward I_{Na} drops, and the residual K^+ current through other channels causes the cell to hyperpolarize and generate graded receptor potential.

The production of graded receptor potential due to hyperpolarization is characteristic of photoreceptor cells. This behavior is different from all other sensory receptors in which receptor potential is generated due to depolarization.



Topic-67 The Color Vision

Types of Cone Cells

The perception of color in human and other vertebrates is based on three types of cone cells.

Each type of cone cell synthesizes only one of the three visual pigments: blue, green or red, making the cones selectively sensitive to different colors.

Visual Pigments: Photopsins

The three visual pigments are called photopsins.

They are formed from binding of retinal to three distinct opsin proteins.

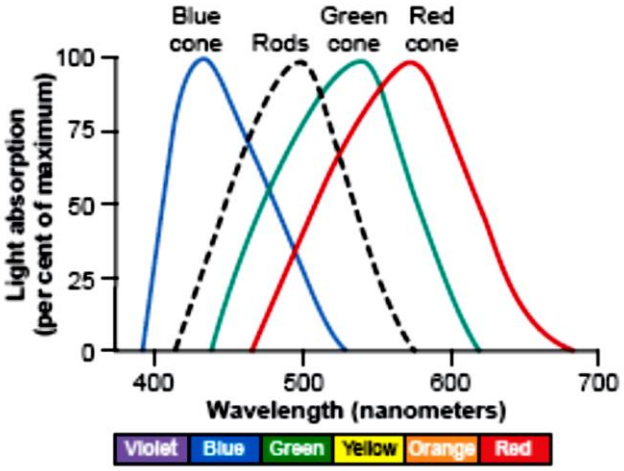
Slight differences in the opsin proteins are sufficient for each photopsin to absorb light optimally at a distinct wavelength.

Perception of Intermediate Hues

The absorption spectra of blue, green and red pigments in the three types of cones show peak absorbance at light wavelengths of 445, 535, and 570 nm, respectively.

However the ranges of spectra overlap which enable brain to perceive intermediate hues on simultaneous stimulation of two or more classes of cones.

For example, when both red and green cones are stimulated, we may see yellow or orange, depending on which class is more strongly stimulated.



Genetic Basis of Color Blindness

The three types of opsins found in color pigments are encoded by three different genes.

The gene encoding the opsin in blue-absorbing pigment is located on an autosomal chromosome. The genes for red-absorbing and green-absorbing pigments are closely linked on the X chromosome.

Color blindness is caused due to a mutation in one of the cone opsin genes, resulting in absence of one type of pigmented cones.

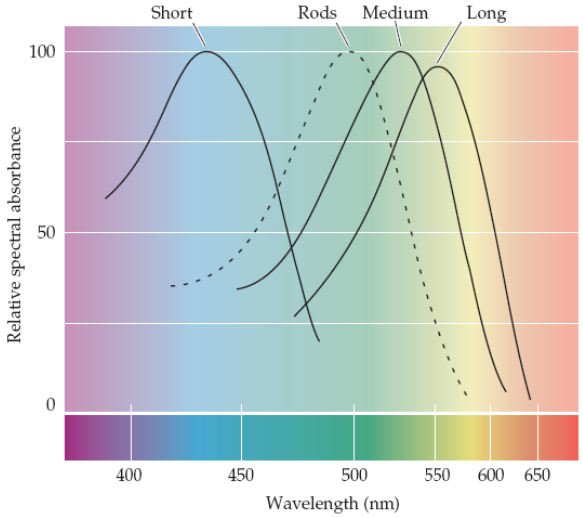
A person missing a single type of color receptive cones is unable to distinguish some colors.

Red-Green Color Blindness

The green, yellow, orange, and red colors between the wavelengths of 525 and 675 nm, are normally distinguished from one another by the red and green cones.

If either of these two cones is missing, the person cannot distinguish these four colors.

The person is especially unable to distinguish red from green and is therefore said to have red-green color blindness.



Protanope and Deuteranope

A person with loss of red cones is called a protanope.

In this type, the overall visual spectrum is shortened at the long wavelength end because of a lack of the red cones.

A color-blind person who lacks green cones is called a deuteranope.

Such a person has a normal visual spectral range because red cones are available to detect the long wavelength red color.

Endocrine Physiology

Topic-68 Glands, Secretions and Secretory Mechanisms

Glands

A gland is a cell or group of cells that secretes a particular chemical substance for use in the body or for discharge into the surroundings.

Every animal has a large number of glands, which differ in structure and type of secretion.

Secretions

Secretions are the chemical substances, synthesized by glandular cells and released from the gland in response to an appropriate stimulus.

The nature and amount of the secretion and the form of stimulus vary greatly among different glands.

Types of Glandular Secretions

Secretions can be categorized by the distance at which they have an effect.

- Autocrine secretions
- Paracrine secretions
- Endocrine secretions
- Exocrine secretions

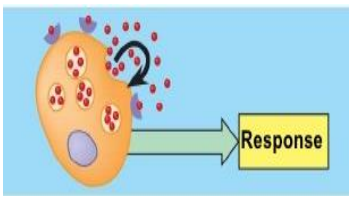
Autocrine Secretions

The secreted substance binds to autocrine receptors on the same cell, leading to changes in the cell.

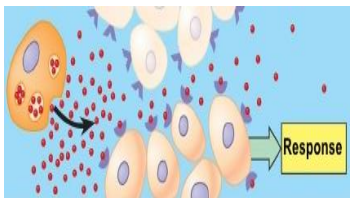
Paracrine Secretions

The paracrine secretion refers to a substance that acts locally, having effect on neighboring cells.

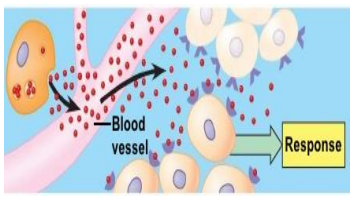
For example, during the inflammatory response localized vasodilation is induced mainly by histamine released from mast cells in the area of tissue damage.



Autocrine secretions



Paracrine secretions

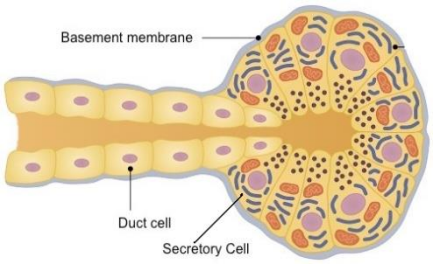


Endocrine secretions

Endocrine Secretions

Endocrine secretions refer to the substances that are released into the bloodstream and act on distant target tissues. The endocrine secretions are generally known as hormones.

Exocrine Secretions



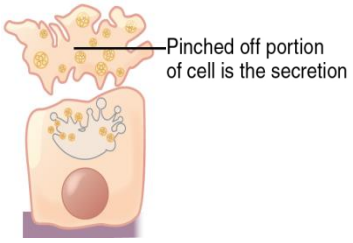
An exocrine secretion refers to a substance that is released via a duct leading from the gland to the external surface of the animal or internal surfaces of the gut and other structures. Various exocrine secretions include digestive secretions, milk, tears, perspiration and fluid that contains sperms.

Secretory Mechanisms

The substances to be exported out of the cell are stored in the form of secretory vesicles. These secretory vesicles are released by various mechanisms in different tissues. These mechanisms can be classified into three types:

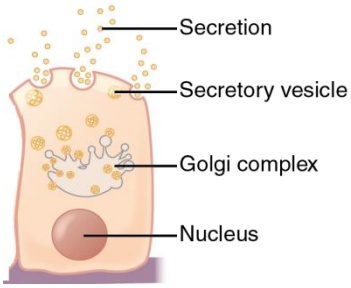
- apocrine Release
- merocrine Release
- holocrine Release

Apocrine Release



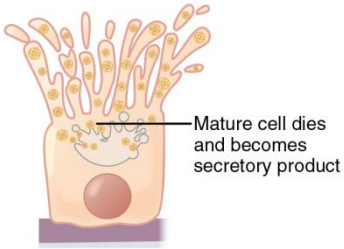
In apocrine secretion, the apical portion of the secretory cell which contains the secretory material, pinches off and enters the lumen. It loses part of its cytoplasm along with the secretion. The cell then reseals at its apex. Mammary glands of mammals are apocrine glands.

Merocrine Release



The secretions of the cell are released by exocytosis into the lumen.
The gland releases its product and no part of the cell is lost or damaged.
It is the most common method of secretion.
This is characteristic of sweat glands and many digestive glands in mammals. Arthropod and annelid exocrine glands also utilize this mechanism.

Holocrine Release



In holocrine secretion, the entire cell is cast off and breaks up to release its contents. This occurs in some insect and molluscan exocrine tissues and is characteristic of mammalian sebaceous glands in the skin.

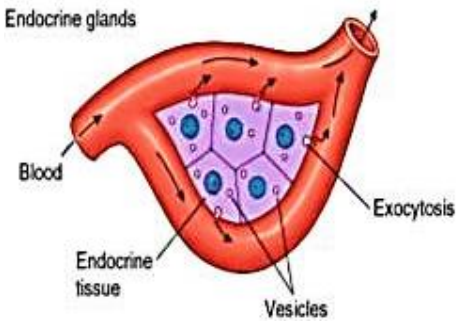
Topic-69 Types of Glands

Glands are broadly classified into two types:

- Endocrine glands
- Exocrine glands

Endocrine Glands

Endocrine glands are the ductless glands that secrete their products i.e. hormones directly into the circulatory system.



Various endocrine tissues are structurally and chemically diverse. They do not exhibit a common morphologic plan or distinctive gross morphologic feature except that such tissues are richly vascularized. For this reason, identifying and locating the endocrine tissues has been a difficult task in some cases.

Some endocrine glands contain more than one type of secretory cells, each producing a different hormone.

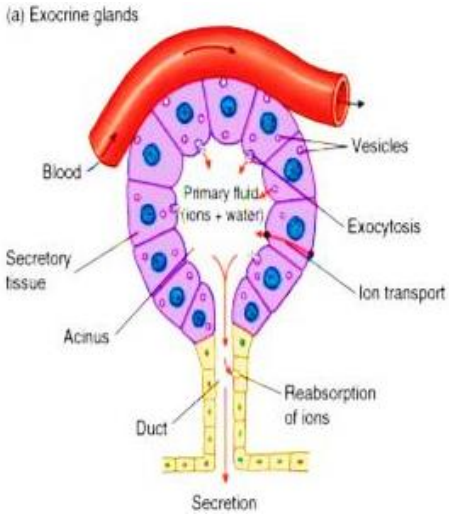
The endocrine glands belong to the body's control system. The endocrine secretions play role in chemical coordination of the body and modulate short-term and long-term physiological processes.

Examples

Pituitary, thyroid and adrenal glands.

Exocrine glands

Exocrine glands produce fluid secretions that are delivered through ducts onto the epithelial surfaces of the body.



Exocrine glands are more easily identified than endocrine glands because of their duct leading to the body surface.

The fluid secretions may be either proteins (enzymes) or mucous or both.

Examples:

- Salivary glands produce saliva that is delivered to the oral cavity for partial digestion of food through parotid and submandibular ducts.
- Pancreas produces enzyme-containing pancreatic juice that is delivered to the small intestine through pancreatic duct.
- Lacrimal glands produce tears that is delivered through lacrimal duct on the surface of eye to provide lubrication.
- Mammary glands produce milk that is delivered through lactiferous ducts to the nipples for nourishing the young.

Topic-70 Vertebrate Endocrine System: An Overview

Endocrine Glands

Vertebrates have a large number of endocrine glands and tissues that produce hormones.

Some glands are distinct and easily identifiable.

However a large number of tissues with endocrine properties are embedded in organs with nonendocrine functions.

Most hormones are produced by only one particular gland located at specific site. However some hormone-like substances e.g. prostaglandins and leukotrienes, are produced by all or nearly all tissues. Others, including some growth factors and the endorphins, are produced by many selected tissues.

Endocrine Glands and Their Secretions

The Table summarizes the major endocrine glands and tissues in vertebrates, the hormones produced by each, and their physiological role.

Vertebrate Endocrine Glands and Tissues		
Endocrine Gland	**Hormone**	**Major Physiological Role**
Hypothalamus	Corticotropin releasing hormone (CRH)	Stimulates ACTH release
	GH releasing hormone	Stimulates growth hormone release
	Gonadotropin releasing hormone (GnRH)	Stimulates release of FSH and LH
	TSH releasing hormone (TRH)	Stimulates TSH release and prolactin secretion
	MSH inhibiting hormone (MIH)	Inhibits melatonin stimulating hormone's secretion
	Prolactin inhibiting hormone (PIH)	Inhibits prolactin release
	Somatostatin	Inhibits release of growth hormone
Pituitary (Anterior)	Growth hormone (GH)	Promotes growth of body tissues Protein synthesis
	Prolactin (PRL)	Promotes milk production
	Thyroid stimulating hormone (TSH)	Stimulates thyroid hormone release
	Adrenocorticotropic hormone (ACTH)	Stimulates release of glucocorticoid hormones by adrenal cortex
	Follicle-stimulating hormone (FSH)	Stimulates gamete production (both ova and sperm); secretion of estradiol
	Luteinizing hormone (LH)	Stimulates androgen production by gonads; ovulation, secretion of progesterone
	Melanocyte-stimulating	Stimulates melanocytes of the skin increasing

	hormone (MSH)	melanin pigment production.
Pituitary (Posterior)	Antidiuretic hormone (ADH)	Stimulates water reabsorption by kidneys Increases blood pressure by vasoconstriction
	Oxytocin	Stimulates uterine contractions during childbirth; milk ejection; stimulates ductus deferens and prostate gland contraction during emission
Thyroid (Follicular cells)	Thyroxine, Triiodothyronine	Maintain metabolic rate and oxygen consumption; Growth and development
Thyroid (Parafollicular cells)	Calcitonin	Reduces blood Ca^{2+} levels
Parathyroid	Parathormone (PTH)	Increases blood Ca^{2+} levels; decreases blood phosphate level
Adrenal (Cortex)	Aldosterone	Increases blood Na^{+} levels; increase K^{+} secretion
	Cortisol, corticosterone, cortisone	Role in carbohydrate metabolism increase blood glucose levels anti-inflammatory effects
Adrenal (Medulla)	Epinephrine, Norepinephrine	Stimulate fight-or-flight response; increase blood glucose levels; increase metabolic activities
Pancreas (Islets of Langerhans)	Insulin	Reduces blood glucose levels; stimulates protein, glycogen and fat synthesis
	Glucagon	increases blood glucose levels; enhances gluconeogenesis and glycogenolysis
Pineal gland	Melatonin	Regulates some biological rhythms and protects CNS from free radicals Inhibits gonadal development (Antigonadotropic action)
Testes (Leydig cells)	Testosterone	Development of male secondary sexual characteristics
Testes (Sertoli cells)	Inhibin	Decreases pituitary FSH secretion
Ovaries	Estradiol	promotes uterine lining growth; female secondary sexual characteristics
	Progesterone	promote and maintain uterine lining growth
Placenta	Chorionic gonadotropin	Increases progesterone synthesis by corpus luteum
	Placental lactogen	Stimulates fetal growth and development Increases mammary gland development in mother
Gastrointestinal tract	Cholecystokinin	Stimulates secretion of enzymes by pancreatic acinar cells Stimulates gall bladder contraction
	Chymodenin	Stimulates secretion of chymotrypsinogen from pancreas
	Gastrin	Stimulates HCl secretion in stomach
	Secretin	Stimulates secretion of bicarbonate
	Substance P	Acts as enteric neurotransmitter for feeling of pain

	Motilin	Increases motility of intestinal villi
Heart (Atrium)	Atrial natriuretic factor	Increases salt and water excretion by kidney to control blood volume and pressure
Most or all tissues	Leukotrienes	Control nucleotide formation
	Prostacyclins	Stimulate cAMP formation
	Prostaglandins	Stimulate cAMP formation
	Thromboxanes	Stimulates cGMP formation
Selected tissues	Endorphins	Produce pain killer effect
	Epidermal growth factor	Promotes epidermal cell proliferation
	Fibroblast growth factor	Promotes fibroblast proliferation
	Nerve growth factor	Promotes development of dendrites and axons
	Somatomedins	Promote cellular growth and proliferation

Topic-71 Hormones and Their Properties

Hormones

Hormones are signaling molecules produced by endocrine glands which are transported by the circulatory system to distant target organs and regulate physiology and behavior of the animal.

Properties of Hormones

- Hormones act only on specific target cells/tissues

  Although hormone molecules come into contact with all the tissues in the body during transport through blood, only the cells that contain receptors specific for a particular hormone are affected by it, and generate response.

- Hormonal action depend on the type of receptor

  The action of a hormone depends on the nature of enzyme cascade linked to the hormone's receptor, as well as the effector molecules expressed in a particular tissue.

  For this reason, a hormone can act on two or more different types of tissues and generate different types of responses.

  For example Antidiuretic hormone stimulates water reabsorption in the nephron of kidney while the same hormone produces vasoconstriction and increases blood pressure by acting on the walls of arteries. The receptors in kidney nephron tubule and arterial receptors are different, causing the same hormone to generate different responses.

- Hormones are active at very low concentration

  The amount of hormone produced by an endocrine gland is small. It is further diluted in the blood and interstitial fluid. The available concentration for the target cell lies between 10^{-8} to 10^{-12} M and the hormone is still effective at this very low concentration.

  The high sensitivity of hormonal signaling is due to the high affinity of target cell receptors for hormones.

- Hormonal effects are amplified

  Binding of a hormone molecule to its receptor leads to a cascade of enzymatic steps that amplify the effect; thus just a few hormone molecules can influence thousands or millions of molecular reactions within a cell.

Topic-72 Chemical Types and Functions of Hormones

Chemical Types of Hormones

Based on their structure and pathway for synthesis, hormones are often divided into four groups:

- Peptide and protein hormones
- Amine hormones
- Steroid hormones
- Prostaglandins

Peptide and protein hormones

These hormones are composed of amino acids. These hormones range in size from small peptides with as few as 3 amino acids (thyrotropin-releasing hormone, TRH) to proteins with almost 200 amino acids (growth hormone and prolactin).

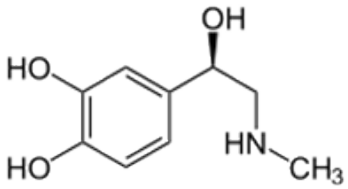
In general, polypeptides with 100 or more amino acids are called proteins, and those with fewer than 100 amino acids are referred to as peptides.

Examples: hormones of the anterior and posterior pituitary gland, hormones of pancreas (insulin and glucagon) and the parathyroid hormone.

Amine hormones

Amines include the catecholamines (epinephrine and norepinephrine) and thyroid hormones (thyroxine and triiodothyronine).

They are small molecules synthesized from a single amino acid tyrosine.

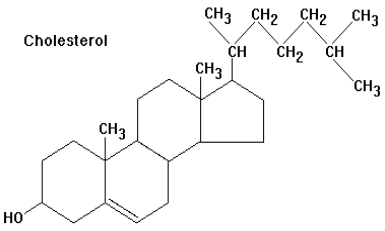


Epinephrine

Steroid hormones

Steroid hormones are synthesized from the precursor steroid cholesterol.

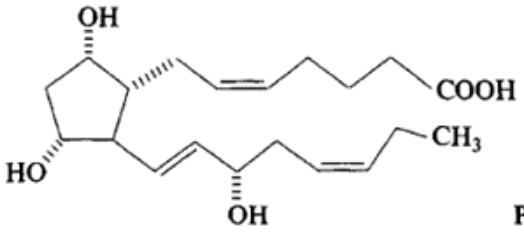
They consist of four fused carbon rings including three cyclohexyl rings and one cyclopentyl ring combined into a single structure.



They include the hormones secreted by the adrenal cortex (cortisol and aldosterone) hormones of ovaries (estrogen and progesterone) and testes (testosterone).

Prostaglandins

Prostaglandins are cyclic unsaturated hydroxy fatty acids synthesized in membranes from 20- carbon fatty acid chains.



Prostaglandin

General Functions of Hormones

Hormones serve a range of functions in the body. To enumerate some:

- Hormones coordinate the long-term functions of animal tissues and organs e.g. growth and maintenance, sexual activity and reproductive cycles and modification of behavior.
- They also perform many regulatory functions e.g. osmoregulation, regulation of blood sugar, metabolic rate.
- Many rhythmic activities of animals are also due to hormones e.g. molting, sleep-wake up cycles, hunger, seasonal reproductive activation, migration in birds etc.
- Moreover, hormones maintain homeostasis, coordinate body's responses to stress and mediate responses to many environmental stimuli.
- One of the most important functions of endocrine hormonal system is that it complements the rapid-acting activity of the nervous system by its slower, more-sustained activity. This coordination between the two systems results in the overall integration of physiological and metabolic functions in a body.

Topic-73 Synthesis of Hormones

Synthesis of Peptide and Protein Hormones

Protein and peptide hormones are synthesized on the rough endoplasmic reticulum of endocrine cells, following the mechanism of protein synthesis.

- They are usually synthesized first as preprohormones which are larger proteins that are not biologically active.
- The preprohormones are cleaved to form smaller prohormones inside the endoplasmic reticulum.
- Prohormones are then transferred to the Golgi apparatus for packaging into secretory vesicles.
- Enzymes in the vesicles cleave the prohormones to produce smaller, biologically active hormones.
- The vesicles are stored within the cytoplasm or remain bound to the cell membrane until their secretion is needed.

Release of Peptide Hormones

Release of hormones occurs when the secretory vesicles fuse with the cell membrane and the contents are extruded into the blood stream by exocytosis.

Synthesis of Steroid Hormones

- Steroid hormones are synthesized from cholesterol instantly when a stimulus is received.
- There is usually very little hormone storage in steroid-producing endocrine cells.
- Rather large stores of cholesterol esters are maintained in the cytoplasmic vacuoles which can be rapidly mobilized for steroid synthesis after a stimulus.
- Much of the cholesterol in steroid-producing cells comes from the plasma, but there is also de novo synthesis of cholesterol in steroid-producing cells.

Release of Steroid Hormones

Steroid hormones are not stored in vesicles.

Once they are synthesized they simply diffuse across the cell membrane and enter the interstitial fluid and then the blood.

Simple diffusion out of the cell is easy because steroids are highly lipid soluble.

Synthesis of Amine Hormones

- Amine hormones including the thyroid and adrenal medullary hormones are derived from amino acid tyrosine.

- They are formed by the actions of enzymes on tyrosine in the cytoplasmic compartments of the glandular cells.
- The synthesized thyroid hormones are incorporated into macromolecules of the protein thyroglobulin.
- Thyroglobulin is stored within the thyroid gland in large follicles.
- Catecholamines (epinephrine and norepinephrine) are formed in the adrenal medulla and stored in vesicles until secreted.

Release of Amine Hormones

- Before secretion, the amines are split from thyroglobulin, and the free hormones are released into the blood stream.
- After entering the blood, most of the thyroid hormones combine with plasma proteins, especially thyroxine-binding globulin, which slowly releases the hormones to the target tissues.
- Catecholamines are released from adrenal medullary cells by exocytosis. Once the catecholamines enter the circulation, they can exist in the plasma in free form or in conjugation with other substances.

Topic-74 Neuro-Endocrine Role of Hypothalamus

Hypothalamus as an Endocrine Tissue

The hypothalamus is a part of brain that has a dual role: neuronal as well as endocrine. It has specialized neurosecretory cells that produce many hormones.

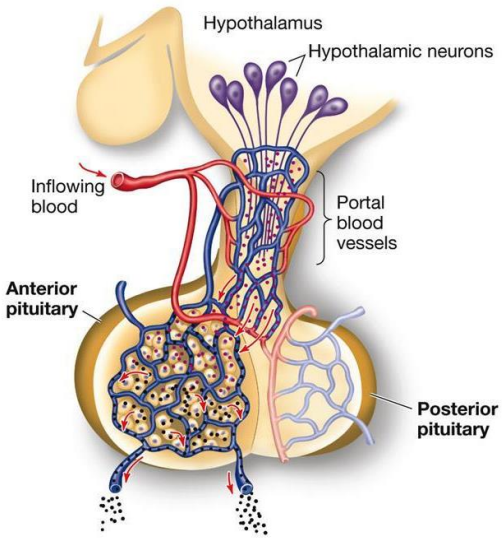
Hormones of Hypothalamus

There are two categories of hypothalamic hormones:

1. **Hypophysiotropic hormones:** Seven hypothalamic hormones act on anterior pituitary gland (adenohypophysis) and regulate the secretion of adenohypophyseal hormones.

   These hormones are of two types:

   - Hypothalamic releasing hormones (RHs) which stimulate the secretory activity of adenohypophysis (anterior pituitary).
     These hormones are:
     - Corticotropin releasing hormone (CRH) that stimulates adrenocorticotropic hormone (ACTH) release from anterior pituitary
     - GH releasing hormone (GHRH) that stimulates release of growth hormone from anterior pituitary
     - Gonadotropin releasing hormone (GnRH) that stimulates the release of FSH and LH from anterior pituitary
     - TSH releasing hormone (TRH) (Thyrotropin) which stimulates TSH and prolactin secretion.
   - Hypothalamic inhibiting hormones (RIHs) which inhibit the secretory activity of adenohypophysis.
     These hormones are:
     - MSH inhibiting hormone (MIH) which inhibits the secretion of melanocyte stimulating hormone from pituitary gland.
     - Prolactin inhibiting hormone (PIH) which inhibits the release of prolactin hormone.
     - Somatostatin that inhibits the release of growth hormone.

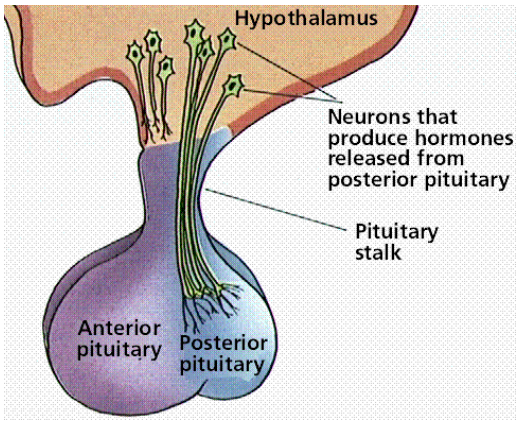


These hormones can produce effects on the anterior pituitary gland in very low concentrations because of close proximity and direct portal connection of hypothalamus and the anterior pituitary gland.

2. Neurohypophyseal hormones

These hormones include Oxytocin and Antidiuretic hormone (Vasopressin).

They are released directly in the posterior pituitary which stores them and releases them as per requirement to act directly on target tissues.

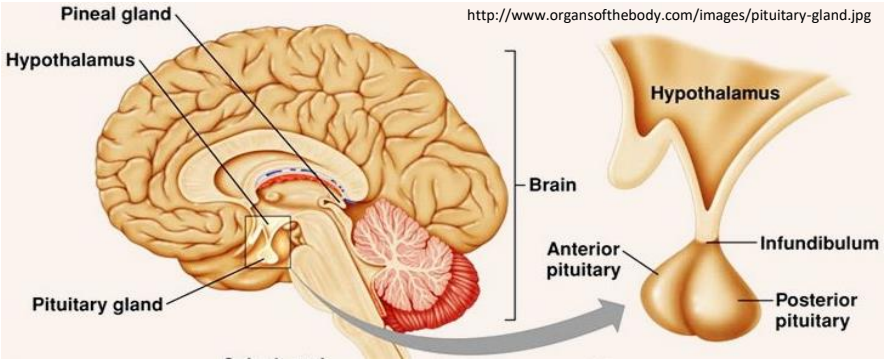


Topic-75 Pituitary Gland and Its Hormones

The pituitary gland, also known as hypophysis is a small gland, about 1 centimeter in diameter and 0.5 to 1 gram in weight.

It lies below the hypothalamus as a small protrusion. It is connected to the hypothalamus by a pituitary stalk or infundibulum.

It is often called as the "master gland" as it secretes nine hormones which affect virtually all tissues of the body, including secretions of many other endocrine glands.



Lobes of the Pituitary Gland

The pituitary gland is composed of three lobes:

- Anterior lobe (adenohypophysis)
- Intermediate lobe (*pars intermedia*)
- Posterior lobe (neurohypophysis)

Anterior Lobe (Adenohypophysis)

The anterior pituitary is fleshy, glandular and highly vascularized in all animals.

It contains five types of glandular cells which are controlled by regulatory hormones of the hypothalamus.

On stimulation of hypothalamic releasing hormones, they synthesize and secrete six hormones.

Glandular Cells and Hormones of Adenohypophysis

1. Somatotropes—produce growth hormone (GH)
2. Corticotropes—produce adrenocorticotropic hormone (ACTH)
3. Thyrotropes—produce thyroid-stimulating hormone (TSH)

4. Gonadotropes—produce gonadotropic hormones (luteinizing hormone, LH and follicle stimulating hormone, FSH)
5. Lactotropes—produce prolactin (PRL)

Roles of Adenohypophyseal Hormones

The ACTH, TSH, LH and FSH are primarily tropic in their actions i.e. they act on other endocrine tissues (e.g., thyroid, gonads, and adrenal cortex), regulating the secretory activity of these target glands.

LH and FSH are referred to as gonadotropins. They act on the gonads and stimulate secretion of gonadal hormones. So, their effect on nonendocrine somatic tissues is indirect, operating through the hormones released from their target glands (gonads).

The growth hormone and prolactin are direct-acting hormones i.e. they act directly on somatic target tissues without causing the release of other hormones.

Intermediate lobe (*pars intermedia*)

The intermediate lobe is avascular and almost absent in human beings.

It is much developed in rodents, mice and rats and produces one hormone known as melanocyte stimulating hormone (MSH).

In humans MSH is secreted by the *pars intermedia*, considered as a part of adenohypophysis.

The secretion of MSH is under the regulation of hypothalamic MIH.

Posterior lobe (neurohypophysis)

The posterior pituitary is non-fleshy and non-glandular.

It has neural composition and is considered as an extension of the hypothalamus.

Hormones of Neurohypophysis

The posterior pituitary gland secretes two peptide hormones:

- Antidiuretic Hormone (ADH) also known as Vasopressin
- Oxytocin

These hormones are synthesized by the cell bodies of neurons in the supraoptic and paraventricular nuclei of the hypothalamus.

These hormones are released in the posterior pituitary gland, which stores and secretes these hormones.

Topic-76 Adenohypophysis: Tropic Hormones

The four hormones secreted by adenohypophysis (anterior Pituitary gland) act on other endocrine tissues and regulate the secretory activity of their target glands. These hormones are:

1. Adrenocorticotropic hormone (ACTH)
2. Thyroid stimulating hormone (TSH)
3. Luteinizing Hormone (LH)
4. Follicle stimulating hormone (FSH)

Adrenocorticotropic hormone (ACTH)

ACTH is a peptide hormone comprising single chain of 39 amino acids.

Functions of ACTH

- Its principal function is to regulate the secretion of corticosteroid hormones by the cortex of the adrenal gland.
- It also stimulates the secretion of androgens by the adrenal cortex.
- It also plays role to maintain the size of zona fasciculata and zona reticularis of adrenal cortex.
- ACTH also stimulates lipoprotein uptake into cortical cells. This increases the bioavailability of cholesterol in the cells of the adrenal cortex.
- In many organisms, ACTH is also related to the circadian rhythms.

Thyroid stimulating hormone (TSH)

The thyroid stimulating hormone or Thyrotropin is a glycoprotein.

The production of TSH by the pituitary gland is stimulated by the thyrotropin-releasing hormone (TRH) from hypothalamus.

TSH is secreted throughout life but particularly reaches high levels during the periods of rapid growth and development.

Functions of TSH

- It controls the rate of secretion of thyroid hormones thyroxine (T_4) and triiodothyronine (T_3) by the follicular cells of thyroid gland. These hormones, in turn, control the rate of metabolic reactions in the body.
- It also helps to maintain the size of thyroid follicular cells.

Gonadotropins (LH and FSH)

LH and FSH are referred to as gonadotropins. Both hormones are glycoproteins that are released under the influence of Gonadotropin-Releasing Hormone (GnRH) from hypothalamus.

Functions of Gonadotropins

- FSH and luteinizing hormone (LH) work together in the reproductive systems of both males and females.
- They act on the gonads and stimulate secretion of gonadal hormones and control growth of the ovaries and testes.
- FSH stimulates the development of ovarian follicles and regulates spermatogenesis in the testes.
- LH stimulates production of estrogen and progesterone by the ovary. It causes ovulation and formation of the corpus luteum.
- In males, LH is also called as interstitial cell–stimulating hormone (ICSH) and stimulates testosterone production by the Leydig cells of testes.

Topic-77 Adenohypophysis: Non-Tropic Hormones

Adenohypophysis secretes three hormones that act directly on their target tissues. These hormones are the melanocyte stimulating hormone (MSH), Prolactin (PRL) and Growth hormone (somatotropin).

Melanocyte Stimulating Hormone (MSH)

Melanocyte-stimulatinghormone (MSH) is a peptide hormone that is released from the intermediate lobe of pituitary that is highly developed and secretes an especially large amount of MSH in lower vertebrates.

In humans, the quantities of MSH released are extremely low and most of skin pigmentation is controlled by ACTH.

Functions of MSH

MSH regulates the activity of pigment-containing cells (melanocytes) in the skin of many vertebrates.

It stimulates the synthesis of black pigment melanin and its dispersal in melanocytes, leading to darkening of the skin.

In mammals, MSH also inhibits hunger by acting on neurons in the brain.

It is also involved in fat metabolism in mammals.

Prolactin

Prolactin (PRL) is remarkable for the diversity of its effects among vertebrate species.

- It regulates fat metabolism and reproduction in birds
- It delays metamorphosis in amphibians.
- It also regulates salt and water balance in freshwater fishes.
- Prolactin stimulates mammary gland growth and milk synthesis in mammals.

These varied roles suggest that prolactin is an ancient hormone with functions that have diversified during the evolution of vertebrate groups.

Growth Hormone

Growth hormone, also called somatotropic hormone or somatotropin, is a protein that contains 191 amino acids in a single chain.

Control of GH secretion

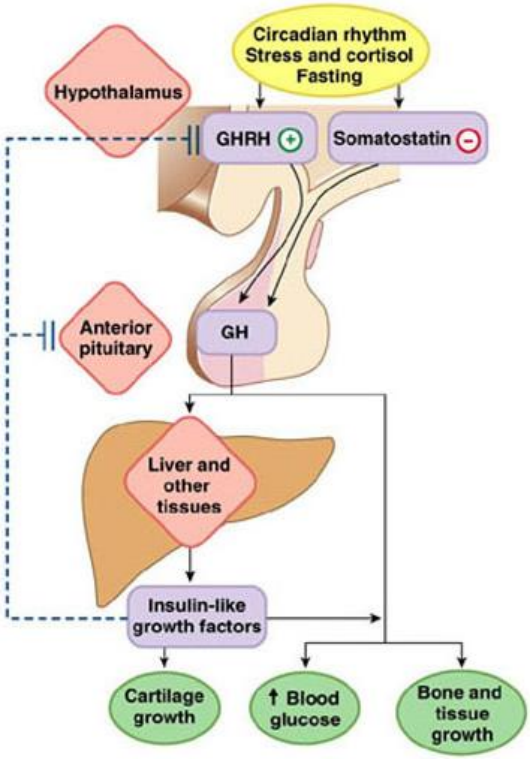
The production and release of growth hormone (GH) in the anterior pituitary gland is under the control of GH releasing hormone (GHRH) and somatostatin (GH-inhibiting hormone GIH). In addition, the release of GHRH and GIH is regulated by such factors as blood glucose levels.

Effects of GH

Growth hormone exerts both metabolic and developmental effects.

Metabolic Effects of GH

- Growth hormone induces the mobilization of stored fat for energy metabolism.
- Growth hormone also stimulates fatty acid uptake in muscles.
- It decreases rate of glucose utilization throughout the body and thus causes an elevation of blood glucose.
- It increases rate of protein synthesis in most cells of the body
- Thus, in effect, growth hormone enhances body protein, uses up fat stores, and conserves carbohydrates.
- It also stimulates insulin secretion both directly, through its action on the pancreatic beta cells (tropic effect of GH), and indirectly, through its effect in elevating plasma glucose levels.



Developmental Effects of GH

- It causes growth of almost all tissues of the body that are capable of growing.
- Growth hormone stimulates RNA and protein synthesis, which result in its developmental effects in promoting the growth of tissues: particularly cartilage and bone.
- GH-stimulated tissue growth occurs by an increase in cell number (i.e., cell proliferation) rather than an increase in cell size.
- It also stimulates the liver to produce other growth-promoting factors, called insulin-like growth factors (lGFs) or somatomedins that act directly on cells to promote growth.
- Thyroid hormones and growth hormone work synergistically to promote tissue growth during development.

Developmental Abnormalities due to GH

Disturbances in the secretion of growth hormone lead to several patterns of abnormal growth and development in humans:

Gigantism: excessive size and stature caused by hypersecretion of growth hormone during childhood (before puberty).

Acromegaly: enlargement of the bones of the head and of the extremities caused by hypersecretion of growth hormone beginning after maturity.

Dwarfism: abnormal underdevelopment of the body caused by insufficient secretion of growth hormone during childhood and adolescence.

Topic-78 Hormones of Neurohypophysis

The posterior lobe of the pituitary gland is also called as neurohypophysis or pars nervosa.

It stores and releases two neurohormones:

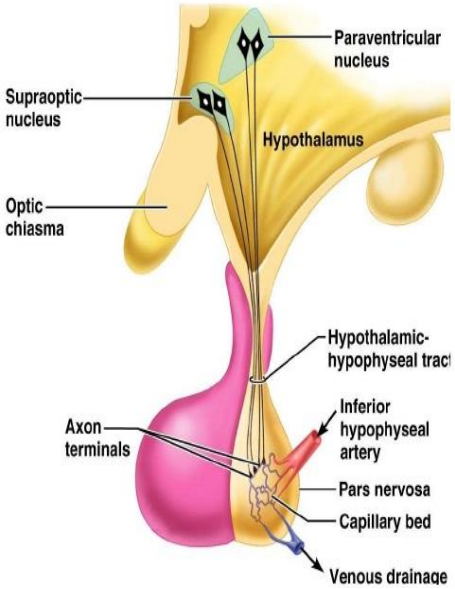
- Oxytocin
- Antidiuretic hormone (ADH) also known as vasopressin

Both these hormones are peptides containing nine amino acid residues.

Synthesis and Release of ADH and Oxytocin

The neurohypophyseal hormones are synthesized and packaged in the cell bodies of two groups of neurosecretory cells in the anterior portion of the hypothalamus: supraoptic and paraventricular nuclei.

After their synthesis, the hormones are transported within the axons of the hypothalamo-hypophyseal tract to nerve terminals in the neurohypophysis, where they are released into a capillary bed.



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Functions of ADH

- The specialized function of ADH is to helps regulate blood osmolarity by promoting water reabsorption in the kidney, thus decreasing urine volume.
- ADH also acts as a vasoconstrictor as it has a potent effect on arterioles which constrict throughout the body in the presence of its high concentration. This effect increases the arterial pressure. For this reason, ADH has been given another name, vasopressin.

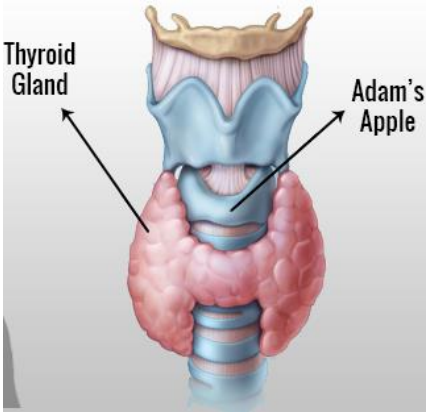
  Intense ADH secretion occurs when blood volume is decreased to 15 to 25 per cent or more. In such conditions, the secretory rate of ADH may rise to as high as 50 times normal.

Functions of Oxytocin

- In mammals, oxytocin is specialized in stimulating uterine contractions during parturition.
- It also stimulates release of milk from the mammary glands during nursing.
- It also functions in regulating mood and sexual arousal in both males and females.
- In birds, it stimulates motility of the oviduct.

Topic-79 Thyroid Gland and Its Hormones

Thyroid Gland

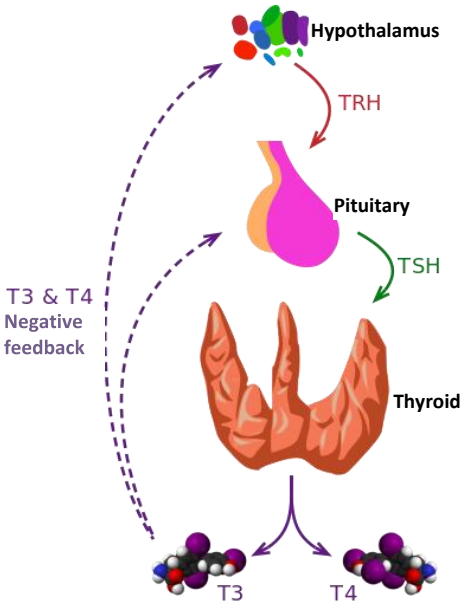


Thyroid gland consists of two lobes on the ventral surface of the trachea.

It has two types of glandular cells:

- Follicular cells which secrete two hormones:
  - Triiodothyronine (T_3)
  - Tetraiodothyronine (T_4) also known as thyroxine
- Parafollicular cells which secrete one hormone:
  - Calcitonin

Secretion of T_3 and T_4



The secretion of T_4 predominates T_3. However the target cells convert most of T_4 to T_3, which is the active form and carries out the major functional roles.

The secretion of these hormones occurs by the stimulation of hypothalamus that releases TSH-releasing hormone (TRH). The stimuli for the release of TRH are stress, cold, low skin temperature and low metabolic rate. TRH acts on anterior pituitary gland that releases thyroid stimulating hormone (TSH). TSH causes the release of thyroid hormones.

Feedback Regulation of T_3 and T_4

The secretion of T3 and T4 is regulated by negative feedback. High concentration of these hormones signals the hypothalamus to reduce the secretion of TRH which, in turn, decreases the secretion of TSH by the pituitary.

Functions of T_3 and T_4

These hormones have diverse effects on the physiology of virtually all tissues of the body.

Their roles can be grouped into metabolic and developmental categories.

Metabolic Roles

- They regulate bioenergetics by stimulating cellular respiration, oxygen consumption and metabolic rate.

- The acceleration of metabolism leads to a rise in heat production. This is of major importance in the thermoregulation of many vertebrates.
- They also sensitize some tissues to epinephrine that helps to maintain normal blood pressure, heart rate and muscle tone.
- They also promote normal motility of gastrointestinal tract and regulate reproductive functions.

Developmental Roles

- The thyroid hormones also significantly affect the development and maturation of vertebrate animals.
- These hormones are required for the normal functioning of bone-forming cells and the branching of nerve cells during embryonic development of the brain.
- Thyroid hormones also control the metamorphosis of a tadpole into a frog.
- The developmental effects of growth hormone occur only in the presence of thyroid hormones.

Hyperthyroidism

Excessive secretion of thyroid hormone is known as hyperthyroidism.

The most common form of hyperthyroidism is Graves' disease. It is an autoimmune disorder in which antibodies that mimic TSH bind to the receptor for TSH and cause sustained thyroxine production.

It leads to high body temperature, profuse sweating, weight loss, irritability, high blood pressure and protruding eyes (exophthalmia).

Hypothyroidism

Hypothyroidism usually results from the lack of dietary iodine. It is characterized by two types of diseases:

Cretinism

Goiter

Cretinism

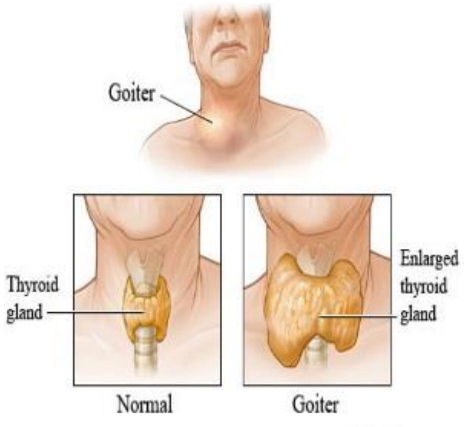
Iodine deficiency during early stages of development results in cretinism.

In cretinism somatic, neural and sexual development is severely retarded, metabolic rate and resistance to infection is reduced.

Goiter

Inadequate production of thyroid hormones in adults leads to excessive production of TSH.

TSH causes overstimulation of thyroid gland resulting in its enlargement (hypertrophy). This condition with enlarged thyroid is called goiter.



Role of Calcitonin

Calcitonin is a protein hormone secreted by the parafollicular cells of the thyroid in response to hypercalcemia (elevated plasma calcium levels).

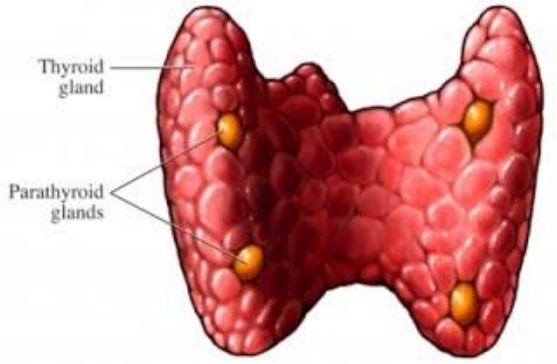
It is an important hormone for calcium metabolism and calcium homeostasis.

Its functions are to:

- Promote calcium deposition in bone matrix.
- Suppress Ca^{2+} loss from bones.
- Enhance Ca^{2+} excretion by the kidneys.

Topic-80 Parathyroid Gland and its Hormones

The parathyroid glands are tiny, pea-sized glands embedded in the thyroid lobes. Usually two glands are embedded in each lobe.



The parathyroids secrete parathormone (PTH) in response to a drop in plasma Ca^{2+} levels.

Physiological Effects of Parathormone

PTH regulates the concentrations of calcium and phosphate ions in the blood.

It acts to increase plasma Ca^{2+} by promoting Ca^{2+} mobilization from bone.

It promotes calcium reabsorption by the kidney tubules to decrease the amount of calcium excreted in the urine.

It also enhances calcium absorption from the small intestine into the blood.

It also regulates phosphate ions in the blood by their absorption into the bones and enhances their renal excretion.

Role of Calcitriol in the Action of PTH

Parathyroid hormone stimulates 1α,25-hydroxylase activity in kidney that stimulates the production of calcitriol, the active form of vitamin D.

PTH works in conjunction with calcitriol which stimulates calcium reabsorption and phosphate excretion from the kidney, as well as calcium absorption from the gut and release from bone.

Effects of PTH Over Secretion

- Bones become soft and deformed and prone to fracture due to release of calcium from bones.
- Elevation of blood calcium levels (hypercalcemia)
- Suppression of nervous system and weakness of muscles due to high levels of calcium in blood.
- Excessive calcium salts precipitation in kidneys leading to stone formation.

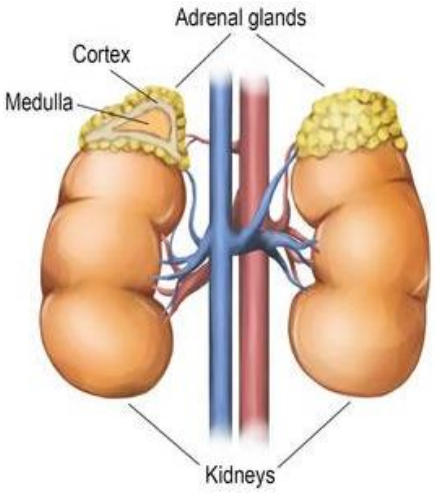
Effects of PTH Under Secretion

- Hypocalcemia.
- Increased excitability of neurons.
- Muscle tetany due to which muscles remain in contracted state.

Topic-81 Adrenal Gland

Mammals have two adrenal glands, one attached to the superior end of each kidney.

Each adrenal gland is in fact two glands in one: an outer layer, the adrenal cortex and an inner, central portion, the adrenal medulla that comprises about 20 per cent of the gland.



Adrenal Cortex and Medulla

The two portions of the mammalian adrenals have different cell types, functions, and embryonic origins.

The cells of the cortex are true endocrine cells, derived from non-neural, mesodermal tissue.

The cells of medulla are derived from the epidermal, neural tissue during embryonic development and are functionally related to the sympathetic nervous system.

Thus, like the pituitary gland, each adrenal gland is a fused endocrine and neuroendocrine gland.

Hormones of Adrenal Cortex

The adrenal cortex produces two major types of steroid hormones: the mineralocorticoids and the glucocorticoids collectively called as corticosteroids. These hormones are involved in blood ion and glucose regulation and anti-inflammatory reactions.

In addition to these, small amounts of sex hormones are also secreted, including androgens, estrogens and progesterone. They exhibit about the same effects in the body as the gonadal hormones.

Hormones of Adrenal Medulla

The cells of the adrenal medulla synthesize and secrete catecholamines, i.e. epinephrine and norepinephrine, under visceral motor stimulation.

Adrenal medulla cells are referred to as chromaffin cells because they stain easily with chromium salts.

The chromaffin cells that produce norepinephrine have dark staining irregular granules, whereas those that produce epinephrine have light-staining, spherical granules.

Chromaffin cells are modified postganglionic sympathetic neurons.

Topic-82 Catecholamines: Synthesis and Release

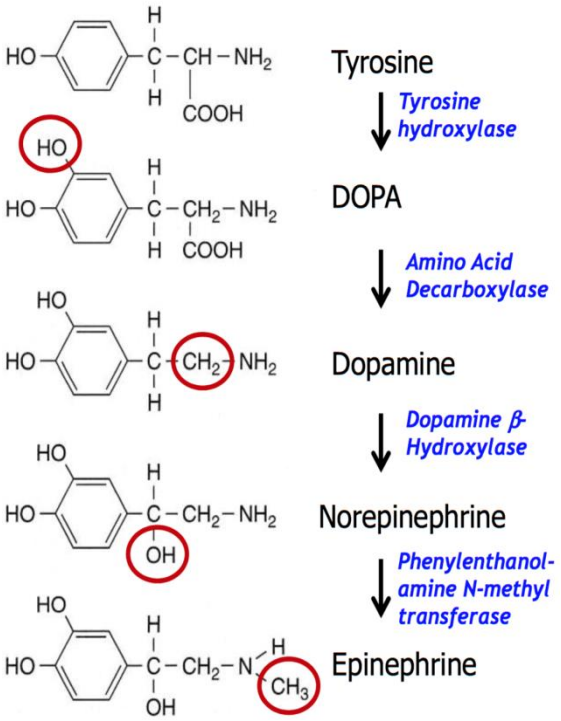
Synthesis of Catecholamines

Norepinephrine is synthesized from tyrosine, with dopa and dopamine as intermediate compounds.

The conversion of tyrosine to dopamine occurs in the cytosol and is catalyzed by tyrosine hydroxylase and dopa decarboxylase enzymes.

Dopamine is then incorporated into the granules and converted to norepinephrine. This reaction is catalyzed by dopamine β-hydroxylase (DBH) contained in the secretory granules.

Norepinephrine is methylated to epinephrine, a reaction catalyzed by phenylethanolamine N-methyl transferase, which is found in the cytosol. Thus, norepinephrine must leave the secretory granules to be converted to epinephrine, which then reenters the granules.



Release of Catecholamines

Catecholamines are released as secretory granules by exocytosis.

The secretory granules within a single chromaffin cell contain either norepinephrine or epinephrine, so each cell secretes either epinephrine or norepinephrine.

The granules also contain enkephalin, ATP, and several acidic proteins called chromogranins to which the catecholamines are bound.

Once a pore is opened in the vesicle, the catecholamines begin to diffuse out, liberating from the chromogranins.

Catecholamine Release Mechanism

Action of preganglionic sympathetic nerves

The release of epinephrine and norepinephrine from the adrenal medulla is controlled by the action of preganglionic sympathetic nerves.

These preganglionic fibers are cholinergic; that is, they release acetylcholine as a neurotransmitter.

When chromaffin cells are stimulated by acetylcholine, their membrane conductance for Ca^{2+} increases, resulting in an influx of Ca^{2+} and elevation of intracellular Ca^{2+} levels.

This rise in intracellular Ca^{2+} causes release of both epinephrine and norepinephrine by exocytosis.

Positive Feedback of Catecholamine Release

Catecholamines cause an increase in blood flow to the adrenals, and this effect also augments catecholamine release from the adrenal medulla. Thus the release of catecholamines has a positive feedback on further catecholamine release.

Control of Catecholamine Release

ATP, which is stored in the granules of chromaffin cells is also released along with catecholamines. ATP and its breakdown product adenosine, inhibit release of catecholamines by reducing calcium influx. This also provide negative-feedback control on catecholamine release from the medulla.

Topic-83 Catecholamines: Effects and Mode of Action

Effects of Catecholamines

- These hormones have numerous cardiovascular and metabolic effects.
- They also affect contraction of smooth muscle, induce vasoconstriction, and stimulate glycolysis and lipolysis.
- **Fight-or-flight response:**
  Catecholamines stimulate the sympathetic nervous system for fight-or-flight response.
  During this type of response, various tissues are activated and the body is mobilized to either attack or flee from the object of stress.
  These effects include dilating the pupil, increasing heart rate, mobilizing energy, and diverting blood flow to skeletal muscles.

Adrenergic Receptors (Adrenoceptors)

Epinephrine and norepinephrine bind to a class of G protein-coupled receptors known as adrenergic receptors or adrenoceptors. They are present on cell membranes of various tissues of the body.

There are two main groups of adrenoreceptors: α and β, each having two subtypes α_1, α_2, and β_1, β_2 in different tissues.

The binding of a catecholamine to its receptor activates one of a number of intracellular second messengers, leading to a particular tissue response.

Mode of Action through α_1-adrenoreceptors

- The α_1-adrenoreceptors mediate smooth muscle contraction in many tissues.
- The α-adrenoreceptors are coupled with an inhibitory G protein.
- Stimulation of these receptors results in a decrease in cAMP and activation of the inositol trisphosphate ($InsP_3$) pathway, leading to elevation of intracellular $InsP_3$.
- Elevated $InsP_3$ causes release of calcium from stores within the cell.
- The resulting rise in cytosolic calcium causes muscle contraction.

Mode of Action through α_2-adrenoreceptors

The α_2-adrenoreceptors located in presynaptic cells at noradrenergic synapses cause inhibition of norepinephrine release.

This action is mediated by an inhibitory effect on adenylate cyclase.

Thus, these receptors are part of a short negative-feedback loop in which the release of norepinephrine inhibits further release of norepinephrine.

This is sometimes referred to as autoinhibition.

The α_2-adrenoreceptors are also located on some postsynaptic sites in liver, brain, and some smooth muscles.

Mode of Action Through β_1-adrenoreceptors

- Stimulation of β_1-adrenoreceptors is largely due to neuronal release of norepinephrine.
- The β_1-adrenoreceptors are coupled to a stimulatory G protein.
- Through these receptors, catecholamines act by activating adenylate cyclase, that leads to an increase in cAMP.
- The elevation of cAMP increases calcium conductance, thereby raising the intracellular calcium level.
- This results in increased contraction of cardiac muscles and the release of fatty acids from adipose tissue.

Mode of Action Through β_2-adrenoreceptors

- The stimulation of β_2-adrenoreceptors is largely due to elevated levels of circulating catecholamines.
- These receptors are also coupled to a stimulatory G protein that causes elevation of cAMP.
- Here, the cAMP causes activation of the calcium pump rather than an increase in calcium conductance.
- As a result, calcium is sequestered within the cell by mitochondria and ER and is also extruded from the cell.
- As a result, intracellular calcium levels fall, promoting muscle relaxation. This smooth muscle relaxation causes bronchodilation and vasodilation.

Topic-84 Adrenal Cortex: Corticosteroids

When stimulated by ACTH, the cells of the adrenal cortex synthesize and secrete a family of steroid hormones collectively called corticosteroids.

These hormones fall into three functional categories:

- Glucocorticoids, which have widespread actions, including mobilization of amino acids and glucose and anti-inflammatory actions
- Mineralocorticoids, which regulate kidney function
- Reproductive hormones

Glucocorticoids

The glucocorticoids include cortisol, cortisone, and corticosterone.

Of these, cortisol is the most important in humans.

Effects of glucocorticoids

1. Gluconeogenesis

- As reflected in their name, glucocorticoids have a primary effect on glucose metabolism.
- The glucocorticoids act on the liver, increasing the synthesis of enzymes that promote gluconeogenesis (synthesis of glucose from substances other than carbohydrates).
- Most of the newly produced glucose is released into the circulation, causing a rise in blood glucose levels.
- Glucocorticoids also act to reduce uptake of glucose into peripheral tissues such as muscle.
- Similarly, uptake of amino acids by muscle tissues is also decreased by glucocorticoids, and amino acids are released from muscle cells into the circulation. This release increases the quantity of amino acids available for deamination and conversion into glucose in the liver under glucocorticoid stimulation.
- The glucocorticoids also stimulate mobilization of fatty acids from stores of fat in adipose tissue. These can be used as substrates for gluconeogenesis in the liver or metabolized directly in muscle to provide energy for contraction.
- All these mechanisms are especially important during starvation and stress as they increase the available quick energy to muscles and critical tissues such as the brain. The end result of this process is the degradation of tissue proteins and stored fat deposits.

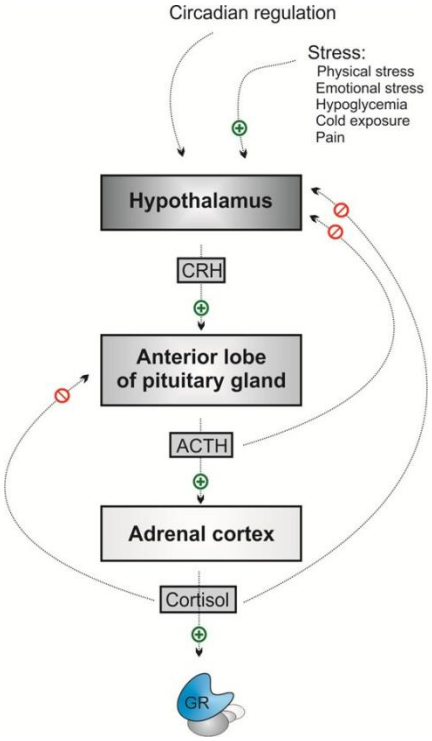
2. The glucocorticoids stimulate gastric secretions.

3. They suppress certain components of immune system and act as anti-inflammatory agents.

Mode of Action

The glucocorticoids, like other lipid-soluble steroid hormones, bind to specific receptors in the cytosol, forming hormone-receptor complexes that enter the nucleus and regulate the transcription of specific genes.

Regulation of Glucocorticoids



The secretion of glucocorticoids is regulated via negative feedback by the hormones themselves on the CRH-secreting neurons of the hypothalamus and the ACTH-secreting cells of the anterior pituitary gland.

The glucocorticoid secretion also undergoes a diurnal rhythm due to cyclic variation in CRH secretion, influenced by an endogenous biological clock.

Glucocorticoid levels in humans are maximal during the early hours of the morning prior to waking, having an adaptive value for energy-mobilizing actions.

In addition to such endogenous regulation of secretion, the adrenal cortex is stimulated to secrete glucocorticoids in response to stress of various types (including starvation). Stress, acting through the nervous system, causes an elevation in ACTH and hence stimulation of the adrenal cortex.

Mineralocorticoids

Mineralocorticoids are named for their effects on mineral metabolism. They act principally in maintaining salt and water balance in the body.

The primary mineralocorticoid hormone is aldosterone.

Aldosterone

It is a steroid hormone and is secreted under the stimulation of ACTH and angiotensin II which is produced during low blood pressure or volume. High blood K^+ also stimulates aldosterone production.

Aldosterone release is subject to negative feedback by the hormone itself on the CRH-secreting neurons of the hypothalamus and on the ACTH-secreting cells of the anterior pituitary gland.

Like other steroid hormones, it affects by binding to intracellular receptors and modifying gene expression.

Effects of Aldosterone

- Aldosterone functions in ion and water homeostasis of the blood.
- It enhances reabsorption of sodium and chloride by the distal tubules and the collecting tubules of the kidney, thereby increasing the osmolarity of the blood.
- It also enhances water reabsorption from the filtrate, contributing to raise blood pressure and volume.
- Aldosterone also functions in the body's response to severe stress.

Adrenal Reproductive Hormones

The adrenal cortex produces small amounts male and female sex hormones i.e. androgens, estrogens and progestins.

The androgens secreted by adrenal cortex include testosterone, Dihydrotestosterone (DHT), Androstenedione (Andro) and dehydroepiandrosterone (DHEA).

Testosterone: is involved in enhancing muscle mass, stimulation of cell growth and development of secondary sex characteristics in males.

Dihydrotestosterone (DHT): is a metabolite of testosterone, and a more potent androgen than testosterone as it binds more strongly to androgen receptors.

Androstenedione (Andro): is an intermediate androgenic steroid that is converted metabolically to testosterone and other androgens. It is also the parent structure of estrone.

Dehydroepiandrosterone (DHEA): It is the primary precursor of natural estrogens.

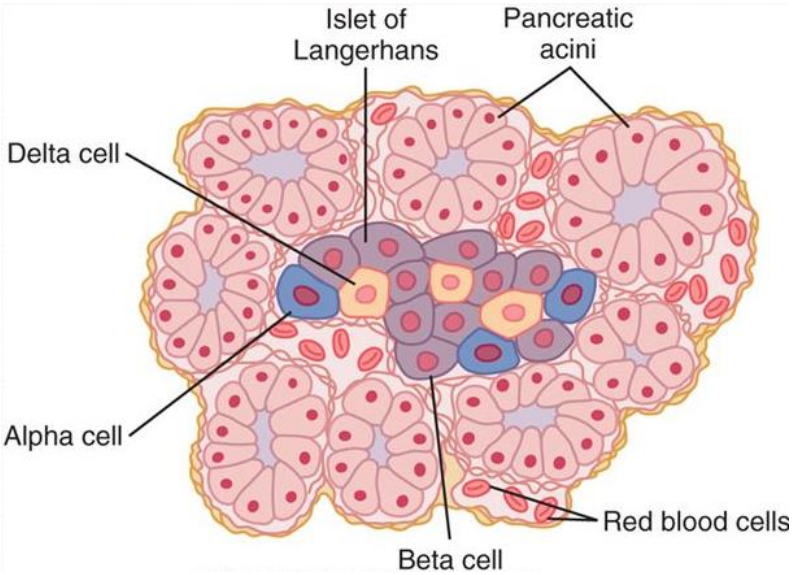
In adult females the adrenal androgens are thought to account for the sex drive.

Topic-85 Pancreas: Insulin and Glucagon Hormones

The pancreas is a dual gland having exocrine as well as endocrine roles. It is composed of two types of tissues:

(1) Acini which secrete digestive juices

(2) Islets of Langerhans which mainly secrete insulin and glucagon along with somatostatin and pancreatic polypeptide hormones.



Textbook of Medical Physiology (11th ed) by Guyton

Islets of Langerhans

Human pancreas has 1 to 2 million islets of Langerhans.

Each islet is about 0.3 millimeter in diameter and organized around small capillaries into which its cells secrete their hormones.

The islets contain four types of cells, alpha, beta, delta and PP cells.

These cells are distinguished from one another by their morphological and staining characteristics.

The beta cells, constituting about 60 per cent of all the cells of the islets, lie mainly in the middle of each islet and secrete insulin.

The alpha cells, about 25 per cent of the total, secrete glucagon.

The delta cells, about 10 per cent of the total, secrete somatostatin that inhibits the secretion of both insulin and glucagon.

The PP cells are present in small number in the islets and secrete a hormone of uncertain function called pancreatic polypeptide.

Stimuli for Release of Insulin

High blood glucose acts as the major stimulus to the pancreatic beta cells to secrete insulin.

The release of insulin is also stimulated by glucagon, growth hormone, gastric inhibitory peptide (GIP, also known as glucose-dependent insulin-releasing peptide), epinephrine, and elevated levels of amino acids.

Effects of insulin

Insulin has important effects on carbohydrate, fat, and protein metabolism.

With regard to carbohydrate metabolism, insulin has two major actions:

- increasing the rate of uptake of glucose into cells of liver, muscle, and adipose tissue.
- stimulating glycogenesis (polymerization of glucose to glycogen).

As for lipid metabolism, insulin stimulates lipogenesis in liver and adipose tissue.

In protein metabolism, insulin stimulates the uptake of amino acids into liver and muscles and the incorporation of amino acids into protein.

Deficiency of Insulin: Diabetes mellitus

Diabetes mellitus in humans is characterized by an absolute or relative deficiency of insulin.

There are two types of Diabetes mellitus: Type I and Type II

Type I diabetes mellitus is associated with a loss of pancreatic beta-cell mass, which leads to diminished or decreased insulin production and secretion (i.e., absolute insulin deficiency).

Type I1 diabetes mellitus is associated with defective insulin receptors (i.e., relative insulin deficiency).

Symptoms of Diabetes mellitus

Both types lead to:

- Hyperglycemia (high levels of blood glucose)
- Glycosuria (spillover of excess glucose into the urine)
- Reduced ability to utilize glucose by the cells.
- Reduced ability to synthesize lipids and proteins, which are broken down to supply energy because cells are deficient in glucose.

- Fat particles that cannot be rapidly metabolized accumulate in the blood as ketone bodies. These are excreted in the urine but can also interfere with liver function.

These disturbances in carbohydrate, lipid, and protein metabolism also produce a large number of complications in various organs (e.g., cataract and cardiovascular and renal diseases).

Glucagon

Glucagon is secreted in response to hypoglycemia (low levels of blood glucose).

Effects of Glucagon

It Increases glucose level in blood by:

- stimulating glycogenolysis in the liver
- stimulating lipolysis, providing lipids for gluconeogenesis (generation of glucose from non-carbohydrate sources).

Antagonistic Actions of Insulin and Glucagon

The antagonistic (opposing) actions of insulin and glucagon are important in maintaining an appropriate blood glucose level, so that adequate glucose is available for all tissues.

Topic-86 Role of Testes as Endocrine Tissue

Testes are the male gonads, primarily involved in the production of male gametes i.e. sperms through a process called spermatogenesis.

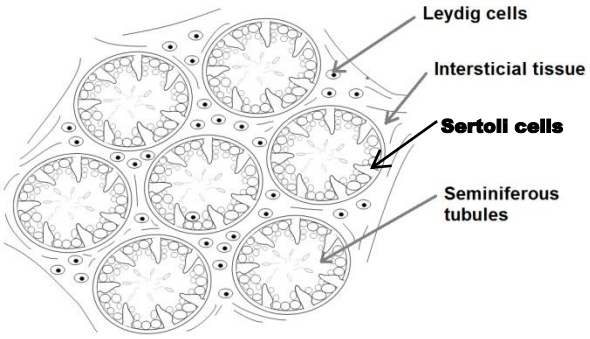
Testes also act as an endocrine tissue and certain cells in them also secrete hormones. These hormones include:

- Inhibin
- Male reproductive hormones collectively called as androgens.

Types of Cells in Testes

In a cross section, testes have two major parts:

- Seminiferous tubules
- Interstitial Tissue



Seminiferous Tubules

The seminiferous tubules of the mammalian testes are lined with germ cells and Sertoli cells.

The germ cells are involved in spermatogenesis.

Sertoli cells support germ cells in spermatogenesis.

Endocrine Role of Sertoli Cells

In addition to supporting spermatogenesis, Sertoli cells synthesize the hormone inhibin, on stimulation from androgens.

Inhibin helps to locally regulate spermatogenesis. It also down-regulates FSH synthesis and inhibits its secretion.

Interstitial Cells

Interstitial cells are lying between the seminiferous tubules and constitute about 20 per cent of the mass of the adult testes. These cells are known as Leydig cells.

Endocrine Role of Interstitial Cells

Leydig cells produce and secrete several male sex hormones which are collectively called androgens.

Androgens include testosterone, dihydrotestosterone, and androstenedione.

Androgens

- Testosterone is the primary sex hormone in males and is much more abundant than the others.
- Dihydrotestosterone is the more active hormone in the target tissues and most of the testosterone is eventually converted into this form.
- Androstenedione is a weak androgen and is formed as an intermediate in the biosynthesis of testosterone.

Regulation of Testosterone Secretion

- The production and secretion of testosterone is promoted by follicle- stimulating hormone (FSH) and luteinizing hormone (LH), which are released from the anterior pituitary in response to the hypothalamic gonadotropin-releasing hormone (GnRH).
- A decrease in blood testosterone stimulates the secretion of GnRH, which promotes the release of FSH and LH which stimulate the production and release of testosterone from Leydig cells.
- An increased testosterone causes more inhibin secretion from sertoli cells.
- Increased levels of testosterone and inhibin provide negative feedback to the hypothalamic centers controlling GnRH production and hence diminish release of the gonadotropins FSH and LH from the anterior pituitary gland.

Topic-87 Role of Ovaries as Endocrine Tissue

Ovaries produce and release two groups of female sex hormones:

Progesterone

Estrogens (include: Estradiol, Estrone and Estriol)

In addition ovaries also secrete:

- Relaxin which is released by the ovaries prior to giving birth.
- Inhibin which is important for signaling to the pituitary to inhibit FSH.

Roles of Progesterone and Estrogens

These hormones work together to:

- Promote the development of female sex characteristics during puberty.
- Maintain the uterine and ovarian cycles
- Help in fertility

Uterine and Ovarian Cycles

These are two closely linked reproductive cycles in human females.

The cyclic changes in the uterus define the uterine cycle, also called the menstrual cycle. Menstrual cycle averages 28 days.

The cyclic events that occur in the ovaries define the ovarian cycle. This is characterized by the ovarian follicle growth and ovulation.

Hormone activity links the two cycles, synchronizing ovarian follicle growth and ovulation with the establishment of a uterine lining that can support embryonic development.

Secretion of Estradiol in Ovarian Cycle

The ovarian cycle begins with the release of GnRH from the hypothalamus. GnRH stimulates the anterior pituitary to secrete small amounts of FSH and LH. These hormones stimulate follicle growth.

The theca interna cells of growing follicles start to secrete estradiol, an estrogen.

The amount of estradiol rises slowly during the follicular phase till the maturation of oocyte.

At high estrogen levels just prior to ovulation, estrogen activates the hypothalamus and anterior pituitary gland, producing a surge in release of FSH and LH, an example of positive feedback. This FSH accelerates maturation of the developing follicles.

When follicle completes its maturation, it ruptures at the surface of the ovary, releasing the ovum. This happens under the influence of LH.

Secretion of Inhibin

FSH stimulates the secretion of inhibin from the granulosa cells of the ovarian follicles in the ovaries.

Its secretion reaches a peak near ovulation.

It acts on the anterior pituitary, and suppresses the release of FSH (but not LH).

Secretion of Progesterone and Estrogens by Corpus Luteum

Immediately after release of ovum, luteal phase begins. In this phase, estrogen secretion declines and LH transforms the ruptured follicle into a temporary endocrine tissue, the corpus luteum.

The corpus luteum secretes estrogens and progesterone, which exert negative feedback on GnRH release by the hypothalamus, leading to decreased secretion of FSH and LH.

Synchrony of Ovarian and Uterine Cycles

The increase in estrogens during the follicular phase simultaneously stimulates proliferation of the endometrium, the tissue that lines the uterus.

Progesterone stimulates secretion of endometrial fluid by the endometrial tissue, preparing it for implantation of a fertilized ovum.

In the absence of fertilization and implantation of an ovum, the corpus luteum degenerates after about 14 days in humans, and secretion of estrogen and progesterone subsides.

In humans and some other primates, this precipitates the shedding of the uterine lining commonly called menses.

With the reduction in estrogen, progesterone, and inhibin levels, FSH and LH secretion by the pituitary increases again, initiating a new cycle.

Role of Corpus Luteum in Pregnancy

If the released ovum is fertilized and becomes implanted in the endometrium, the developing placenta begins to produce chorionic gonadotropin hormone that maintains an active corpus luteum, so that estrogen and progesterone secretion continues until the placenta fully takes over the production of these hormones, at which time the corpus luteum degenerates.

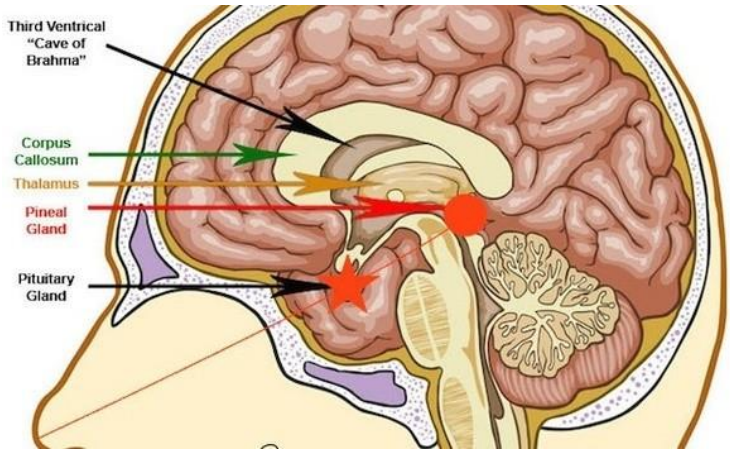
In many other mammals, such as the rat, the corpus luteum, stimulated by prolactin, continues to grow and secrete estrogen and progesterone throughout the gestation period.

Topic-88 Pineal Gland

Pineal gland is a small gland on the dorsal surface of the vertebrate forebrain.

The shape of the gland resembles a pine cone, hence its name.

The gland is reddish-gray and about the size of a grain of rice (5–8 mm) in humans.



Light Sensitivity of Pineal Gland

The pineal gland represents a kind of shrunken photoreceptor.

In some species of amphibians and reptiles, it is linked to a light-sensing organ, known as the parietal eye, which is also called the pineal eye or third eye.

In birds and mammals, it contains light sensitive cells or has nervous connections from the eyes that control its secretory activity.

Hormone Melatonin

The pineal gland synthesizes and secretes the hormone melatonin.

Melatonin is synthesized from serotonin, which itself is synthesized from the amino acid tryptophan.

Functions of Melatonin: Biorhythms

Melatonin is involved in the regulation of biorhythmic functions in animals. These biorhythms are related to light and to seasons marked by changes in day length.

Melatonin production is stimulated by darkness and inhibited by light.

Melatonin is secreted at night, and the amount released depends on the length of the night.

In winter when days are short and nights are long, more melatonin is secreted.

The main target of melatonin is a group of neurons in the hypothalamus called the supra-chiasmatic nucleus (SCN), which functions as a biological clock. Melatonin seems to decrease the activity of the SCN, and this effect may be related to its role in mediating rhythms.

Role in Sleep-Wake Cycles

All birds and mammals show characteristic sleep/wake cycles. Melatonin plays an important role in these cycles. It modulates the brainstem circuits that govern the sleep–wake cycle.

Melatonin synthesis increases as the light in the environment decreases and reaches a maximum between 2 A.M. and 4:00 A.M.

In the elderly, the pineal gland produces less melatonin that explains why older people sleep less at night and are more often afflicted with insomnia. Melatonin has been used to promote sleep in elderly insomniacs and to reduce disruption of the biological clocks.

Role in Regulating Seasonal Fertility in Animals

The pineal gland plays a regulatory role in seasonal sexual and reproductive activities of animals.

Melatonin causes a decrease in gonadotropic hormone secretion from the anterior pituitary gland.

Thus, in the presence of pineal gland secretion, gonadotropic hormone secretion is suppressed in some species of animals, and the gonads become inhibited and even partly involuted. This is what presumably occurs during the early winter months when there is increasing darkness. But after about 4 months of dysfunction, gonadotropic hormone secretion breaks through the inhibitory effect of the pineal gland and the gonads become functional once more, ready for a full springtime of activity.

Melatonin Effect on Human Sexual Development

The abundant melatonin levels in children are believed to inhibit sexual development. When puberty arrives, melatonin production is reduced.

The pineal gland also plays some role in controlling sexual drive and reproduction in humans.

Topic-89 Placental Hormones

In pregnancy, the placenta secretes large quantities of hormones which are essential for maintenance of pregnancy.

These hormones include:

- Human chorionic gonadotropin
- Estrogens
- Progesterone
- Human chorionic somatomammotropin

Human Chorionic Gonadotropin

Human chorionic gonadotropin is a glycoprotein.

It has similar molecular structure and function as luteinizing hormone secreted by the pituitary gland.

The secretion of this hormone starts 8 to 9 days after ovulation i.e. shortly after the blastocyst implants in the endometrium.

The rate of secretion rises rapidly and reaches a maximum at about 10 to 12 weeks of pregnancy and decreases back to a lower value by 16 to 20 weeks. It continues at this level for the remainder of pregnancy.

Functions of Human Chorionic Gonadotropin

It causes persistence and growth of the corpus luteum.

It causes corpus luteum to grow about twice its initial size and secrete larger quantities of progesterone and estrogens up to the 12th week, till the placenta starts to secrete sufficient quantities of these hormones.

It also helps to prevent menstruation.

It also causes the endometrium to continue to grow and store large amounts of nutrients.

Effect of Human Chorionic Gonadotropin on the Fetal Testes

Human chorionic gonadotropin also exerts an interstitial cell–stimulating effect on the testes of the male fetus, resulting in the production of testosterone in male fetuses until the time of birth.

This small secretion of testosterone during gestation causes the fetus to grow male sex organs instead of female organs. It also causes the testes to descend into the scrotum.

Secretion of Estrogens by the Placenta

The placenta secretes both estrogens and progesterone.

Toward the end of pregnancy, the daily production of placental estrogens increases to about 30 times the mother's normal level of production.

Functions of Estrogens in Pregnancy

During pregnancy, estrogens exert mainly a proliferative function on most reproductive and associated organs of the mother. They cause:

(1) enlargement of mother's uterus

(2) enlargement of mother's breasts and growth of breast ductal structure

(3) enlargement of mother's external genitalia.

They also relax the pelvic ligaments of the mother, so that the pubic symphysis becomes elastic. These changes allow easier passage of the fetus through the birth canal.

Secretion of Progesterone by the Placenta

Progesterone is secreted in tremendous quantities by the placenta, averaging about a 10-fold increase during the course of pregnancy.

Functions of Progesterone in Pregnancy

The special effects of progesterone that are essential for the normal progression of pregnancy are as follows:

1. Progesterone causes decidual cells to develop in the uterine endometrium, and these cells play an important role in the nutrition of the early embryo.
2. Progesterone decreases the contractility of the uterus, thus preventing uterine contractions from causing spontaneous abortion.
3. Progesterone contributes to the development of the conceptus even before implantation, because it specifically increases the secretions of the mother's fallopian tubes and uterus to provide appropriate nutritive matter for the developing morula and blastocyst.
4. The progesterone secreted during pregnancy helps the estrogen prepare the mother's breasts for lactation.

Human Chorionic Somatomammotropin

It is a protein with a molecular weight of about 38,000. Its secretion begins by the placenta at about fifth week of pregnancy.

Secretion of this hormone increases progressively throughout the remainder of pregnancy in direct proportion to the weight of the placenta.

Functions of Human Chorionic Somatomammotropin

- It is involved partially in the development of animal's breasts.
- In some instances, it also causes lactation.
- It promotes the formation of protein tissues just like the growth hormone.
- It causes decreased insulin sensitivity and decreased utilization of glucose in the mother, thereby making larger quantities of glucose available to the fetus.
- The hormone promotes the release of free fatty acids from the fat stores of the mother, thus providing this alternative source of energy for the mother's metabolism during pregnancy.

Therefore, it appears that human chorionic somatomammotropin is a general metabolic hormone that has specific nutritional implications for both the mother and the fetus.

Topic-90 Metabolic and Developmental Hormones

Several hormones regulate metabolism and affect developmental processes.

These hormones are secreted by different endocrine glands and belong to different chemical categories (e.g., proteins, steroids and amines).

A tabular summary of the properties of the major metabolic and developmental hormones is as follows:

Hormone	Insulin
Tissue of Origin	Pancreas (beta cells)
Chemical Category	Protein
Target Tissue	All tissues, except most neural tissues
Primary Actions	Increases glucose and amino acid uptake by cells
Regulation	Secreted in response to high plasma glucose and ammo acid levels. Secretion is lowered with low glucose level and inhibited by somatostatin.

Hormone	Glucagon
Tissue of Origin	Pancreas (alpha cells)
Chemical Category	Protein
Target Tissue	Liver, Adipose tissue
Primary Actions	Release of glucose from liver by stimulating glycogenolysis. Also promotes lipolysis
Regulation	Low serum glucose increases secretion, somatostatin inhibits release

Hormone	Glucocorticoids (cortisol, cortisone, corticosterone)
Tissue of Origin	Adrenal cortex
Chemical Category	Steroid
Target Tissue	Liver, Adipose tissue
Primary Actions	Stimulate mobilization of amino acids from muscles and fatty acids from adipose tissue to liver for gluconeogenesis that raises blood glucose. Also exhibit anti-inflammatory actions.
Regulation	Physiological stress increases secretion. Negative feedback and biological clock regulate secretion via CRH and ACTH.

Hormone	Catecholamines (Epinephrine, norepinephrine)
Tissue of Origin	Adrenal medulla (chromaffin cells)
Chemical Category	Amine
Target Tissue	Most tissues
Primary Actions	Increase cardiac activity. Induce vasoconstriction. Increase glycolysis and lipolysis causing hyperglycemia.

Regulation	Sympathetic stimulation increase secretion. Self-control mechanisms through simultaneous release of ATP control its secretion

Hormone	Thyroxine
Tissue of Origin	Thyroid gland
Chemical Category	Amine
Target Tissue	Most cells, specially muscles, heart, Liver and kidney
Primary Actions	Increases metabolic rate and thermogenesis. Promotes growth and development. Promotes amphibian metamorphosis
Regulation	TSH induces release. Negative feedback controls secretion by affecting pituitary TSH and hypothalamic TRH.

Hormone	Growth hormone
Tissue of Origin	Adenohypophysis
Chemical Category	Protein
Target Tissue	All tissues
Primary Actions	Stimulates RNA and protein synthesis. Promotes tissue growth Increases transport of glucose and amino acids into the cells. Increases lipolysis. Stimulates antibody formation
Regulation	Reduced plasma glucose and increased plasma amino acid levels stimulate release via GHRH. Somatostatin inhibits release

Integration of Metabolism and Development

The growth and development of animals is related to the metabolic activities. These processes are controlled and integrated by coordinated activity of these hormones.

Topic-91 Hormones for Water Regulation and Ion Balance

The major organs involved in the regulation of water and ion balance in vertebrates are the kidney, intestine and bone. They also include gills in fishes.

In these organs, epithelial cells are responsible for the uptake or excretion of water and electrolytes. So, most of the hormones that regulate water and electrolyte balance act on these epithelial tissues.

A tabular summary of the hormones that play a major role in maintaining water and electrolyte balance is as follows:

Hormone	Antidiuretic hormone (ADH), or vasopressin
Tissue of Origin	Neurohypophysis
Chemical Category	Nonapeptide
Target Tissue	Kidneys
Primary Actions	Increases water reabsorption
Regulation	Increased plasma osmotic pressure or decreased blood volume stimulates release

Hormone	Aldosterone (mineralocorticoid)
Tissue of Origin	Adrenal cortex
Chemical Category	Steroid
Target Tissue	Distal kidney tubules
Primary Actions	Promotes reabsorption of Na^+ from urinary filtrate
Regulation	Angiotensin II stimulates secretion

Hormone	Atrial natriuretic Hormone
Tissue of Origin	Heart (atrium)
Chemical Category	Peptide
Target Tissue	Kidneys
Primary Actions	Reduces Na^+ and water reabsorption
Regulation	Increased venous pressure stimulates release

Hormone	Calcitonin
Tissue of Origin	Thyroid (parafollicular cells)
Chemical Category	Peptide
Target Tissue	Bones, kidneys
Primary Actions	Decreases release of Ca^{2+} from bone. Increases renal Ca^{2+} and PO_4^{3-} excretion
Regulation	Increased plasma Ca^{2+} stimulates secretion

Hormone	Parathormone (PTH)
Tissue of Origin	Parathyroid gland

Chemical Category	Peptide
Target Tissue	Bones, kidneys, intestine
Primary Actions	Increases release of Ca^{2+} from bone. Increases intestinal Ca^{2+} absorption with calcitriol Decreases renal Ca^{2+} excretion
Regulation	Decreased plasma Ca^{2+} stimulates secretion

Topic-92 Reproductive Hormones

The reproductive hormones of vertebrates belong to two chemical categories:

- Steroid Sex Hormones
- Peptide Hormones

Steroid Sex Hormones

In vertebrates, steroid hormones estrogens, androgens and progesterone are the reproductive hormones.

They are produced by the gonads i.e. testes and ovaries and by adrenal cortex of both sexes in varying quantities. Androgens predominate in the males, whereas estrogens predominate in the females.

Peptide Hormones

Two peptide hormones produced in the pituitary gland function in parturition (child birth) and lactation.

These hormones are:

- Prolactin
- Oxytocin

Synthesis of Steroid Sex Hormones

- All the steroid hormones are synthesized from cholesterol.
- Cholesterol is first converted to progesterone.
- Progesterone is then transformed into the androgens (androstenedione and testosterone).
- Androgens are then converted into the estrogens, of which estradiol-17β is the most potent.

Importance of Steroid Sex Hormones

The estrogens and androgens are important in both sexes in various aspects of growth, development, and morphologic differentiation, as well as in the development and regulation of sexual and reproductive behaviors and cycles.

Roles of Androgens in Males

The androgens trigger development of the primary male sexual characteristics (e.g., testes, penis, vas deferens, seminal vesicles, prostate gland, epididymis) in the embryo.

They produce male secondary sexual characteristics (e.g., the lion's mane, the rooster's comb and plumage, and facial hair in men, voice coarseness and body musculature) at the time of puberty.

Androgens particularly testosterone stimulate spermatogenesis by acting on the germinal cells of testicles.

They also contribute to general growth and protein synthesis-in particular, the synthesis of myofibrillar proteins in muscle, as evidenced by the greater muscularity of the males relative to the females in many vertebrate species.

Roles of Steroid Sex Hormones in Females

Estrogens and progesterone are the primary steroid sex hormones in females.

Estrogens stimulate development of female primary sexual characteristics e.g. uterus, ovaries and vagina.

They are also responsible for the development of secondary female sex characteristics e.g. breast.

They regulate the reproductive cycles which are menstrual cycle in human and some other primate females and estrous cycle in other mammalian females.

Reproductive Role of Peptide Hormones

Prolactin stimulates mammary gland growth and milk synthesis in mammals.

Oxytocin is specialized in stimulating uterine contractions during parturition.

Oxytocin also stimulates release of milk from the mammary glands during nursing.

Topic-93 Prostaglandins

Prostaglandins are about 16 hormone-like local regulators substances that constitute a family of cyclic, long-chain, unsaturated, hydroxy fatty acids.

Synthesis

Prostaglandins are produced by all or nearly all tissues.

They are synthesized in membranes from arachidonic acid, which is produced by cleavage of membrane phospholipids by phospholipases.

Mode of Action

In some cases, they act locally as paracrine agents and in other cases they act on distant target tissues in endocrine fashion.

They have a rapid, short-lasting effect, similar to that of lipid-insoluble hormones.

They bind to cell-surface receptors linked to the cAMP pathway.

Functions

Prostaglandins have diverse actions on a variety of tissues, particularly involving smooth muscles.

1. **Role in Fertilization**
   Prostaglandins present in semen aid in fertilization by reacting with the female cervical mucus to make it more receptive to sperm movement. They also stimulate the smooth muscles of the female's uterine wall to contract, helping sperm reach an egg.
2. **Aid During Labor**
   Certain prostaglandins are secreted by the placenta at the onset of childbirth. They make the muscles of uterus more excitable, enhancing uterine contractions during labor.
3. **Role in Immune Response**
   The damaged tissues, that induce immune response, produce prostaglandins. Some prostaglandins act as local regulators of inflammation, promoting fever and inflammation and also intensify the sensation of pain. They worsen pain by increasing nociceptor sensitivity to noxious stimuli. The interleukin-1, produced in immune response, causes fever by inducing the formation of a prostaglandin E_2 which acts in the hypothalamus to elicit the fever reaction.
   The anti-pyretic, anti-inflammatory and pain-relieving effects of aspirin and ibuprofen are actually due to the inhibition of prostaglandin synthesis by these drugs.
4. **Blood Clot Formation**
   Prostaglandins also help the platelets to aggregate and form blood clots.
   This is the basis of use of aspirin by patients at risk for a heart attack due to formation of clots.

5. **Stomach Lining**

   Prostaglandins also help maintain a protective lining in the stomach.

   As aspirin interferes with prostaglandin synthesis, long-term aspirin therapy can result in damage to this protective lining, causing debilitating stomach irritation.
6. **Production of Erythropoietin**

   Several prostaglandins stimulate the production of erythropoietin by kidneys. Erythropoietin is a hormone that stimulates the production of erythrocytes.
7. **Blood Pressure Regulation**

   Some prostaglandins produced in the kidney also act on the smooth muscles of blood vessels and regulate blood pressure by vasodilation and vasoconstriction.
8. Prostaglandins also modify the actions of some hormones.

Topic-94 Feedback Mechanisms

A feedback mechanism connects the response to the initial stimulus through a feedback loop/circuit.

Feedback loops are characteristic of controlled pathways of hormones through which secretion is modulated by one or more consequences of the secreted hormone.

Types of Feedback Loops

Feedback circuits/loops may follow negative or positive pathways.

Negative Feedback

The secretory activities of most endocrine tissues, especially those involved in maintaining homeostasis, are modulated by negative feedback.

In this type of feedback, the hormone itself or products resulting from its action tend to suppress its further release.

Negative feedback mechanisms ensure a proper level of hormone activity at the target tissue and prevent its over-activity by over-secretion.

How –ve Feedback Operates

Feedback may result in the regulation of hormones at any level e.g.

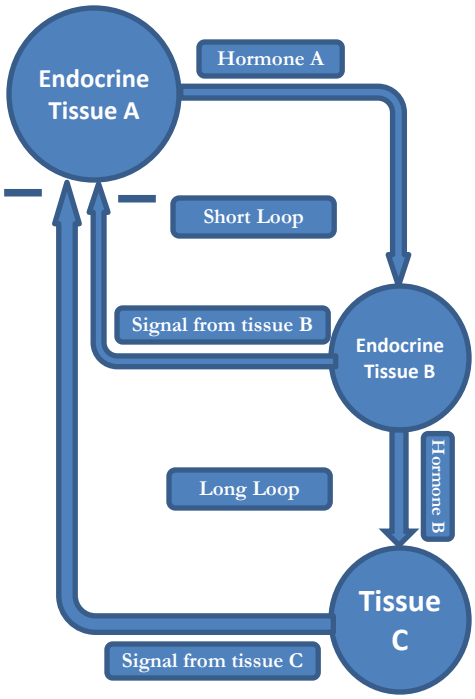
- Synthesis of hormone may be stopped by regulating gene transcription and translation steps.
- Steps involved in the activation of hormone may be regulated.
- Releasing of hormones may be blocked.

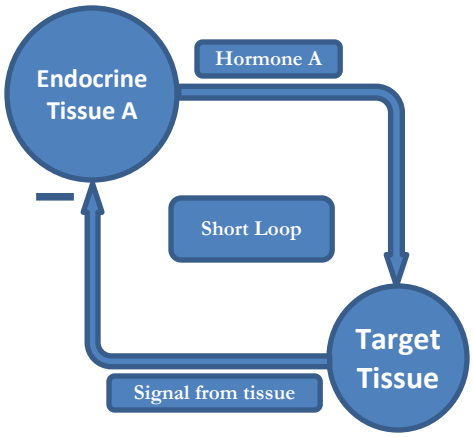
Short and Long Loops of –ve Feedback

Negative feedback involves either a short loop or long loop.

In short-loop feedback, the concentration of the hormone itself, or a byproduct of its activity, acts back directly on the endocrine tissue to reduce secretion, thereby keeping hormone secretion in check.

Long-loop feedback operates on similar principles, but it includes more than one endocrine gland and hormone in the feedback pathway.





Positive Feedback

In this type of feedback, the secretion of a hormone leads directly or indirectly to its increased secretion.

This happens when an extremely rapid or strong response is required.

Positive feedback is also common in the early phases of response in most cases of hormonal action.

Example of Positive Feedback

Increase in the level of luteinizing hormone before ovulation as a result of the stimulatory effect of estrogen on the anterior pituitary.

The secreted LH acts on the ovaries to stimulate additional secretion of estrogen. This estrogen, in turn, causes more secretion of LH.

The positive feedback is ultimately countered by a negative feedback that ends the rapid increase e.g. when LH reaches an appropriate concentration, typical negative feedback control of hormone secretion is exerted to lower LH and estrogen concentrations.

Topic-95 Mechanisms of Hormone Action

The action of hormone can be divided into two phases:

1. Forming the hormone-receptor complex
2. Producing the effect/response

Hormone-receptor complex

The first step of a hormone's action is to bind to specific receptors at the target cell forming the hormone-receptor complex.

Hormone receptors are large proteins and each target cell usually has some 2000 to 100,000 receptors. Cells that lack receptors for the hormones do not respond.

Locations of hormone receptors

The receptors for lipid-insoluble, hydrophilic hormones e.g. protein, peptide, and catecholamine hormones are present on the cell surface. These hormones, being lipid-insoluble, cannot penetrate the plasma membrane and bind to the surface receptors.

The primary receptors for different steroid hormones are present in the cytoplasm while their secondary receptors are in the nucleus. These hormones, being lipid soluble, can readily penetrate the plasma membrane and bind to receptors inside the cell.

The receptors for the thyroid hormones are found in the nucleus.

Producing the effect/response

When the hormone-receptor complex is formed, it initiates a cascade of reactions in the cell.

The intracellular mechanism of action of hormones binding to cytoplasmic and cell-surface receptors varies.

Mechanism of action of lipid-soluble hormones

Steroids and lipid-soluble thyroid hormones, which bind to cytoplasmic or nuclear receptors, form hormone-receptor complexes that translocate to the nucleus and act directly on the DNA of the cell to cause changes in gene expression. These effects are long-term and last for hours or days.

Mechanism of action of lipid-insoluble hormones

Lipid-insoluble hormones, which bind to cell-surface receptors, often lead to production of one or more second messengers, which amplify the signal and mediate rapid, short-lived responses via various effector proteins.

Mechanism of action of Prostaglandins

Prostaglandins, although lipid-soluble, bind to cell-surface receptors and produce a rapid, short-lasting effect, similar to that of lipid-insoluble hormones.

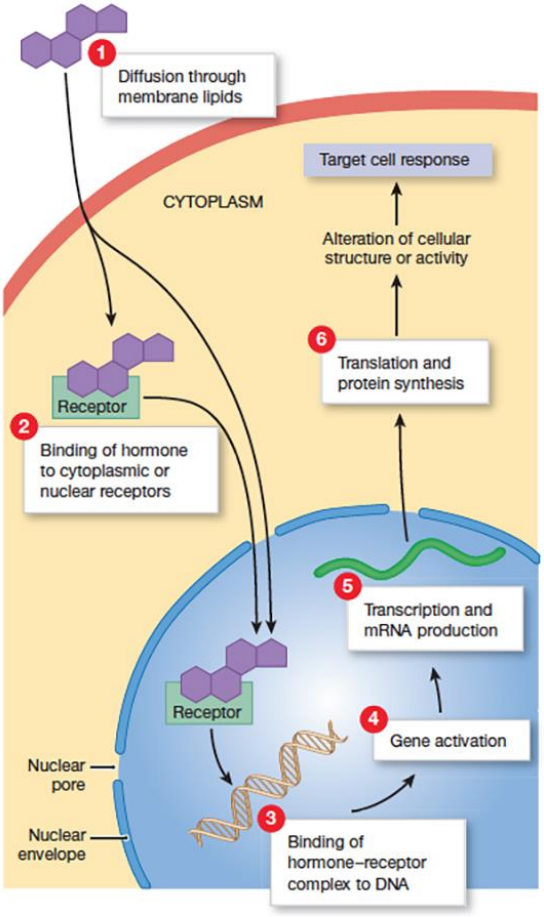
Topic-96 Lipid Soluble Hormones: Mechanism of Action

Transport of lipid soluble hormones

When the lipid-soluble steroid and thyroid hormones are released into the bloodstream, they form complexes with carrier proteins. These complexes are carried by blood to the target tissues. These carrier proteins are necessary because blood is an aqueous solution and only small amounts of lipid-soluble hormones can dissolve in it. In such un-dissolved form, these hormones would be taken up completely by the first encountered lipids in the circulation. The binding ensures adequate rates of hormone delivery to all target tissues.

Entry into the Target Cells

Once these hormones reach their target tissues, they dissociate from their carrier proteins and readily enter the cells by diffusing across the plasma membrane.



Receptors for Lipid-Soluble Hormones

The receptors for steroid hormones are present in the target cell cytoplasm, where hormone-receptor complexes are formed. These complexes then move into the nucleus.

The receptors for non-steroid lipid soluble thyroid hormones are present in the nucleus and hormone-receptor complexes are formed inside the nucleus.

Characters of Receptors for Lipid-soluble Hormones

All the cytoplasmic receptors that bind lipid-soluble hormones share a highly conserved DNA-binding domain. In the absence of hormone, these receptors are bound to an inhibitor protein that blocks the DNA binding domain of the receptor, making it inactive. Binding of hormone to the receptor causes the inhibitor protein to dissociate, thereby exposing its DNA-binding site and activating the receptor.

Action of Hormone in the Nucleus

Inside the nucleus, the DNA-binding domain of the receptor binds specific regulatory sequences within the DNA, thereby regulating the transcription of specific genes causing synthesis of specific proteins.

Since the lipid-soluble hormones act on the cell's DNA to stimulate or inhibit production of particular proteins, their effects persist for hours to days, whereas the effects of lipid-insoluble hormones usually last only minutes to hours.

Topic-97 Lipid Insoluble Hormones and Intracellular Signaling

The water soluble hormones do not penetrate the cell. Their receptors are present in the plasma membrane. So, the hormone-receptor complexes are formed on the cell membrane of target cell.

Signaling Through Second Messengers

The binding of hormone to its receptor results in the activation of many cellular proteins that result in a cascade of enzymatic reactions in the cell which produce a second messenger.

The second messenger causes subsequent intracellular effects that transduce the extracellular hormonal signal into a specific intracellular response.

Diverse Responses of Water-Soluble Hormones

The response may be the activation of an enzyme, a change in the uptake or secretion of specific molecules, or a rearrangement of the cytoskeleton. In addition, some cell-surface receptors cause proteins in the cytoplasm to move into the nucleus and alter transcription of specific genes.

Second Messenger Types

The second messengers involved in signal transduction fall into three distinct groups:

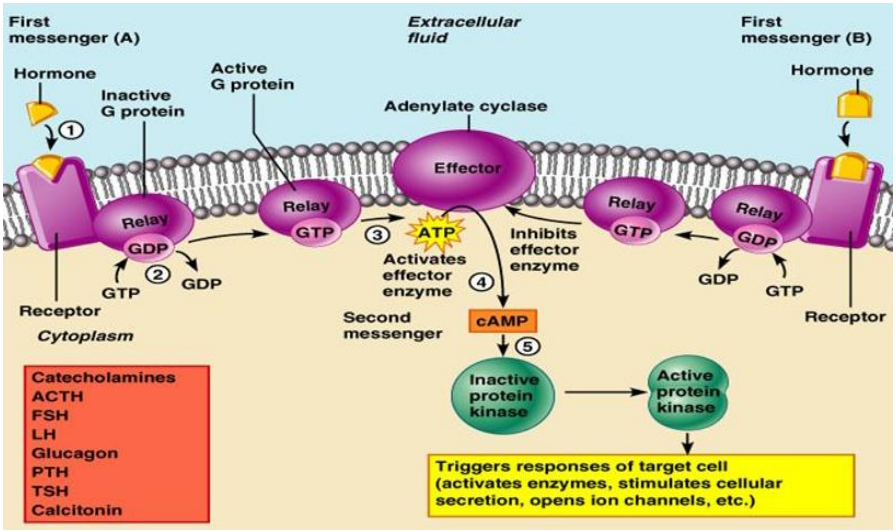
- Cyclic nucleotide monophosphates e.g. cAMP (cyclic adenosine monophosphate) and cGMP (cyclic guanosine monophosphate).
- Inositol phospholipids e.g. inositol trisphosphate ($InsP_3$) and diacylglycerol (DAG)
- Ca^{2+} ions and associated calmodulin

Topic-98 Cyclic Nucleotide Signaling Systems

Water-soluble hormones exert intracellular actions by stimulating the formation of a second messenger inside the cell. The most common second messengers are the cyclic nucleotides cAMP and cGMP. These cyclic nucleotides cause subsequent intracellular effects of the hormone.

The Signaling System of cAMP

Many hormones use the adenylate cyclase–cAMP second messenger system to stimulate their target tissues.



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The hormone binds with the receptor that is coupled to a G protein. The G protein stimulates the membrane-bound adenylate cyclase enzyme. Activated adenylate cyclase catalyzes the conversion of adenosine triphosphate (ATP) into cAMP in the cytoplasm.

The cAMP then activates an enzyme called cAMP-dependent protein kinase. This enzyme phosphorylates specific proteins in the cell, triggering a cascade of biochemical reactions that ultimately lead to the cell's response to the hormone.

Action of cAMP Varies with Cell-Type

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

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

cGMP as a second messenger

Many animal cells also use cyclic GMP (cGMP) as a second messenger. The pattern of cGMP activities is similar to that of cAMP. However, the cGMP signaling pathway differs in some respects pertaining to specific enzymes and factors stimulating these enzymes.

A few of such differences include:

- The production of cGMP is catalyzed by guanylate cyclase enzyme from GTP.
- Guanylate cyclase occurs in two forms: one bound to the plasma membrane and one free in the cytoplasm. In contrast, adenylate cyclase is always bound to the plasma membrane.
- Guanylate cyclase becomes active as the Ca^{2+} concentration is increased within the cell, while adenylate cyclase activity is increased when Ca^{2+} conc. is low.
- cGMP activates a specific protein kinase, protein kinase G instead of protein kinase A.

Amplification of the Effect

The importance of this mechanism involving a cascade of biochemical reactions is that each activated enzyme stimulates many more molecules of the next enzyme. This is like a chain reaction that can initiate a powerful cascading activity in the cell even in the presence of slightest amount of the hormone.

Topic-99 Inositol Phospholipid and Ca^{+2} Signaling Systems

Inositol Phospholipid Signaling System

Some hormones use the inositol phospholipid pathway to produce their effect. These hormones include: Angiotensin II, Catecholamines, Gonadotropin-releasing hormone (GnRH), Growth hormone–releasing hormone (GHRH), Oxytocin, Thyroid-releasing hormone (TRH) and Vasopressin.

Mechanism of Inositol Phospholipid Signaling System

The hormone binds to the transmembrane receptors that are linked to G proteins. These G proteins activate the enzyme phospholipase C. The enzyme phospholipase C catalyzes the breakdown of some phospholipids in the cell membrane, especially phosphatidylinositol biphosphate (PIP_2) into two different second messenger products: inositol trisphosphate ($InsP_3$) and diacylglycerol (DAG).

Role of $InsP_3$

The $InsP_3$ mobilizes calcium ions from intracellular calcium stores (mitochondria and endoplasmic reticulum). These calcium ions have their own second messenger effects, such as smooth muscle contraction and changes in cell secretion.

Role of DAG

DAG (diacylglycerol) activates the enzyme protein kinase C (PKC), which then phosphorylates a large number of proteins, leading to the cell's response.

In addition to these effects, the lipid portion of DAG is arachidonic acid, which is the precursor for the synthesis of prostaglandins and other local hormones that cause multiple effects in tissues throughout the body.

Ca^{+2} Signaling Systems

Some hormones interact with membrane receptors that open calcium channels.

Calcium entering through these channels acts as a second messenger.

On entering a cell, calcium ions bind with the protein calmodulin.

This protein has four calcium sites, and when three or four of these sites have bound with calcium, the calmodulin changes its shape and initiates multiple effects inside the cell, including activation or inhibition of protein kinases.

Activation of calmodulin-dependent protein kinases causes, via phosphorylation, activation or inhibition of proteins involved in the cell's response to the hormone.

Example

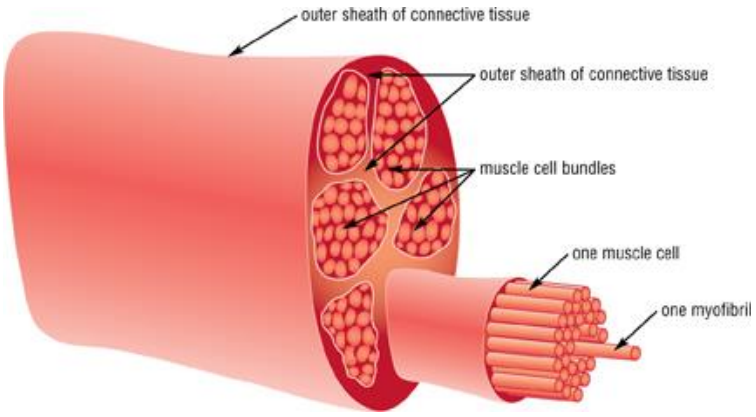
Calcium-calmodulin pathway is used to activate myosin kinase, which acts directly on the myosin of smooth muscle and causes smooth muscle contraction.

Topic-100 The Structure of Muscle

The Muscle Cells (Myofibers)

Each muscle consists of hundreds to thousands of long, cylindrical, multinucleated cells called muscle fibers or myofibers, which are arranged in bundles called fascicles.

Skeletal muscle fibers range from 5 to 100 μm in diameter, and may be many centimeters in length.



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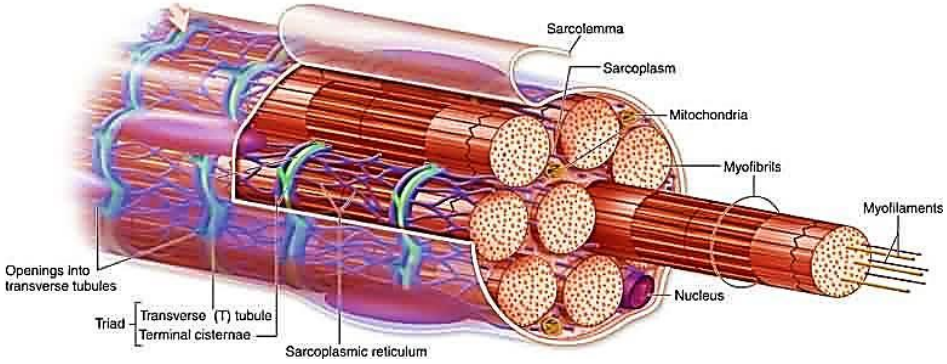
The membrane of the cell is called sarcolemma, its cytoplasm is called sarcoplasm and its endoplasmic reticulum is known as sarcoplasmic reticulum.



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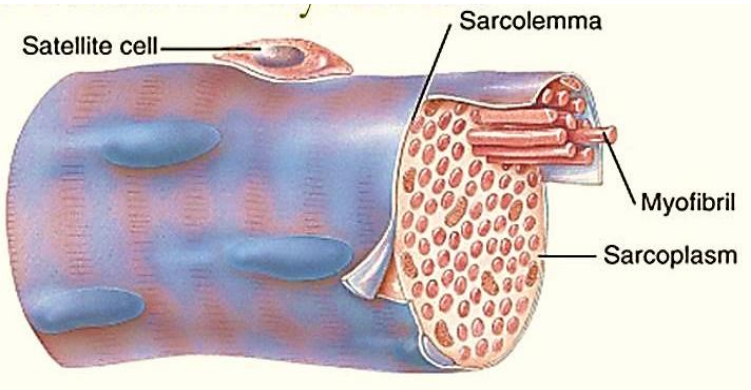
Myofibrils

Within each muscle fiber, numerous myofibrils run in parallel fashion. Myofibrils are 1-2 μm in diameter and extend the entire length of the cell.



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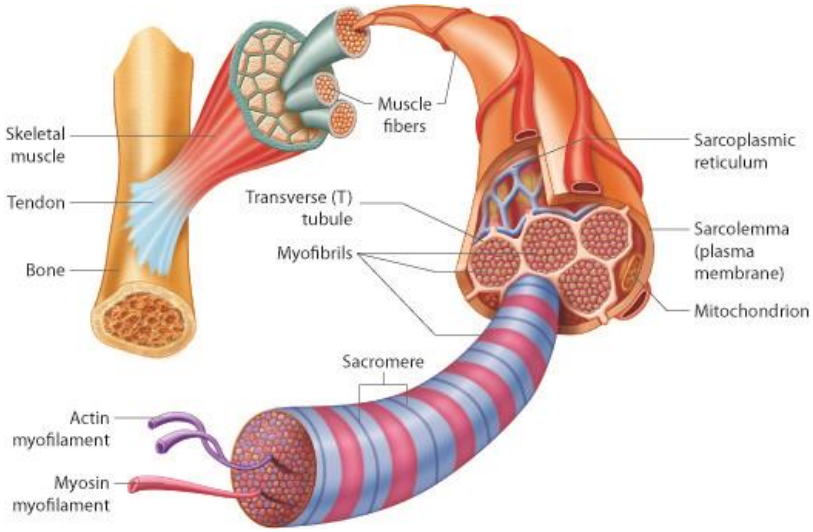
Myofilaments

Each myofibril is composed of myofilaments. Myofilaments are of two types, thin filaments and thick filaments.

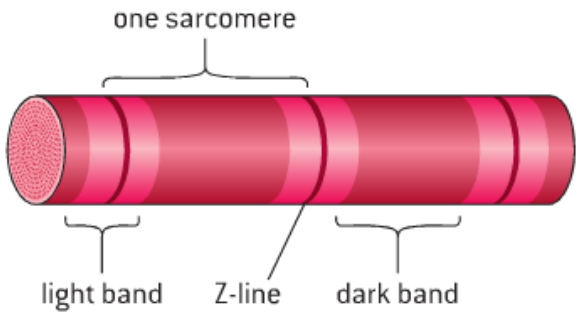
Thin filaments are composed of actin while the thick filaments are composed of myosin molecules.



Sarcomere

The regular arrangement of the thick and thin filaments creates a pattern of repeating light and dark bands.

This pattern gives a striped appearance to the muscle cell.

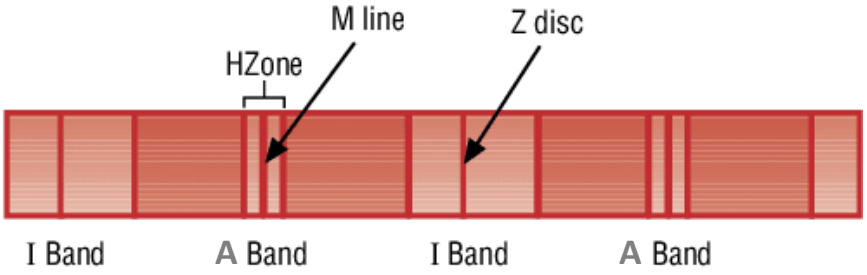


Each repeating unit is called a sarcomere and is the basic functional contractile unit of the muscle.

Structure of Sarcomere

- Each dark band in a sarcomere is called A band. This band is anisotropic i.e. it polarizes visible light.
- Each A band has a lighter stripe in its center which is called H-zone.
- The H-zone is bisected by a dark line called M-line.
- The light band is called I band. It is isotropic i.e. non-polarizing.
- The I band has a mid-line called Z-line.

A sarcomere is the region of a myofibril between two successive Z-lines.

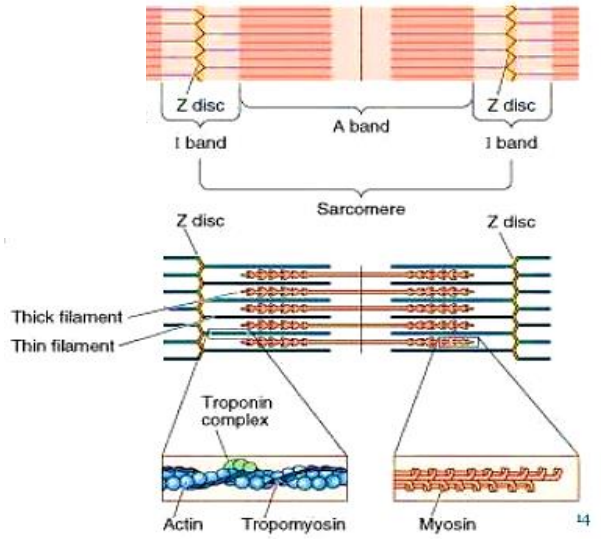


Topic-101 Myofilament Substructure

Myofilament is made up of thick and thin filaments.

Thick Filaments

- Thick filaments extend the entire length of A band.
- These filaments are about 16 nm in diameter and are composed of about 300 myosin molecules.



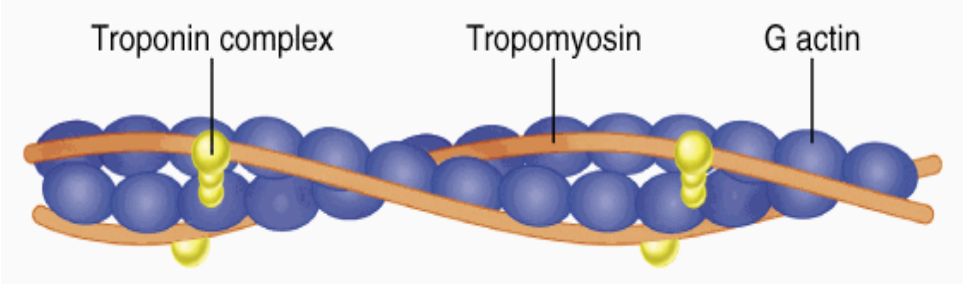
Myosin Molecule

- Each myosin molecule consists of two identical heavy chains which are coiled together to form a long tail. It also has two globular heads which are made from two heavy chains plus three or four calcium-binding light chains.
- The heads form cross bridges between the thick and the thin myofilaments during contraction.

Thin Filaments

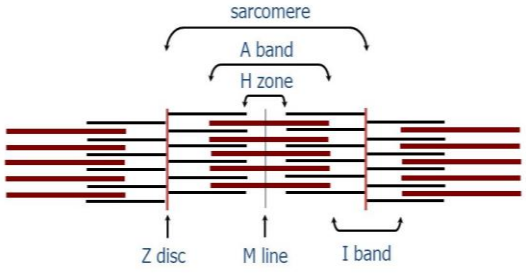
- The thin filaments are 7-8 nm thick and extend across the I band.
- They are composed chiefly of actin molecules.

- Thin filaments also overlap myosin filaments in the peripheral darker regions of the A band. In these regions, six actin filaments surround each myosin filament while each actin filament is surrounded by three myosin filaments.
- In thin filaments, actin molecules are arranged in two chains which twist around each other.
- Two strands of another protein tropomyosin twist around the actin and help to stiffen it. In a relaxed muscle fiber, they block myosin binding so that the myosin heads can not bind to the thin filaments.
- Thin filaments also have a three polypeptide complex troponin at intervals of about 40nm along the thin filament.
- One of the troponin polypeptides (TnI) is an inhibitory subunit that binds to actin, other (TnT) binds to tropomyosin and helps position it on actin while third (TnC) binds the calcium ions.
- Both troponin and tropomyosin help control the myosin-actin interactions involved in contractions.



The H Zone

- The center of A band appears lighter than the other regions in a relaxed sarcomere.
- This region is called H zone and contains only thick filaments. There are no overlaps between the actin and myosin in this region.
- The H zone is bisected by a dark line, the M line which contains enzymes important in energy metabolism.



Topic-102 Contraction of Muscle: Sliding Filament Theory

Sliding Filament Theory

H. E. Huxley and A. F. Huxley proposed the sliding filament theory of muscle contraction in 1954.

This theory states that during muscle contraction the thin and thick filaments in sarcomeres slide and undergo shifting.

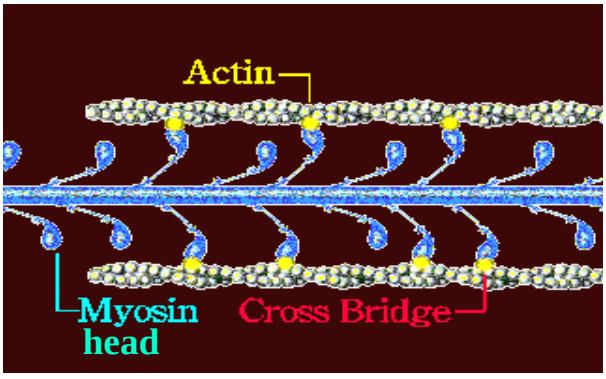
When a muscle contracts, the thin actin filaments actively slide along between the thick myosin filaments and move closer to the center of the sarcomere. As a result, the sarcomere becomes shorter.

When a muscle relaxes or is stretched, the overlap between thin and thick filaments is reduced, and the sarcomere elongates.

The changes in sarcomere length during contraction and stretch of a muscle, correspond to changes in muscle length.

Explanation

- In a relaxed muscle fiber, the thick and thin filaments overlap only at the ends of A band. But when muscle fibers are stimulated by the nervous system, myosin heads are attached to the myosin-binding sites on actin in the thin filaments, i.e. cross bridges are formed and the sliding begins.



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- During contraction, the A bands (myosin filaments) maintain a constant length, whereas the I bands and the H zone (zones where actin and myosin filaments do not overlap) become shorter and Z lines get closer.
- When the muscle is stretched, the A band again maintains a constant length, but the I bands and H zone become longer.

- Neither the myosin thick filaments nor the actin thin filaments change their lengths when a sarcomere shortens or is stretched. It is the extent of overlap between actin and myosin filaments that changes.

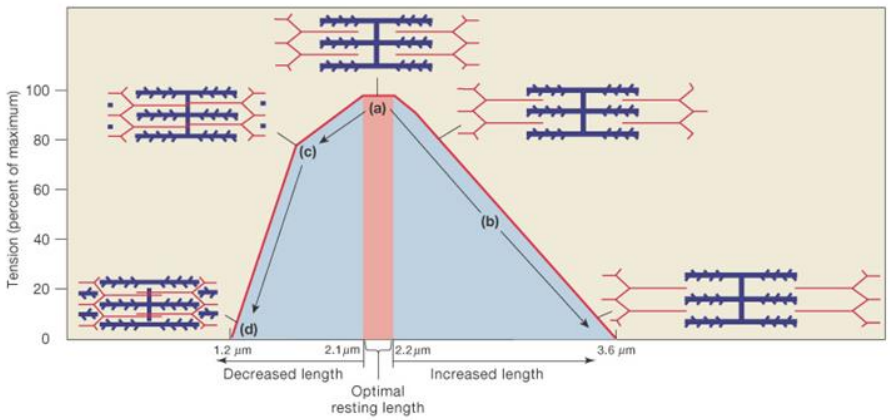
Length-Tension Curve

One of the strongest pieces of evidence in support of the sliding filament theory comes from the length-tension relation of a sarcomere.

Experimental measurement of the shortening of length of sarcomere during contraction and resulting force generates a length-tension curve. This curve explains the assumptions of sliding-filament theory.

Explanation of the Curve

- The tension produced by the muscle is maximal when the overlap between thick and thin filaments allows the largest number of cross-bridges to be formed between actin and myosin.
- Tension drops off with increased length of sarcomere, because the thick and thin filaments overlap less and fewer crossbridges can be formed.
- It also drops off with decreased length, because thin filaments begin to collide with one another, preventing further shortening.
- The curve also predicts the consequence of sliding filament theory that no active tension will develop if a sarcomere is stretched so far that there remains no overlap between actin and myosin filaments, making it impossible to develop any crossbidges.



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Conclusion

This curve shows that the tension produced by a sarcomere is proportional to its shortening which is due to sliding of thick and thin filaments and formation of cross bridges in the sarcomere during contraction. These were the proposals of sliding filament theory. So length-tension curve provides a practical proof of this theory.

Topic-103 Role of ATP in Cross Bridge Working

Cyclic Attachment and Detachment of Cross-Bridges

- Myosin cross-bridges must attach to binding sites on actin filaments in order to generate force.
- However, the cross-bridges must also be able to detach because attached cross-bridges would prevent filaments from sliding past one another, locking the muscle at one length.
- In addition, detachment of cross-bridges from actin is necessary for the muscle to relax.
- So, during contraction, the cross-bridges must attach and detach from the thin filaments in a cyclic fashion.

Role of ATP in Cross-Bridge Detachment

- This cyclic attachment and detachment happens due to the activity of ATP.
- Cross bridges are formed when actin (A) and myosin (M) bind and form a stable complex called actomyosin (AM). This happens in the absence of ATP.
- Cross-bridge detachment occurs in the presence of ATP. ATP causes the AM complex to rapidly dissociate into actin and myosin-ATP:

$$\mathbf{A + M = AM}$$

$$\mathbf{AM + ATP = A + M\text{-}ATP}$$

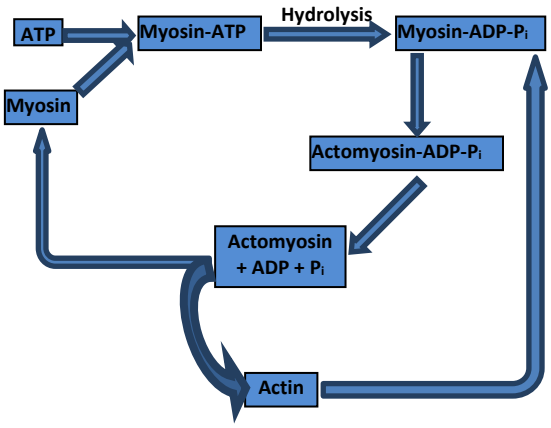
Cyclic Activity of AM complex

- The Myosin-ATP complex hydrolyzes to form myosin-ADP-P_i complex.
- However, ADP and P_i unbind from myosin very slowly.
- The release of ADP and P_i is greatly speeded up when actin binds to myosin in the myosin-ADP-P_i complex.
- This binding of actin results in the formation of another actomyosin complex. This reaction is kinetically favored as it releases energy.

$$\mathbf{M\text{-}ATP \longrightarrow M\text{-}ADP\text{-}P_i \xrightarrow{\text{Very slow}} M + ADP + P_i}$$

$$\mathbf{M\text{-}ADP\text{-}P_i + A \xrightarrow{\text{Fast}} AM + ADP + P_i}$$

Combining these reactions produces a cycle of binding and unbinding of myosin with actin with a net use of one molecule of ATP per cycle.



Rigor Mortis

After death, human and other animal's bodies gradually become rigid. This condition is called rigor mortis.

This rigidity happens because ATP's are not available in dead body for detachment of actin and myosin, so muscles cannot relax.

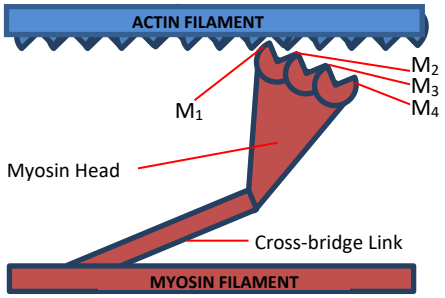
Topic-104 Production of Force for Sliding of Filaments

Force is Produced by Rotation of Myosin Head

During muscle contraction, myosin heads make cross-bridges with actin filaments that pull the thin filament toward the center of sarcomere. The force for pulling is produced by the partial rotation of myosin heads.

How Rotation is Produced?

The rotation is produced when the four sites M_1 to M_4 of myosin head interact sequentially with the binding sites of actin filament.



Energy Storage in the Link

As the myosin head rotates against the actin filament, the link is stretched elastically and stores mechanical energy in the link due to tension developed in it.

Transmission of Force to Thick Filament

The tension thus produced is transmitted to the thick filament through the neck of the myosin molecule. This tension provides force to shorten the sarcomere.

Detachment of Myosin Head

When the rotation of the head is complete, the myosin head dissociates from the actin filament and rotates back to its relaxed position.

The myosin head detaches from actin when Mg^{2+} and ATP bind to the head. The ATP is then hydrolyzed, which is accompanied by a conformational change in the myosin head, leaving the head in an energized state, ready to rebind to a little farther site on the actin filament.

This cycle is repeated over and over, and the filaments slide past one another in small incremental steps of attachment, rotation, and detachment of the many cross-bridges on each thick filament.

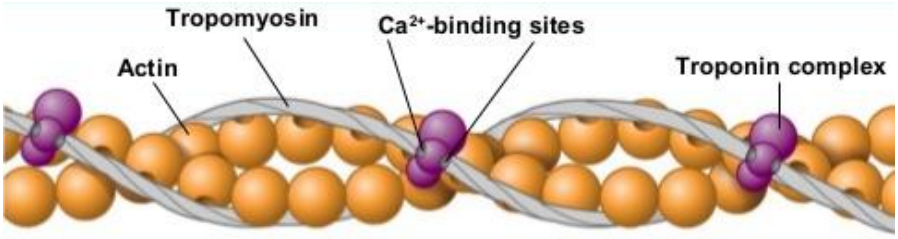
Topic-105 Role of Calcium in Contraction

Role of Calcium in Cross-bridge Attachment

Ca^{2+} plays a crucial role in regulating the contractile activity of muscles as it helps to expose the myosin binding sites of actin. This exposure induces cross bridge formation, necessary for contraction.

Ca^{2+} Plays Role by Interacting with Troponin and Tropomyosin

- Ca^{2+} induces contraction with the help of two regulatory proteins troponin and tropomyosin, associated with actin filaments.
- In a relaxed myofibril, tropomyosin coils around the actin filament and sterically (physically) covers the myosin binding sites of actin, thus preventing actin and myosin from interacting.
- Troponin complex binds to tropomyosin about every 40 nm along the thin actin filament.



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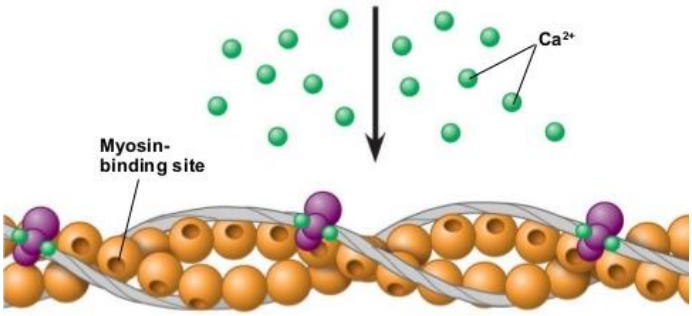
Binding of Ca^{2+} to Troponin

- Troponin has a high binding affinity for Ca^{2+} and each troponin complex binds four Ca^{2+} ions.
- When Ca^{2+} binds to troponin, the troponin molecule undergoes a change in conformation.
- This causes a shifting in the position of tropomyosin. Tropomyosin movement exposes the myosin binding sites on the thin actin filament.



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Thus, when Ca^{2+} binds to troponin, it removes the inhibition of attachment between myosin cross-bridges and thin filaments. So the thin and thick filaments can slide past each other, and the muscle fiber contracts.

The role of Ca^{2+} in regulating the actin-myosin interaction via troponin and tropomyosin applies to vertebrate skeletal and cardiac muscle.

Required Concentration of Ca^{2+} for Contraction

The required concentration of Ca^{2+} ions in cytosol for binding of cross-bridges to actin is above 10^{-7} M.

Topic-106 Excitation Contraction Coupling

Action Potentials Trigger Muscle Contraction

The skeletal muscles contract in response to an action potential (nerve impulse) that arrives at the neuromuscular junction.

Acetylcholine Neurotransmitter

At the neuromuscular junction, motor neurons release the neurotransmitter, acetylcholine.

Acetylcholine binds to the receptors in postsynaptic muscle fibers. These receptors are ligand-gated ion channels. Opening of these channels causes movement of sodium (Na^+) and potassium (K^+) ions.

End-plate Potential

The ionic movements cause change of potential in the muscle cell membrane resulting in membrane excitation. The potential of excited muscle fiber membrane is known as end-plate potential. Membrane excitation results in the triggering of an all-or-none AP in the fiber membrane.

The AP propagates away, exciting the entire membrane of the muscle fiber and setting in motion the sequence of events leading to contraction.

Excitation-Contraction Coupling

The sequence of events that convert an action potential to muscle contraction is known as excitation-contraction coupling.

Latency period

It takes several milliseconds to begin contraction after the arrival of an AP.

This latency is because of the large size of skeletal muscle fibers which cannot contract unless action potential spreads deep into the fiber to the vicinity of each myofibril.

During this latent period, action potential is transmitted along the transverse tubules (T tubules) deep within the fiber.

Release of Ca^{2+} and Contraction

Transmission of action potential through T tubules results in the release of calcium ions form stores of sarcoplasmic reticulum.

This increases Ca^{2+} concentration inside the muscle fiber in the immediate vicinity of the myofibrils.

These calcium ions cause the contraction to begin.

The net effect of excitation-contraction coupling is to link an AP in the plasma membrane of the muscle fiber to the concentration of free Ca^{2+} in the cytosol that initiate contraction.

Topic-107 T-tubules: Propagation of Action Potential into the Myofibril

Large Size of Muscle Fiber: A Problem in Propagation of AP

An action potential arriving at the neuromuscular junction causes a potential difference across the surface membrane of muscle cell. This potential difference can directly affect less than a micrometer area of the membrane.

The skeletal muscle fiber is quite large i.e. 50-100 μm in diameter. So, the small action potentials spreading along its surface membrane can cause almost no current flow deep within the huge muscle fiber.

Spread of Depolarization in Muscle Fiber

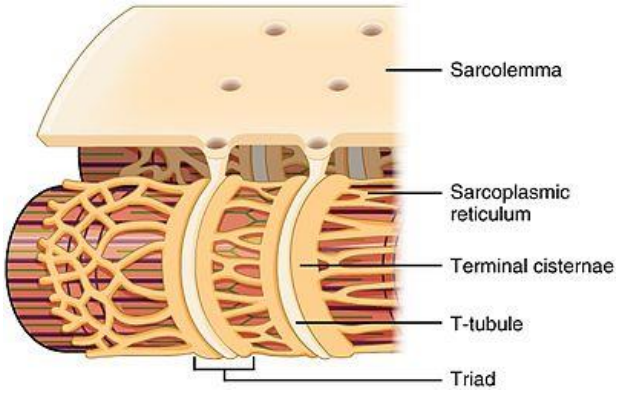
To spread depolarization deep within the muscle fiber, there needs to be a mechanism that couples depolarization of the surface membrane to the myofibrils.

This is achieved by transmission of action potentials along transverse tubules (T tubules).

T Tubules

T tubules are thin internal extensions of the cell membrane that are less than 0.1 μm.

They innervate the cell at the level of Z disk and make branching networks around the perimeter of each myofibril.



Role of T Tubules

The T tubule system provides the anatomic link between the surface membrane and the myofibrils deep inside the muscle fiber.

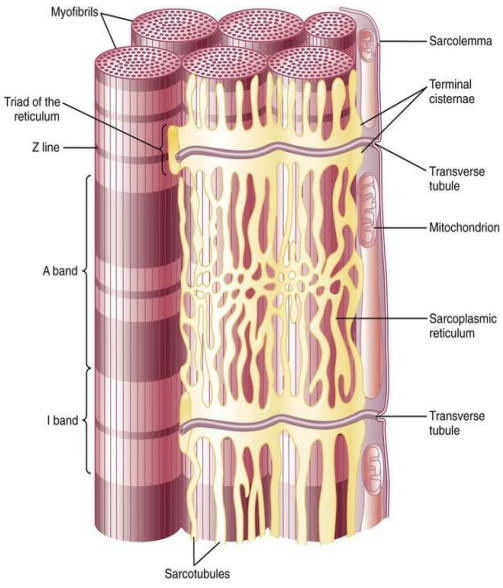
When an action potential spreads over a muscle fiber membrane, a potential change also spreads along the T tubules to the deep interior of the muscle fiber.

In the cell interior, T tubes are linked to the sarcoplasmic reticulum which, on excitation, releases Ca^{2+}, permitting myosin cross-bridges to attach to the actin thin filaments and generate force for contraction.

Topic-108 Sarcoplasmic Reticulum

Sarcoplasmic Reticulum

- The sarcoplasmic reticulum (SR) is a network of membrane-bound tubules that extends throughout muscle cells on either side of a Z disk and extends from one Z disk to the next as well.
- In many features, it is similar to the endoplasmic reticulum in other cells.
- The SR has a special organization that is extremely important in controlling muscle contraction.
- That is why the rapidly contracting types of muscle fibers have extensive network of sarcoplasmic reticulum.



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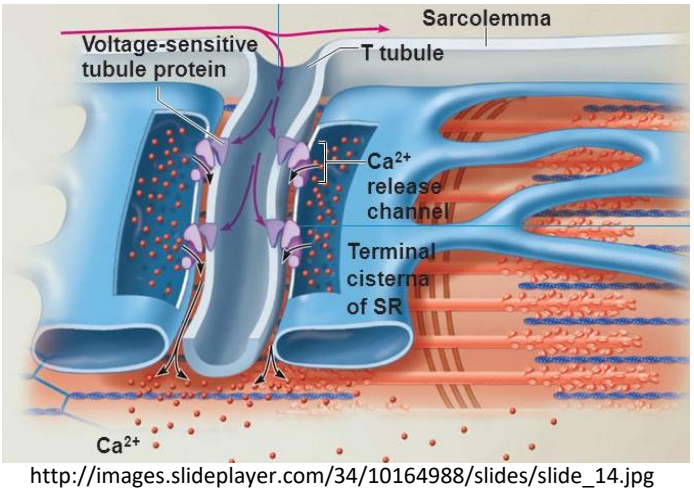
Structure of SR

SR is composed of two major parts:

(1) Terminal cisternae which are larger chambers. T-tubules are closely associated with terminal cisternae (with a separating distance of about 12 nanometers). These are the primary site of calcium release as they have voltage sensitive channel proteins that open when action potential in T tubules activates them.

(2) Long longitudinal tubules that run between the terminal cisternae and surround the myofibrils. These are the locations where ion channels necessary for calcium ion absorption (calcium pumps) are most abundant.



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Calcium Sequestering by SR

The main function of the SR is to sequester and store calcium (Ca^{2+}) ions.

Sarcoplasmic reticulum takes up Ca^{2+} ions due to the activity of calcium ion pumps in its membrane that actively transport Ca^{2+} ions from the sarcoplasm and concentrate it inside the reticular tubules.

Role of Calsequestrin

Inside the SR, Ca^{2+} is stored bound to a protein called calsequestrin.

Each molecule of this protein can bind around 50 Ca^{2+}.

This decreases the amount of free Ca^{2+} within the SR and enhances the capacity of SR to store more calcium ions.

Importance and Role of Ca^{2+} Sequestering

Due to calcium sequestering by SR, Ca^{2+} levels in the cytosol are kept below 10^{-7} M.

This concentration is required to remove Ca^{2+} bound to troponin and preventing contraction.

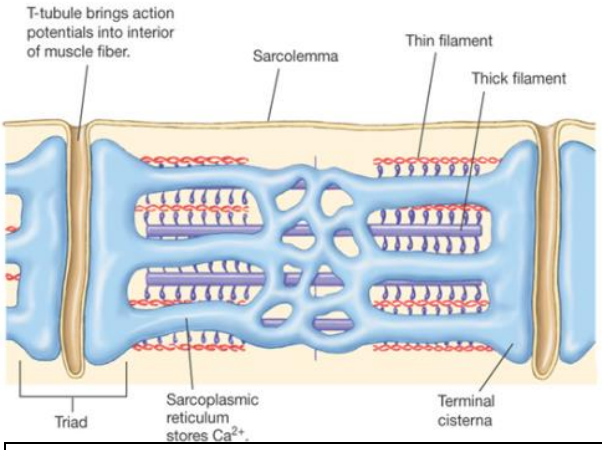
When an AP arrives to cause contraction, it is conducted within the muscle fiber through T tubules. Action potential in T tubules causes opening of calcium channels in the terminal cisternae of SR and large quantities of stored Ca^{2+} ions are released.

When Ca^{2+} ions are released, contraction is activated.

Topic-109 Membrane Receptors in Triads

Triads

In the skeletal muscle fiber, a T tubule is associated with two terminal cisternae of sarcoplasmic reticulum on its both sides. This arrangement of three associated tubes or sacks forms a structure that is called a triad.



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Each skeletal muscle fiber has many thousands of triads which are visible in longitudinal sections of muscle fiber.

Triads are typically located at the junction between the A and I bands of the sarcomere.

Function of Triads

Triads form the anatomical basis of excitation-contraction coupling, due to which a stimulus excites the muscle and causes it to contract.

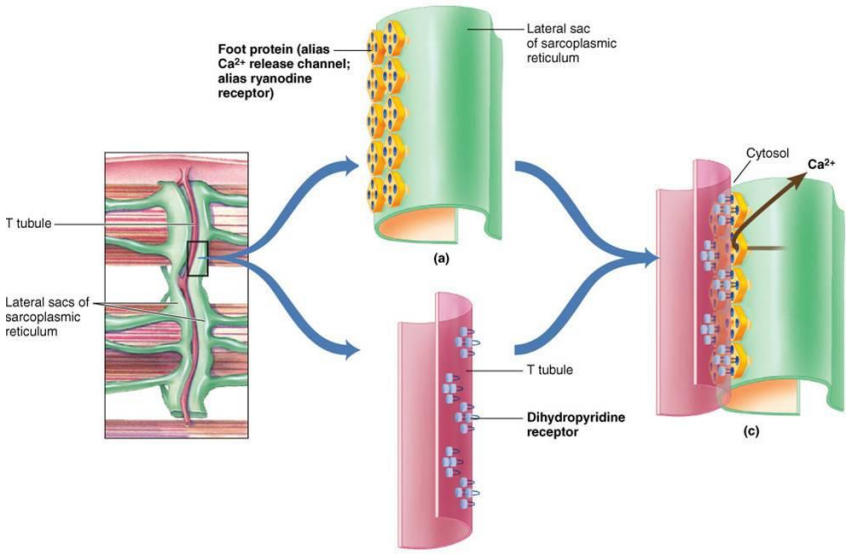
It is due to the close proximity of T tubules and sarcoplasmic reticulum at the triads that an AP in T tubule causes the SR to release Ca^{2+}.

Receptors in Triads and Release of Ca^{2+}

The membrane of SR in the triad region has specialized Ca^{2+} ion channel proteins called ryanodine receptors. When they open, Ca^{2+} ions are released from the sarcoplasmic reticulum.

Opening of Ryanodine Receptors

- Ryanodine receptors open when a cluster of proteins called dihydropyridine receptors in the T-tubule membrane are activated.
- The dihydropyridine receptors are voltage-sensitive receptors which are activated by action potential in the T tubule.
- Activation of these receptors causes a change in their conformation.
- In the activated state, these receptors mechanically interact with ryanodine receptors causing conformational change in them too.
- This results in the opening of ryanodine receptors which allow release of calcium ions from SR. Release of calcium ions causes contraction to happen.



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Topic-110 Summary of Muscle Contraction Mechanism

Contraction-Relaxation Cycle

Starting with a relaxed skeletal muscle, the following sequence of events leads to contraction and then relaxation of a skeletal muscle fiber:

1. The surface membrane of the fiber is depolarized by an AP due to neuronal input.
2. The AP is conducted deep into the muscle fiber along the T tubules.
3. In response to depolarization of the T-tubule membrane, voltage-sensitive dihydropyridine receptors in the T-tubule membrane undergo a conformational change that-through direct mechanical linkage to ryanodine receptors in the SR membrane-causes opening of Ca^{2+} channels in the SR membrane.
4. As Ca^{2+} flow out from the lumen of sarcoplasmic reticulum, the free Ca^{2+} concentration of the myoplasm increases from a resting value of below 10^{-7} M to an active level of about 10^{-6} within a few milliseconds.
5. Most of the Ca^{2+} ions that enter the myoplasm bind rapidly to troponin, inducing a conformational change in the troponin molecule. This conformational change causes a change in the position of the tropomyosin, eliminating steric hindrance and allowing myosin cross-bridges to bind to actin thin filaments.
6. Myosin cross-bridges attach to the actin filaments. Myosin heads rotate against the actin filaments producing force that pulls the thin filaments toward the center of the sarcomere, causing the sarcomere to shorten.
7. ATP binds to the ATPase site on the myosin head causing the myosin head to detach from the thin filament.
8. ATP is then hydrolyzed, and the energy of the hydrolysis is stored as a conformational change in the myosin molecule, which then reattaches to the next site along the actin filament and the cycle of binding and unbinding is repeated.
9. Finally, calcium pumps in the SR membrane actively transport Ca^{2+} from the myoplasm back into the SR. As the concentration of free Ca^{2+} in the myoplasm drops, Ca^{2+} bound to troponin is released, allowing tropomyosin again to inhibit cross-bridge attachment, so the muscle relaxes. The muscle remains relaxed until the next depolarization.

Topic-111 Isometric and Isotonic Contractions

Muscle contractions are categorized into two types based on two variables: force (tension) and length (shortening or lengthening):

1. Isotonic contraction
2. Isometric contraction

Isotonic Contraction (Constant Tension)

If the muscle length changes while muscle tension remains constant, the contraction is called an isotonic contraction (tonic = tension).

Isotonic contractions occur because the force exerted by muscle contraction is greater than the external force against it.

The change in length of the muscle results in the movement of a body part. Therefore, this type of muscle contractions are produced during locomotion.

Types of Isotonic Contractions

Based on how the length changes, isotonic contractions are further classified into two types:

- Concentric contractions
- Eccentric contractions

Concentric Contractions

If the muscle generates tension and the entire muscle shortens then it is a concentric contraction.

An example would be lifting a weight from your waist to your shoulder; the bicep muscle used for this motion would undergo a concentric contraction.

Eccentric Contractions

If the muscle generates tension and the entire muscle lengthens, it is a eccentric contraction.

For example, lowering the weight from the shoulder to the waist, the bicep muscles would generate force but the muscle would be lengthening.

Eccentric contractions work to decelerate the movement at the joint.

Eccentric contractions can generate more force than concentric contractions.

Isometric Contraction

When the tension in a muscle increases without a corresponding change in length, the contraction is called an isometric contraction (iso = same, metric=length).

Isometric contractions occur because the force exerted by the muscle contraction is only equal to the opposing external force.

Isometric contractions are important in maintaining posture or stabilizing a joint.

An example of an isometric contraction is when one grips something hard, for example a book. There is no movement of the arm or the book, but the muscles in the arm contract to provide a force to keep the book in place against gravity.

Topic-112 Muscle Twitch and Tetanus

Muscle Twitch

A muscle twitch is a single contraction in response to a single action potential.

Components of a single muscle twitch

A single muscle twitch has three components:

- The latent period, or lag phase
- The contraction phase
- The relaxation phase

The Latent Period

The latent period is a short delay from the time when the action potential reaches the muscle until tension can be observed in the muscle.

This is the time required for calcium to diffuse out of the SR and bind to troponin, tropomyosin moves off the active sites and cross bridges are formed.

The Contraction Phase

The contraction phase is when the muscle is generating tension.

It is associated with cycling of the cross bridges that result in the shortening of sarcomeres.

The Relaxation Phase

Relaxation phase is the time for the muscle to return to its normal length.

Length of a twitch

The length of the twitch varies between different muscle types and could be as short as 10 milliseconds or as long as 100 ms.

Tetanus

A tetanic contraction is a sustained muscle contraction evoked by stimulation from simultaneous multiple impulses. Each stimulus causes a twitch.

A tetanic contraction can be either unfused (incomplete) or fused (complete).

An unfused tetanus is when the muscle fibers do not completely relax before the next stimulus because they are being stimulated at a faster rate.

Fused tetanus is when there is no relaxation of the muscle fibers between stimuli and the twitches overlap. It occurs during a high frequency of stimulation.

A fused tetanic contraction is the maximal possible contraction.

During tetanized state, the contracting tension in the muscle remains constant in a steady state.

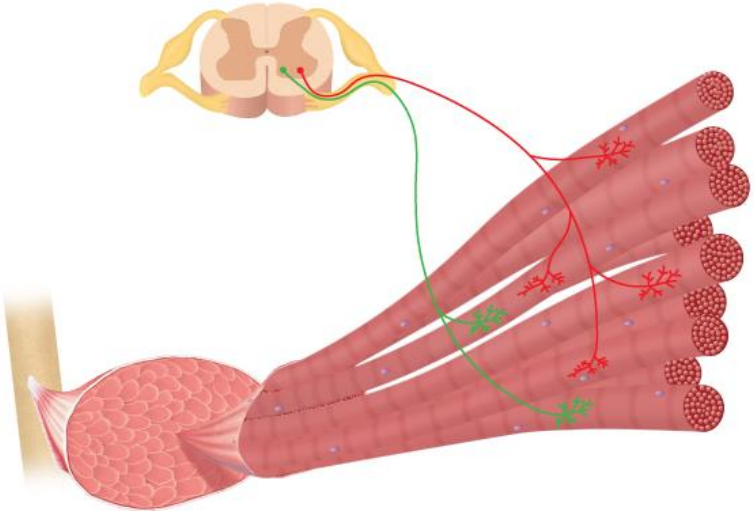
Topic-113 Neural Control of Muscle Contraction

Neural Control of Coordination of Muscle Contraction

- Effective animal movement requires the contractions of many fibers within a muscle-and of many muscles within the body.
- These contractions need to be correctly timed with respect to one another.
- This coordination is generated within the nervous system which sends neuronal impulses at the neuromuscular junctions of the muscle and coordinates the timing of muscle contractions.
- Moreover, the nervous system also regulates the strength of contractions by determining the number and type of fibers to be activated simultaneously.

Spinal Motor Neurons

- All vertebrate skeletal muscles are innervated by motor neurons whose cell bodies are located in the ventral horn of the gray matter of the spinal cord.
- Axons of these motor neurons leave the spinal cord by a ventral root. Peripheral nerves carry these axons to the muscles where they branch off repeatedly. The branches of each motor neuron innervate hundreds of skeletal muscle fibers.



- A motor neuron and the muscle fibers that it innervates form a motor unit.
- Spinal motor neurons, themselves, receive an enormous number of synaptic inputs from sensory neurons and interneurons. These spinal motor neurons are the only means available for controlling contraction of the muscles, so they have been called "the final common pathway" of neuronal output.

Fine Motor Control of Muscle Contraction

- An AP is initiated in a motor neuron as a consequence of synaptic inputs. The AP spreads into all of its terminal branches, activating all of its endplates.
- All vertebrate spinal *a* motor neurons produce the neurotransmitter acetylcholine (ACh) which is released onto all of the fibers in the neuron's motor unit.
- Each time a motor neuron fires an AP, all of the muscle fibers in its motor unit contract. The frequency of APs generated in the motor neuron determines whether single twitches or sustained tetanic contractions are produced.

Topic-114 Muscle Fatigue

Muscle Fatigue

Fatigue is a condition in which a skeletal muscle is no longer able to contract optimally.

Usually prolonged and strong contraction of a muscle leads to the state of muscle fatigue.

Muscle fatigue has physiological causes. It can occur anywhere between the neuromuscular junction and the contractile elements of the muscle.

Physiological Causes of Fatigue

1. Transmission of nerve signals through the neuromuscular junction diminishes after intense prolonged muscle activity. This happens because of impaired membrane excitability as a result of imbalances of ions. Potential causes are inadequate functioning of the Na^+/K^+ pump, subsequent inactivation of Na^+ channels and impairment of Ca^{2+} channels. If this is the reason, muscles can recover quickly, usually within 30 minutes or less.
2. Fatigue may also occur due to interruption in excitation-contraction coupling with impaired Ca^{2+} release. This cause takes from 24 hours to 72 hours to recover from fatigue.
3. Interruption of blood flow through a contracting muscle leads to almost complete muscle fatigue because of the loss of nutrient supply, especially loss of oxygen.
4. Other potential fatigue contributors include:
    - Accumulation of inorganic phosphates
    - Metabolic acidosis due to hydrogen ion accumulation and subsequent pH change that disrupts tissue metabolism
    - Glycogen depletion
    - depletion of ATP
    - Imbalances in K^+
5. Lactic acid accumulation has been quoted as the major cause of muscle fatigue. However recent researches have not proved this factor to contribute to fatigue.

Topic-115 Lever System of the Body

Lever System of the Body

Bones, ligaments, and muscles are the structures that form levers in the body to create human movement.

Muscles operate by applying tension to their points of insertion into bones, and the bones in turn form various types of lever systems.

In simple terms, a joint (where two or more bones join together) forms the axis (or fulcrum), and the muscles crossing the joint apply the force to move a weight or resistance.

Kinesiology

The study of different types of muscles, lever systems, and their movements is called kinesiology and is an important scientific component of human physioanatomy.

Types of Levers in Body

Levers are typically labeled as first class, second class or third class levers depending on:

(1) the point of muscle insertion
(2) its distance from the fulcrum of the lever
(3) the length of the lever arm

All three types are found in the body, but most levers in the human body are third class.

First-Class Lever

A first-class lever has the axis (fulcrum) located between the weight (resistance) and the force.

An example of a first-class lever is a pair of scissors.

First-class levers in the human body are rare. One example is the joint between the head and the first vertebra (the atlanto-occipital joint). The weight (resistance) is the head, the axis is the joint, and the muscular action (force) come from the posterior muscles attaching to the skull.

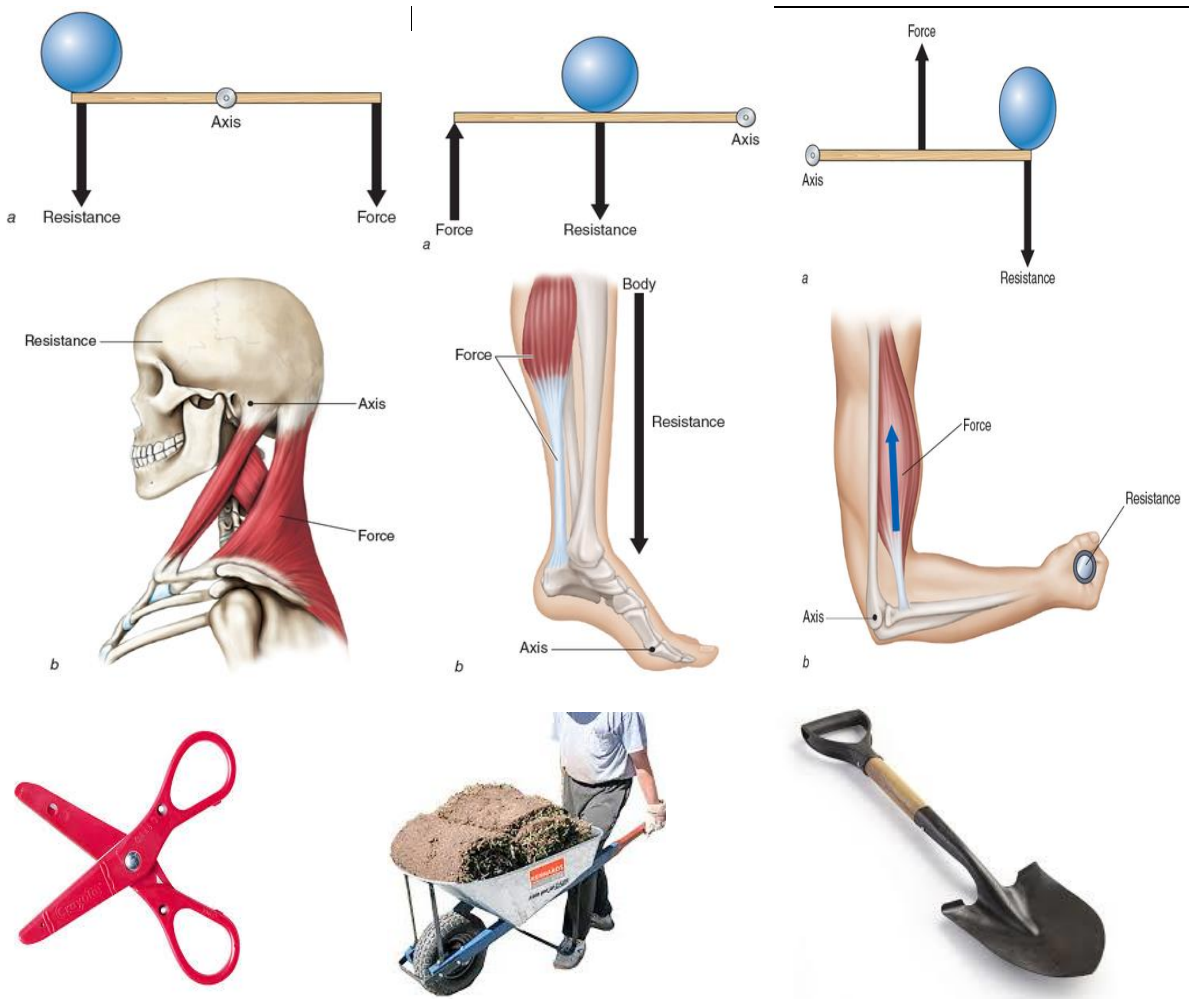
Second-Class Lever

In a second-class lever, the weight (resistance) is located between the axis (fulcrum) and the force.

The most obvious example is a wheelbarrow, where a weight is placed in the bed of the wheelbarrow between the wheel (axis) and the hands of the person using the wheelbarrow (force).

In the human body, an example of a second-class lever is found in the lower leg when someone stands on tiptoes. The axis is formed by the metatarsophalangeal joints, the resistance is the weight

of the body, and the force is applied to the calcaneus bone (heel) by the gastrocnemius and soleus muscles (calf muscles) through the Achilles tendon.



Third-Class Lever

In a third-class lever, the most common in the human body, force is applied between the resistance (weight) and the axis (fulcrum).

Picture someone using a shovel to pick up an object. The axis is the end of the handle where the person grips with one hand. The other hand, placed somewhere along the shaft of the handle, applies force. At the other end of the shovel (the bed), a resistance (weight) is present.

There are numerous third-class levers in the human body. One example can be illustrated in the elbow joint. The joint is the axis (fulcrum). The resistance (weight) is the forearm, wrist, and hand. The force is the biceps muscle when the elbow is flexed.

Topic-116 Cardiac Muscles

Cardiac Muscles

Cardiac muscles are found only in the heart.

These muscles are striated muscles which share many characteristics with skeletal muscle but differ in several important ways.

Features of Cardiac Muscles

- A cardiac muscle cell (myocyte) contains one nucleus, whereas skeletal muscle cells are multinucleate.
- Skeletal muscle fibers are individually innervated by an excitatory motor axon, whereas cardiac muscle fibers are innervated only diffusely by neurons of the sympathetic (excitatory) and parasympathetic (inhibitory) nervous system.
- The cardiac innervation is modulatory only and does not produce discrete postsynaptic potentials. Its actions are to increase or decrease the strength of spontaneous myogenic contractions, which are induced by the electrical activity within the pacemaker region of the heart.
- Cardiac muscle cells are connected electrically by intercalated disks so that an AP initiated in the pacemaker region spreads rapidly from cell to cell, through fast-conducting pathways to all muscle cells within the heart.

Contractile Mechanism of Cardiac Muscles

- The contractile mechanism of vertebrate ventricular muscle fundamentally resembles that of skeletal twitch muscle, however their membrane APs differ.
- In contrast to the very short duration of the AP in skeletal muscle, the AP in cardiac muscle has a plateau phase that is hundreds of milliseconds long.
- The long duration of the cardiac-muscle AP and the associated long refractory period of several hundred milliseconds prevent tetanic contraction and permits the muscle to relax, allowing the ventricle to fill with blood between APs.
- As a result of regularly paced, prolonged APs, the heart contracts and relaxes at a rate suitable for its function as a pump.
- As in skeletal twitch muscle, contraction of cardiac muscle is activated by an increase in the cytosolic Ca^{2+} concentration. The rise in cytosolic Ca^{2+} depends both on influx across the

plasma membrane and release from the sarcoplasmic reticulum. The cells of mammalian cardiac muscle possess an elaborate sarcoplasmic reticulum and system of T tubules.

Topic-117 Smooth Muscles

General Features of Smooth Muscles

- These are the least specialized muscle fibers that have myosin similar to the form found in contractile nonmuscle cells.
- Smooth muscle fibers lack the characteristic striations produced by the organized groups of actin and myosin filaments in sarcomeres.
- Smooth muscle of vertebrates is under autonomic and hormonal control and is not "voluntary".
- Smooth muscle cells contract and relax far more slowly than striated muscle fibers and generally are capable of more sustained contractions.

Types of Smooth Muscles

Vertebrate smooth muscles are categorized into two types:

- single-unit smooth muscles
- multi-unit muscles

Single-Unit Muscles

- Individual muscle cells are small, spindle shaped and mononucleate.
- They are coupled with one another through electrically conducting gap junctions.
- So, if only a few cells are excited and generate contraction, the entire muscle mass contracts as the wave of depolarization is passed from one cell to the other through gap junctions.
- Neurons synapse onto single-unit muscle cells and can modulate the rate and strength of contraction, but neuronal input is not required for contraction.
- Single-unit smooth muscle forms the walls of vertebrate visceral organs e.g., alimentary canal, urinary bladder, ureters, and uterus.

Multi-Unit Muscles

- In multi-unit muscles each cell acts independently and contracts only when it receives synaptic input from neurons.
- The muscles in the iris of the eye that regulate the diameter of the pupil are multi-unit muscles.
- They also found in the walls of blood vessels.

Excitation-Contraction Coupling In Smooth Muscles

- Excitation-contraction coupling in smooth muscle occurs by different mechanisms.

- Smooth muscles have a poorly developed sarcoplasmic reticulum. So the surface membrane of smooth-muscle cells performs calcium-regulating functions similar to those of SR membranes in striated muscles.
- They also lack troponin and tropomyosin.
- Rather, they have an elongated protein called caldesmon, which in the absence of Ca^{2+}, binds to actin thin filaments and restricts myosin-actin interactions, inhibiting muscle contraction.
- During excitation-contraction coupling, Ca^{2+} bind to calmodulin forming a Ca^{2+}/calmodulin complex.
- When this complex binds to caldesmon, inhibition on myosin-actin interactions is removed.

Cardiovascular Physiology

Topic- 118 Excitatory and Conductive System of Heart

Excitatory and Conductive System

The heart has a specialized system for generating rhythmic electrical impulses. It also has the system to conduct these impulses rapidly throughout the heart muscles. These impulses cause and control the contractions of the heart muscles rhythmically.

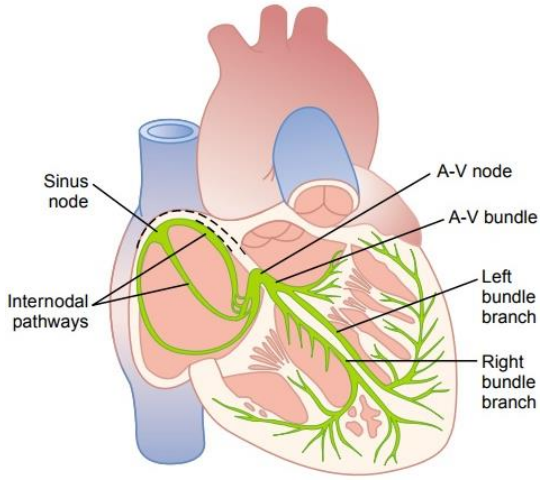
Effects of Rhythmic of Electrical Impulses

The rhythmicity of electrical impulses generated by the heart implies that the contraction of atria occurs about one sixth of a second ahead of contraction of ventricles. This time lapse allows filling of the ventricles before they contract and pump blood into the lungs and peripheral circulation.

Another special importance of this system is that it allows all portions of the ventricles to contract almost simultaneously. This feature is essential for generating effective pumping pressure in the ventricular chambers.

Components of Excitatory and Conductive System

The excitatory system of the heart comprises of the pacemaker region (also called sinoatrial or S-A node), in which the rhythmical impulses are generated.



The conductive system includes:

- The atrial internodal pathways that conduct impulse from the S-A node to the atrioventricular (A-V) node.
- The A-V node, in which the impulse from the atria is delayed before passing into the ventricles.
- The A-V bundle, which conducts the impulse from the atria into the ventricles.
- The left and right bundle branches of A-V bundle.
- Purkinje fibers, which branch off from bundle branches and conduct the cardiac impulse to all parts of the ventricles.

Topic-119 Pacemakers

Pacemaker

The pacemaker is the excitatory region which generates the rhythmical impulses that control the rhythmicity of cardiac chambers.

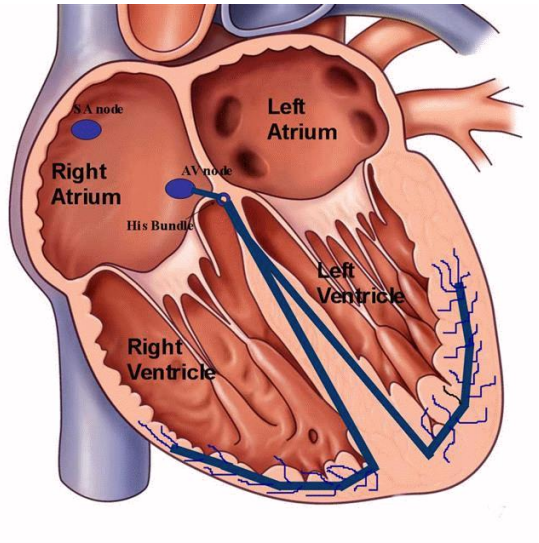
Neurogenic and Myogenic Pacemakers

In many invertebrate hearts, the pacemaker is neurogenic that consists of neurons. These hearts are known as neurogenic hearts.

The pacemaker in some invertebrate and all vertebrate hearts is myogenic i.e. consists of specialized self-excitatory muscle cells. Such hearts are known as myogenic hearts.

Vertebrate Myogenic Pacemaker

The pacemaker is situated in the sinus venosus in those vertebrates which have it as a chamber of heart. In amniotes, it is located in a vestigial remnant of sinus venosus as the sinoatrial node (SA node), situated in the superior posterolateral wall of the right atrium.



Characteristics of Pacemaker

The sinoatrial node consists of small, flattened and weakly contractile specialized muscle cells that are capable of self-excitation.

The S-A node in human heart is about 3 millimeters wide, 15 millimeters long, and 1 millimeter thick.

The fibers of this node are non-muscular and have almost no contractile elements.

These fibers connect directly with the atrial muscle fibers, so that any action potential that begins in the sinus node spreads immediately into the atrial muscle wall.

Topic-120 Autorhythmicity of Pacemaker

Autorhythmicity

Automaticity is the ability of certain cardiac cells to spontaneously and repetitively generate an electrical impulse (depolarization or action potential) without a stimulus from the nervous system.

Cardiac cells normally capable of generating an impulse are the sinoatrial node, cells of the AV node, the bundle of His and Purkinje cells.

Cardiac cells that can generate an impulse to maintain a heart rate are called pacemaker cells.

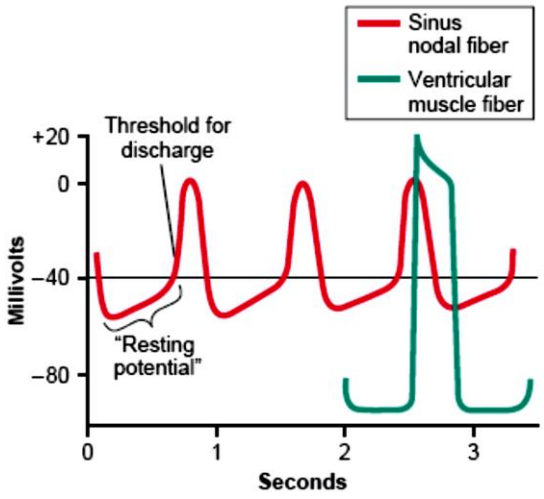
Normally, the rhythmical discharge of sinoatrial node is faster (70 to 80 times per minute) than that of any other part of the heart, so it normally controls the beat of the heart and is virtually always the pacemaker of the normal heart. However, if SA node stops functioning, other autorhythmic components may take control of the rhythmicity of the heart, at a slower rate. Such pacemakers are known as ectopic pacemakers.

The rhythmic discharge rate of A-V nodal fibers is 40 to 60 times per minute, and the Purkinje fibers discharge at a rate between 15 and 40 times per minute.

Pacemaker Potentials and Autorhythmicity

The autorhythmicity of pacemaker is due to an important characteristic of pacemaker cells i.e. the absence of a stable resting potential. The "resting membrane potential" of the sinoatrial nodal fibers is about -55 to -60 millivolts, in comparison with -85 to -90 millivolts for the ventricular muscle fibers.

This is because the cell membranes of the sinoatrial fibers are naturally leaky to sodium and calcium ions.



Consequently, the membranes of cells in pacemaker tissue undergo a steady depolarization, termed as pacemaker potential.

When the pacemaker potential reaches the threshold level, it gives rise to an all-or-none cardiac action potential that spreads to the whole cardiac tissue and cause contraction.

Cardiac Action Potential and Heart Rate

The interval between cardiac APs determines the heart rate. This interval depends on:

- the rate of depolarization of the pacemaker
- the extent of repolarization
- the threshold potential for the cardiac AP.

A faster depolarization brings the membrane to a firing level sooner and thus increases the frequency of firing, leading to a faster heart rate, whereas a slower depolarization does the opposite.

Topic-121 Role of Ion Channels in Self Excitation

Basis of Self-Excitation

The inherent leakiness of the sinoatrial nodal fibers to sodium and calcium ions is the basis of their self-excitation. The leakiness of these fibers is due to the presence of three types of ion channels in their membranes. These channels play important role in causing the self-excitation of these fibers. These channels are:

(1) Fast sodium channels
(2) Slow sodium-calcium channels
(3) Potassium channels

These channels activate and deactivate at a pace that have two important effects:

- They keep the RMP much less negative i.e. only -55 millivolts as compared to -90 millivolts in the ventricular muscle fiber
- The RMP is not stable. It keeps on rising due to continuous influx of sodium and calcium ions.

Role of Fast Sodium Channels

The fast sodium channels open when the membrane potential goes less negative than -55 millivolts.

These channels remain open for only a few milliseconds, as Na^+ immediately move inside the cell because of high sodium ion concentration in the extracellular fluid outside the nodal fibers.

This sodium ion influx prevents developing a more negative RMP found in other cells.

The fast sodium channels become "inactivated" and blocked above -55mV as the inactivation gates on the inside of the cell membrane close these channels.

Role of Slow Sodium-Calcium Channels

At -55 mV and above, the slow sodium-calcium channels start to open.

Thus positive sodium ions tend to leak to the inside and the membrane potential gradually rises, preventing to establish a stable RMP.

As soon as the V_m reaches a threshold voltage of about -40 millivolts, maximum sodium-calcium channels become activated and cause influx of sodium and calcium ions, triggering the action potential.

As the rise in membrane potential is slower in the range of -55 to -40 mV, the atrial nodal action potential is slower to develop than the action potential of the ventricular muscle.

Role of Potassium Channels

After the action potential, the K^+ channels open slowly and cause the return of membrane potential to its negative state.

Topic-122 Transmission of Excitation Over the Heart

Gap Junctions

Electrical activity, initiated in the pacemaker region of the heart, spreads over the entire heart from one cell to another because the cells are electrically coupled via membrane gap junctions.

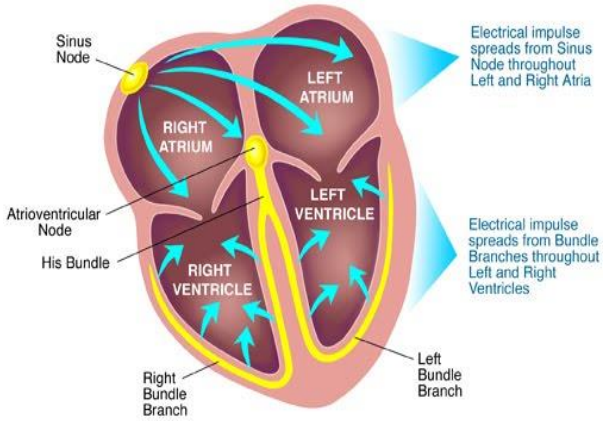
Gap junctions are regions of low resistance between cells and allow current flow from one cell to the next across intercalated disks.

Transmission of Cardiac Impulse Through the Atria

The ends of the sinoatrial nodal fibers connect directly with surrounding atrial muscle fibers.

The wave of excitation spreads from the sinoatrial node over both atria in a concentric fashion.

The velocity of conduction in most atrial muscle fibers is about 0.3 m/sec, but conduction is more rapid, about 1 m/sec, in several small bands of atrial fibers.



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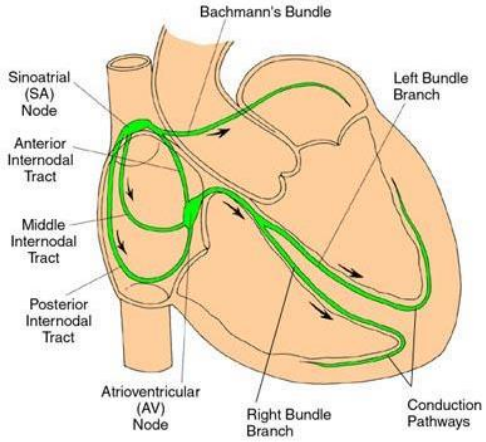

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Internodal Pathways

The excitation spreads from the atrial musculature to the atrioventricular node (A-V node) through small junctional fibers that form internodal pathways.

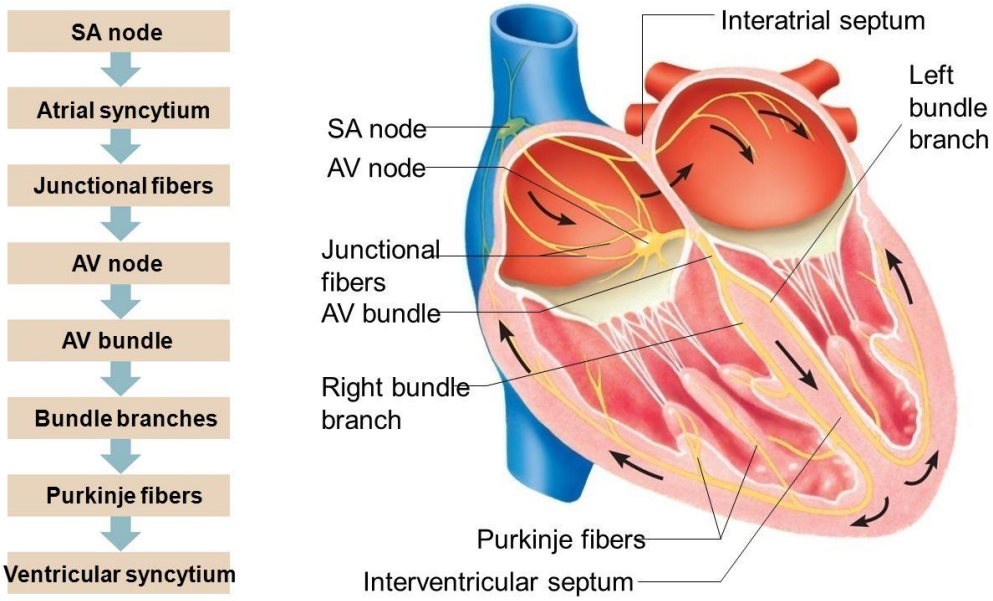
These pathways include:

- The anterior interatrial band that passes through the anterior walls of the atria to the left atrium.
- Three other small bands that curve through the anterior, lateral, and posterior atrial walls and terminate in the A-V node.

Delay in Impulse Conduction

The velocity of wave of excitation in junctional fibers is slow and is about 0.05 m/s.

This slowness causes the delay in cardiac impulse conduction to the ventricles. This delay allows atrial contractions to precede ventricular contractions and also allows time for blood to move from the atria into the ventricles.



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Conduction Through Bundle of His and Purkinje Fibers

The AV nodal fibers are connected via transitional fibers to the bundle of His (atrioventricular bundle).

This structure branches into right and left bundles, which subdivide into Purkinje fibers that extend into the myocardium of the two ventricles.

Conduction is rapid through the bundle of His and Purkinje fibers (4-5 m/s).

The bundle of His and the Purkinje fibers deliver the wave of excitation to all regions of the ventricular myocardium, causing all the ventricular muscle fibers to contract together.

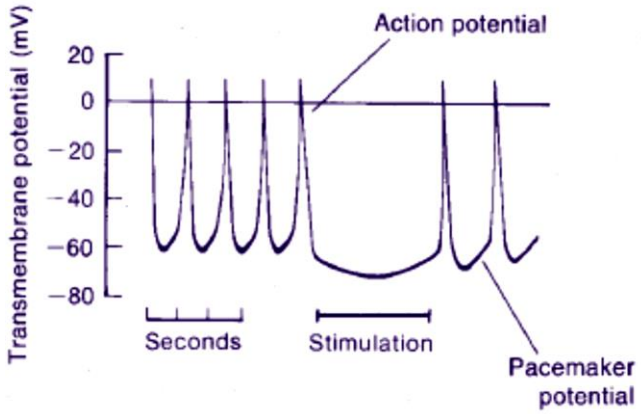
The velocity of transmission through the ventricular muscle mass to the epicardial surfaces is only 0.3 to 0.5 m/sec i.e. one sixth that in the Purkinje fibers.

Topic-123 Effect of Acetylcholine and Catecholamines on Excitation

Effect of Acetylcholine on Pacemaker Potentials

Parasympathetic cholinergic fibers of the vagus nerve (tenth cranial nerve) innervate the S-A and A-V nodes of the heart.

Acetylcholine, released from the terminals of these nerve fibers slows the heart rate by increasing the interval between APs of pacemaker cells.



It increases potassium conductance of the pacemaker cells that keeps the membrane potential near the potassium equilibrium potential for a longer time, thereby slowing the pacemaker depolarization and delaying the onset of the next upstroke.

This decrease in heart rate is referred to as a negative chronotropic effect.

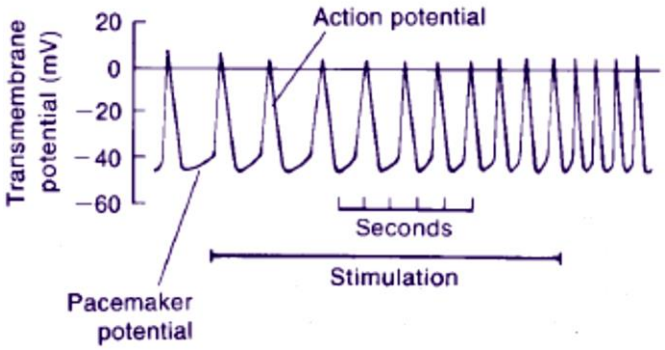
As the heart rate slows, acetylcholine also reduces the velocity of conduction from the atria to the ventricles through the atrioventricular node.

Effect of Catecholamines on Pacemaker Potentials

Norepinephrine is released from adrenergic nerve fibers that innervate the sinoatrial node, atria, atrioventricular node and ventricles.

It has three distinct positive effects on heart function:

- Increased rate of myocardium contraction.
  This happens because Norepinephrine causes increased sodium and calcium conductance, so it accelerates the pacemaker depolarization, increasing the heart rate. This is called as positive



chronotropic effect.

- Increased force of contraction of the myocardium (positive inotropic effect) due to a general effect on all myocardial cells.
- Increased speed of conduction of the wave of excitation over the heart (positive dromotropic effect)

Topic-124 Cardiac Output and Stroke Volume

Cardiac Output

Cardiac output is the quantity of blood pumped into the aorta each minute by the heart. This is also the quantity of blood that flows through the circulation.

The average cardiac output for the resting adult is often stated to be almost exactly 5 L/min.

Factors Affecting Cardiac Output

Cardiac output varies widely with the level of activity of the body.

The following factors directly affect cardiac output:

(1) Basic level of body metabolism
(2) Physical activity of the body
(3) Age
(4) size of the body

Stroke Volume

The volume of blood ejected by each beat of the heart is termed the stroke volume.

Stroke volume is the difference between the volume of the ventricle just before contraction (end-diastolic volume) and the volume of the ventricle at the end of a contraction (end-systolic volume).

Measurement of Stroke Volume

The mean stroke volume can be determined by dividing cardiac output by heart rate.

Changes in stroke volume may result from changes in either end-diastolic or end-systolic volume.

Determining the End-Diastolic Volume

The end-diastolic volume is determined by four parameters:

- Venous filling pressure
- Pressures generated during atrial contraction
- Distensibility of the ventricular wall
- The time available for filling the ventricle

Determining the End-Systolic Volume

The end-systolic volume is determined by two parameters:

- The pressures generated during ventricular systole
- The pressure in the outflow channel from the heart (aortic or pulmonary artery pressure)

Topic-125 Changes in Pressure and Flow During One Beat

Contractions of the heart chambers during each heart beat cause fluctuations in pressure and volume.

These fluctuations are related to the events that occur during a single heartbeat in sequence.

1. During diastole aortic valves are closed. This maintains a large pressure difference between the relaxed ventricles and systemic and pulmonary arteries. Atrioventricular valves remain open, so blood flows directly from the venous system through the atria into the ventricles by venous filling pressure.
2. When atria contract and pressures rise in them, blood is ejected into the ventricles. In the mammalian heart, the volume of blood forced into the ventricle by atrial contraction is about 30% of the total ventricular output. Thus, ventricular filling is largely determined by the venous filling pressure. Atrial contraction simply tops off the nearly full ventricles with blood.
3. As the ventricles begin to contract, pressure rises in them. At this point, the atrioventricular valves close, thus preventing backflow of blood into the atria. As the aortic valves are also closed, so the ventricles form sealed chambers and pressure in them rises due to contracting muscles without a volume change. So, the ventricular contraction is isometric.
4. When the pressure within the ventricles exceeds those in the aorta and pulmonary arteries, the aortic valves open, and blood is ejected into the aorta and pulmonary arteries. This results in a decrease in ventricular volume.
5. As the ventricles begin to relax, intraventricular pressures falls, aortic valves close and atrioventricular valves open. Ventricular filling starts again, and the cycle is repeated.

Topic-126 Work Done by the Heart

Work

In physics, work is the product of force and distance. Therefore, considering a solid object of a given mass, the work done is the force applied to the object multiplied by the distance that the objects moves.

Work Done by the Heart

In the case of heart, the work is to move a volume of fluid i.e. blood.

So, work is defined as the product of the volume of blood and the pressure required to move it.

The heart, working as a pump, continuously increases and decreases the pressure on blood. During diastole, blood flows into the atria and ventricles, and during systole blood is pumped out.

The total mechanical energy involved in this process can be calculated by multiplying the ventricular pressure of the blood with the volume of blood ejected from the ventricle (stroke volume).

In a normal heart, the ventricular pressure is approximated by the mean arterial pressure. So, the work done by the heart during one stroke (SW) is the product of stroke volume (SV) and mean arterial pressure (MAP).

$$SW \cong SV \times MAP$$

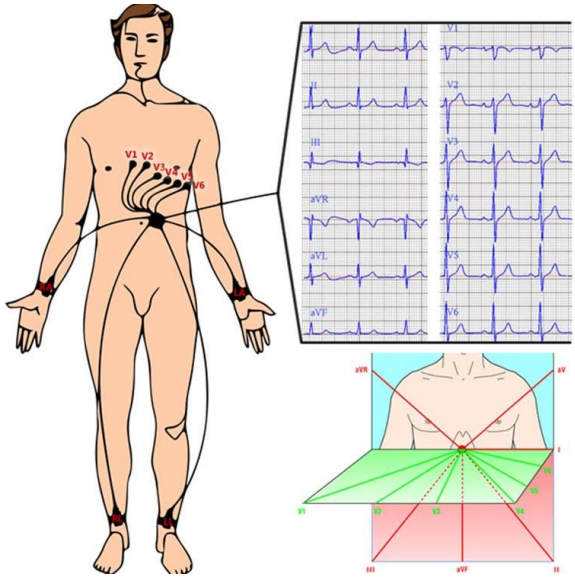
Work Done By the Two Ventricles

The work done differs for the right and left ventricles of a mammalian heart.

The two ventricles eject equal volumes of blood, but the pressures generated in the pulmonary circuit (right ventricle) are much lower. Consequently, the external work done by the right ventricle is much less than that done by the left ventricle.

Topic-127 Electrocardiogram (ECG)

Basis of Electrocardiogram

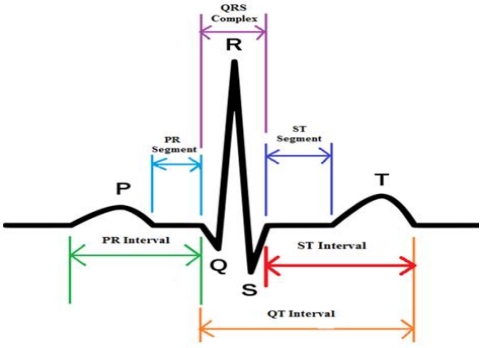


When the cardiac impulses pass through the heart, electrical changes result from depolarization and repolarization of cardiac muscle fibres.

The electrical current spreads from the heart into the adjacent tissues. A small portion of the current also spreads all the way to the surface of the body.

If electrodes of an instrument called the electrocardiograph are placed on the skin on opposite sides of the heart, electrical potentials generated by the current can be recorded. This recording is known as an electrocardiogram (ECG).

An Electrocardiogram



An electrocardiogram reflects both depolarization and repolarization waves.

In a normal electrocardiogram, wave deflections, designated as P wave, a QRS complex, and a T wave are produced as specific events of the cardiac cycle occur.

P Wave

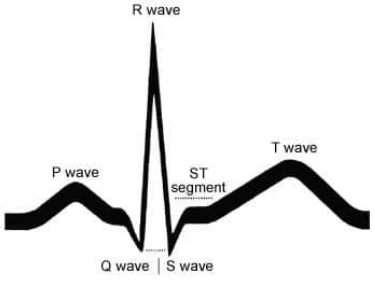
The P wave is caused by electrical potentials generated when the atria depolarize.

It occurs just prior to contraction of the atria.

The ventricles of the heart are in diastole during the expression of the P wave.

The P-R Interval

On the ECG recording, the P-R interval is the period of time from the start of the P wave to the beginning of the QRS complex.



This interval indicates the amount of time required for the SA depolarization to reach the ventricles.

QRS Complex

The QRS complex comprises of three separate waves. This complex begins as a short downward deflection (Q-wave),

continues as a sharp upward spike (R wave), and ends as a downward deflection (S wave).

The QRS complex indicates the depolarization of the ventricles.

During this interval, the ventricles are in systole and blood is being ejected from the heart.

T Wave

The T wave is caused by potentials generated as the ventricles recover from the state of depolarization and repolarize. So, T wave is known as a repolarization wave.

S-T Segment

The time duration known as S-T segment represents the period between the completion of ventricular depolarization and initiation of repolarization.

Uses of Electrocardiogram

Any heart disease that disturbs the electrical activity will produce characteristic changes in one or more of these waves. So understanding the normal wave-deflection patterns is clinically important and is used to diagnose:

- Conduction defects
- Cardiac arrhythmias
- Myocardial hypertrophy
- Ischemia or infarction (decrease in oxygen content)
- Electrolyte imbalance
- Toxicity of certain drugs

Topic-128 Kymography

Kymograph

A kymograph is a device that graphically records changes in the mechanical activities of animal tissues in the physiological experiments.

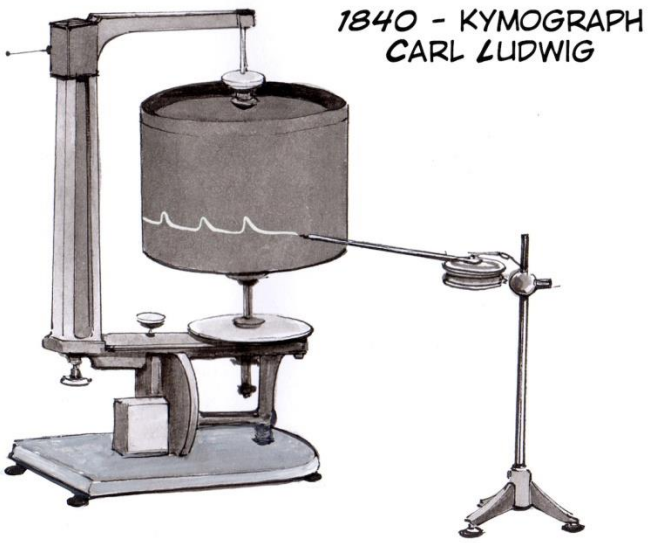
Uses of Kymograph

Since its invention in the 1840s, the kymograph has been used most commonly in the field of medicine to study various physiological and muscular processes.

It has been used to study the skeletal muscle contractions (twitch and tetanus) as well as the cardiac muscle activities (cardiac cycle).

It is also used to measure blood pressure and rate of respiration.

Kymograph Apparatus



A kymograph consists of a drum to which a writing stylus is attached.

The stylus records the changes on a paper wrapped around the drum as the drum revolves.

The term kymograph comes from Latin and translates as "wave writer" referring to the graphical record produced by the instrument, where the stylus traces a pattern of the changes as they occur.

This record provides a representation of changes over time, with time intervals usually marked on the paper.

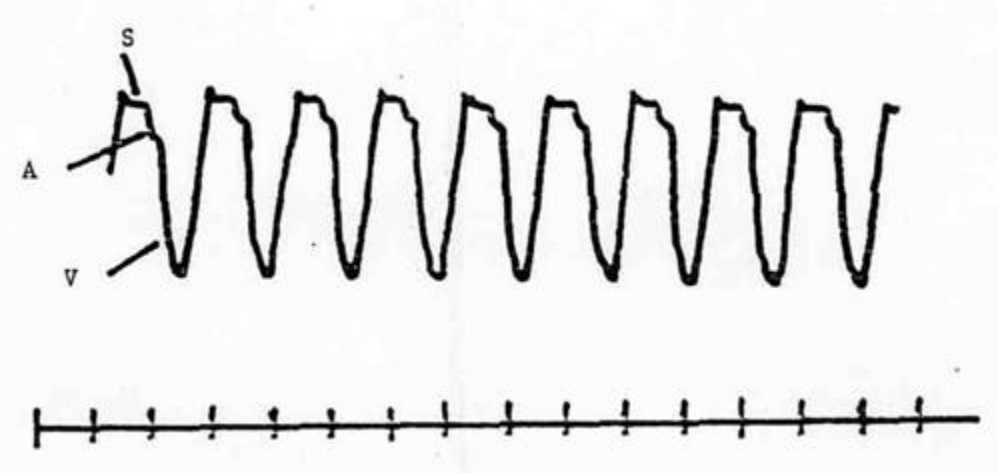
The graphic record generated by the kymograph instrument is commonly translated into a graph, showing changes in pressure or motion on the horizontal x-axis, and time elapsed on the vertical y-axis.

Kymography of Heart of Frog

The frog's heart kymography is generally carried out in physiology labs.

The results provide us understanding of the cardiac cycle of frog giving clues of the site of origin of the heart beat, how it is controlled and how the contractions of the different chambers of the heart are coordinated.

It also helps to study the effects of temperature, various ions, acetylcholine and epinephrine on cardiac output.



A typical kymograph of frog's heart beat showing sinus (s) auricular (a) and ventricular (v) beats. (http://player.slideplayer.com/15/4693551/data/images/img4.jpg)

Topic-129 Introduction to Hemodynamics

Hemodynamics

Hemodynamics is the study of physical laws that explain the relationship between pressure and flow of blood through blood vessels of the circulatory system.

Principles of Hemodynamics

1. Blood Returned = Blood Pumped

In vertebrates and other animals with a closed circulation, the blood flows in a continuous circuit. Since blood is an incompressible fluid, the volume of blood returning to the heart each minute must be equal to the cardiac output i.e. volume pumped out each minute.

2. Velocity of Flow

The velocity of flow at any point is inversely related to the total cross-sectional area of the blood vessel.

This is mathematically expressed as:

$$V = Q/A$$

where

V = velocity (cm/s)

Q = blood flow (ml/s)

A = cross sectional area (cm^2)

The highest velocities of blood flow occur where the total cross-sectional area is smallest and the lowest velocities occur where the cross-sectional area is largest.

The arteries have the smallest total cross-sectional area, whereas the capillaries have the largest. Thus, the highest velocities occur in the aorta and pulmonary artery in mammals; then velocity falls markedly as blood flows through the capillaries, but it rises again as blood flows through the veins.

The slow flow of blood in capillaries is of functional significance, because it is in capillaries that the time-consuming exchange of substances between blood and tissues takes place.

3. Vascular Resistance

Vascular resistance is the resistance of blood vessels to flow of blood.

It is related to vessel radius, vessel length, and blood viscosity.

VR must be overcome to push blood through the circulatory system and create flow.

Vascular resistance is used in calculations of blood pressure, blood flow, and cardiac function. Vasoconstriction and greater viscosity increases VR, whereas vasodilation and lower viscosity decreases VR.

4. Blood Pressure

The blood pressure in circulatory system is principally due to the pumping action of the heart.

As the pumping action of the heart is pulsatile, systemic arterial blood pressure varies between a maximum (systolic) and a minimum (diastolic) pressure during each heartbeat.

Topic-130 Laminar and Turbulent Flow

Blood flow is affected by the smoothness of the vessels, resulting in either turbulent or laminar (smooth) flow.

Laminar Flow in Smaller Vessels

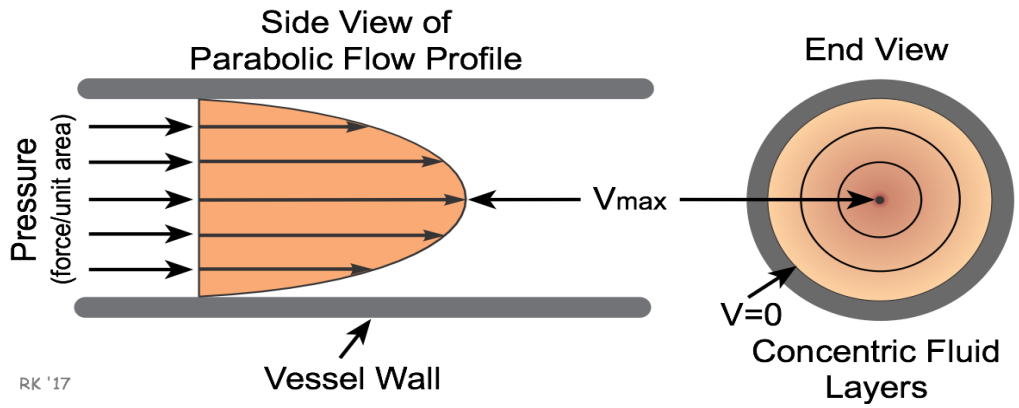
In smaller vessels of the circulation, blood flow is streamlined and continuous.

Such laminar flow is characterized by a parabolic velocity profile across the vessel.

Blood flows in layers at different velocities.

Flow is zero at the wall and maximal at the center along the axis of the vessel.

A pressure difference supplies the force required to slide adjacent layers past each other.



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Laminar Flow in Larger Vessels

The large arteries have pulsatile laminar flow.

It has a more complex velocity profile than the continuous laminar flow characteristic of smaller vessels.

In large arteries, blood is first accelerated and then slowed with each heartbeat.

Since the vessel walls are elastic, they expand and then relax as pressure oscillates with each heartbeat.

Close to the heart, the direction of flow reverses each time the aortic valves shut.

The end result is that the velocity across large arteries has a much flatter profile than the velocity across more peripheral blood vessels and the direction of flow oscillates.

Turbulent Flow

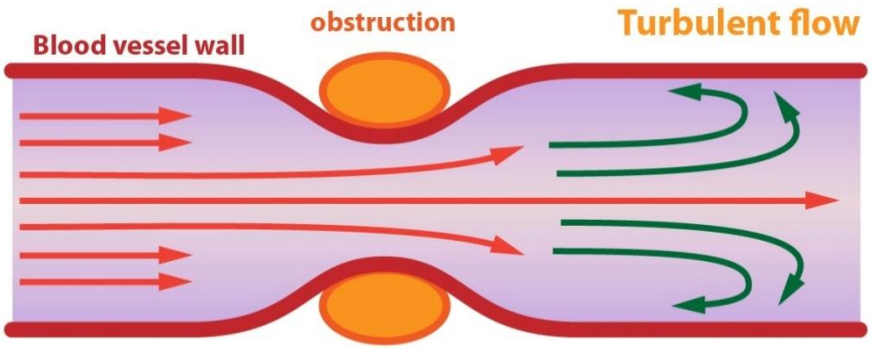
In turbulent flow fluid moves in directions not aligned with the axis of the flow.

Turbulent flow is uncommon in the peripheral, undivided vessels with smooth walls. However, it occurs in some situations e.g. during very high blood velocities associated with strenuous exercise.

The highest turbulence is observed in the proximal portions of aorta and pulmonary artery at the time of ventricular contraction and during backflow of blood when the aortic and pulmonary valves close.

Turbulence in blood vessels may also happens if smoothness is reduced by any obstruction in the blood vessels e.g. buildup of fatty deposits on the arterial walls.

Turbulence requires higher energy to move blood through a vessel.



Topic-131 Relationship Between Pressure and Flow

Blood flow occurs because of a difference in pressure between two sites.

Difference in pressure between two points in a flow path establishes a pressure gradient and therefore the direction of flow is determined from high to low pressure.

When the heart contracts, pressure in the ventricles increases. This pressure is used to overcome the resistance to flow through the vessels.

Role of kinetic energy

Energy is expended in setting the blood into motion. As the blood is ejected into the aorta, pressure is converted into kinetic energy. So, the flow of blood depends on both pressure and kinetic energy.

Kinetic energy is highest in the aorta. In the capillaries the kinetic energy is negligible, so the velocity of flow in capillaries is very low (about 1 mm/s).

Poiseuille's law

The relationship between pressure and continuous laminar flow of fluid in a rigid tube is described by Poiseuille's law.

It states that the flow rate of a fluid, Q, is directly proportional to:

- the pressure difference ($P_1 – P_2$) along the length of the tube
- the fourth power of the radius of the tube (r^4)

and inversely proportional to:

- the tube length (L)
- fluid viscosity (η)

$$\dot{Q} = \frac{(P_1 - P_2)\pi r^4}{8L\eta}$$

As Q is proportional to r^4, very small changes in r will have a profound effect on Q.

A doubling of vessel diameter, for instance, will lead to a 16-fold increase in flow if the pressure difference (P_1 - P_2) along the vessel remains unchanged.

Application of Poiseuille's equation on Blood Flow

Although Poiseuille's equation applies to steady flows in straight rigid tubes, it has been used, with some limitations, to analyze the relationship between pressure and flow in small arteries (arterioles), capillaries, and veins, even though these are not "rigid" tubes.

Blood pressure and flow are pulsatile, and the blood vessel walls are not rigid, the oscillations in the pressure and flow of blood are not in phase. So, the relationship between the two is not accurately described by Poiseuille's law. The extent of the deviation of the relationship between pressure and flow from that predicted by Poiseuille's law is indicated by the value of a nondimensional constant α:

$$\alpha = r\frac{\sqrt{2\pi nf\rho}}{\eta}$$

In this equation:

- ρ = density of blood
- η = viscosity of blood
- f = frequency of oscillation
- n = order of the harmonic component
- r is the radius of the vessel

Topic-132 Vascular Resistance to Flow

Vascular resistance is the resistance that must be overcome to push blood through the circulatory system and create flow.

The resistance offered by the systemic circulation is known as the systemic vascular resistance (SVR) while the resistance offered by the pulmonary circulation is known as the pulmonary vascular resistance (PVR).

Systemic vascular resistance is used in calculations of blood pressure, blood flow, and cardiac function.

Factors affecting Resistance

Vascular resisance is determined mainly by the muscle tone in the smooth muscle tissue of the tunica media and the elasticity of the elastic fibers there.

Vasoconstriction (i.e., decrease in blood vessel diameter) increases SVR, whereas vasodilation (increase in diameter) decreases SVR.

Calculation of vascular Resistance

Vascular resistance is calculated by a modified form of the Poiseuille equation:

$$R = 8L\eta / \pi r^4$$

Where

R = resistance to blood flow

L = length of the vessel

η = viscosity of blood

r = radius of the blood vessel

From this equation, it is evident that the resistance to flow is inversely proportional to the fourth power of the radius of the vessel. Due to this factor, the resistance to blood flow is minimal in larger blood vessels, but maximum in narrow capillaries.

Topic-133 Viscosity of Blood

Viscosity of Blood

- Plasma has a viscosity of about 1.8 relative to water.
- Viscosity increases with the addition of blood cells.
- Relative viscosity of mammalian and bird blood at 37°C is between 3 and 4. Thus, blood is three or four times more viscous than water.

Effects of Blood Viscosity on Flow

- According to Poiseuille's law, the flow of blood is inversely related to its viscosity.
- Due to high viscosity, larger pressure gradients are required to maintain flow of blood through vascular system.

Blood Viscosity and Flow in Arterioles

Blood flowing through small vessels (arterioles) behaves as if its relative viscosity is much reduced.

In vessels less than 0.3 mm in diameter, the apparent relative viscosity of blood approaches the viscosity of plasma i.e. 1.8 only.

It happens due to plasma skimming i.e. RBCs accumulate in the center of blood vessel during flow and the walls remain relatively free of cells. This causes difference in viscosity between the center and the walls and results in increase in velocity of blood flow.

This phenomenon is called the Fahraeus-Lindqvist effect.

It reduces the energy required to drive blood through microcirculation.

Blood Viscosity and Flow in Capillaries

In very small vessels (diameters 5 to 7 μm) Fahraeus-Lindqvist effect is inverted i.e. apparent viscosity of blood increases. In these vessels, red blood cells move in a queue, pressing against the walls. So blood flow is slowest in capillaries.

Topic-134 Compliance in Circulatory System

Compliance

- Blood vessels contain elastic fibers that enable them to distend. As the pressure in a vessel increases, its walls are stretched and the volume of the vessel increases.
- The ratio of change in volume to change in pressure is termed as compliance of the system.
- The compliance of a system is related to its size and elasticity of its walls.
- The greater the initial volume and elasticity of the walls, the greater is the compliance of a system.

Compliance in Venous System

- Venous system is very compliant because a small change in pressure produces large change in volume. Similarly large changes in volume have little effect on venous pressure.
- Due to greater compliance, venous system acts as a volume reservoir without causing a significant change in blood pressure.

Compliance in Arterial System

- Arterial system is less compliant than the venous system. It acts as a pressure reservoir in order to maintain capillary blood flow.
- Some portions of arterial system are more elastic e.g. near the heart. They help to reduce the oscillations in pressure generated by contractions of the heart and to maintain flow in distal arteries during diastole.

Topic-135 Peripheral Circulation

Vascular Pathways

Cardiovascular system includes two pathways of blood circulation:

- Pulmonary circuit that circulates blood through lungs
- Systemic or peripheral circuit

Peripheral Circulation

The pathway followed by blood pumped from the left ventricle of the mammalian heart till its return to the right atrium is known as peripheral or systemic circulation.

Pathway of Peripheral Circulation

- The oxygenated blood is pumped by the left ventricle into the aorta which is the largest artery in the peripheral circulation.
- Branches from aorta form the arterial system and supply blood to the organs and major body regions.
- Arteries branch to form capillary beds in the tissues where oxygen is exchanged for carbon dioxide.
- The deoxygenated blood returns through the venous system to the superior and inferior vena cavae which open into the right atrium.

Blood Vessels

Three types of blood vessels carry blood during circulation:

- Arteries which carry blood away from the heart to organs and tissues.
- Veins which return blood to the heart.
- Capillaries which have thin walls formed of only a single layer of endothelial cells and permit exchange of materials between blood and tissues.

Topic-136 Blood Pressure

Contraction of the ventricle of heart generates blood pressure. This pressure causes the blood to flow in the arteries away from the heart from higher pressure to lower pressure areas.

Changes in Blood Pressure during Circulation

The pressure is highest in the aorta and decreases during circulation through tiny arterioles and capillaries which offer substantial resistance to flow due to narrow diameters. Blood pressure is almost nonexistent in the venous system.

Changes in Blood Pressure With Cardiac Cycle

Arterial blood pressure is highest during ventricular systole. The pressure at this time is called systolic pressure.

This pressure causes the arteries to stretch.

During diastole, when the ventricles are relaxed, pressure drops. However, a lower pressure (diastolic pressure) is maintained in the arteries due to contraction of elastic walls of arteries.

Regulation of Blood Pressure

Blood pressure fluctuates with vasoconstriction and vasodilation due to contraction or relaxation of smooth muscles in arteriole walls.

Vasoconstriction narrows the arterioles and increases the blood pressure while vasodilation causes an increase in diameter of arterioles that causes blood pressure to fall.

Contraction of smooth muscles of arteriole walls is regulated through chemical, nervous and hormonal controls. These controls are also affected by physical or emotional states e.g. exercise and stress

Chemical Control of Blood Pressure

- Hormones that affect body state during stress also act to cause vasodilation or vasoconstriction and, thereby, regulate blood pressure. These hormones include cortisol, epinephrine and norepinephrine.
- The renin-angiotensin-aldosterone system of the kidneys that regulates blood volume also regulates blood pressure.
- Nitric oxide (NO) serves as a major inducer of vasodilation in the cardiovascular system.
- A peptide, endothelin is a potent inducer of vasoconstriction.

Topic-137 Effect of Gravity on Pressure and Flow

Effect of Gravity on Arterial blood Pressure

Gravity affects the column of blood in larger arteries. So pressure in limbs and head region varies in different positions of the body.

In lying down position, the heart is at the same level as the limbs and head with respect to gravity. So, blood pressure in the arteries of head and limbs is equal.

In a standing position, the relationship between the head, heart, and limbs changes with respect to gravity.

In this position heart is below the head and about a meter above the lower limbs. So, the arterial pressure in lower limbs increases while in the head region, it decreases.

Effect of Gravity on Venous Flow

Because the vascular system is elastic, an increase in absolute pressure expands blood vessels, particularly the veins which are more compliant.

Thus, pooling of blood tends to occur in veins, in different regions of the body.

Pooling of blood causes difficulty in maintaining capillary flow in those regions that may have severe physiological consequences e.g. change in kidney filtration rates.

Such problems are particularly acute in species with long necks and limbs e.g. giraffe, camels and dinosaurs.

Regulation of Blood Pressure in Distant Body Regions

The pressure generated by heart is regulated with position of the neck.

When the neck is raised, heart pumps blood at much higher pressure through aorta (195-300 mm Hg) to maintain arterial pressure in the brain at around 98 mm Hg.

When the neck is lowered to the ground, aortic pressure is reduced to maintain a relatively constant blood flow to the brain.

This wide variation in aortic pressure as the giraffe moves its head position can lead to extensive pooling of blood (head raised) or decreased flow (head lowered) in arterioles of regions between head and chest.

In these regions, pooling is prevented by vasoconstriction of peripheral vessels when the head is raised. When the head is lowered, extensive vasodilation of arterioles leading to capillary beds maintains flow despite the lower aortic pressure.

Arterial pressures in the legs of giraffe become higher than aortic pressures due to gravity and cause pooling.

To deal with pooling of blood, the giraffe has large quantities of connective tissue surrounding the limb vessels.

Topic-138 Counter Current Exchangers

Counter Current Exchangers

- Circulatory system controls heat flow between the interior and exterior of the body through special arrangements of blood vessels.
- In these special arrays of blood vessels, arterial and venous blood flows in opposite direction in close proximity.
- Such systems are known as counter current exchangers.

Significance

Counter current exchange systems are adaptive features that play a significant role in thermoregulation.

These help to exchange heat between the bloods flowing in arteries and veins and regulate the rate of heat loss via the limbs.

Additionally, they serve to exchange gases and ions between arterial and venous systems.

Principle of Counter Current Exchangers

They work by:

- Regulating the extent of blood flow near the body surface
- Trapping heat within the body core.

Presence of Exchangers

Countercurrent exchangers are formed in specific parts of an animal due to an arrangement of small arteries and veins in which blood flows in opposite directions.

They are common in the limbs of birds and mammals. In fishes they are extensively distributed in body.

In humans, this type of countercurrent exchanger is found only in the kidney.

Rete Mirabile

A countercurrent network arrangement of arterial and venous capillaries is referred to as a rete mirabile.

Before entering a tissue, an artery divides into a large number of small capillaries that parallel a series of venous capillaries leaving the tissue.

The arterial capillaries are surrounded by venous capillaries.

This arrangement forms an extensive exchange surface between inflowing and outflowing blood.

Examples

Tuna (fish) have a large number of rete mirabile, which are used to regulate the temperature of the brain, muscles, and eyes.

The rete mirabile leading to the swimbladder of some fish (e.g. eels) function as a carbon dioxide countercurrent exchanger.

Topic-139 Capillaries and Microcirculation

Capillaries

- Capillaries are microscopic vessels about 1 mm long and 3 - 10 μm in diameter.
- They have very thin, porous walls which are completely devoid of connective tissue and smooth muscle.
- They consist of a single layer of endothelial cells surrounded by a basement membrane of collagen and mucopolysaccharides.

Capillary Beds

- In the tissues, small terminal arteries subdivide to form arterioles, which in turn subdivide to form metarterioles which subsequently form capillaries.
- Networks of these capillaries are called capillary beds or microcirculatory beds.
- The microcirculatory beds infiltrate each tissue such that any tissue cell is not more than three or four cells away from a capillary.

Material Transfer across Capillary Walls

- The endothelium composing the capillary wall is highly permeable.
- It allows substances to move with relative ease in and out of capillaries.
- Due to this, exchange of chemicals, nutrients, waste products and gases between the blood and tissue cells occurs across the walls of capillaries by diffusion.

Permeability of Capillaries

The capillaries in various tissues differ considerably in permeability.

These permeability differences are associated with the structure of endothelium.

Types of Capillaries

Based on their wall structure, capillaries are classified into three types

Continuous capillaries: They are least permeable and have a continuous basement membrane. Their endothelium is about 0.2-0.4 μm thick. They are located in muscle, nervous tissue, lungs, connective tissue and exocrine glands.

Fenestrated capillaries: They are perforated by pores in some regions and exhibit intermediate permeability. They are found in the renal glomerulus, intestines and endocrine glands.

Sinusoidal capillaries: They are the most permeable as they have large paracellular gaps that extend through the basement membrane. They are present in the liver, bone marrow, spleen, lymph nodes and adrenal cortex.

Topic-140 Capillary Pressure and Flow

Precapillary Sphincter

The arterioles have smooth muscle that becomes discontinuous in the metarterioles and ends in a smooth muscle ring, the precapillary sphincter.

Control of Circulation in Capillary Beds

The innervated smooth muscle of the arterioles and the precapillary sphincter control blood distribution to each capillary bed and thus alter the blood distribution within the tissue.

Capillaries Open to Flow

Different tissues have varying numbers of capillaries open to flow. Most issues have about 30%-50% capillaries that are open at a time.

In many tissues, most of the capillaries tend to be open (e.g., in the brain) while in many other tissues e.g., in the skin, they remain closed for considerable periods.

Pressure and Flow in Capillary Beds

All capillaries in a network are only a short distance from an arteriole.

So, the pressure and flow are fairly uniform throughout the capillary bed.

Transmural pressures in capillaries are about 10 mm Hg.

Higher pressures inside a capillary result in the filtration of fluid from blood into the interstitial space.

In most tissues, there is only a small net movement of fluid across capillary walls and tissue volume remains constant

Rise in Capillary Pressure

A rise in capillary pressure, owing to a rise in either arterial or venous pressure, will result in increased loss of fluid from the blood, thus causing tissue edema.

In general, arterial pressure remains fairly constant to prevent large oscillations in tissue volume.

High Capillary Pressure in Kidneys

In the kidney, capillary pressure is high. It is called filtration pressure that helps formation of an ultrafiltrate in the kidney tubule that eventually forms urine. The kidney is encapsulated to prevent swelling of the tissue in the face of ultrafiltration.

Topic-141 Regulatory Controls of Circulation

Requirement of Circulatory Regulation

Regulation of circulation is necessary to:

- Assure adequate supply of blood to the vital organs: brain and heart
- Supply adequate blood to other organs of the body according to their activity level
- Control capillary pressure to maintain tissue volume and maintain composition of interstitial fluid within reasonable ranges

Regulatory Mechanisms

The regulatory mechanisms focus on controlling cardiac output and blood pressure.

They include:

- Autoregulation
- Neural Mechanisms
- Endocrine Mechanisms

Autoregulation

- Autoregulation causes immediate, localized homeostatic adjustments.
- Chemical factors in interstitial fluids change the pattern of blood flow locally at the tissue level within capillary beds.
- These factors include local vasodilators and vasoconstrictors that act on precapillary sphincters causing them to open and close.
- Local vasodilators include:
  - Decreased tissue oxygen levels or increased CO_2 levels.
  - Lactic acid or other acids generated by tissue cells.
  - Nitric oxide (NO) released from endothelial cells.
  - Rising concentrations of potassium ions or hydrogen ions in the interstitial fluid.
  - Elevated local temperature.
- Local vasoconstrictors include:
  - Prostaglandins and thromboxanes released by activated platelets and white blood cells
  - Endothelins released by damaged endothelial cells.
- If autoregulation fails to normalize conditions at the tissue level, neural mechanisms and endocrine factors are activated.

Neural Mechanisms

Neural mechanisms respond to changes in arterial pressure or blood gas levels sensed at specific sites.

When those changes occur, the cardiovascular centers in the medulla oblongata and pons adjust cardiac output and peripheral resistance to maintain blood pressure and ensure adequate blood flow.

Endocrine Mechanisms

The endocrine system releases hormones that enhance short-term adjustments and that direct long-term changes in cardiovascular performance.

Topic-142 Central Control of Cardiovascular System

Cardiovascular Center

The sensory inputs of cardiovascular system are integrated in the cardiovascular center of the brain.

This center is located in the medulla oblongata and pons.

It induces reflex effects to maintain an adequate arterial pressure.

Sensory Receptors of Cardiovascular System

The body employs a variety of sensory receptors for monitoring the status of cardiovascular system.

(1) Baroreceptors: monitor blood pressure at various sites in the cardiovascular system
(2) Chemoreceptors: monitor CO_2, O_2, and pH of the blood.
(3) Cardiac mechanoreceptors
(4) Thermoreceptors

Sensory input from these receptors is transmitted to the medullary cardiovascular center.

The medullary cardiovascular center also receives inputs from:

- Medullary respiratory center
- Hypothalamus
- Amygdala nucleus
- Cortex

Role of Cardiovascular Center

- The output from the medullary cardiovascular center is fed to sympathetic and parasympathetic autonomic motor neurons.
- These neurons innervate the heart and smooth muscles of arterioles and veins. They also link to the other areas of brain e.g. medullary respiratory center.

Sympathetic Control

Stimulation of sympathetic nerves increases the rate and force of contraction of the heart and causes vasoconstriction.

It results in a marked increase in arterial blood pressure and cardiac output.

Parasympathetic Control

Stimulation of parasympathetic nerves causes reverse effects.

It results in a drop in arterial blood pressure and cardiac output.

Topic-143 Arterial Baroreceptors

Baroreceptors

The baroreceptor system is a simple and rapidly acting control mechanism that contributes to the regulation of arterial blood pressure.

Baroreceptors in Vertebrates

Baroreceptors are widely distributed in the arterial system of vertebrates.

- The central cardiovascular system of amphibia, reptiles and mammals has unmyelinated baroreceptors.
- These unmyelinated baroreceptors only respond to pressures above normal, initiating reflexes that reduce arterial blood pressure and thus protect the animal from damaging increases in blood pressure.
- Mammals also have myelinated baroreceptors which respond to blood pressures below normal, thus protecting the animal from prolonged periods of reduced blood pressure.
- The myelinated baroreceptors are present in the mammalian carotid sinus, aortic arch, subclavian artery, pulmonary arteries and the wall of right atrium.
- Aortic baroreceptors monitor blood pressure within the ascending aorta. Any changes trigger the aortic reflex, which adjusts blood pressure in the systemic circuit.
- Carotid sinus baroreceptors are extremely sensitive and trigger reflexes that maintain adequate blood flow to the brain.

Working Mechanism of Baroreceptors

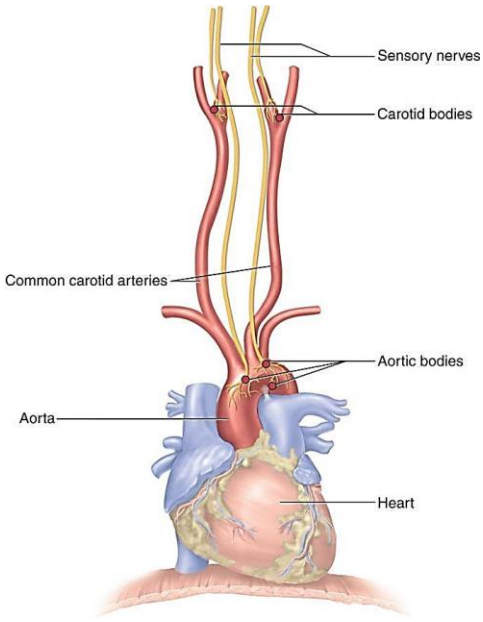
Baroreceptors are stimulated by stretch of the arterial wall.

When the arterial pressure rises too high, the baroreceptors send nerve impulses to the medulla of the brain which produces two major effects that lead to a decline in blood pressure to normal levels:

(1) A decrease in cardiac output, due to parasympathetic stimulation and the inhibition of sympathetic activity. This happens due to the release of acetylcholine at the sinoatrial node.
(2) Widespread peripheral vasodilation, due to the inhibition of excitatory neurons in the cardiovascular center.

Topic-144 Arterial Chemoreceptors

Arterial Chemoreceptors



Arterial chemoreceptors are located in the carotid and aortic bodies.

They are primarily important in regulating ventilation, but they are important in the function of cardiovascular system which requires close relationship with the respiratory system.

Chemoreceptors in the cardiovascular system monitor chemical characteristics of the blood to help regulate function of both cardiovascular and respiratory systems

These chemoreceptors respond to an increase in CO_2 or to decrease in O_2 and pH of the blood.

Arterial Chemoreceptors: Effects

Chemoreceptor stimulation has a direct effect on heart rate and breathing rate.

They enhance both heart rate and breathing rate if levels of carbon dioxide are high. This helps to eliminate CO_2 from the blood.

They slow down the heart rate, if the animal is not breathing (e.g. during dive).

They also cause peripheral vasoconstriction while the cardiac output is reduced.

It increases arterial blood pressure.

It also ensures maintenance of blood pressure in arteries leading to the brain, ensuring blood flow to brain.

Topic-145 Cardiac Receptors

Cardiac Receptors

- The information about the state of the heart is collected by mechanoreceptive and chemoreceptive afferent nerve endings which innervate the atria and ventricles of heart.
- They transmit signals via the spinal cord to the medullary cardiovascular center and other regions of the brain.
- In addition, stimulation of some cardiac receptors causes hormone release either directly from the atria or from other endocrine tissues within the body.
- These hormones regulate heart rate and blood pressure.

Atrial Receptors

The atrial walls contain many mechanoreceptive afferent fibers. These include:

- Myelinated A-type afferent fibers
- Myelinated B-type afferent fibers
- Unmyelinated C-type afferent fibers
- Stretch-sensitive secretory cells

Myelinated A-type Afferent Fibers

Myelinated A-type afferent fibers respond to changes in heart rate

Myelinated B-type Afferent Fibers

- Myelinated B-type afferent fibers respond to increases in the rate of filling and volume of the atria.
- The central cardiovascular centers, in return, generate two major effects:
  (i) increased heart rate
  (ii) increase in urine excretion (diuresis) mediated by a decrease in antidiuretic hormone (ADH) levels in the blood.

Unmyelinated C-type Afferent Fibers

- Unmyelinated C-type afferent fibers innervate the junction of the veins and atria.
- Their stimulation affects both heart rate and blood pressure.
- If heart rate is low, distension of this region results in an increase in heart rate.
- If heart rate is high, stimulation results in a fall in heart rate and blood pressure.

Stretch-sensitive Secretory Cells

The stretch-sensitive secretory cells produce atrial natriuretic peptide (ANP).

This hormone causes an increase in urine production and sodium excretion, thereby effectively reducing blood volume and therefore blood pressure.

Mode of Action of ANP

- ANP inhibits release of renin by the kidney and production of aldosterone by the adrenal cortex.
- It thus diminishes the renin-angiotensin-aldosterone system, which stimulates sodium resorption and an increase in blood volume
- ANP also inhibits release of ADH and acts directly on the kidney to increase water and sodium excretion.

Ventricular Receptors

- The endings of both myelinated and unmyelinated sensory afferent fibers are also embedded in the ventricle.
- They are stimulated by interruption of coronary blood flow.
- At low stimulation levels, these fibers cause increased sympathetic outflow and decreased vagal outflow to the heart, raising cardiac contractility as well as blood pressure.
- At higher stimulation levels, these fibers are necessary for the perception of pain in the heart.

Topic-146 Nervous Control of Microcirculation

Role of Nervous System in Maintaining Blood Pressure

Nervous control serves to maintain arterial pressure by:

- Adjusting resistance to blood flow in the peripheral circulation.
- controlling the number of capillaries open at any moment

The nervous control of capillary flow ensures that if arterial pressure falls, blood flow to the gut, liver, and muscles is reduced to maintain flow to the brain and heart.

Nervous Innervations of Arterioles

- Most arterioles are innervated by sympathetic nerves, which release norepinephrine at their endings.
- Some arterioles are innervated by parasympathetic nerves, which release acetylcholine at their endings.

Sympathetic Nerve Stimulation

- Stimulation of sympathetic nerves causes release of norepinephrine.
- Binding of the norepinephrine to α-adrenoreceptors in the smooth muscle of arterioles causes vasoconstriction and therefore a decrease in diameter of the arterioles.
- This decrease in diameter causes an increase in resistance to flow, thus reducing blood flow through that capillary bed.

Microcirculation of Heart

- The action of norepinephrine is extensively modulated by neuropeptide Y in the microcirculation of heart.
- The atrial and ventricular myocardium and the coronary arteries are surrounded by nerve fibers that contain neuropeptide Y.
- Neuropeptide Y decreases coronary blood flow and the contraction of cardiac muscle.

Parasympathetic Stimulation

Arterioles of the brain and lungs are innervated by parasympathetic nerves.

These nerves contain cholinergic fibers, which release acetylcholine from their nerve endings.

In mammals, parasympathetic nerve stimulation causes vasodilation in arterioles.

Topic-147 Local Control of Microcirculation

Many compounds influence capillary blood flow locally within a tissue.

These can be grouped into three categories:

- Endothelium-produced compounds
- Inflammatory mediators
- Metabolites and other secretions

Endothelium-produced Compounds

The vascular endothelium releases nitric oxide, endothelin, and prostacyclin that affect vascular smooth muscle and, therefore, capillary blood flow.

- Nitric oxide is produced and released continuously by the vascular endothelium. It causes relaxation of vascular smooth muscle and acts as vasodilator.
- Endothelins are proteins that cause vasoconstriction.
- Prostacyclin causes vasodilation and acts as an anticoagulant.

Inflammatory Mediators

- Thromboxane A, formed in the plasma by platelets causes vasoconstriction.
- Histamine released from connective tissue and white blood cells in injured tissues in mammals causes a marked vasodilation of vessels
- Plasma kinins (e.g. bradykinin) are another group of potent vasodilators in damaged tissues.

Metabolites and other Secretions

- Norepinephrine released from sympathetic nerves acts as vasoconstrictor.
- Angiotensin II formed primarily in the lungs and circulates in the blood acts as vasoconstrictor.
- Serotonin acts as a vasoconstrictor or vasodilator, depending on the vascular bed and concentration. It is found in high concentration in the gut and blood platelets.

Respiratory Physiology

Topic-148 Respiration: General Considerations

Gas Exchange

Animals take in oxygen from the environment and give off CO_2. This exchange of oxygen and carbon dioxide with the environment is called gas exchange or external respiration or breathing.

Oxygen is used for cellular respiration. Carbon dioxide is generated as waste during this process. Removal of CO_2 is important because its accumulation in the body causes the pH to fall that may be lethal.

Gas Exchange Mechanism

Oxygen and carbon dioxide are transferred passively by diffusion from the environment across the respiratory surface which may be skin or special respiratory epithelium.

Features of Respiratory Surfaces

A respiratory surface has specialized features that facilitate gas exchange.

1. Large Surface Area and Low Diffusion Distance
2. Thin epithelium
3. High vascularization

Surface Area of Respiratory Epithelium

An animal's O_2 requirement and CO_2 production increase as a function of mass.

However, the rate of gas transfer across the body surface is related primarily to surface area and diffusion distance.

To facilitate the rate of gas transfer, surface area of respiratory epithelium should be large and diffusion distances as small as possible.

In very small animals the distances for diffusion are small, and the ratio of surface area to volume is large. For this reason, diffusion across the body surface is sufficient in small animals, such as rotifers and protozoa, which are less than 0.5 mm in diameter.

Increase in size results in increase in diffusion distances and reductions in the ratio of surface area to volume.

Large surface-area-to volume ratios are maintained in larger animals with the evolution of specialized respiratory organs with extensive respiratory epithelium for the exchange of gases.

This surface comprises the major portion of the total body surface. In humans, for instance, the respiratory surface area of the lung is between 50 and 100 m^2.

Thin Epithelium

The surface specialized for gas exchange is made up of a thin layer of cells, the respiratory epithelium, which is 0.5 to 15 μm thick.

Vascularization

A respiratory surface should have an extensive capillary network just beneath it. Blood flowing through the capillaries reduces diffusion distances required for the diffusion of gases.

Gas Transfer System

A gas-transfer system in animals takes in oxygen from the environment takes it to the issues through blood and brings CO_2 from tissues, transporting it to the gas exchange surface and removes it by diffusion.

Such a system involves four basic steps:

1. Breathing movements, which assure a continual supply of air or water to the respiratory surface (e.g., lungs or gills)
2. Diffusion of O_2 and CO_2 across the respiratory epithelium
3. Bulk transport of gases by the blood
4. Diffusion of O_2 and CO_2 across capillary walls between blood and mitochondria in tissue cells

Topic-149 Respiratory Pigments

Respiratory Pigments

- Respiratory pigments are the substances that transport respiratory gases, oxygen and CO_2 in the blood.
- They are complexes of proteins and metallic ions.
- Each respiratory pigment has a characteristic color that changes with its O_2 content.
- The color of the pigment is reflected in the color of blood.

Types of Respiratory Pigments

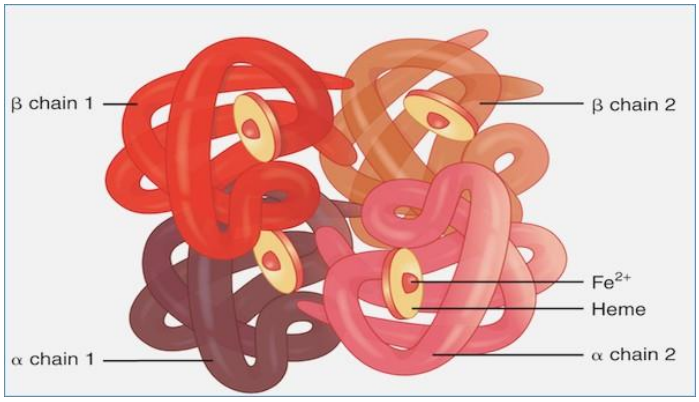
Various respiratory pigments found in animal kingdom include: hemoglobin, myoglobin, hemocyanin, hemerythrin and chlorocruorin.

Hemoglobin

- Hemoglobin is the most common respiratory pigment found in all vertebrate and many invertebrate groups.
- Its color is bright red when loaded with O_2 and dark maroon when deoxygenated.
- If O_2 is bound, the molecule is referred to as oxyhemoglobin; if O_2 is absent, it is called deoxyhemoglobin.

Structure of Hemoglobin

- A Hemoglobin molecule contains four iron containing heme groups, associated with a tetrameric globin protein.
- Iron, in hemoglobin, is in the ferrous state (Fe^{2+}).



Oxygen Carrying Capacity of Hemoglobin

- Hemoglobin (and other respiratory pigments) increases the O_2 binding capacity of the blood.
- The concentration of oxygen in blood with hemoglobin is 20 ml per 100 ml blood at 37°C at atmospheric pressure.
- It is a 70 times increase in capacity as compared to a blood without hemoglobin i.e. 0.3 ml O_2 per 100 ml blood.

Formation of Methemoglobin

- Binding of O_2 to hemoglobin to form oxyhemoglobin does not oxidize ferrous iron (Fe^{2+}) to ferric iron (Fe^{3+}).
- Certain substances oxidize the ferrous iron in hemoglobin to the ferric state. This oxidation produces methemoglobin.
- Methemoglobin is nonfunctional and does not bind O_2. So, higher concentration of methemoglobin in blood impairs oxygen transport.
- Red blood cells contain an enzyme methemoglobin reductase, which reduces methemoglobin to the functional ferrous form, hemoglobin.
- Certain compounds (e.g., nitrites and chlorates) act either to oxidize hemoglobin or to inactivate methemoglobin reductase, thereby increasing the level of methemoglobin.

Hemoglobin Inhibition by Carbon Monoxide

- The affinity of hemoglobin for carbon monoxide is about 200 times greater than its affinity for oxygen.
- Carbon monoxide displaces oxygen and saturates hemoglobin, even at very low partial pressures of carbon monoxide. This causes a marked reduction in oxygen transport to the tissues.
- Hemoglobin saturated with carbon monoxide is called carboxyhemoglobin.
- Saturation of hemoglobin with CO has effects similar to that of oxygen deprivation on oxidative metabolism. This condition is called anoxia which may impair brain functions and prove lethal.

Myoglobin

- Myoglobin is a respiratory pigment that stores O_2 in vertebrate muscles.
- It has a much higher oxygen affinity than hemoglobin.

Hemocyanin

- Hemocyanin is a large, copper-containing respiratory pigment found in many molluscs and Arthropods.
- Unlike hemoglobin, hemocyanin is not packaged in cells.

- In its oxygenated form, it is light blue and colorless in its unoxygenated form.

Hemerythrin

- Hemerythrin is used for oxygen transport by members of two phyla of marine invertebrates (Priapulida and Brachiopoda) and only one member of Annelida.
- It is colorless when deoxygenated, but turns violet-pink in the oxygenated state

Chlorocruorin

- It is found free floating in the blood plasma of many annelids, particularly marine polychaetes.
- It is a dichromatic compound that appears green in dilute solutions and light-red in concentrated solutions.

Topic-150 Transport of Oxygen in Blood

Transport of Oxygen

Oxygen is absorbed from the respiratory epithelium by the blood. In the blood most of oxygen binds with hemoglobin (97%) which carries and transports oxygen as oxyhemoglobin.

A small proportion (3%) of O_2 also gets dissolved in the plasma.

Oxygen Capacity of Hemoglobin

The ability of hemoglobin to bind with oxygen is called oxygen carrying capacity of the blood.

This capacity is directly proportional to the partial pressure of oxygen, P_{O2}.

Each hemoglobin molecule can combine with four oxygen molecules, each heme combining with one molecule of oxygen.

If all sites on the hemoglobin molecule are occupied by O_2, the blood is 100% saturated and the oxygen content of the blood is equal to its oxygen capacity.

Hemoglobin can absorb maximum O_2 at the sea level. The maximum amount of O_2 which normal human blood absorbs and carries at the sea level is about 20 ml/100 ml of blood, which is the oxygen capacity.

Liberation of Oxygen in Tissues

Oxyhemoglobin is unstable and dissociates rapidly into hemoglobin and oxygen at low oxygen concentration and less pressure.

This forms the basis of liberation of oxygen in the tissues.

When oxygen pressure falls below 60 mm Hg, as in many cells and tissues, the splitting of oxygen from hemoglobin occurs very sharply.

Carbonic anhydrase enzyme present in RBC's facilitates this activity.

Factors Affecting Oxygen Carrying Capacity

The hemoglobin-oxygen affinity is labile and depends on three important factors:

1. Temperature: Rise in temperature causes a decrease in oxygen carrying capacity of blood.
2. Carbon dioxide Concentration: O_2 tension decreases as CO_2 pressure increases and the capacity of hemoglobin to hold oxygen becomes less. In this way increased CO_2 tension favors the greater liberation of O_2 from the blood in the tissues.

3. pH: As the pH of blood declines, the affinity of oxygen to bind hemoglobin also declines. This phenomenon is termed as Bohr effect, or Bohr shift.
   This occurs because decreased pH results from an increase in hydrogen ions and the hydrogen ions combine with the protein parts of the hemoglobin molecules, causing a decrease in the ability of hemoglobin to bind oxygen.
   Conversely, an increase in blood pH results in an increased ability of hemoglobin to bind oxygen.

Topic-151 Transport of Carbon Dioxide in Blood

Carbon dioxide dissolves freely in the tissue fluid surrounding the cells. From the tissue fluid, dissolved Carbon dioxide passes to the plasma within the blood capillaries.

Carbon dioxide is transported in the blood, to the capillaries of the lungs, in several different states.

1. About 23% of Carbon dioxide is carried as carboxyhemoglobin. Carboxyhemoglobin is formed when carbon dioxide combines with amino group of globin part of hemoglobin.
2. About 7% Carbon dioxide is carried by binding to plasma proteins.
3. About 70% Carbon dioxide is carried as bicarbonate ion in the plasma.
   As carbon dioxide from tissue fluid enters the capillaries, it combines with water to form carbonic acid.

$$CO_2 + H_2O \rightleftharpoons H_2CO_3$$

The carbonic acid is an unstable compound and splits quickly and ionizes to produce hydrogen ions and bicarbonate ions.

$$H_2CO_3 \rightleftharpoons H^+ + HCO_3^-$$

HCO3- ions travel through circulation to the lungs
In the lungs, all these reactions occur in reverse order

Bicarbonate ions combine with hydrogen ions to form carbonic acid which splits into water and carbon dioxide.

$$\mathbf{HCO_3^- + H^+ \longrightarrow H_2CO_3 \longrightarrow H_2O + CO_2}$$

Carbon dioxide diffuses out from the capillaries of the lungs into the space of alveolar sac.

Topic-152 Vertebrate Lungs

Lungs in Vertebrates

Terrestrial vertebrates (amphibians, reptiles, birds, and mammals) use a pair of lungs to exchange oxygen and carbon dioxide between their tissues and the air.

Basic Plan of Vertebrate Lung

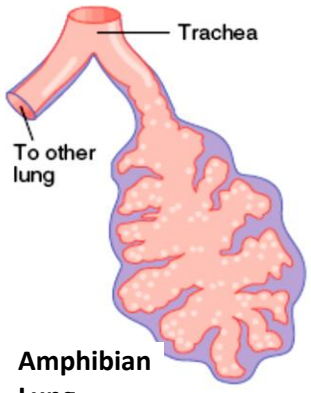
Considerable structural variations occur among the four groups.

The generalized vertebrate lung consists of a complex network of tubes and sacs or air spaces.

The sizes of terminal air spaces become progressively smaller in the order: amphibians, reptiles, and mammals. However the total number of air spaces per unit volume becomes greater.

Alveoli make the respiratory epithelium of lungs. Respiratory epithelium is thin and well vascularized.

Amphibian Lungs



Amphibian Lung

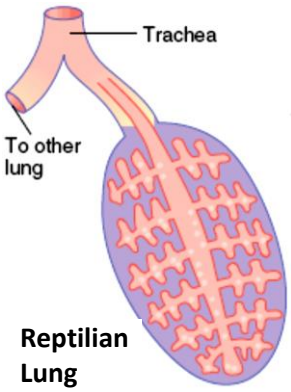
The structure of amphibian lungs vary in sub-groups.

In some urodeles, it is just like a smooth-walled pouch.

Gas exchange is limited to the outer surface of the lung.

Lungs in frogs and toads are balloon-like which are subdivided by septa and folds into numerous interconnected air sacs.

Reptilian Lungs



Reptilian Lung

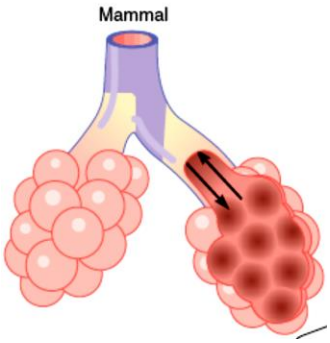
The lungs of most reptiles have a single bronchus running down the centre, from which numerous branches reach out to individual pockets throughout the lungs.

These pockets are similar to alveoli in mammals, but much larger and fewer in number. These give the lung a sponge-like texture.

Mammalian Lungs

Subdivision of lungs in mammals is much more than any other group.

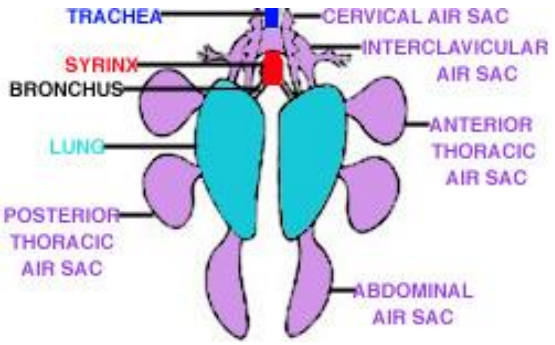
The trachea subdivides to form bronchi, which branch repeatedly, leading eventually to terminal bronchioles and finally respiratory bronchioles, each of which is connected to a terminal spray of alveolar ducts and sacs.



Subdivision of lungs, forming smaller sacs, results in an increase in respiratory surface area per unit volume of lung.

Birds Lungs

Lungs of birds are relatively small, but are connected to 8 or 9 air sacs that extend through much of the body. These air sacs are connected to air spaces within the bones.



The lungs contain millions of tiny parallel passages called parabronchi. Like the alveoli in other lungs, they are the site of gas exchange.

The air sacs, which hold air, do not contribute much to gas exchange, as they are poorly vascularised.

Parabronchi allow a unidirectional flow of air. This enables the bird's lungs to remove 90% of oxygen from air with each breath, whereas a mammal can remove only 25%.

Topic-153 Functional Anatomy of Mammalian Lungs

Air Pathway to Lungs

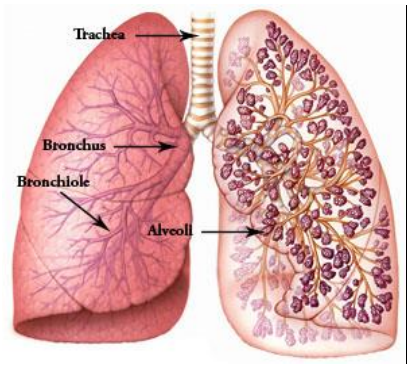
Lungs are located in the thoracic cavity.

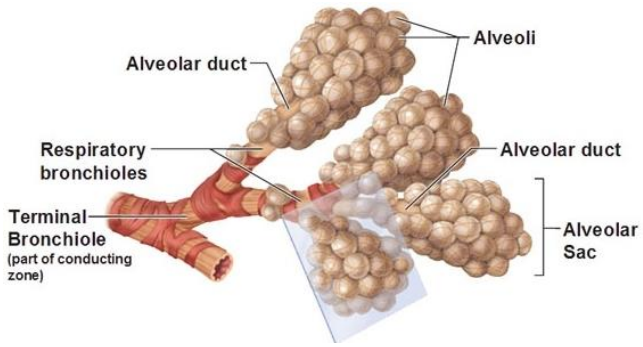
Air enters through the nostrils and enters trachea through the pharynx.

A system of branching ducts conveys air to the lungs.

Functional Anatomy of Mammalian Lungs

Trachea subdivides to form bronchi, which branch repeatedly, leading eventually to terminal bronchioles and finally respiratory bronchioles. Each respiratory bronchiole is connected to a terminal cluster of alveolar ducts and sacs (alveoli). The terminal bronchioles, the respiratory bronchioles, the alveolar ducts, and the alveolar sacs constitute the respiratory portion of the lung.





Cross Sectional Area of Airways

Although the diameter of individual air ducts decreases from the trachea to the terminal bronchioles, total cross-sectional area of the airways increases rapidly as a result of extensive branching.

Gas Exchange Surface

Gases are transferred across the thin-walled alveoli. The airways leading to the terminal bronchioles constitute the non-respiratory portion of the lung.

Prevention from Collapse

Air ducts leading to the respiratory portion of the lung contain cartilage and a little smooth muscle. This prevents air ways from collapse.

Topic-154 Lung Volumes and Capacities

Lung Volumes and Capacities

Lung volumes and lung capacities refer to the volume of air associated with different phases of the respiratory cycle.

Lung volumes are directly measured; Lung capacities are inferred from lung volumes.

Lung Volumes

Lung volumes are of five types:

1. Resting Tidal volume
2. Inspiratory reserve volume
3. Expiratory reserve volume
4. Residual volume
5. Minimal volume

Resting Tidal Volume

The amount of air that moves into or out of lungs during a single respiratory cycle under quiet, resting conditions. The resting tidal volume averages about 500 mL in human male and female both.

Inspiratory Reserve Volume

The amount of air that can be inhaled by maximum inspiratory effort. On average, the lungs of males are larger than those of females. For this reason, the inspiratory reserve volume of males averages 3300 mL, while in females, it is 1900 mL.

Expiratory Reserve Volume

The amount of air that can be voluntarily expelled after tidal volume by maximum expiratory effort. A male human can expel an additional 1000 mL of air with maximum use of the accessory muscles. Female expiratory reserve volume averages 700 mL.

Residual Volume

The amount of air that remains in lungs even after a maximal exhalation.

It is typically about 1200 mL in males and 1100 mL in females.

Minimal Volume

The minimal volume is a component of residual volume. It is the amount of air that would remain in lungs if they are allowed to fully collapse. The minimal volume ranges from 30 to 120 mL.

Unlike other volumes, it cannot be measured in a healthy person.

Lung Capacities

Respiratory capacities can be calculated by adding the values of various volumes. These include:

Inspiratory Capacity

The sum of tidal volume and inspiratory reserve volume. It is the amount of air that can be drawn into lungs after a complete respiratory cycle.

Functional Residual Capacity

FRC is the sum of the expiratory reserve volume and the residual volume.

It is the amount of air remaining in lungs after a complete respiratory cycle.

Vital Capacity

It is the maximum amount of air that can be moved into or out of lungs in a single respiratory cycle.

It is the sum of the expiratory reserve volume, the tidal volume, and the inspiratory reserve volume. It averages around 4800 mL in males and 3400 mL in females.

Total Lung Capacity

It represents the total volume of lungs.

It is calculated by adding the vital capacity and the residual volume.

The total lung capacity averages around 6000 mL in males and 4200 mL in females.

Topic-155 Mechanism of Lung Ventilation in Mammals

Lung Ventilation

Lung ventilation or breathing is a mechanical process that consists of two phases: Inspiration and expiration.

During inspiration, fresh air moves in and in expiration air with low oxygen and high CO2 content is moved out of the lungs.

Anatomical Features for Breathing in Mammals

Certain anatomical features help the lungs of mammals to carry out ventilation.

1. Lungs are spongy in nature. They neither pull air in nor push it out. During inspiration, passive expansion of elastic lungs occurs and expiration is due to a passive contraction of lungs.
2. At the floor of thoracic cavity, in which lungs are situated, is a diaphragm. Diaphragm is a muscular sheet. The shape of diaphragm is domelike when its muscles are relaxed. When the muscles of diaphragm contract, its shape becomes less domelike.
3. Walls of the thoracic cavity are composed of ribs. Between the ribs, external and internal intercostal muscles are present which act as antagonistic pair. Contractions or relaxations of these muscles cause the rib cage to elevate or drop and increasing or decreasing pressure on the lungs.

Mechanism of Inspiration

During inspiration, the space inside the thoracic cavity is increased in two ways:

Firstly, the external intercostal muscles contract and cause the ribs to move forward and upward, elevating the rib cage.

Secondly, the muscles of diaphragm also contract, making the diaphragm less domelike.

The combined effect of these two actions is the expansion of thoracic cavity, resulting in decrease of air pressure inside the lungs which, in turn, expand.

With the expansion of lungs, vacuum is created inside the lungs and air rushes passively into them from outside due to higher atmospheric pressure i.e. inspiration happens.

Mechanism of Expiration

During expiration, the external intercostal muscles relax and the ribs move downward and inward.

At the same time, muscles of the diaphragm also relax making it more domelike.

The combined effect of both these actions is the reduction in the volume of thoracic cavity.

This exerts pressure on the lungs, causing higher pressure in them resulting in moving out of the air passively i.e. expiration.

Topic-156 Mechanism of Ventilation in Birds

Birds' respiratory system consists of lungs and large air sac (numbering 7 or 9).

Air Sacs of Birds

- Two posterior (abdominal)
- Two anterior thoracic (cranial)
- Two posterior thoracic (caudal)
- Two cervical (these are not present in some species)
- One interclavicular

The air sacs have branches which also extend into the bones.

Respiratory cycle of a bird

Respiration in birds requires two ventilation cycles to move the air through the entire respiratory system. A breath of inhaled air remains in the respiratory system for two complete inhalation and exhalation cycles before it is fully used and exhaled out the body.

First Inspiration

During the first inspiration, the air travels through the nostrils, and passing through the larynx enters the trachea.

From the trachea air does not go directly to the lung, but instead travels to the posterior abdominal air sacs.

Simultaneously, a small amount of air passes through the posterior abdominal air sacs to the lung through the ventrobronchi and dorsobronchi.

In the lungs, these bronchi continue to divide into smaller diameter parabronchi and air capillaries.

Blood capillaries flow through the air capillaries and this is where the oxygen and carbon dioxide are exchanged.

First Expiration

During the first expiration, the spent air in the lungs flows out the body through the trachea. This air is replaced by the fresh air from the posterior air sacs.

Second Inspiration

When the bird inspires the second time fresh air again enters both the posterior sacs and the lungs. Spent air in the lungs is again displaced by incoming air, but it cannot exit through the trachea because fresh air is flowing inward. Instead, the spent air from the lungs enters anterior thoracic (cranial) air sacs.

Second Expiration

On the second expiration, the air moves out of the cranial air sacs and the lungs, and flows out through the trachea. Fresh air in the posterior sacs again enters the lungs for gas exchange.

Maintenance of Air Flow: Ventilation

Birds do not have a diaphragm.

Air is moved in and out of the respiratory system through pressure changes in the air sacs.

Muscles in the chest cause the sternum to be pushed outward. This creates a negative pressure in the air sacs, causing air to enter the respiratory system.

Expiration is not passive, but requires certain muscles to contract to increase the pressure on the air sacs and push the air out.

Efficiency of Birds Lung Ventilation System

The respiratory system of birds is more efficient than that of mammals, transferring more oxygen with each breath.

This pattern of airflow through the respiratory system creates unidirectional (one-way) flow of fresh air over the gas exchange surfaces in the lungs. Furthermore, fresh air passes over the gas exchange surfaces during both inhalation and exhalation, resulting in a constant supply of fresh air enabling the bird to experience a near-continuous state of gas exchange within the lungs.

Topic-157 Mechanism of Lung Ventilation in Reptiles

Thoracic Cavity in Reptiles

The ribs of reptiles like snakes, lizard and crocodilians, form a thoracic cage around the lungs like those of mammals. In tortoises and turtles, the ribs are fused to a rigid shell.

Reptiles do not possess a diaphragm. However, pressure differences between the thoracic and abdominal cavities occur, indicating a functional separation of these cavities.

Breathing in Snakes and Crocodilians

Inhalation

During inhalation, posterior movement of the ribs causes expansion of thoracic cavity.

Expansion of thoracic cavity reduces pressure in the lungs below atmospheric pressure. Air is drawn passively into the lungs by passing through open nares and glottis.

Exhalation

Elastic recoil of the lungs and the movement of ribs and body wall, compress the lungs and air is expelled.

Breathing in Tortoises and Turtles

The ribs of turtles are a part of the shell; thus, movements of the body wall to which they attach are impossible.

Turtles exhale by contracting muscles that force the viscera upward, compressing the lungs.

They inhale by contracting muscles that increase the volume of the visceral cavity, creating negative pressure to draw air into the lungs.

Topic-158 Mechanism of Ventilation of Lungs in Frogs

Respiratory Apparatus of Frog

In frogs, the nose opens into a buccal cavity. Buccal cavity is connected to paired lungs via the glottis.

The lungs are balloon shaped. Each lung consisting of small thin walled chambers called alveoli. Alveoli increase the surface area of the lungs.

Inspiration

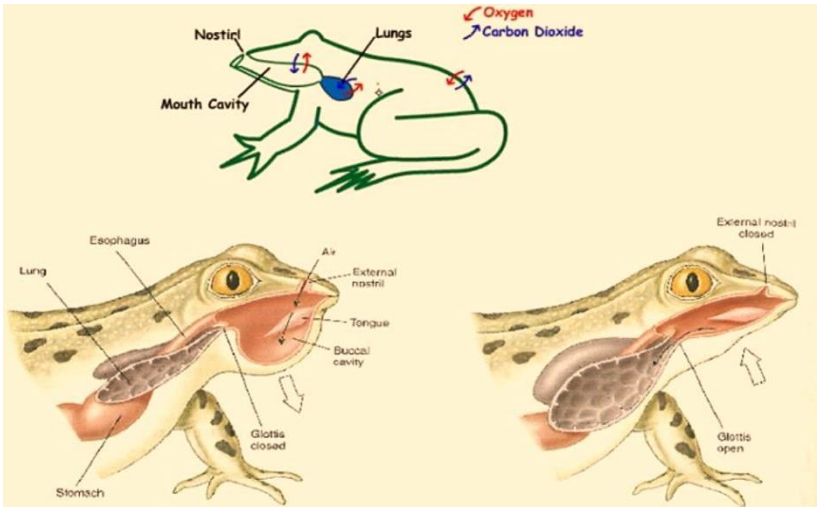
Frogs use positive pressure pumping mechanism in which air is pushed into the lungs by the pumping pressure of buccal cavity.

The frog can open and close its nares and glottis independently.

Steps of Inspiration

- Air is drawn into the buccal cavity with the nares open and glottis closed. Floor of the mouth is lowered.
- Then the nares are closed, glottis is opened, and the buccal floor is raised.
- This forces the air from the buccal cavity into the lungs.

This lung-filling process may be repeated several times in sequence, before ventilation cycle begins.



Expiration

Expiration is complex and occurs in steps. The lungs release air in portions to the buccal cavity.

Expiration may not be complete, so that some of the air from the lung is mixed with ambient air in the buccal cavity and then pumped back into the lungs.

During repeating sequence of inspirations, when fresh air is drawn into the buccal cavity, opening of glottis occurs. This opening of glottis causes back flow of air from lungs into the buccal cavity. As the floor of buccal cavity is raised and fresh air is pushed into the lungs, the exhaled air also pumped back into the lungs.

That is, a mixture of pulmonary air, presumably low in O_2 and high in CO_2 is mixed with fresh air in the buccal cavity and returned to the lungs.

The reason for this complex method of lung ventilation may be directed toward reducing oscillations in CO_2 levels in the lungs in order to stabilize and regulate blood P_{CO2} and control blood pH.

After few cycles, a full ventilation cycle (exhalation) happens that repeats the inhalation steps in reverse order.

Topic-159 Pulmonary Surfactants and Alveolar Collapse

Tension in Lung's Wall

Lungs have the ability to stretch and expand due to tension in the lung wall.

The tension in lung wall depends on:

- Properties of the alveolar wall that allow stretching
- Surface tension at the liquid-air interface that causes resistance to stretch

Pulmonary Surfactants

The alveoli of a healthy lung have relatively low surface tension due to the presence of surfactants.

Surfactants are lipoprotein complexes that bestow a very low surface tension on the liquid-air interface of alveoli.

Lung surfactants not only reduce the effort associated with breathing but also help prevent collapse of alveoli.

Surfactants are produced by type II cells within the alveolar lining and have a half-life of about 12 hours in mammals.

Surfactants are found in the lungs of all terrestrial vertebrates i.e. amphibians, reptiles, birds, and mammals.

Alveolar Collapse

Alveoli are very small bubble-like structures that are inflated and deflated alternately.

The continuous inflation and deflation creates mechanical problems that might cause them to collapse.

The air pressure inside the alveoli with thin walls may cause them to burst or join with other larger alveoli with lower pressure, forming larger sacs. This is known as alveolar collapse.

It results in reduced surface area available for gas exchange.

Prevention of Alveolar Collapse

Alveolar collapse normally does not occur in the lung for two reasons:

- surrounding tissue helps prevent overexpansion of alveoli
- presence of pulmonary surfactants

Role of Pulmonary Surfactants in Preventing Collapse

Due to presence of surfactant on the surface of alveoli, the wall tension increases when the surface film is expanded and decreases when it is compressed.

When their volume decreases (deflation), alveoli fold and the layer of surfactant between the folds becomes thick.

Thick layer of surfactant reduces the surface tension. This permits easy inflation of folded alveoli.

This effect of surfactants also minimizes pressure differences between large and small alveoli, thus reducing the chance of collapse.

Topic-160 Neural Control of Breathing

Central Processor of Breathing

The integration of breathing movements in all air-breathing vertebrates results from the central processing of many sensory inputs.

The central processor consists of:

- a pattern generator that determines the depth and amplitude of each breath
- a rhythm generator that controls breathing frequency

Medullary Respiratory Centers

The central rhythm generator that maintains breathing rhythm in human is located in the ventral medulla.

Rhythmic activity is enhanced by neurons in the pons and medulla. Some neurons just anterior to the medulla cause prolonged inspiration in the absence of rhythmic drive from the pons.

Thus the medulla contains a central rhythm generator that drives the pattern generator within the medullary respiratory center to cause breathing movements.

Neural Control of Mammalian Lung

Mammalian lung is ventilated by the action of diaphragm and muscles between the ribs.

These muscles are activated by spinal motor neurons and the phrenic nerve, which receive inputs from medullary respiratory centers.

The control of respiratory muscles can be very precise, allowing extremely fine control of air flow, as is required for such complex actions in humans as singing, whistling, and talking, as well as simply breathing.

Inspiratory and Expiratory Neurons

The medullary respiratory center contains inspiratory neurons, whose activity coincides with inspiration, and expiratory neurons, whose activity coincides with expiration.

Respiratory rhythm depends primarily on the activity of inspiratory neurons.

Exhalation is a passive process, which does not depend on activity in expiratory neurons.

Expiratory neurons become active only when inspiratory neurons are inactive, and then they show a burst pattern somewhat similar to that of inspiratory neurons.

Roles of Central Processor

- Receives pH input and adjusts ventilation to maintain blood pH.
- Integrate breathing movements with feeding, talking and singing, or other body movements.
- Generate coughing or sneezing reflexes to protect respiratory epithelium from environmental hazards.
- Optimize breathing patterns to minimize energy expenditure.

Topic-161 Factors Affecting Breathing Rate and Depth

Factors Affecting Breathing Rate and Depth

Chemical stimuli affecting ventilation are changes in pH and concentration of O_2,and CO_2.

Rate and depth of ventilation is also changed with emotions, sleep, lung inflation and deflation, lung irritation, variations in light and temperature and requirements for speech.

Breathing rate and depth can also be controlled consciously.

Receptors of Respiratory Stimuli

Several types of receptors respond to these stimuli and send information to the medullary respiratory center for integration. Medullary respiratory center causes reflex changes in the rate and/or depth of breathing.

Monitoring O_2, CO_2 and pH Levels

Three types of chemoreceptors monitor changes in O_2 and CO_2 and pH levels in arterial blood:

- Peripheral Chemoreceptors
- Central Chemoreceptors
- Type-J Chemoreceptors

Peripheral Chemoreceptors

They are found in the carotid bodies and aortic bodies of mammals, in the carotid body of birds, and in the carotid labyrinth of amphibians.

In teleost fishes, chemoreceptors are located in the gills.

In all cases, the chemoreceptors are innervated by branches of ninth (glossopharyngeal) or tenth (vagus) cranial nerve.

Peripheral chemoreceptors respond to falling O_2 levels in water and blood and are important in increasing ventilation during periods of hypoxia.

Central Chemoreceptors

They are found in mammals and many other air breathing vertebrates. They are located in the medulla and respond to decrease in the pH of the cerebrospinal fluid (CSF) due to high CO_2 levels. Stimulation of these H^+-sensitive receptors causes reflex increase in breathing.

Type-J Chemoreceptors

A third group of receptors are present in the lung. They are positioned close to the pulmonary capillaries in interstitial spaces. These are called juxtapulmonary capillary receptors, or type J receptors.

Stimulation of type J receptors elicits a sensation of breathlessness. Violent exercise results in a rise in pulmonary capillary pressure and an increase in interstitial volume, which could cause stimulation of type J receptors and therefore breathlessness.

Topic-162 Respiratory Responses to Hypoxia

Hypoxia is a condition in which the body or a region of the body is deprived of adequate oxygen supply.

Respiratory Responses of Aquatic Animals to Hypoxia

Oxygen level in aquatic environment varies frequently. Aquatic animals are subjected to more frequent and rapid changes in oxygen levels.

Many aquatic animals can withstand very long periods of hypoxia. Many of these animals utilize a variety of anaerobic metabolic pathways to survive the period of reduced oxygen availability.

Many animals adjust the respiratory and cardiovascular systems to maintain oxygen delivery during reduced oxygen availability. For example, many fishes increase gill ventilation rate in hypoxic conditions. Ram ventilators (e.g. tuna) swim forward with their mouth open, increase the size of gap during hypoxia to increase water flow over the gills.

Responses to Hypoxia by Animals at High Altitudes

There is a gradual reduction in oxygen concentration with altitude.

Animals vary in their capacity to climb to high altitudes and withstand the reduced ambient oxygen levels.

A reduction in environmental oxygen results in a decrease in blood P_{O2}.

This stimulates the carotid and aortic body chemoreceptors, causing an increase in lung ventilation in mammals.

Rise in lung ventilation leads to an increase in CO_2 elimination and a decrease in blood P_{CO2} that leads to an increase in pH of the CSF.

Increase in CSF pH tends to reduce ventilation, thereby attenuating the hypoxia-induced increase in lung ventilation.

If hypoxic conditions are maintained, both blood and CSF pH are returned to normal levels by the excretion of bicarbonate.

This acclimatization takes about one week in humans.

Topic-163 Respiratory Responses to Hypercapnia

Hypercapnia

Hypercapnia is a condition of abnormally elevated carbon dioxide levels in the blood.

Animal Responses to Hypercapnia

In many animals, hypercapnia results in an increase in ventilation, in proportion to the rise in CO_2. A marked increase in ventilation occurs almost immediately in response to a rise in CO_2 and is maintained for long periods till compensatory mechanisms take control.

Receptors of Hypercapnia

Increase in ventilation rate is mediated by the activity of several receptors that send messages to the medullary respiratory center. These receptors include the chemoreceptors of the aortic and carotid bodies and the mechanoreceptors in the lungs.

Hypercapnia and pH Fall

An increase in carbon dioxide levels in the blood also cause the pH to fall. This change in pH is responded by the central H^+ receptors which also cause increase in ventilation rate.

Normalization: Role of Bicarbonates

Ventilation rate eventually returns to a level slightly above the level that prevailed before hypercapnia.

This return to a value only slightly greater than the initial ventilation level is related to increases in levels of plasma bicarbonate and CSF bicarbonate.

Increase in bicarbonate level brings the pH to normal even though the raised CO_2 levels are maintained. Correction of CSF pH is very important in the return of ventilation to normal.

Topic-164 Respiratory Responses to Diving

Diving

Many air-breathing vertebrates (e.g. dolphins, whales and water birds) that live in water may go under water (submerge or dive) for varying periods of time.

They have to rise to the surface to breathe. The time between breaths varies with the diver, but is mostly around 10-20 minutes for many diving vertebrates.

Dealing with Hypoxia and Anoxia during Dive

Diving mammals and birds are subjected to periods of hypoxia during submergence. The mammalian central nervous system (CNS) cannot withstand anoxia and must be supplied with oxygen throughout the dive.

Diving animals solve the problem by utilizing oxygen stores in the lungs, blood, and tissues.

Many diving animals have high hemoglobin and myoglobin levels, and their total oxygen stores generally are larger than those in nondiving animals.

To minimize depletion of available stores, oxygen is preferentially delivered to the brain and the heart during a dive. Blood flow to other organs may be reduced, and these tissues may adopt anaerobic metabolic pathways.

During prolonged dives, metabolic rates and thus oxygen needs often are reduced in such animals (e.g., elephant seals).

Control of Inhalation and Exhalation during Dive

Receptors that detect the presence of water and that inhibit inspiration during a dive are situated near the glottis and near the mouth and nose (depending on the species).

The decrease in blood O_2 levels and increase in CO_2 levels that occur during a dive do not stimulate ventilation because inputs from the chemoreceptors of the carotid and aortic bodies are ignored by the respiratory neurons while the animal is submerged.

Topic-165 Gas Exchange across Gills of Fishes

Gills as Respiratory Organs of Fishes

Fishes live in an environment that contains less than 2.5% of the oxygen present in air.

To maintain adequate levels of oxygen in their bloodstream, fishes must pass large quantities of water across gill surfaces and extract the small amount of oxygen present in the water.

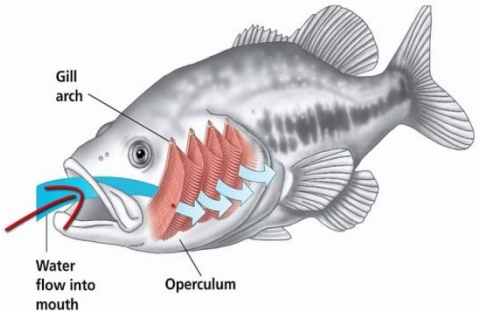
Fishes have gills which are efficient respiratory organs for gas exchange in water.

Flow of Water over Gills in Bony Fishes

Most of bony fishes (teleosts) have a muscular pumping mechanism to move water over the gills.

This branchial pump is powered by the skeletal muscles surrounding the pharynx and opercular (branchial) cavity.

Water is drawn into the mouth, passes over the gills, and exits through the gill clefts.



Flow of Water over Gills in Cartilaginous Fishes

Cartilaginous fishes don't have an operculum.

Many of them have gill bars with external flaps that can close and form a cavity functionally similar to the opercular cavity of bony fishes.

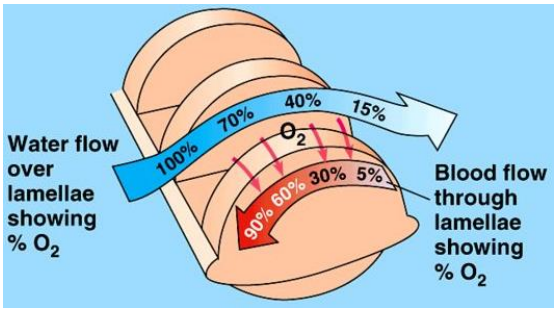
Some elasmobranchs and open-ocean bony fishes (e.g. tuna), maintain water flow over gills by ram ventilation. They keep their mouths open while swimming so as to ventilate the gills by the forward motion of the body. These fishes must keep moving to survive.

Gas Exchange across Gills

Gas exchange across gill surfaces is very efficient.

Gas exchange occurs as blood and water move in opposite directions on either side of the lamellar epithelium.

This countercurrent exchange mechanism provides very efficient gas exchange.



It maintains oxygen concentration gradient between the blood and water over the entire length of the capillary bed.

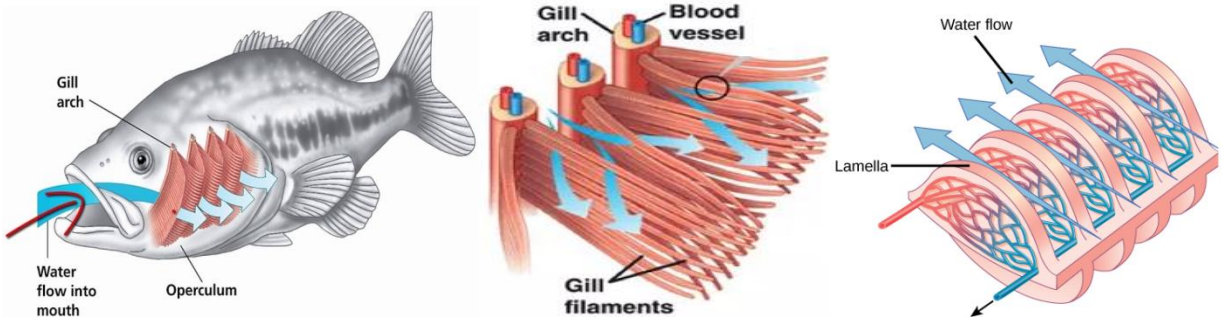
This arrangement provides the greatest possible extraction of oxygen from water.

Topic-166 Functional Anatomy of Gills of Fishes

Gills

Gills are effective respiratory organs for gas exchange in water.

They have a thin, moist and highly vascularized layer of epidermis that permits gas exchange through water medium.



Anatomy of Fish Gills

Each gill consists of two rows of thin, dorsoventrally flattened filaments supported by a gill arch.

Each filament has an upper and a lower row of vascular folds of epithelium, called pharyngeal lamellae.

Pharyngeal Lamellae

Pharyngeal lamellae represent the respiratory portion of the gill.

Each gill lamella is covered by a thin sheet of epithelial cells.

The inner lamellar wall is formed by pillar cells. Pillar cells are associated with an extensive collagen network, which gives them support.

Branchial arteries that carry blood to the gills break into capillary beds in pharyngeal lamellae.

The lamellae of successive filaments in a row are in close contact so that the whole gill forms a sievelike structure.

Lamellar Channels

Successive lamellae form slitlike channels between them through which water flows.

These channels are about 0.02-0.05 mm wide and about 0.2-1.6 mm long.

Due to the small size of channels, water flows in thin sheets between the lamellae. As a result diffusion distance between water and blood flowing in capillaries is reduced to a maximum of 0.01 - 0.025 mm.

Topic-167 Osmoregulation and Excretion

Osmoregulation and Excretion

Water is the solvent in the cells that makes solutions with solutes i.e. salts, electrolytes and ions. Each cell is adapted to a defined quantity of water in relation to salts in it to perform its functions. Changes in the concentration of either water or solutes in it disturb the homeostatic balances. Osmoregulation and excretion are the homeostatic mechanisms that maintain water and solute balance.

The mechanism of regulation of solutes and concentration of water in the cells and body fluids of animal is called osmoregulation.

The mechanism which eliminates nitrogenous wastes is referred as excretion.

Correlation of Osmoregulation and Excretion

Metabolic nitrogenous wastes e.g. ammonia and urea disturb the osmotic balance of the cells at toxic levels. Their removal is called excretion and is necessary to maintain osmotic balances. So, osmoregulation and excretion are correlated processes.

Osmolarity

Cells consistently encounter changing extracellular environment.

An external medium that is dilute as compared to the cell concentration is designated as hypotonic environment.

The more concentrated external environment is termed as hypertonic environment.

The environment whose solute concentration resembles to that of cell's internal solution is termed as isotonic.

Effects of Osmolarity

Hypotonic environments osmotically cause entry of water into the cell and dilute the cell solution. The cell may become turgid or swells and even burst.

Hypertonic environment causes the cells to lose water and renders cell solutions concentrated.

Importance of Osmoregulation

Animal cells require critical balance of water and solutes in the body as they cannot survive a net water gain or loss. Water continuously enters and leaves the cells, however, the quantity of water and solutes is kept in balance through osmoregulation.

Topic-168 Osmoregulators and Osmoconformers

Osmoregulators

Animals whose body fluid concentrations differ noticeably from the outside environment are called osomoregulators.

They actively regulate water and salt to maintain an internal osmolarity different from the medium in which they are living.

They discharge excess water in hypotonic environment and excrete salts in hypertonic conditions.

Their internal tissues are sensitive to minor changes in extracellular osmolarity. So they need to actively regulate water and electrolytes to maintain cell volume.

Animals living in different environments e.g. marine, freshwater and terrestrial environments have distinct adaptations to regulate osmotic balance.

Most vertebrates are osmoregulators. Only exceptions are elasmobranchs and hagfishes.

Marine vertebrates keep their blood solute concentration hyposmotic to seawater while fresh water fishes maintain hyperosmotic composition as compared to freshwater.

Among invertebrates, some fresh water and many terrestrial invertebrates are osmoregulators.

Osmoconformers

Animals whose body fluids are kept isotonic to the external environment are called osmoconformers.

They do not actively control the osmotic condition of their body fluids and conforms to the osmolarity of the ambient medium.

All marine invertebrates are osmoconformers i.e. in osmotic balance with seawater. Ionic concentrations in their body fluids parallel the seawater in which they live.

Among vertebrates elasmobranchs and hagfishes are osmoconformers.

Osmoconformers display a high degree of cellular osmotic tolerance.

Their cells can cope with high plasma osmolarities and maintain cell volume.

They do so by increasing their intracellular osmolarities with intracellular organic osmolytes. Osmolytes e.g. urea and trimethylamine oxide, utilized by marine elasmobranchs, are substances which reduce the need to maintain osmotic pressure with inorganic ions.

Topic-169 Osmoregulation in Aquatic Environments

Environmental Osmolarities and Osmotic Problems

Animals face distinct osmotic problems related to water and salt exchange in aqueous environments.

The osmolarities of aqueous environments range from a few milliosmoles per liter in freshwater lakes to about 1000 mosm/L in ordinary seawater, or even more in landlocked salt seas.

Intermediate environments, such as brackish bogs, marshes, and estuaries, have salinities ranging between these extremes.

As a rule, animal body fluids (i.e. interstitial fluids and blood) tend away from the environmental osmotic extremes.

The nature of osmotic problems faced by freshwater and marine animals and their mechanisms for dealing with them are different.

Stenohaline Animals

Most oceanic invertebrates can tolerate only a narrow osmotic range and have very limited abilities to withstand osmotic change.

They cannot tolerate substantial changes in external osmolarity and are said to be stenohaline.

If they are exposed to dilute seawater, they die quickly because their body's cells cannot tolerate dilution and are helpless to prevent it. So, these animals are restricted to living in a narrow salinity range.

An example is the marine spider crab.

Euryhaline Animals

Euryhaline animals can survive large fluctuations in external osmolarity. They can tolerate a wide range of salinities and demonstrate varying powers of osmotic regulation with changing salt concentration in water.

Euryhaline animals are found along coasts and in estuaries and river mouths where conditions are much less constant than those of the open ocean. Here animals must be able to withstand large and often abrupt changes in salinity as the tides ebb and flow and mix with fresh water draining from rivers.

They include certain osmoconformers and osmoregulators. Many barnacles and mussels are euryhaline osmoconformers while striped bass and the various species of salmon are euryhaline osmoregulators.

Topic-170 Osmoregulation in Fresh Water Animals

Osmolarity of Freshwater Animals

The body fluids of freshwater animals, including invertebrates, fishes, amphibians, reptiles, and mammals, are generally hyperosmotic to their aqueous surroundings.

Freshwater vertebrates have blood osmolarities in the range of 200 to 300 mosm/L, while the osmolarity of freshwater is generally less than 50 mosm/L.

Osmotic Problems of Freshwater Animals

They face two kinds of osmoregulatory problems in hyposmotic aqueous surroundings:

- They are subject to osmotic flooding of body fluids which results in swelling.
- They are subject to continuous loss of body salts to the surrounding medium.

Osmoregulatory Needs of Freshwater Animals

Freshwater animals need to:

1. Prevent net gain of water and get rid of excess water
2. Prevent loss of salts and gain salts to replace for net loss

Osmoregulatory Strategies of Freshwater Animals

Almost all fresh water animals are osmoregulators.

- Freshwater protozoa (Amoeba, paramecium) have contractile vacuoles for pumping out excess water.
- As a general rule, vertebrates living in freshwater refrain from drinking water, to reduce excess water entry into the body.
- Most freshwater vertebrates (fishes and amphibians) produce a copious amount of dilute urine to avoid a net gain of water. The nephrons of freshwater fishes possess large glomeruli for more filtration and relatively short tubule systems that allow little water reabsorption.
- The useful salts are largely retained by reabsorption into the blood from the ultrafiltrate in the tubules of the kidney.
- Yet, some salts pass out in the urine that causes a potential problem of loss of biologically important salts such as KCl, NaCl, and $CaCl_2$.
- Lost salts are replaced, in part, from ingested food.
- Salts are also actively transported across the epithelium of skin (in amphibians) or gills (in fishes) from the external dilute medium.

- In some freshwater animals, especially reptiles, birds, and mammals, water uptake and salt loss are minimized by an integument having low permeabilities to both salts and water.

Topic-171 Osmoregulation in Marine Animals

Osmoregulation in Marine Invertebrates

The body fluids of marine invertebrates and ascidians (primitive chordates) are maintained at similar levels (isosmotic) to seawater both in osmolarity and in the plasma concentrations of individual major inorganic salts.

Such animals need not expend much energy in regulating the osmolarity of their body fluids.

Osmoregulation in Marine Vertebrates: Hagfishes

Plasma of hagfishes is isosmotic with marine water.

However, the concentration of individual ions is regulated. They maintain their blood Ca^{2+}, Mg^{2+} and SO_4^- ions at significantly lower concentrations than seawater. They also maintain Na^+ and Cl^- at higher levels than sea water.

Osmoregulation in Marine Vertebrates: Cartilaginous Fishes

Cartilaginous fishes such as sharks, rays, and skates have plasma that is approximately isosmotic to seawater.

However they maintain far lower concentrations of electrolytes (i.e., inorganic ions).

They excrete excess inorganic electrolytes such as NaCl via the kidneys and also by means of a special excretory organ, the rectal gland, located at the end of the alimentary canal.

They maintain an isotonic osmolarity with sea water due to organic osmolytes such as urea and trimethylamine oxide (TMAO).

High urea concentration tends to cause the breakup of proteins, whereas trimethylamine oxide has the opposite effect. So, it stabilizes protein structure in the face of high urea levels.

Osmoregulation in Marine Vertebrates: Teleost Fishes

The body fluids of marine teleosts (modern bony fishes) are hypotonic to seawater.

These fishes have a tendency to lose water, especially across the gill epithelium.

To replace the lost volume of water, they drink saltwater that also results in excess salt uptake.

Most of the excess salts are subsequently eliminated from the blood. Na^+, Cl^- and some K^+ are eliminated by active transport across the gill epithelium. Ca^{2+}, Mg^{2+}, and SO_4^- are excreted in urine through the kidneys.

The urine produced is isotonic to the blood, but rich in salts.

The net result of the combined osmotic work of gills and kidneys in the marine teleosts is a net retention of water.

Topic-172 Osmoregulation in Terrestrial Animals

Osmoregulatory Problems in Terrestrial Environment

The terrestrial animals often face the problem of both water and salt losses.

Water loss occurs due to:

- Water permeable epidermis
- Respiratory epithelia
- Sweat and urine excretion

Salt loss is caused due to:

- Sweat
- Urine excretion

Maintaining Water and Salt

- Terrestrial animals maintain a balance between water and salt loss and gain.
- These animals feed on food materials which are moist and rich in salts to compensate the deficiency of water and salts.
- They either drink large amount of water to replenish the lost water or conserve water by physiological and behavioral means.

Physiological Adaptations

Physiological adaptations to meet the osmotic problems in terrestrial animals (e.g. reptiles, birds, mammals, some crustaceans and annelids) are:

- The body is usually covered by a water proof material which prevents the evaporation of water from the body. This covering may be of horny scales (as in certain reptiles), feathers (as in birds) and hair or fur (as in mammals).
- The loss of water through urine and feces is checked by various mechanisms. Water is absorbed from feces by rectum and cloaca and water from urine is absorbed by loop of Henle in the kidney.
- Many terrestrial animals, which do not drink water directly, such as birds, snakes and lizards excrete a semisolid urine containing uric acid crystals, thus minimizing water loss.
- The animals of extreme terrestrial habitat, the dry hot desert, have developed special means of water conservation.

Topic-173 Osmoregulation in Desert Living Animals

Challenges of Desert Environment

The animals living in desert are faced with excessive heat, evaporative water loss and near absence of free freshwater.

Such animals have special physiological adaptations for survival in hot and dry environment.

Kangaroo Rat—Model of Desert Adaptations

Kangaroo rats live in some of the hottest and driest desert environments. They eat only dry seeds and never drink water. Their survival strategies include a variety of osmoregulatory physiological adaptations characteristic of many small desert mammals.

- They have adapted a nocturnal lifestyle i.e. remaining in burrows during daylight and coming out only at night. This reduces evaporative water loss. The cool burrows reduce the animal's temperature load and also reduce respiratory water loss.
- Their nasal epithelium has cooling properties and has a countercurrent mechanism for absorbing respiratory moisture.
- They have adapted to utilize metabolic water in place of drinking water.
- They excretes a highly concentrated urine and also absorb water from the feces in the rectum to produce essentially dry fecal pellets.

By using all these adaptations for desert survival, the kangaroo rat greatly reduces its potential water loss, required for survival.

Camels—Large Desert Mammals

- Large mammals like camels can go for long periods without water in hot and dry deserts.
- Their primary adaptation is their ability to withstand extreme body dehydration. A camel can lose as much as 40 per cent of the water in its body fluids and still survive.
- When deprived of drinking water, camels allow their body temperature to rise during hot day time rather than losing water by evaporative cooling or sweating.
- During the cooler night, their body temperature drops.
- The body temperature of a dehydrated camel may vary from 35°C at night to 41°C during the day.
- This strategy of heating during the day and cooling at night is impossible in small rodents, whose body temperatures oscillate much more rapidly than in the larger animals.
- The camel also reduces heating by orienting to give minimal surface exposure to direct sunlight.
- The camel, like other desert animals, produces dry feces and concentrated urine.

- When water is not available the camel does not produce urine but stores urea in the tissues.
- They can tolerate not only dehydration but also high urea levels in the body.
- When water becomes available, they rehydrate by drinking larger amounts of water.

Topic-174 Osmoregulation in Marine Mammals

Osmoregulatory Challenges of Marine Mammals

Marine mammals, such as whales, porpoises, sea lions and seals face osmoregulatory problems similar to those of desert animals because they live in an environment without available drinking water.

They avoid drinking seawater as they lack extrarenal salt-secreting glands. Their physiological responses, although different in detail, are generally similar to those of desert mammals.

Osmoregulatory Strategies of Marine Mammals

- They lose water through excretion and through moisture in the exhaled air. So, their basic osmoregulatory emphasis is on water conservation.
- They get their water entirely from their food intake and its subsequent metabolism.
- They depend primarily on their kidneys for maintaining osmotic balance. They have highly efficient kidneys capable of producing very hypertonic urine.
- To reduce water loss via ventilation, seals have a characteristic labyrinth-like proliferation of epithelial surfaces in the nasal passages. Whales and dolphins have a blow hole which cools the air passing through it. Many have an ability to suspend breathing for quite longer time (up to 40 minutes) with and alternating deep breathing period of about 5 minutes. This strategy reduces respiratory water loss.
- The females have an additional water loss in their milk when they are nursing young, but this loss is counterbalanced by a concentration of milk. The milk of these mammals is about ten times as concentrated in fat as is cow's milk.

Topic-175 Osmoregulation in Terrestrial Arthropods

Osmoregulatory Challenges

Terrestrial environments are highly desiccating. The major challenges for insects and other arthropods are:

- Acquisition of water
- Conservation of water

Acquisition of Water

- Insects do not take water directly through drinking.
- Most insects obtain water from their food.
- Some insects and arthropods have the ability to extract water vapor directly from the air.

Extraction of Water Vapors from Air

- The terrestrial arthropods having the ability to extract water vapors from the air include certain arachnids (ticks, mites) and a number of wingless forms of insects, primarily larvae.
- In these arthropods, the site of entry of water vapors is the rectum and mouth.
- The principle of absorption of water in vapor form is that highly concentrated salt solutions absorb water from air.
- Insects create very concentrated salt solutions in their rectum and mouth that can absorb water from air.
- In the rectum this role is played by NaCl while in the mouth, salivary glands secrete a highly concentrated solution of KCl to absorb water from the air.

Water Conserving Strategies

Arthropods have developed better water conservation strategies in terrestrial habitats. These include:

- Presence of exoskeleton of chitin that prevents evaporative water loss.
- Production of highly concentrated or nearly dry digestive excreta in the rectum.
- Use of uric acid as metabolic excretory product. The association of excretory malpighian tubules with the gut prevents water loss involved in nitrogenous waste excretion.
- Prevention of respiratory water loss through evolution of tracheal system for respiration.

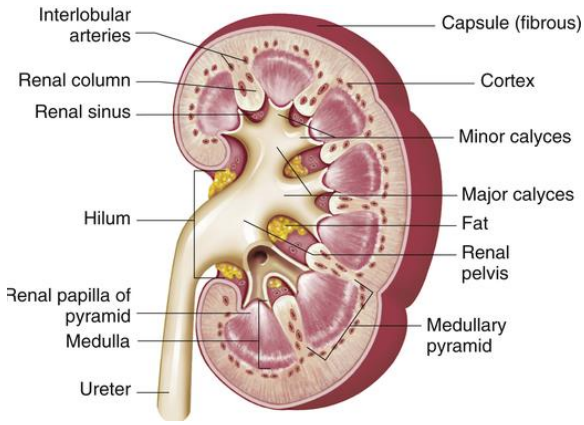
Topic-176 Mammalian Kidney: Anatomy

Kidney is the osmoregulatory organ of mammals.

Anatomy of the Mammalian Kidney

A kidney is a reddish brown bean shaped organ.

A fibrous connective tissue layer called the fibrous capsule encloses each kidney.



http://physiologyplus.com/wp-content/uploads/2017/08/Kidney-Structure.png

Hilus (Hilum)

The lateral surface of each kidney is convex but its medial side is deeply concave. This forms a medial depression known as the hilus.

Through the hilus, the renal artery and nerves enter and the renal vein and the ureter exit.

Cortex and medulla

The kidney is divided into two functional layers that contain the functional urine forming units—nephrons. The outer layer is called renal cortex while the inner layer is renal medulla.

Renal Pyramids

The renal medulla consists of a number of cone shaped renal pyramids. The base of each pyramid is located at the boundary between renal cortex and the renal medulla.

The tips of the conical pyramids are called renal papillae. They are pointed towards the center of the kidney, projecting into the pelvis.

The parts of cortex which are projected between the renal pyramids are called renal columns.

The spaces between any two renal columns are called minor calyces.

Each renal papilla is pierced by tiny opening that leads into the minor calyx.

The minor calyces from several pyramids join together to form large funnel shaped spaces called major calyces.

The major calyces converge to form an enlarged channel called renal pelvis.

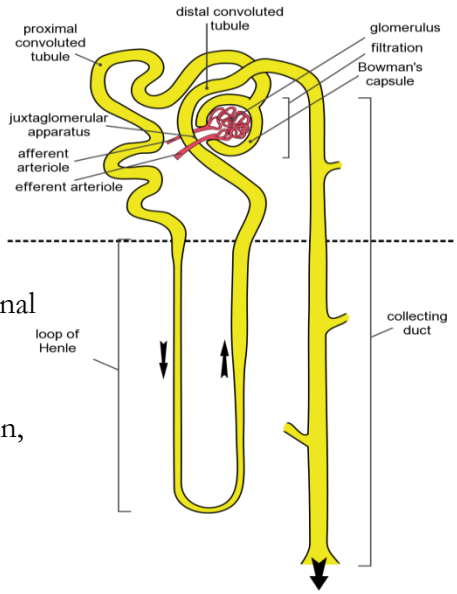
Urine formed within the kidneys passes from renal papillae into the minor calyces, then into the major calyces.

From the major calyces, urine is collected in the renal pelvis and exits the kidney through ureter.

Topic-177 Mammalian Kidney: Anatomy of Nephron

Nephron

The nephron is the functional unit of mammalian kidney. The number of nephrons per kidney varies from several hundred in lower vertebrates to many thousands in small mammals, and a million or more in humans and other large species.



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Structure of Nephron

The nephron consists of a renal corpuscle and a renal tubule.

Renal Corpuscle

The renal corpuscle is an expanded part at the closed end of renal tubule. It is composed of a network of capillaries called glomerulus which is responsible for the first step in urine formation i.e. ultrafiltration. Glomerulus is surrounded by a thin, double-walled, cup-shaped structure called Bowman's capsule.

Renal Tubule

It leads away from the Bowman's capsule.
The wall of the renal tubule is only one cell thick.

It has three portions:

- Proximal convoluted tubule
- Loop of Henle
- Distal convoluted tubule

The first portion of the tubule called proximal convoluted tubule is highly coiled.

The proximal convoluted tubule dips towards the renal pelvis into the medulla forming a sharp loop called loop of Henle.

It consists of a descending limb and an ascending limb.

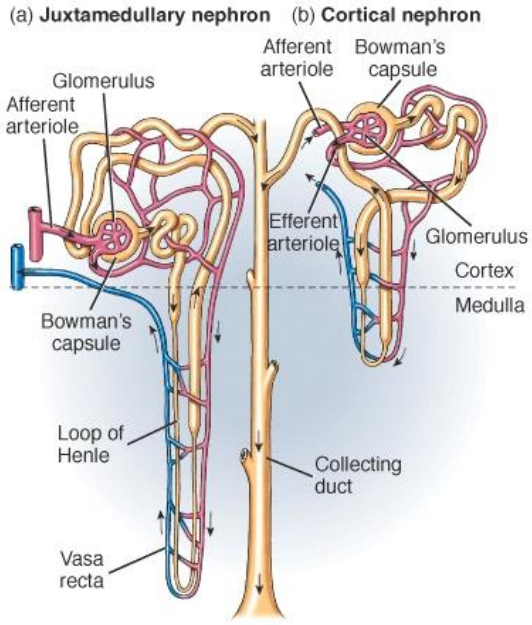
The ascending limb returns to the region of the renal corpuscle, where it becomes highly coiled again, and is called the distal convoluted tubule which is connected to the collecting duct.

Arrangement of Nephrons in Kidney

The glomeruli are found in the renal cortex, and the loops of Henle reach down into the papillae of the medulla; thus the nephrons are arranged in a radiating fashion within the kidney.

Based on the location of glomeruli and loop of Henle, nephrons are divided into two groups:

- Juxtamedullary nephrons, which have their glomeruli in the inner part of the cortex and long loops of Henle that plunge deeply into the medulla. These nephrons are specifically instrumental in the production of concentrated urine.
- Cortical nephrons, which have their glomeruli in the outer cortex and relatively short loops of Henle that extend only a short distance into the medulla



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Topic-178 Blood Supply to the Nephron

Blood Supply to Kidneys

Kidneys are about 1 % of total body weight in humans. In comparison to their small size, the kidneys receive a remarkably large blood flow, i.e. 20%-25% of the total cardiac output.

Due to high blood supply, kidneys filter the equivalent of the blood volume every 4-5 minutes.

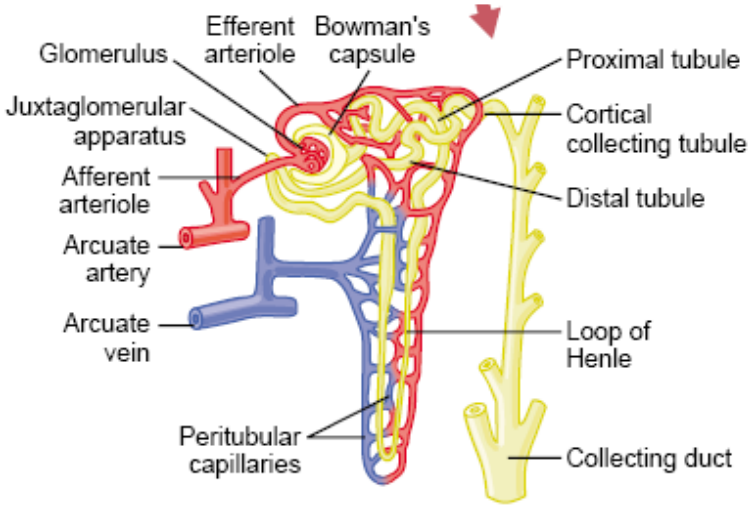
Blood Supply to the Nephron

Blood is supplied to the kidneys through renal artery.

Renal artery gives rise to branches called interlobular arteries which project into the cortex.

Interlobular arteries subdivide to form a series of short afferent arterioles.

Afferent arterioles supply blood to the renal corpuscle of each nephron and form glomerular capillaries.



Text book of medical physiology, Guyton. 11th ed. 2005

The capillaries of the glomerulus recombine to form an efferent arteriole; unlike most other vessels, which join to form veins.

Flow in the efferent arteriole is less than that in the afferent arteriole. So the glomerular capillaries have higher pressures than other capillaries because of the low-resistance input pathway and high resistance output pathway.

The efferent arteriole then subdivides once again to form another plexus of capillaries called peritubular capillaries that surround proximal and distal convoluted tubules and the loop of Henle.

The hairpin-loop like specialized part of peritubular capillaries that surround the loop of Henle is called vasa recta. It starts in the cortex region and then enters medulla along the descending loop of Henle and then re-enters cortex with ascending loop.

The peritubular capillaries drain into interlobular veins, which drain into renal vein which leaves the kidney.

Topic-179 Urine Production: Overview

Role of Kidneys

Kidneys function as excretory and osmoregulatory organs.

Their excretory functions include the filtration of nitrogenous wastes from blood and their removal in the form of urine.

Being osmoregulatory organs, kidneys control the amount of water excreted in the urine.

They produce dilute urine when body is flooded with water and form concentrated urine when body is dehydrated.

Urine Formation by Kidneys

The formation of urine involves three main processes:

- Glomerular filtration
- Tubular reabsorption
- Tubular secretion

Glomerular Filtration (Ultrafiltration)

- Glomerular filtration of plasma to form an ultrafiltrate is the first step in urine formation.
- It takes place in the renal corpuscle under pressure.
- The pressure comes from glomerular capillaries which have exceptionally high blood pressure than any other capillary bed in the body.
- Due to high filtration pressure, water and small solute molecules are filtered out of the glomerular capillaries.
- This filtrate is collected in the Bowman's capsule.
- Large molecules like proteins as well as blood cells and platelets are left behind in the blood.
- The filtered fluid in the Bowman's capsule is called glomerular filtrate.
- It has a chemical composition similar to that of blood plasma.

Tubular Reabsorption (Selective Reabsorption)

Approximately 99% of the water and most of the useful substances are selectively reabsorbed from the ultrafiltrate in the tubular part of the nephron into the blood in surrounding peritubular capillaries.

The major reabsorbed molecules include glucose, amino acids, vitamins and inorganic salts.

Due to reabsorption, the filtrate is converted into urine that has only left over nitrogenous and other waste substances when it leaves the tubule.

Tubular Secretion

- The epithelial cells of convoluted tubule secrete certain substances by active transport into the ultrafiltrate passing through the nephron's tubular part.
- e.g. ammonium and hydrogen ions
- Main purpose of this secretion is to maintain the pH of the urine.

Topic-180 Glomerular Filtration

Urine formation begins when a large amount of fluid that is virtually free of protein is filtered from the glomerular capillaries into Bowman's capsule.

Most substances in the plasma, except for proteins, are freely filtered, so that their concentration in the glomerular filtrate in Bowman's capsule is almost the same as in the plasma.

Filtration takes place in the renal corpuscle as fluids move across the three layered wall of the glomerulus and into the capsular space.

The process of ultrafiltration in the glomerulus is entirely passive and depends on three factors:

(1) Hydrostatic pressure difference between the lumen of the capillary and the lumen of Bowman's capsule, which favors filtration. The reason for hydrostatic pressure is the small diameter of efferent arteriole which offers considerable resistance. Relatively higher pressures are needed to force blood into it. As a result, glomerular pressures are high i.e. about 50 mm Hg, instead of 35 mm Hg typical of peripheral capillaries.

(2) The colloidal osmotic pressure that arises because of the separation of proteins during the filtration process. This pressure opposes filtration.

(3) The permeability of the three-layered glomerular filtration membrane separating these two compartments. This membrane acts as a molecular sieve, excluding almost all proteins from the ultrafiltrate based mainly on molecular size, but also on shape and charge. There is a bulk flow of water through the sieve carrying with it ions, glucose, urea, and many other small molecules.

Topic-181 Tubular Reabsorption

Tubular Reabsorption

As the glomerular filtrate enters the renal tubules, it flows sequentially through the successive parts of the tubule.

Along this course, some useful substances are selectively reabsorbed from the tubules back into the blood.

Reabsorption takes place in every segment of the renal tubule, however, the substances absorbed and their relative concentration changes from segment to segment.

Reabsorption at the PCT

The cells of the proximal convoluted tubule normally reabsorb 60–70 percent of the volume of the ultrafiltrate.

The PCT reabsorbs more than 99 percent of the glucose, amino acids, and other organic nutrients in the fluid. This reabsorption involves a combination of facilitated transport and cotransport.

The PCT actively transports several ions, including sodium, potassium, magnesium, phosphate, bicarbonate and sulfate ions. It also absorbs some ions passively.

Much of water is also reabsorbed from PCT.

The reabsorbed materials enter the peritubular fluid, diffuse into peritubular capillaries, and are quickly returned to the circulation.

Reabsorption in Loop of Henle

Reabsorption of water continues in the descending limb of the loop of Henle that is freely permeable to water due to numerous water channels formed by aquaporin proteins.

In contrast, there is a near absence of channels for salt and other small solutes, resulting in a very low permeability for these substances.

Unlike the descending limb, the ascending limb contains ion channels, but not water channels.

Overall, the loop of Henle reabsorbs about half of the water and two-thirds of the sodium and chloride ions from the filtrate entering it.

This reabsorption takes place efficiently by countercurrent exchange.

Reabsorption at the DCT

Only 15–20 percent of the initial filtrate volume reaches the distal convoluted tubule.

Throughout most of the DCT, the tubular cells actively transport Na^+ and Cl^- out of the tubular fluid.

Tubular cells along the distal portions of the DCT also contain ion pumps that reabsorb tubular Na^+ in exchange for K^+.

DCT also reabsorbs bicarbonate ions to regulate the pH of urine.

Topic-182 Tubular Secretion

The blood entering the peritubular capillaries still contains a number of potentially undesirable substances that did not cross the filtration membrane at the glomerulus.

Such substances are secreted directly through the tubular cells into the tubules into the out going urine.

Secretion takes place in every segment of the renal tubule. However, most substances are secreted in the PCT and DCT.

Secretion at the PCT

The proximal tubule is an important site for secretion of organic acids and bases, bile salts, oxalate, urate, and catecholamines.

Many end products of metabolism, harmful drugs and toxins that must be rapidly removed from the body through urine are also secreted through the tubular cells into the tubules.

Secretion at the DCT

The distal convoluted tubule is involved in the secretion of potassium and hydrogen ions.

Ammonium ions are also pumped into the tubular fluid by sodium-linked countertransport.

Secretion of Potassium Ions

Tubular cells secrete excess potassium ions in body fluids by exchanging them with sodium ions which are reabsorbed. These potassium ions diffuse into the lumen of the DCT through potassium leak channels at the apical surfaces of the tubular cells.

Secretion of Hydrogen Ions

Hydrogen ion secretion is also associated with the reabsorption of sodium. H^+ secretion involves generation of carbonic acid by the enzyme carbonic anhydrase. Carbonic acid dissociates to generate hydrogen ions which are secreted in exchange for Na^+ in the tubular fluid.

Hydrogen ion secretion acidifies the tubular fluid while elevating the pH of the blood. Hydrogen ion secretion speeds up when the pH of the blood falls.

Topic-183 Glomerular Filtration Rate

The Glomerular Filtration Rate (GFR)

The glomerular filtration rate (GFR) is the amount of filtrate the kidneys produce each minute.

Each kidney contains about 6 m^2 of filtration surface, and the GFR averages an astounding 125 mL per minute. This means that roughly 10% of the fluid delivered to the kidneys by renal arteries leaves the bloodstream and enters the capsular spaces.

In the course of a single day, the glomeruli generate about 180 liters (48 gal) of filtrate, roughly 70 times the total plasma volume. But as filtrate passes through the renal tubules, about 99 percent of it is reabsorbed.

Factors Affecting GFR

1. **Net filtration pressure**
   The glomerular filtration rate depends on the net filtration pressure across glomerular capillaries.
   Any factor that alters the net filtration pressure also alters the GFR and affects kidney function.
   One of the most significant factors is a drop in renal blood pressure.
   If blood pressure at the glomeruli drops by 20 percent (from 50 mm Hg to 40 mm Hg), kidney filtration ceases, because the net filtration pressure is 0 mm Hg.
   For this reason, the kidneys are sensitive to changes in blood pressure that have little or no effect on other organs.
2. Hemorrhaging, shock, and dehydration are relatively common clinical conditions that can cause a dangerous decline in the GFR and lead to acute renal failure.

Importance of GFR

- Glomerular filtration is the vital first step for all other kidney functions.
- If filtration does not take place, waste products are not excreted and pH control is lost.

Control of the GFR

A variety of regulatory mechanisms ensure that GFR remains within normal limits.

Three interacting levels of control stabilize GFR:

(1) Autoregulation, at the local level. It involves changes in the diameters of afferent arterioles, efferent arterioles, and glomerular capillaries to maintain GFR.
(2) Hormonal regulation, initiated by the kidneys through renin–angiotensin system and the natriuretic peptides.

(3) Autonomic regulation, primarily by the sympathetic division of the autonomic nervous system.

Topic-184 Regulation of pH by Kidneys

Importance of pH Regulation

Within the human body, blood must be maintained within the narrow alkaline pH range of 7.35 to 7.45. Outside that range, pH becomes incompatible with life as proteins are denatured and enzymes lose their ability to function.

Role of Kidneys in pH Regulation

Kidneys play important role in maintaining pH by two ways:

1. Bicarbonate buffering system
2. Removal of fixed acids and H^+

1 Bicarbonate Buffering System

- Buffer systems minimize changes in pH.
- Most important buffer system is the CO_2/HCO_3^- buffer.
- By adjusting the level of HCO_3^- the kidney is able to adjust pH, without elimination of excess hydrogen
- Under normal circumstances all filtered HCO_3^- is reabsorbed from the filtrate in kidney.

Bicarbonate Reabsorption

- Kidneys reabsorb 4,000 to 5,000 mmol of the filtered bicarbonate ions daily which is equivalent to the removal of the same amount of H^+.
- About 85 to 90% of the filtered bicarbonate is reabsorbed in the proximal tubule while the rest is reabsorbed by the thick ascending limb, distal tubule and collecting ducts.

Bicarbonate Reabsorption Mechanism

- Absorption of bicarbonate is facilitated by the secretion of H^+ in the PCT lumen by the A-type cells.
- H^+ ions are secreted by three mechanisms:
  - Via a Na^+-H^+ antiporter in the PCT and ascending limb
  - Via H^+-ATPase (proton pump) in the PCT and DCT
  - H^+-K^+ ATPase in the collecting duct
- Secreted H^+ ions combine with filtered HCO_3^- to form CO_2 and H_2O. The CO_2 is lipid soluble and diffuses into the tubular cell. In the cell, it combines with OH^- to produce bicarbonate.
- The HCO_3^- crosses the basolateral membrane via a Na^+-HCO_3^- symporter that transfers three HCO_3^- into the blood for every one Na^+.

This mechanism does not lead to the net excretion of any H^+ from the body as the secreted H^+ is consumed in the reaction with the filtered bicarbonate in the tubular lumen.

Removal of Fixed Acids and H^+

- Kidneys are also responsible for the excretion of fixed acids i.e. acidic anions (citrate, acetate, gluconate, lactate) and associated H^+.
- Kidneys excrete about 70-100 mmols of fixed acids per day. This helps to maintain the plasma $[H^+]$ of only 40 nanomoles/litre.

Mechanisms for Removal of H^+

H^+ ions (acids) are removed as:

1. Ammonium ions
2. Bound to filtered buffers

Excretion of Ammonium Ions

- Ammonium ions (NH_4^+) are produced from glutamine.
- Filtered glutamine is absorbed into proximal tubular cells and metabolized to NH_4^+ (ammonium) and HCO_3^-.
- HCO_3^- diffuses into blood, and the NH_4^+ is secreted into the tubule via the NH_4^+-Na^+ antiporter and eliminated in urine.
- As NH_4^+ is formed of NH_3+H^+, so causes removal of acidic H^+ ions.

Removal of H^+ Bound to Filtered Buffers

- Secreted H^+ may also combine with a filtered buffer (e.g. PO_4^{3-}).
- These H^+ ions are not reabsorbed.
- About 36 mmol of H^+ is eliminated with filtered PO_4^{3-} each day, with each PO_4^{3-} binding two H^+ ions.

Topic-185 Urine Concentrating Mechanisms

Production of Hypertonic Urine

- Mammalian kidneys can produce hypertonic urine as compared to blood plasma.
- The loop of Henle is considered to be of central importance in concentrating the urine.
- Vertebrates that lack the loop of Henle are incapable of producing hyperosmotic urine.
- The animals which produce very concentrated urine (such as desert animals) have very long loops of Henle capable of creating a very large osmotic gradient.

Countercurrent Multiplication in Loop of Henle

- Efficiency of reabsorption in loop of Henle is due to a countercurrent exchange system between its descending and ascending limbs.
- Both limbs lie very close together and are separated by a peritubular fluid.
- Filtrate moves in opposite directions in both limbs.
- During the movement, exchange of water and salts occurs between the filtrate in two limbs and peritubular fluid.
- This exchange is referred to as countercurrent multiplication.

Countercurrent Multiplication: Mechanism

- The two parallel limbs of the loop of Henle have very different permeability characteristics.
- The descending limb is permeable to water but impermeable to solutes. Thus water moves through the tubular wall into the peritubular space. This makes the filtrate hypertonic. This filtrate enters the ascending limb.
- The ascending limb is impermeable to water but permeable to solutes.
- From the filtrate in ascending limb, Na^+, Cl^-, and K^+ are actively transported out into the peritubular space.
- This makes fluid in peritubular space hypertonic and creates an osmotic pressure.
- Osmotic pressure causes more water to be drawn out of the descending limb into the peritubular space.
- This makes filtrate in the descending limb more hypertonic.
- Arrival of a highly concentrated solution in the thick ascending limb speeds up transport of sodium and chloride ions out into the peritubular fluid.
- Thus countercurrent flow within the descending and ascending limb increases, or multiplies the osmotic gradient between tubular fluid and interstitial space, causing osmotic removal of more and more water from the filtrate.

Role of Vasa Recta

Absorbed water enters into the circulatory system from the interstitium via the vasa recta, which surround the loop of Henle.

Role of ADH

The amount of water reabsorbed and concentration of urine is controlled by antidiuretic hormone, which affects the water permeability of renal tubules.

Topic-186 Renal Regulatory Mechanisms

The osmoregulatory function of mammalian kidney is regulated by a combination of nervous and hormonal controls.

Nervous Controls

The kidney is innervated with efferent sympathetic nerve fibers reaching the renal vasculature, the tubules, the juxtaglomerular granular cells, and the renal pelvic wall.

Stimulation of efferent renal sympathetic nerve reduces renal blood flow, urinary sodium excretion and increase renin secretion.

Kidneys are also supplied with renal sensory nerves which mainly innervate the renal pelvic wall.

Activation of the sensory nerves elicits an inhibitory reflex that causes a decrease in efferent renal sympathetic nerve activity leading to natriuresis (excretion of sodium in the urine).

Hormonal Controls

The Hormones affecting kidney function include:

- Antidiuretic hormone (ADH)
- Renin-Angiotensin-Aldosterone System
- Atrial natriuretic peptide (ANP)

Antidiuretic Hormone (ADH)

Osmoreceptor cells in the hypothalamus monitor the osmolarity of blood and regulate release of ADH from the posterior pituitary.

ADH is released in response to an increase in osmolarity above the set point of 300 mosm/L.

When ADH reaches the kidney, its main targets are the distal tubules and collecting ducts. ADH makes the epithelium more permeable to water, resulting in increased water reabsorption and concentration of urine, reduced urine volume, and lowering blood osmolarity back toward the set point.

A reduction in blood osmolarity below the set point has the opposite set of effects.

Renin-Angiotensin-Aldosterone System (RAAS)

The RAAS is present in a specialized tissue called the juxtaglomerular apparatus (JGA), located near the afferent arteriole that supplies blood to the glomerulus.

When blood pressure or blood volume in the afferent arteriole drops JGA releases the enzyme renin. Renin initiates chemical reactions that yield a peptide angiotensin II.

Angiotensin II raises blood pressure by constricting arterioles, decreasing blood flow to the nephrons. It also stimulates the adrenal glands to release aldosterone. Aldosterone acts on distal tubules, making them reabsorb more sodium (Na^+) and water, thus increasing blood volume and pressure.

Atrial Natriuretic Peptide (ANP)

The walls of the atria of the heart release ANP in response to an increase in blood volume and pressure.

Atrial natriuretic peptide (ANP), opposes the RAAS.

It inhibits the release of renin from the JGA, inhibits NaCl reabsorption by the collecting ducts, and reduces aldosterone release from the adrenal glands.

These actions lower blood volume and pressure.

Topic-187 Nitrogenous Wastes in Animals

Nitrogenous Wastes

Catabolism of nitrogen containing macromolecules results in formation waste and toxic byproducts.

The major nitrogenous waste is the amino group ($–NH_2$) which is produced by the catabolism of amino acids during deamination. It is highly toxic and is removed by the animals in three forms: Ammonia, urea and Uric acid.

Many other nitrogenous waste metabolic byproducts are produced in lower quantities. These include: creatinine, creatine and trimethylamine oxide.

Metabolism of purine and pyrimidine bases produces significant amount of nitrogenous wastes: hypoxanthine, xanthine and allantoin in addition to uric acid, urea and ammonia.

Major Nitrogenous Wastes

The byproducts of amino acid metabolism i.e. ammonia, urea and uric acid are considered as the major nitrogenous wastes which are excreted by animals in large quantities.

Ammonia

Ammonia is highly toxic and needs to be immediately excreted out of the body. It requires large amount of water for its excretion. Excretion of one gram of ammonia requires about 0.5 liters of water. So, only aquatic animals use it as major excretory product.

Urea

Terrestrial animals convert ammonia into urea or uric acid which can be excreted with less water loss.

Urea is less toxic than ammonia. It requires only 0.05 liters of water to excrete 1 g of urea, i.e. only 10% as compared to ammonia. Urea synthesis, however, consumes ATP that is energetically costly.

Uric Acid

Excretion of uric acid requires even less water i.e. only 0.001 liter for 1 g uric acid which is only 1% as compared to ammonia.

Uric acid is only slightly soluble in water and is excreted as a white pasty precipitate.

Evolutionary Trends in Excretion of Nitrogenous Wastes

In the course of evolution, different animal groups have adapted to produce mainly one of these forms for excretory purposes during whole or part of their life cycles.

In general, water availability and habitat determines the nature and pattern of nitrogenous waste excretion.

Topic-188 Excretion of Ammonia: Ammonotelic Animals

Ammonotelic Animals

- Animals which excrete their nitrogenous wastes principally as ammonia are called ammonotelic animals.
- Most teleost fishes and aquatic invertebrates are ammonotelic. They produce little or no urea, as they have plenty of water for removal of ammonia.

Formation of Ammonia

- The deamination of amino acids in cells removes amino group (NH_4^+).
- The amino groups are transferred to glutamate with the aid of a transaminase enzyme.
- Glutamate is deaminated in the liver to form ammonium ions and α-ketoglutarate.
- In mammals and urea excreting animals, most of these ammonium ions are converted to urea by urea cycle in liver. However small amounts of ammonia are left which are excreted in their urine.
- In fishes and other ammonotelic animals, ammonium ions dissolve in plasma water to form ammonia which is excreted either through gills or kidneys.
- Liver also converts glutamate to glutamine, which is much less toxic than ammonia. Glutamine is released from the liver into the blood.

Excretion of Ammonia through Kidneys

- Glutamine is taken up by the kidneys.
- Cells of the kidney tubules deaminate glutamine, liberating ammonia into the tubular fluid.
- The excreted ammonia in tubular fluid takes up a proton to form the NH_4^+, which cannot diffuse back into the tubular cells and thus leaves the body via the urine.
- In this way, glutamine, which is nontoxic, acts as the amino-group carrier through blood and tissues until its deamination in the kidney.

Excretion of Ammonia through Gills

- Most of ammonia excretion in fishes occurs by passive diffusion through gill surfaces. Gill membranes permit diffusion as they are highly permeable to ammonia.
- As H^+ and carbon dioxide are also excreted through gill surface, they acidify the water next to gill surface. Acidified water traps NH_3, so ammonia excretion is enhanced.

Toxicity of Ammonia

- A blood concentration of only 0.05 mmol/L ammonia is toxic to most animals, causing convulsions, coma and death.

- The toxicity of NH_3 is due in part to the elevation of pH it produces, which causes changes in the tertiary structure of proteins.
- Ammonia also interferes with some ion-transport mechanisms, because NH_4^+ substitutes for K^+ in some cases.
- Ammonia can also affect brain blood flow and some aspects of synaptic transmission, particularly glutamate metabolism.

Topic-189 Excretion of Urea: Ureotelic Animals

Ureotelic Animals

Animals which excrete nitrogenous wastes as urea are known as ureotelic animals.

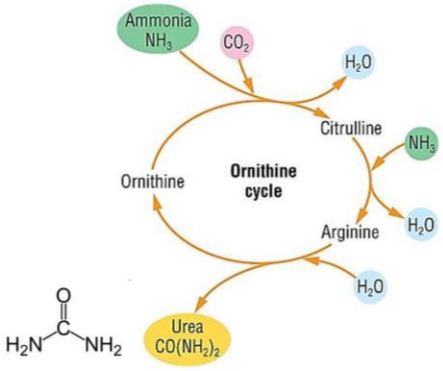
Urea is far less toxic than ammonia, and requires much less water for excretion.

A urea molecule contains two nitrogen atoms, so excreting urea has double efficiency in removal of nitrogenous waste as compared to ammonia.

Formation of Urea

Urea is formed from ammonia. Ureotelic animals utilize one of two pathways for urea formation:

- Ornithine-urea cycle
- Uricolytic pathway

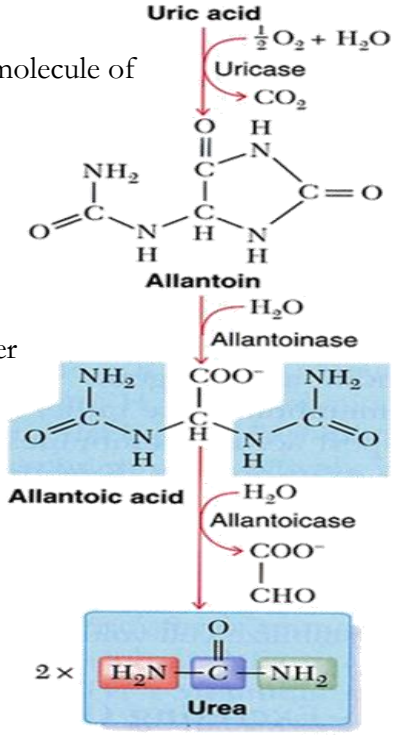


Ornithine-Urea Cycle

- All vertebrates except most teleost fishes, synthesize urea primarily in the liver via the ornithine-urea cycle.
- In this cycle, two ammonia and one CO_2 molecule are added to ornithine to form arginine.
- Arginine is cleaved by the enzyme arginase, to remove a molecule of urea and regenerate ornithine.

Uricolytic Pathway

- Most teleosts and many invertebrates utilize the uricolytic pathway.
- In this pathway, urea is produced from uric acid that either arises from a transamination via aspartate or is produced during nucleic acid metabolism.
- Uric acid is first converted to allantoin with the help of enzyme uricase. Allantoin is converted to allantoic acid with the help of enzyme allantoinase.
- Allantoic acid is then converted to urea using allantoicase enzyme.



Most mammals don't have uricase, allantoicase and allantoinase enzymes and thus excrete uric acid as an end product of nucleic acid metabolism.

Topic-190 Excretion of Uric Acid: Uricotelic Animals

Uricotelic Animals

Animals which excrete nitrogen chiefly in the form of uric acid or the closely related compound guanine are known as uricotelic animals.

In general, uricotelic animals are adapted to conditions of limited availability of water.

They include: birds, reptiles, and most terrestrial arthropods.

Uric acid and guanine have the advantage of carrying away four nitrogen atoms per molecule.

Formation of Uric Acid

Uric acid is formed by the conversion of ammonia and urea in uricotelic animals.

It is also formed during the metabolic breakdown of the amino acids glycine, aspartate, and glutamine.

It is also formed by the breakdown of purine and pyrimidine bases of nucleic acids.

Transport and Excretion of Uric Acid

Uric acid is transported from the blood into the cells of the renal tubule via a urate-anion exchanger or via a urate uniporter.

It then moves from the cells into the lumen of the tubule down an electrochemical gradient and is excreted in the urine.

Uric acid, because of its low solubility, precipitates and is excreted with very little urinary water.

Physiology of the Digestive Tract

TOPIC-191 Overview of the Alimentary Systems

Roles of Alimentary Systems

Alimentary systems procure food for the animal and convert it to usable form by the body of an animal through the process collectively called as nutrition.

The major steps of animal nutrition include:

- Digestion of food
- Absorption of digested food
- Egestion (Removal of indigestible wastes)

Types of Alimentary Systems

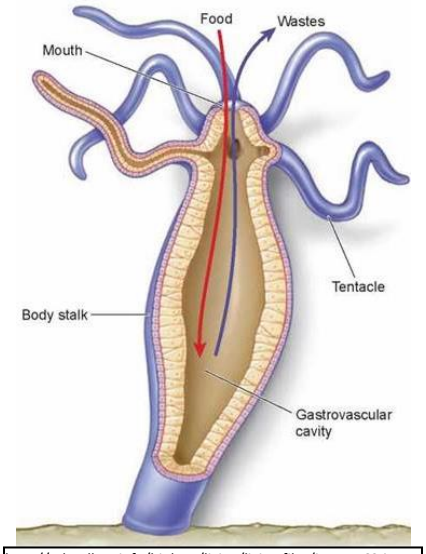
There are two basic plans of alimentary systems observed in animals:

1. **Sac-like Gastrovascular Cavity**
2. **Tubular Alimentary Canal or Gut**

1. Sac-like Gastrovascular Cavity

The sac-like gastrovascular cavity is characteristic feature of Cnidarians.

This cavity has only one opening, the mouth that serves for both ingestion as well as egestion.



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2. Tubular Alimentary Canal or Gut

The complex bilateral animals have a hollow, tubular cavity which is open at both ends with two openings: mouth for ingestion and anus for egestion.

Such a tube is called a complete digestive tract or alimentary canal.

Alimentary Canal allows unidirectional flow of food materials, increasing the efficiency of digestive and absorptive processes.

The food passes through the canal through various regions that have specializations for different types of digestive actions involving:

- mechanical, chemical and bacterial treatment of the food for digestion
- absorption of products of digestion
- storage of undigested waste materials

TOPIC-192 Generalized Alimentary Canal

The alimentary canal of all animals has a basic tubular organization that extends between two openings, a mouth and an anus.

Mammalian Digestive Tract

The mammalian digestive tract is a representative example of an alimentary canal.

Regions of the Alimentary Canal

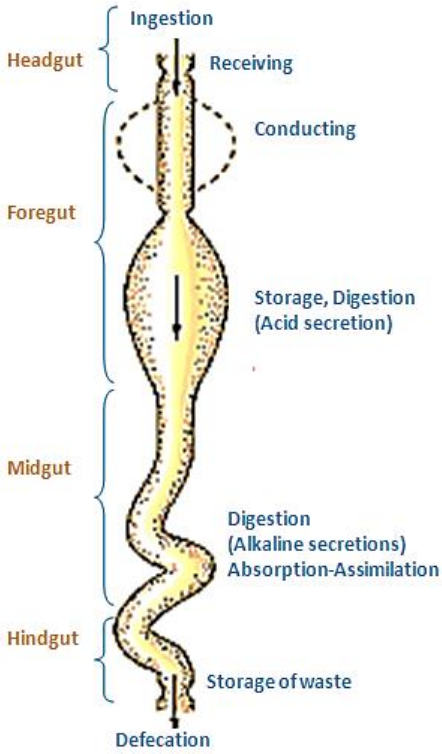
In general, alimentary canals can be divided on a structural and functional basis into four major divisions:

(1) Headgut: specialized for receiving ingested material. Includes Buccal cavity and pharynx

(2) Foregut: specialized for conducting, storing, and digesting ingested material. Includes esophagus and stomach. Also includes crop in some animals.

(3) Midgut: specialized for digesting and absorbing nutrients. Includes small intestine: duodenum, jejunum and ileum.

(4) Hindgut: specialized for absorbing water and defecating. Includes large intestine: colon, cecum, rectum and anus.



Regional Specialization

Alimentary canal's specialized regions allow particular digestive tasks to be carried out in a stepwise fashion.

Ingested material is subjected to various mechanical, chemical, and bacterial treatments as it passes through this canal, and digestive juices, primarily enzymes and acids, are mixed with the ingested material at appropriate regions in the alimentary canal.

It also allows both acidic and alkaline secretions to occur at the same time in different parts.

Accessory Glands

In mammals, the alimentary canal is associated with various accessory glands that secrete digestive juices through ducts into the gut.

The accessory glands of the mammalian digestive system are:

- Three pairs of salivary glands
- Gastric glands
- Pancreas
- Liver

- Gallbladder

TOPIC: 193 Headgut

Headgut is the anterior region of the alimentary canal that receives food through ingestion.

It consists of organs and structures for feeding and swallowing.

The major organs of headgut include:

- Buccal cavity with associated structures mouthparts, teeth, tongue, and salivary glands
- Pharynx

Buccal Cavity

Buccal cavity is the space behind mouth. It has teeth, tongue, and salivary glands.

Functions of Buccal Cavity

Buccal cavity performs many important functions:

1. Food selection

Buccal cavity selects food through taste and feeling.

The food entering the buccal cavity is selected and swallowed if its taste and feeling is good. Otherwise it is rejected.

2. Food handling and Mastication

Teeth and tongue play role in food handling and mastication.

Teeth are present in all vertebrates. They are used for holding or tearing the prey. In most mammals, they also grind the food by the process known as mastication.

Tongue is also present in vertebrates and assists in grasping, handling and rolling the food during mastication.

Tongue is also important in the swallowing process.

Tongue is also used in chemoreception as it bears taste buds which are gustatory receptors.

3. Lubrication and chemical digestion:

Salivary glands produce saliva that lubricates the food material. Lubrication assists swallowing.

Saliva also contains digestive enzyme, salivary amylase, which helps in semi-digestion of starch content in food.

Swallowing

Swallowing is the process that allows the bolus of food to pass from the buccal cavity through the pharynx into the esophagus.

It involves integrated movements of muscles in the tongue and pharynx, as well as peristaltic movements of the esophagus.

Process of Swallowing

Swallowing occurs in following steps:

(a) Tongue pushes the bolus to the back of mouth.
(b) Soft palate moves upwards and to the rear. This action closes the nasal cavity.
(c) Larynx moves upward and forces the cartilaginous epiglottis into horizontal position. Thus glottis, the opening of trachea is closed. This step is very crucial to prevent the entry of bolus into the trachea----which may be life-threatening.

The beginning of swallowing action is voluntary, but once food reaches the back of buccal cavity, swallowing becomes involuntary, under direct neural control of the medulla oblongata of the brain.

TOPIC-194 Foregut: Esophagus and Crop

The foregut consists of the food conducting region i.e. esophagus and storage region i.e. stomach. In some animals it also includes a crop.

Esophagus

After being swallowed, food enters the esophagus which is a tube that leads from the pharynx to the stomach which is a storage as well as digestive region.

Esophagus does not produce any digestive secretion or enzymes and only the previous digestive actions of saliva continue during this conduction.

Peristalsis

The esophagus conducts the bolus by peristaltic movement.

Peristaltic movements are the waves of contraction and relaxation in the smooth muscles of alimentary canal walls.

These movements start from oral cavity and end at the distal end of rectum.

Crop

In some animals, esophagus contains a sac-like expanded section, the crop, which is used to store food before digestion.

Crop is generally found in those animals that feed infrequently. It allows quantities of food to be stored for digestion at a later time.

Crop—Examples:

Many birds e.g. chicken.

Leeches, which feed very infrequently, with weeks or months between feeding periods.

In some animals crops are also used to ferment or digest foods for purposes other than normal digestive process. For example some parent birds prepare food in this way to be regurgitated for their nestlings e.g. pigeon's milk.

Topic-195 Foregut: Stomach

Functions of Stomach

1. Stomach is the part of foregut that serves as a food storage organ.
2. In many vertebrates it also carries out initial stages of protein digestion by secreting the enzyme pepsinogen (pepsin) in a highly acidic environment (due to hydrochloric acid) required for pepsin activation.
3. It is also involved in mechanical grinding and mixing of food contents by contraction of its muscular walls.

Types of Stomach in Vertebrates

Based on the number of chambers, stomachs are classified as:

- Monogastric stomachs
- Digastric stomachs

Monogastric Stomachs

A monogastric stomach consists of a single strong muscular tube or sac.

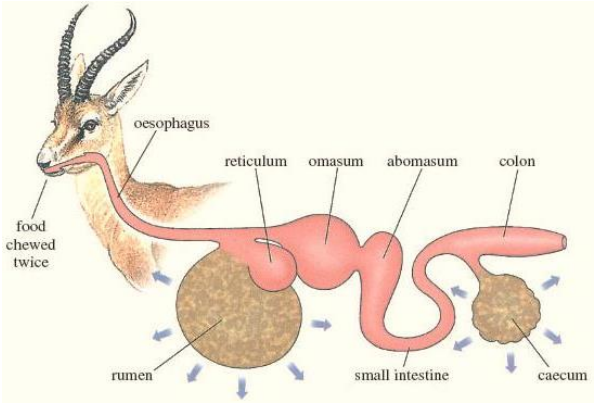
Carnivorous and omnivorous vertebrates have a monogastric stomach.

Digastric Stomachs

Digastric stomachs are multichambered and are found in ruminant mammals of order Artiodactyla e.g. deer, giraffe, sheep, cattle, camel, llama etc.

These stomachs have four chambers which are separated into two divisions.

- The first division consists of fermentation chambers called rumen and reticulum.
- The second division comprises the omasum and abomasum (true stomach).



Fermentation Chambers

The rumen and reticulum receive grazed vegetation and act as fermentation chambers.

These chambers have bacteria and protozoans that cause extensive digestive breakdown by fermentation of carbohydrates.

Omasum

Symbiotic microorganisms grown in the rumen, along with undigested particles, are passed into the omasum and then into the abomasum.

Abomasum

Abomasum is homologous to the monogastric stomach of non-ruminants that secretes digestive enzymes.

Stomach of Birds

The stomach of birds has two chambers:

- A highly muscular grinding chamber, the gizzard (also known as the muscular stomach or ventriculus). It also contains swallowed sand, pebbles, or stones which aid in the grinding of seeds and grains.
- The secretory true stomach called the proventriculus

Some fishes, insects and decapod crustaceans also have variation of this pattern.

Topic-196 Midgut: Small Intestine

In vertebrates, midgut comprises of the small intestine which is the major site for chemical digestion and absorption of food.

While digestion occurs in acidic medium in stomach, in small intestine, it occurs in an alkaline environment.

Divisions of Midgut

The vertebrate midgut or small intestine is typically divided into three distinct portions:

- **Duodenum.** The first, shorter section (25 centimeters in human). It receives food from stomach through pyloric sphincter. It secretes mucus and enzymes and receives bile salts from gall bladder to assist in emulsification of fats and enzyme-containing pancreatic juice from pancreas which aid in digestion.
- **Jejunum.** A longer part (about 2.5 meters long in human) Also secretes enzymes and is involved in digestion and absorption.
- **Ileum.** Acts primarily to absorb nutrients digested in the duodenum and jejunum. It also secretes some enzymes which complete the digestion of food.

Length of the Small Intestine

The length of human small intestine is about 6 meters.

Carnivorous vertebrates have shorter and simpler intestines than herbivores.

It reflects the shorter time required to digest meat than vegetation.

For example, a tadpole, which is herbivore, has a longer intestine than the adult frog, which is carnivorous.

Intestinal Symbionts

Intestine of most animals contains large numbers of bacteria, protozoans, and fungi.

These microorganisms contribute enzymatically to digestion.

Another important function of some intestinal symbionts is the synthesis of essential vitamins.

Topic-197 Absorptive Epithelium of Intestine

Absorption

Digested nutrients in the lumen of alimentary canal need to be absorbed to reach body tissues.

Most of the absorption occurs by crossing the epithelial lining of ileum of small intestine.

The epithelial lining of ileum is specialized for absorptive functions. These specializations include an increase in the surface area for absorption and supply of transport system to carry the absorbed nutrients.

Adaptations to Increase Surface Area

Intestinal folds

The luminal wall of small intestine has numerous circular folds.

These folds increase the surface area of the intestine.

Villi

Each circular fold has thousands of finger-like projections called villi.

Each villus is about 1 mm long.

Due to villi, internal surface of ileum exhibits velvety appearance.

Epithelial Cells of Villi

Each villus has a covering of epithelial cells which make the actual absorptive surface of the small intestine.

Microvilli

Each epithelial cell has several thousand, closely packed cylindrical processes on its apical surface called microvilli, exposed to the intestinal lumen. Each microvillus is 0.5 to 1.5 µm long and about 0.1 µm wide.

Large number of microvilli, laying side-by-side, gives the intestinal epithelium a brush-like appearance that is generally referred to as brush border.

The microvilli greatly increase the total capacity for nutrient absorption.

Supply of Transport System

Internally, it has a network of blood vessels-arterioles, capillaries and venules-and a network of lymph vessels, the largest of which is the central lacteal.

Nutrients taken up from the intestine are transferred into these blood and lymph vessels for transport to other tissues; the central lacteal can, in addition, take up larger particles.

Surface Area for Absorption

The intestinal folds, villi and microvilli collectively increase the surface area available for absorption more than 500 times. The total area for absorption in small intestine of human is 200-300 m^2 as compared to the small intestine's gross cylindrical area of 0.4 m^2.

Topic-198 Hindgut: Large Intestine

Hindgut includes the large intestine which is comprises of colon, cecum, and rectum.

Junction of Small and Large intestine

The small intestine connects to the large intestine through the ileocolic sphincter that controls the movement of material entering the large intestine. It opens and closes time to time to allow small amount of residue from ileum to enter the large intestine.

The junction of small and large intestine forms a T, having a sac-like cecum on one side and the longer colon on the other side.

Cecum

The cecum is a blind sac that is large and functional in non-ruminant herbivore mammals. It harbors bacteria and microorganisms for fermenting plant material.

Humans have a relatively small cecum with a finger-like extension, the appendix which is about 9 cm long.

Appendix has no role in digestion or absorption but has an undefined role in immunity as it has many lymph nodes.

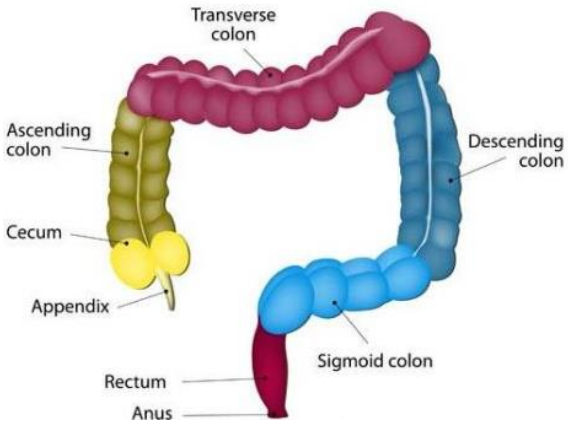
Colon

The colon is about 1.5 m long and consists of four parts: ascending colon, transverse colon, descending colon and sigmoid colon.

Colon receives the undigested part of the food along with inorganic ions and excess water.

Ions and water are absorbed by the colon.

As water is absorbed, indigestible wastes become increasingly solid and are converted into feces as they move along the colon by peristalsis.



It takes approximately 12-24 hours for material to travel the length of the colon and reach the rectum for elimination through the anus.

Rectum

The terminal portion of the large intestine is the rectum which is a straight muscular tube that begins at the termination of sigmoid colon and ends at the anal canal.

In the rectum, feces are stored until they can be eliminated.

Anal Canal

The last 2-3 cm of the digestive tract forms the anal canal.

It begins at the inferior end of the rectum and ends at the anus.

Anal Sphincters

There are two sphincters between the rectum and the anus. The inner sphincter is formed from smooth muscle and is involuntary and the outer one is formed from skeletal muscle and is voluntary.

Defecation Reflex

Periodic strong contractions of the colon cause defecation reflex, opening of the anal sphincters that creates an urge to defecate.

Topic-199 Motility of the Alimentary Canal

The ability of the alimentary tract to contract and propel ingested material along its length is called motility.

The motility depends on the activity of smooth muscle walls and/or ciliary lining of the digestive tract.

Motility of alimentary canal is important for many digestive functions to happen.

It is significant for:

1. Conduction/translocation of food
2. Mechanical treatment of food
3. Prevent Scumming

Conduction of Food

Correctly timed translocation of food along the entire length of the alimentary canal is necessary.

Due to this translocation, food reaches the various parts that have specialized surfaces for secretion of digestive enzymes, absorption of the products of digestion and absorption of water and ions.

It is also important for the expulsion of fecal material.

Mechanical treatment of food

Ingested food materials include larger components. It is necessary to breaking them into smaller soluble forms on which enzymes and bile salts can act.

This involves grinding and kneading actions due to the muscular activity of the alimentary canal.

Muscular activity is also necessary to mix the digestive juices with the food contents.

Mixing of the luminal contents is achieved primarily by a process called segmentation.

Segmentation consists of asynchronous contractions of the circular muscle layer that occur along the wall of gut at various points without participation of the longitudinal muscle.

Prevent Scumming

Motility ensures mixing of the contents so that there is continuous renewal of material in contact with the absorbing and secreting surfaces of the epithelial lining of alimentary canal.

This is important to prevent any layer formation and clogging of the surfaces that may reduce the absorptive or secretory area.

Topic-200 Muscular and Ciliary Motility

Motility of alimentary canal is achieved by two different mechanisms:

- Muscular motility
- Ciliary motility

Muscular Motility

Muscular motility is involved in the transport of food content by muscle contraction of the walls of the alimentary canal.

Muscular mechanisms permit handling of harder and larger pieces of food.

It is the only mechanism found in arthropods and chordates.

In chordates, motility is achieved strictly by smooth muscle fibers. The rhythmic contraction and relaxation of smooth muscles of the alimentary canal is called peristalsis that pushes the food throughout the digestive tract.

In many arthropods motility is achieved by contraction of striated fibers (skeletal muscles).

Ciliary Motility

Ciliary motility involves beating of the cilia lining the digestive tract.

Cilia generate fluid currents that propel food within the digestive tube.

Ciliary motility is the only mechanism used to translocate food along the alimentary canals of annelids, many mollusks, tunicates, and cephalochordates.

Muscular digestive tracts are lined by cilia in echinoderms and most mollusks. So, they use both mechanisms simultaneously.

Topic-201 Peristalsis

Peristalsis—Definition

The continuous contractions and relaxations of the circular and longitudinal muscles that produce alternating waves of constriction and distension in the lumen of the alimentary canal are known as peristalsis.

Peristalsis starts from the buccal cavity and continues along the esophagus to the stomach and then along the whole alimentary canal till the rectum.

Peristalsis—Mechanism

The arrangement of the alimentary smooth musculature in vertebrates consists of an inner circular layer and an outer longitudinal layer.

The contraction of the inner circular layer is coordinated with relaxation of the outer longitudinal layer. This coordination produces constriction in the lumen.

Alternatively, contraction of the longitudinal layer with relaxation of the circular layer produces distension.

Peristalsis—Roles

1. **Push the food**
   Peristalsis results in pushing the food along the alimentary canal in the direction of the peristaltic wave.
   It pushes the food from mouth to anus, inducing swallowing and culminating in defecation.
2. **Regurgitation and Vomiting**
   Regurgitation occurs when peristalsis takes place in the reverse direction, moving the luminal contents back into the buccal cavity.
   Ruminants regularly use regurgitation to bring up the unchewed food for further chewing.
   Reverse peristalsis in non-ruminants results in emesis (vomiting).

Topic-202 Control of Alimentary Canal Motility

Alimentary canal motility in vertebrates involves coordinated contractions of circular and longitudinal smooth muscle layers.

This coordination is regulated by a combination of intrinsic and extrinsic (neural and hormonal) mechanisms.

Intrinsic Mechanisms

- The smooth muscle tissue in the wall of the alimentary tract is myogenic.
- It is capable of producing an intrinsic cycle of electrical activity that leads to muscle contraction without external neural stimulation.
- This cycle occurs due to rhythmic depolarizations and repolarizations called the basic electric rhythm (BER).
- This rhythm consists of spontaneous slow waves of depolarization that progress slowly along the muscle layers.
- Some of these slow waves give rise to action potentials (APs) produced by an inward current carried by calcium ions.
- These calcium currents lead to contractions of the smooth muscle cells.
- The amplitude of the slow-wave BER is modulated by:
    - local influences such as stretching of the muscle tissue by contents in its lumen.
    - chemical stimulation of the mucosa by substances in the chyme.

Extrinsic Hormonal Mechanisms

A chemical stimulant in the chyme causes the release of a local gastrointestinal peptide hormone which, in turn, modulates the motility of the muscle tissue.

Extrinsic Neural Mechanisms

Postganglionic neurons of sympathetic and parasympathetic autonomic nervous system along with aminergic and peptidergic neurons diffusely innervate throughout the smooth muscle layers of intestinal tract and influence the intestinal motility.

Parasympathetic Network

The parasympathetic network is made up of cholinergic neurons and receives input via branches of the vagus nerve.

Acetylcholine released by their nerve endings mediates excitatory actions i.e., increased motility and gastrointestinal secretion.

Sympathetic Network

Adrenergic postganglionic neurons of the sympathetic division directly innervate all the tissues of the gut wall.

These innervations have inhibitory effect on motility of the stomach and intestine.

They release norepinephrine which inhibits the smooth muscle cells to develop action potentials.

Role of Aminergic and Peptidergic Neurons

Smooth muscles in the alimentary canal of vertebrates are also regulated by non-adrenergic, non-cholinergic neurons that release a variety of peptides and purine nucleotides.

These neurons include aminergic neurons that release ATP, 5-HT, dopamine and GABA.

Peptidergic neurons release enkephalins, vasoactive intestinal polypeptide (VIP), substance P, gastrin-releasing peptide, neurotensin, cholecystokinin (CCK), and neuropeptide Y (pancreatic polypeptide).

This host of transmitter substances allows very fine control over the numerous interacting functions of the alimentary canal.

Topic-203 Gastrointestinal Secretions

The alimentary canal in many animals has been described as the "largest endocrine and exocrine gland of the body" as its secretions include both endocrine and exocrine secretions.

Endocrine Secretions of GI Tract

Endocrine secretions of digestive tract include many gastrointestinal hormones that are liberated directly into the bloodstream.

These hormones are produced by the enteroendocrine cells spread throughout the digestive tract e.g. in the stomach, pancreas, and small intestine.

These hormones act on tissues of the alimentary canal and control various functions of the digestive organs.

Gastrointestinal Hormones

The gastrointestinal hormones include.

1. Gastrin
2. Cholecystokinin
3. Secretin
4. Glucagon
5. Vasoactive intestinal peptide (VIP)
6. Gastric inhibitory peptide (GIP)
7. Somatostatin
8. Motilin
9. Substance P
10. Ghrelin—a peptide hormone released from stomach and liver and is often referred to as the "hunger hormone". Its high levels are found in individuals that are fasting.

Many gut peptides, such as secretin, cholecystokinin and substance P are also found to play a role of neurotransmitters and neuromodulators in the central and peripheral nervous systems.

Exocrine Secretions of GI Tract

Exocrine tissues of the gastrointestinal tract include the salivary glands, secretory cells in the stomach and intestinal epithelium, and secretory cells of the liver and pancreas.

Exocrine gastrointestinal secretions are not composed of a single species of molecule. They usually consist of aqueous mixtures of substances including enzymes, water, mucous, inorganic salts and ions.

The digestive tract of human secretes about seven liters of exocrine fluids in a day.

Enzymes in Exocrine Secretions of GI Tract

Exocrine secretions of GI tract contain digestive enzymes which catalyze the hydrolysis of large food molecules into simpler compounds that can be absorbed through the cells lining the intestine.

The digestive enzymes belong to three major groups: proteases, carbohydrases, and lipases corresponding to the three major types of foodstuffs.

Some others classes of enzymes are present in the secretions of intestinal cells and are specialized to digest specific components of food e.g.

- Nucleases, nucleotidases and nucleosidases which hydrolyze nucleic acids and their residues.
- Esterases which hydrolyze esters present in ripe fruits.

Topic-204 Exocrine Secretions—Water, Mucus and Ions

There are large variations in the composition of exocrine secretions from different glands of the alimentary canal.

However, all these secretions usually contain large amount of water, mucus, salts and ions in addition to enzymes.

Water

Water makes most of the volume of these secretions, as these are water-based fluids.

To prevent a huge water loss, the distal portions of the gut reabsorb most of this secreted water.

Mucus

Mucus is also an important constituent of all GI secretions.

It is composed of a specific family of glycoproteins termed mucins and is generally very viscous.

Mucus is made by two types of specialized cells termed mucus cells in the stomach and goblet cells in the intestines.

The salivary glands and pancreas secrete a thinner mucoid solution while the mucus produced in the stomach and intestinal secretions is thicker.

Mucus serves to lubricate and prevent mechanical and enzymatic injury to the lining of the gut.

Ions and Electrolytes

The ions secreted in exocrine fluids are primarily H^+, Cl^-, and HCO_3^- along with Na^+ and K^+.

H^+ and Cl^- are secreted by the parietal cells into the lumen of the stomach creating acidic conditions with a low pH of 1.

HCO_3^- ions are present in the salivary and pancreatic secretions. They neutralize the acid secretions entering the duodenum of small intestine.

Pancreatic HCO_3^- comes from acinar cells in the form of $NaHCO_3$. $NaHCO_3$ dissociates and results in the high concentration of both HCO_3^- and Na^+ present in the pancreatic duct.

Topic-205 Exocrine Secretions—Bile and Bile Salts

The vertebrate liver secretes bile that does not contain any digestive enzymes. However, it contains many salts which are essential for the digestion of fats.

Composition of Bile

Bile consists of water and a weakly basic mixture of cholesterol, lecithin, inorganic salts, organic salts, and bile pigments.

The bile organic salts are manufactured by the liver from cholesterol and amino acids complexed with sodium.

The bile pigments are derived from biliverdin and bilirubin, which are products of the breakdown of hemoglobin coming from ruptured red blood cells.

Storage and Concentration of Bile

Bile produced in the liver is transported via the hepatic duct to the gallbladder.

Gallbladder concentrates and stores bile.

Concentration involves osmotic removal of water, followed by active transport of Na^+ and Cl^- from the bile across the gallbladder epithelium.

Functions of Bile

Bile serves numerous functions important to digestion.

- In the initial segment of small intestine, high alkalinity of bile neutralizes the highly acidic food coming from stomach.
- Bile salts act as a detergent for the emulsification of fats dispersing them in aqueous solution. This process facilitates enzymatic fat digestion
- Bile salts also disperse lipid-soluble vitamins for transport in the blood.
- Bile fluid contains waste substances removed from the blood by the liver, such as hemoglobin pigments, cholesterol, steroids, and drugs. These substances are either broken down by digestive enzymes or excreted in the feces.

Topic-206 Digestive Enzymes: Proteases

Proteases

Proteases are proteolytic enzymes which digest proteins by breaking the peptide bonds of proteins and polypeptides.

Types of Proteases

Proteases are categorized as:

- Endopeptidases
- Exopeptidases

Endopeptidases confine their attacks to bonds well within the protein molecule, breaking large peptide chains into shorter polypeptide segments. These shorter segments provide a much greater number of sites of action for the exopeptidases.

Exopeptidases attack only peptide bonds near the end of a peptide chain, releasing free amino acids, dipeptides and tripeptides.

Specificity of Proteases

Some proteases exhibit marked specificity for particular amino acid residues located on either side of the bonds they attack.

Examples

The endopeptidase trypsin attacks only those peptide bonds in which the carboxyl group is provided by arginine or lysine, regardless of where they occur within the peptide chain.

The endopeptidase chymotrypsin attacks peptide bonds containing the carboxyl groups of tyrosine, phenylalanine, tryptophan, leucine, and methionine.

Proteases in Digestive Tract

Pepsin

In mammals, protein digestion usually begins in the stomach by the action of the gastric protease pepsin.

Pepsin functions best at a low pH value of 1-2, maintained by the secretion of gastric HCl.

Action of pepsin results in the hydrolysis of proteins into polypeptides and some free amino acids.

Proteases in Pancreatic Juice

Pancreas produces several proteases which are secreted in the pancreatic juice.

These include trypsin, chymotrypsin and carboxypeptidase.

These enzymes continue the proteolytic process, yielding a mixture of free amino acids and small peptide chains.

Intestinal Proteases

Many proteolytic enzymes (e.g. Erepsin) are secreted by the epithelium of the intestinal wall.

These proteases act on polypeptides and hydrolyze them into short oligopeptides consisting of two to three amino acids residues, and then further break them into individual amino acids.

Topic-207 Digestive Enzymes: Carbohydrases and Lipases

Carbohydrases

Carbohydrases are the enzymes which digest carbohydrates by hydrolysis.

They can be divided functionally into two groups:

- Polysaccharidases
- Glycosidases

Polysaccharidases

Polysaccharidases hydrolyze the glycosidic bonds of long-chain carbohydrates such as cellulose, glycogen, and starch.

The most common polysaccharidases are the amylases which are secreted in vertebrates by the salivary glands and pancreas. They hydrolyze all but the terminal glycosidic bonds within starch and glycogen, producing disaccharides and oligosaccharides.

Glycosidases

Glycosidases act on disaccharides such as sucrose, maltose and lactose.

They hydrolyze the alpha-1,6 and alpha-1,4 glycosidic bonds present in the disaccharides, releasing their constituent monosaccharides.

Lipases

Lipases are lipid and fat digesting enzymes, secreted in the pancreatic juice and intestinal epithelium.

They act on emulsified fat droplets and hydrolyze fat molecules into monoglycerides and diglycerides and finally into free fatty acids and glycerol.

Emulsification by bile salts is necessary for lipases to hydrolyze lipids. If there are insufficient bile salts, fats in food are not emulsified and fat digestion by the lipases remains incomplete.

Topic-208 Proenzymes

Proenzymes

Certain digestive enzymes, in particular proteolytic enzymes, are synthesized, stored, and released in an inactive molecular form known as a proenzyme or zymogen.

Packaging of the enzyme in an inactive form prevents self-digestion of releasing tissues/cells by the enzyme.

The proenzyme is activated by the removal of a portion of the molecule, either by the action of another enzyme specific for this purpose or through a rise in ambient acidity.

Examples

Pepsinogen-Pepsin

Pepsin is the gastric proteolytic enzyme.

It is produced by the chief cells of stomach in its inactive form known as pepsinogen, which is a proenzyme.

Pepsinogen is activated in the lumen of stomach through a rise in acidity by HCl into its active form, pepsin.

Trypsinogen-Trypsin

Trypsinogen is secreted in pancreatic juice as a proenzyme.

The proenzyme trypsinogen is a 249-residue inert polypeptide. It is activated in the duodenum when a 6-residue segment is cleaved from the amino terminal end.

This cleavage is achieved either by the action of an intestinal proteolytic enzyme, enterokinase or another activated trypsin molecule.

Chymotrypsinogen-Chymotrypsin

Chymotrypsinogen is also secreted as proenzyme in pancreatic juice.

It is activated by trypsin into its hydrolytic active form chymotrypsin.

Topic-209 Control of Digestive Secretions

The secretory rate and quantity of digestive secretions is regulated through several interacting features.

These include:

1. Complex involuntary neural and hormonal controls
2. Presence of food
3. Cognition or thought processes

1. Involuntary neural and Hormonal Controls

- Salivary secretions are very rapid and entirely under involuntary neural control.
- Gastric secretions are under hormonal as well as neural control.
- Intestinal secretions are slower and are primarily under hormonal control.

As in other systems, neural control predominates in rapid reflexes, whereas endocrine mechanisms are involved in reflexes that develop over minutes or hours.

2. Role of Presence of Food

Among vertebrates, the primary stimulus for secretion of digestive juices in a given part of the digestive tract is the presence of food.

The presence of food molecules stimulates chemosensory endings, which leads to the reflex activation of autonomic efferents that activate or inhibit motility and exocrine secretion.

Appropriate food molecules also directly stimulate epithelial endocrine cells by contact with their receptors, causing reflex secretion of gastrointestinal hormones into the local circulation.

These reflexes permit secretory organs outside the alimentary tract (liver and pancreas) to be properly coordinated with the need for digestion of food.

3. Role of Cognition or Thought Processes

In mammals, cognition or thought processes also control the digestive secretions.

Cephalic influences such as mental images of food as well as learned behaviors stimulate digestive secretions.

Topic-210 Control of Salivary and Gastric Secretions

Control of Salivary Secretions

Salivary glands produce a slow flow of saliva in the absence of food.

Secretion of saliva is stimulated by the presence of food in the mouth.

Food stimulates cholinergic parasympathetic nerves in the salivary glands which result in increase in salivary secretion.

Cognitive awareness of food also results in rapid secretion of saliva.

Gastric Secretions

The gastric juice contains HCl, Pepsin and mucus which are synthesized and secreted separately by three different types of cells present in the gastric glands located in the wall of stomach.

- HCl is secreted by parietal or oxyntic cells.
- Mucus is synthesized and secreted by goblet cells.
- Pepsin is secreted in its inactive form pepsinogen by the chief cells.

Control of Gastric Secretions

Gastric secretion in mammals occurs in three distinct phases:

- Cephalic phase
- Gastric phase
- Intestinal phase

Cephalic Phase

In the cephalic phase, gastric secretion occurs in response to the sight, smell, and taste of food, or in response to conditioned reflexes.

This phase is mediated by the brain (hence the term cephalic) and is blocked by section of the vagus nerve.

Gastric Phase

The gastric phase is mediated by the hormone gastrin and the compound histamine.

The gastric secretion is stimulated directly by the presence of food in the stomach, which stimulates both chemoreceptors and mechanoreceptors.

Secretagogues in food, such as caffeine, alcohol, and active ingredients of spices increase gastric secretion.

Intestinal Phase

The intestinal phase of gastric secretion is more complex.

It is controlled by gastrin, as well as the hormones secretin, vasoactive intestinal peptide (VIP), and gastric inhibitory peptide (GIP).

As food enters the duodenum of the small intestine, partially digested proteins in acidic chyme directly stimulate the duodenum's mucosa to secrete enteric gastrin.

Enteric gastrin has the same action as stomach gastrin, stimulating the gastric glands to increase their rate of secretion.

GIP is liberated by endocrine cells in the mucosa of the upper small intestine in response to the entry of fats and sugar into the duodenum. GIP inhibits secretion of gastric glands.

Topic-211 Control of Intestinal and Pancreatic Secretions

Intestinal Secretions

The epithelium of the mammalian small intestine secretes intestinal juice which is a mixture of two fluids secreted by Brunner's glands and crypts of Lieberkuhn (mucosal glands).

Brunner's glands Secretion

Brunner's glands are present in the first part of the duodenum between the pyloric sphincter and the pancreatic duct.

They secrete a viscous, enzyme-free, alkaline mucoid fluid.

This fluid enables the duodenum to withstand acidic chyme coming from the stomach until it can be neutralized by the alkaline pancreatic and biliary secretions coming from the pancreatic duct.

Secretion of Crypts of Lieberkuhn

Crypts of Lieberkuhn (mucosal glands) in the intestinal folds produce a thinner, enzyme-rich alkaline fluid.

This fluid mixes with duodenal secretions.

Control of Intestinal Secretions

The secretion of intestinal juice is regulated by several hormones, including secretin, gastric inhibitory peptide (GIP), and gastrin.

It is also under neural control as vagus nerve innervation stimulates secretion.

Distension of the wall of the small intestine also elicits a local secretory reflex.

Secretions of Pancreas

The exocrine tissue of pancreas produces pancreatic juice that enters the duodenum through the pancreatic duct.

Pancreatic juice contains several digestive enzymes in an alkaline, bicarbonate-rich fluid.

The pancreatic enzymes include: alpha-amylase, trypsin, chymotrypsin, elastase, carboxypeptidases, aminopeptidases, lipases, and nucleases. These enzymes show optimum activity at a neutral or slightly alkaline pH.

Control of Pancreatic Secretions

Pancreatic secretions are controlled by a variety of hormones including peptide hormones, gastrin, cholecystokinin, somatostatin and enkephalins.

Effect of Peptide Hormones

Acid chyme reaching the small intestine from the stomach stimulates the release of peptide hormones secretin and vasoactive intestinal peptide (VIP) by endocrine cells in the upper small intestine.

These peptides stimulate secretion of pancreatic enzymes.

Effect of Gastrin

Gastrin secreted from the stomach lining also elicits a small flow of pancreatic juice in anticipation of the food coming in the duodenum.

Effect of Cholecystokinin

Secretion of pancreatic enzymes is also elicited by the upper intestinal hormone cholecystokinin that is secreted in response to fatty acids and amino acids in the intestinal chyme.

This hormone also stimulates contraction of the smooth muscle wall of the gallbladder, forcing bile into the duodenum.

Effect of Somatostatin and Enkephalins

Somatostatin inhibits gastric and pancreatic secretions.

Enkephalins inhibit gastric acid secretion but stimulate pancreatic enzyme secretion.

Topic-212 Absorption of Food in Intestine

The breakdown products of digestion (amino acids, glucose, fatty acids etc.) are absorbed from the gut in to the bloodstream and transported to animal's tissues and cells.

Most absorption occurs through ileum of the small intestine. Ileum is specialized for absorptive functions as it has villi. Each villus is richly supplied with blood capillaries and a lacteal of lymphatic system. A villus also has a covering of absorptive epithelial cells with microvilli in their apical membrane.

The microvilli have specialized features including a glycocalyx, digestive enzymes associated with the membrane, and specific intramembrane transporter proteins. All these features make them specialized structures to absorb all types of digested food products.

Absorption of Sugars and Amino Acids

Microvilli take up simple sugars and amino acids by diffusion or active transport into the epithelial cells from where they are diffused into the blood capillaries of villi.

Absorption of Fatty Acids and Glycerol

As the fats and lipids are digested in the small intestine, bile salts aggregate around the products of digestion and form micelles.

Micelles pass by simple diffusion into the epithelial cells.

In the epithelial cell, fatty acids and glycerol recombine to form triacylglycrerol. Proteins combine with triacylglycrerol to form chylomicrons (lipoproteins). These chylomicrons leave the epithelial cells and enter the lacteals of villi and are transported by the lymphatic system.

These lipoproteins are passed into the blood stream via thoracic lymphatic duct.

In the blood, these lipoproteins are hydrolyzed by plasma enzymes into fatty acids which can enter the tissue cells.

Topic-213 Absorption Mechanisms

Absorption of products of digestion in small intestine involves several transfer processes.

These include:

- Simple passive diffusion
- Carrier mediated facilitated diffusion
- Co-transport and counter-transport
- Active transport
- Endocytosis

The type of transfer mechanism used depends on the type of molecule being transported during the absorption process.

Simple Diffusion

Simple diffusion can take place across the plasma membrane of epithelial cells either through lipid bilayer or through water-filled pores.

Lipid soluble substances e.g. fatty acids, monoglycerides and cholesterol can diffuse through the lipid bilayer.

Substances that pass through water-filled pores include water and water soluble nonelectrolytes and alcohols. Their net diffusion rate is proportional to their chemical concentration gradient.

Certain electrolytes are also absorbed through diffusion. Their net diffusion rate is proportional to their electrochemical gradient.

Carrier Mediated Transport

Some monosaccharides (e.g. fructose) and few amino acids cannot pass through water-filled pores by simple diffusion, although they are water soluble. It is because they bear charges and are usually larger than the pore size.

They are absorbed across the absorptive cell membrane by carrier mediated transport (facilitated diffusion) with the help of specific channel proteins located in the membranes.

Topic-214 Absorption by Active Transport and Endocytosis

Absorption by Active Transport

Many nutrients, including amino acids, vitamins and most glucose molecules, are pumped actively against concentration gradients by the epithelial cells of the villus.

Active Transport of Glucose and Amino Acids

The energy for the transport of glucose, amino acids, dipeptides and tripeptides is supplied by a sodium co-transport mechanism.

The molecules to be absorbed bind to a specific transport protein present in the membrane of microvilli.

This transport protein requires sodium binding before transport can occur.

After binding, the sodium ion moves down its electrochemical gradient to the interior of the cell and pulls the glucose, amino acid or peptide along with it.

In this way, both the sodium ion and glucose molecule are transported together to the interior of the cell. This is called co-transport (or secondary active transport).

At least five types of transport proteins have been found in the luminal membranes of intestinal epithelial cells for the transport of amino acids, peptides and glucose. Each type is specific for diverse binding properties of different substances that are to be carried into the cell.

Endocytosis

Some oligopeptides are taken up by absorptive cells through endocytosis.

In newborn mammals this process is responsible for the uptake in the intestine of immunoglobulin molecules derived from the mother's milk.

Once inside the absorptive cell, nutrients pass through the basolateral membranes of the absorptive cell into the interior of the villus and then move from the interstitial fluid into the circulatory system.

Topic-215 Transport of Nutrients

Digestion products absorbed enter either the blood or the lymphatic circulation in the villi.

Blood Transport of Sugars and Amino Acids

Sugars and amino acids primarily enter the capillaries of the villi.

These capillaries are drained by venules that lead into the hepatic portal vein.

The hepatic portal vein takes the blood from the intestine directly to the liver.

In the liver, much of the glucose is taken up by hepatocytes and, under the influence of insulin, is converted into glycogen granules for storage. Only a controlled quantity is released into the circulation to be utilized by tissues.

Lymphatic Transport of Fats

In vertebrates about 80% of the chylomicrons enter the lacteals of villi and are carried by lymphatic vessels. The remaining 20% enter the blood directly.

The lymph is poured into the bloodstream via thoracic lymphatic vessel which delivers fats to the blood for circulation.

Topic-216 Water and Electrolyte Absorption

Release of Water in Alimentary Secretions

In the process of producing and secreting various digestive juices, the exocrine tissues of alimentary canal and accessory organs release a large amount of water and electrolytes.

In humans, this amount is over 7 liters per day that is about 1.5 times the total blood volume.

This huge quantity of water along with electrolytes cannot be lost from the body with the feces.

Reabsorption of Water

Nearly all secreted water and electrolytes are recovered by uptake in the intestine.

Water is reabsorbed throughout the intestine; however, most of the reabsorption takes place in the lower part of the small intestine and colon.

Osmotic pressure is the motive force leading to net water movement from the intestinal lumen to the interior of the villus, this movement is entirely passive.

The osmotic gradient driving water from the lumen into the villus is set up primarily by the active transport of substances from the lumen into the villus, in particular the transport of salt, sugar, and amino acids.

The elevated osmotic pressure within the villus that results from this active transport draws water osmotically.

Control of Water Absorption

Excessive uptake of water from the lumen across the intestinal wall results in abnormally dry lumen contents that result in constipation.

This situation is normally prevented by an inhibitory action on electrolyte and water uptake by some of the gastrointestinal hormones.

Gastrin acts indirectly to inhibit water absorption from the small intestine, while secretin and CCK reduce the uptake of Na^+, K^+, and Cl^- in the upper jejunum.

Bile acids and fatty acids also inhibit the absorption of water and electrolytes.

Absorption of Na^+ and Cl^-

Most of Na^+ are actively absorbed by cells located at the tip of each villus.

Cl^- ion follow passively Na^+ ions.

The absorption of Na^+ and Cl^- into the villus is enhanced by high concentrations of glucose in the intestinal lumen, which stimulate sodium-sugar co-transport.

Absorption of Ca^{2+}

Ca2+ requires a special active transport mechanism for absorption from the gut.

The calcium ion is first bound to a calcium-binding protein in the microvillus and is then transported as a complex into the absorptive cell by an energy-consuming process.

From the absorptive cell the Ca^{2+} then passes into the blood.

The presence of calcium-binding protein is regulated by the hormone calcitriol, vitamin D_3.

The release of Ca^{2+} from the absorptive cell into the blood is accelerated by parathyroid hormone.

Absorption of Vitamin B_{12}

Vitamin B_{12} (molecular weight of 1357) is the largest water-soluble essential nutrient taken up intact across the intestinal lumen in the distal ileum.

Thermoregulation

Topic-217 Homeotherms and Poikilotherms

On the basis of stability of body temperatures, animals have been traditionally classified into two types:

- Homeotherms
- Poikilotherms

Homeotherms

Homeotherms can regulate their body temperatures within a narrow physiological range by controlling heat production and heat loss.

They are able to maintain body temperatures in spite of variation in ambient (environmental) temperatures.

Examples

- **Mammals:** can maintain their core body temperature between 37°C to 38°C.
- **Birds:** can maintain their core body temperature closer to 40°C.
- Some other vertebrates and some invertebrates can control their body temperatures during periods of activity or rapid growth.

Poikilotherms

Poikilotherms are the animals which lack high rates of heat production and their body temperatures tend to fluctuate with the ambient temperature.

Warm Blooded and Cold Blooded

The general terms "warm blooded" and "cold blooded" have been traditionally used for homeotherms and poikilotherms respectively.

Early comparative physiologists considered all fishes, amphibians, reptiles and invertebrates to be poikilotherms (cold blooded) and birds and mammals to be homeotherms (warm blooded).

However these terms are not considered physiologically correct because thermal behaviors of animals are quite variable. Many poikilotherms can become quite warm and endotherms may become cold regionally or temporally. So the use of these terms has been abandoned in scientific literature.

Topic-218 Endotherms and Ectotherms

Physiologists classify animals into endotherms and ectotherms on the basis of source of body heat.

Endotherms

Endotherms are animals that generate their own body heat through metabolism and elevate their body temperatures considerably above ambient temperatures.

They also have relatively low thermal conductivity because of good insulation with fur, feathers or sub-cutaneous fat. This insulation enables them to conserve heat in spite of a high temperature gradient between body and environment.

Homeothermic and Heterothermic Endotherms

- Mammals and birds regulate their temperatures within relatively narrow limits. They are said to be homeothermic endotherms.
- A few large fishes (sharks and tuna) and some flying insects maintain regions of their body above ambient temperatures, for short periods of time under specific circumstances. They are known as regional heterothermic endotherms.

Significance of Endothermy

As endotherms can maintain their body temperatures well above the ambient temperatures in cold climates, they have been able to invade habitats that are too cold for most ectotherms.

Ectotherms

Ectothermic animals produce metabolic heat at comparatively low rates and rely almost entirely on environmental sources of heat for warming their bodies.

They also have high thermal conductance as their bodies are poorly insulated. As a result, heat derived from metabolic processes is quickly lost to cooler surroundings.

However, high thermal conductance allows ectotherms to absorb heat readily from their surroundings.

Behavioral Temperature Regulation in Ectotherms

Ectotherms regulate their body temperatures principally by means of behavioral temperature regulation.

In colder environment, many ectotherms behave in a way that facilitates heat absorption from the environment

In hotter environments, they tend to dissipate heat to the environment or minimizes heat uptake from the environment.

Examples

A lizard or a snake may bask in the sun with its body oriented for maximal warming until it achieves a temperature suitable for efficient muscular function.

Small ectotherms in hot environments (lizards, ants) often elevate their bodies to avoid hot surfaces over which they are moving.

The most effective thermoregulatory action taken by ectotherms is movement into a suitable microclimate in the environment. For example, keep hiding in the burrows having moderate temperatures during the heat of the day and coming out at night.

Topic-219 Heterotherms

Heterotherms are animals capable of varying degrees of endothermic heat production, but generally do not regulate body temperatures within a narrow range.

They may be divided into two groups:

- Temporal heterotherms
- Regional heterotherms

Temporal Heterotherms

Temporal heterotherms are animals whose temperatures vary widely over time on daily basis or on annual basis.

These animals have accurate temperature control mechanisms and so are basically homeothermic. Yet, they behave like temporal heterotherms because they allow their body temperatures to undergo daily cyclical fluctuations, having endothermic temperatures during periods of activity and lower temperatures during periods of rest.

Examples

- Monotremes (egg-laying mammals) such as the echidna are temporal heterotherms.
- Some mammals (e.g. bats) and birds (e.g. hummingbirds) which undergo hibernation and daily torpor are also temporal heterotherms.
- Some large endotherms (e.g. ground squirrels) resort to a long winter torpor with reduced body temperature to save energy.

Regional Heterotherms

Regional heterothermy describes organisms that are able to maintain different temperature zones in different regions of the body.

Regional heterotherms include both ectotherms and endotherms.

Many ectotherms can achieve high core temperatures through muscular activity, while their peripheral tissues and extremities approach the ambient temperature.

In many endotherms, temperature of limbs is allowed to fall near the ambient temperature, while keeping the core temperature nearly constant.

Examples

- Regional heterothermy is shown by many flying insects, pythons, and some fishes (mako sharks and tuna) which can raise the temperature of parts of their bodies well above ambient temperature by virtue of heat generated as a by-product of intense muscular activity.

- Some insects prepare for flight by exercising their flight muscles for a time to raise their temperatures before takeoff.
- Some large billfin fishes (e.g., marlin) use specialized ocular muscle called "heater tissue" to elevate brain temperature.
- Another special example of regional heterothermy is seen in the scrotums of some mammals, including canines, cattle, and human beings, which hold the testes outside the body core to keep them at a slightly lower temperature to prevent overheating of the testes which has a harmful effect on sperm production.

Topic-220 Ectotherms in Cold and Freezing Environments

Challenges of Cold Environments

The body temperature of most ectotherms depends on the ambient temperature.

Ectotherms occupying cold environments face two major problems:

1. Maintaining metabolism
2. Freezing threat

Maintaining metabolism in Cold Environments

For animals living in cool environments, survival requires maintaining adequate metabolism. At low temperatures enzyme activity becomes very slow.

Many animals living in cold environments have evolved enzymes that show maximal activity at temperatures many degrees below those of homologous enzymes in animals living in warmer environments.

Freezing Threat

Ectotherms living in freezing environments face freezing threat.

The formation of ice crystals within cells is usually lethal because, as the crystals grow in size, they rupture and destroy the cells.

No animal is known to survive complete freezing of its tissue water.

Animal Strategies to Avoid freezing

If ice crystals form and grow within cells, they damage the tissue by breaking the cells.

In contrast, ice crystals that form outside the cells do little damage.

The adaptiveness of animals living in freezing environments lies in crystal formation in the extracellular space where little tissue damage is caused.

Such animals employ three methods to survive freezing environments:

- Ice-nucleating Agents (INAs)
- Cryoprotectants (antifreeze substances)
- Supercooling

Ice-nucleating Agents (INAs)

Certain animals contain ice-nucleating agents (INAs) in the extracellular fluid.

INAs include many inorganic substances, microorganisms, proteins, and organic residues which can accelerate the process of crystal formation (nucleation).

INAs cause the extracellular fluids to freeze more readily than the intracellular fluids.

Ice Nucleation

As ice forms in the extracellular fluid, the unfrozen extracellular fluid becomes more concentrated with solutes.

This process draws water out of the cells, lowering the intracellular freezing point.

In this way, animals protect their cells from making ice crystals and can withstand freezing temperature.

Example

The freshwater larvae of the midge (fly) Chironomus, can survive freezing at temperatures as low as -32°C.

Antifreeze Substances

The body fluids of some cold-climate ectotherms contain cryoprotectants (antifreeze substances) e.g. glycerol, sorbitol and antifreeze proteins. These substances lower the freezing point of fluids. E.g. glycerol acting as an antifreeze can lower the freezing point of solute to as low as -17°C.

Supercooling

Ice crystals formation requires ice crystals or nuclei as seeds.

The animals which can undergo supercooling keep their bodies free of ice-nucleating agents INAs in a freeze-avoidance strategy.

So, their body fluids can be cooled below freezing temperature, yet remaining unfrozen because ice crystals fail to form.

Examples

- Certain Arctic bottom dwelling fishes live in a continually supercooled state and normally do not freeze unless they brush against frozen ice on the water surface.
- The larvae of parasitic wasp *Brachon cephi* can supercool to -47°C without ice crystal formation.

Topic-221 Ectotherms in Hot Environments

Ectotherms occupying hot environments are particularly vulnerable to warming. They may face daytime summer surface temperatures of nearly 40°C or above.

Most ectotherms have a critical thermal maximum below 45°C, above which long-term survival is not possible.

Above critical thermal maximum, affinity of the respiratory pigment for oxygen is decreased that affects most tissue functions. Moreover proteins are denatured and enzymes fail to function at higher temperatures.

Strategies to Live in Hot Environments

Most ectotherms actively respond to prevent elevation of their body temperatures to the critical thermal maximum. They tend to eliminate excess heat gained from the environmental by behavioral and physiological mechanisms.

Physiological Adaptations

Most ectotherms have high heat conductance that allows them to radiate heat rapidly on moving to less warm places.

Above 40°C many reptiles start panting, just like birds and mammals to increase heat loss through respiratory evaporation that causes cooling.

The marine iguanas can regulate heart rate and flow of blood to the surface tissues to either absorb or eliminate heat.

The Gila monster (*Heloderma suspectum*) evaporates water from its cloaca to cool its internal body temperature—a process similar to sweating in mammals.

Behavioral Adaptations

To avoid heat of the sun, most ectotherms move to shades or burrows that provide cooler microclimates.

The desert iguanas which are efficiently adapted to survive in harsh desert environments exhibit bipedal locomotion to run across hot sands. This behavior allows the abdomen to be raised from the ground, removing its contact from the hot substratum.

When crossing larger stretches of hot sands, they also dig sand at intervals to get cooling from lower cooler sand.

Topic-222 Costs and Benefits of Ectothermy

Ectothermy has its respective advantages and disadvantages relative to endothermy.

The biological costs and benefits of being an ectotherm are the inverse of those of being an endotherm.

In considering the costs and benefits of both, ectothermy and endothermy, we can make certain generalizations as follows.

Benefits of Ectothermy

1. Ectotherms use less energy in maintaining metabolic rate. They can use a large proportion of energy in growth and reproduction (over 50%). Endotherms have to consume major portion of energy (up to 98%) obtained from food in maintaining high metabolic rate and body temperature.
2. They require less food, they need less time spending in foraging. In contrast, endotherms are big consumers, spending more time on obtaining food. Example: A 300 g lizard needs 17 times lesser food per day as does a 300 g rodent living in the same habitat and having the same diet.
3. As they live at cooler places, they face less evaporative water loss, so need not to be massive for reducing surface-to-volume ratio.
4. Low respiratory rates also ensure less water loss.
5. In the tropics, ectotherms (e.g. reptiles) outcompete mammals both in abundance of species and in numbers of individuals. This competitive success is due to greater energy economy of the ectotherms.

Costs of Ectothermy

1. The inability to metabolically regulate body temperature requires behavioral thermoregulatory activities. Behavioral activities are time consuming and have certain limits e.g. basking in the sun is time wasting and is possible only if there is sufficient solar radiation.
2. In energy terms, ectotherms generate and expend lower energy. So, they cannot sustain longer periods of intense activity. In comparison, endotherms have high rates of aerobic respiration and energy yield. So, they can sustain longer periods of intense activity.
3. While constancy of body temperature in endotherms allows enzymes to function more efficiently, ectotherm's enzymes functions intermittently.
4. Ectotherms are more sluggish and less competent as predators in cold climates. So they are less abundant in temperate regions and cold climates. Endotherms have a significant competitive edge over ectotherms in the cold regions because their tissues are kept warm.
5. Because ectotherms tend to lower their activity levels periodically, they are vulnerable to predation. Whether they are basking in the sun or falling asleep because of dropping body temperature, they are at risk of predation.

Topic-223 Temperature Relations of Heterotherms

Heterotherms are animals intermediate between pure ectotherms and endotherms.

Heterotherms generally do not regulate their body temperatures within a narrow range. They mostly depend on external source of heat, like ectotherms. However, they are capable of endothermic heat production through muscular activity to varying extent.

They include certain insects, reptiles and fishes.

Heat Generation in Heterothermic Insects

Some flying insects (e.g. locusts, beetles, arctic flies) behave strictly as ectotherms when inactive.

However, they can raise the core temperatures in their thoracic parts to more or less regulated levels when preparing to fly.

Without this warm up, their flight muscles contract too slowly to produce sufficient power for flight and are unable to take off and fly.

As flight starts, the large thoracic flight muscles (which are among the most metabolically active tissues known) produce enough heat to maintain elevated muscle temperatures.

The thoracic temperature reaches about 40°C and is maintained during flight. At this level of heat generation the insects even have to employs heat-dissipating mechanisms to prevent overheating.

Heat Generation in Heterothermic Reptiles

Muscle-generated heat has been observed in some heterothermal reptiles including the female Indian python.

The brooding female Indian python elevates its body temperature with shivering thermogenesis to provide warmth for the group of eggs around which it coils itself.

The rate of muscle contractions increases with declining ambient temperature and an increased difference between the ambient and body temperatures.

Heat Generation in Heterothermic Fishes

Unlike terrestrial ectothermic vertebrates, which can bask in the sun to warm up, marine ectotherms cannot obtain radiant energy of sun as a source of heat.

Fishes can raise above ambient temperature only through intensive metabolic activity.

Many teleosts are strictly ectothermic, operating at core temperatures close to ambient temperatures.

However, some fishes, such as tunas and Mako sharks, have specializations for generating and retaining sufficient heat to raise the temperature of body muscle, brain, and eyes some 10 degrees or more above their surroundings.

These fishes can therefore be classified as regional heterotherms.

Anatomical Features of Fishes for Heterothermy

Two anatomical features permit heterothermic fishes to maintain temperature of their swimming muscles.

First, the red (dark) aerobic swimming muscles are located relatively deep in the core of a fish's body.

Second, escape of heat through skin and gills is retarded by a countercurrent heat-exchange system composed of rete mirabile.

Topic-224 Thermal Neutral Zone, Lower Critical Temperature (LCT) and Upper Critical Temperature (UCT) for Endotherms

The degree of thermoregulatory activity required by homeothermic endotherms to maintain a constant core temperature varies with environmental temperature.

Thermal Neutral Zone

The range of temperatures at which the basal rate of heat production balances heat loss to the environment is termed as the thermal neutral zone.

Within this range of temperatures, an endotherm does not need to expend energy to maintain its body temperature. It can regulate its body temperature by adjusting the rate of heat loss through alterations in the thermal conductance of the body surface.

These adjustments include:

- Vasomotor responses
- Postural changes to alter exposed areas of surface
- Regulation of insulating effectiveness of the pelage by raising or lowering hairs or feathers.

Lower Critical Temperature (LCT)

Lower critical temperature is the ambient temperature below which an endotherm's basal metabolic rate becomes insufficient to balance heat loss.

Below this temperature, an endotherm must increase heat production by thermogenesis above basal levels to offset heat loss.

Heat production rises linearly with decreasing temperature below the lower critical temperature. This is termed as the zone of metabolic regulation.

If the environmental temperature drops below the zone of metabolic regulation, compensating mechanisms fail, the body cools, and the metabolic rate drops.

If an animal's body temperature falls below its normal values, the animal enters a state of hypothermia. If this condition persists, the animal grows progressively cooler, its metabolic rate falls and it soon dies.

Upper Critical Temperature (UCT)

Temperature zone which activates evaporative heat-dissipating mechanisms.

Animals react to higher temperature by losing heat by active heat-dissipating mechanisms such as sweating or panting.

temperatures above the upper critical temperature lead to hyperthermia. Hyperthermia occurs as the heat production and gain exceeds the rate of heat loss.

If evaporative heat loss mechanisms fail, hypothermia becomes lethal.

Topic-225 Temperature Relations of Endotherms

Maintaining Body Temperature

Homeothermic endotherms include most mammals and birds. They maintain their body temperatures relatively constant within a narrow range that is independent of the surrounding environmental temperature.

Core and Peripheral Temperatures

The core temperatures are maintained nearly constant between 37°C and 38°C in mammals and about 40°C in birds.

The temperatures of peripheral tissues and extremities are held less constant and are sometimes allowed to approach environmental temperatures.

Mechanisms of Endothermy

Endotherms use a variety of mechanisms for heat production (thermogenesis), heat conservation and heat dissipation.

These mechanisms include:

- Homeostatic mechanisms
- Muscular mechanisms (shivering thermogenesis)
- Hormonal mechanisms (non-shivering thermogenesis)
- Counter current exchange mechanisms
- Evaporative cooling mechanisms
- Cooling behaviors

Basal Heat Production and Metabolism

Basal heat production for different homeotherms of a given size is about the same, and the basal metabolic rate can be 10 times as high as the standard metabolic rate of ectotherms of comparable size measured at similar body temperatures.

This elevated basal metabolism, in conjunction with heat conserving and heat-dissipating mechanisms, allows homeotherms to maintain constant body temperatures as much as 30°C or more above ambient temperatures.

Topic-226 Thermogenesis in Endotherms

Endotherms Mechanisms for Thermogenesis

When the ambient temperature drops below the lower critical temperature, an endothermic animal responds by generating large amounts of additional heat, thereby preventing a decrease in the core temperature.

There are two primary means of extra heat production:

- Shivering thermogenesis
- Non-shivering thermogenesis

Both processes convert chemical energy into heat by a normal energy-converting metabolic mechanism involved in primary heat production.

However, all the chemical-bond energy released in this process is essentially used to generate heat rather than to chemical or mechanical work.

Shivering Thermogenesis

Shivering is a means of using muscle contraction to liberate heat.

The nervous system activates groups of antagonistic skeletal muscles so that there is little net muscle movement other than shivering.

The activation of muscle causes ATP to be hydrolyzed. The chemical energy released during contraction appears as heat.

Non-shivering Thermogenesis

In non-shivering thermogenesis, enzyme systems for the metabolism of fats are activated throughout the body, so conventional fats are broken down and oxidized to produce heat.

Non-shivering thermogenesis is activated by the sympathetic nervous system through the release of norepinephrine and thyroid hormones.

Brown Fat

A specialization found in a few mammals for fat-fueled thermogenesis is brown fat, also called brown adipose tissue (BAT).

This fat contains extensive vascularization and so many mitochondria that it is brown (owing largely to mitochondrial cytochrome oxidase).

Oxidation is triggered by thyroid hormones and takes place within the brown fat containing cells, which are richly endowed with fat-metabolizing enzyme systems.

In ordinary body fat, deposits must first be reduced to fatty acids, which enter the circulation and eventually are taken up by other tissues, where they are oxidized.

In this way, brown fat is an adaptation for rapid, massive heat production.

Brown fat heats up significantly during thermogenesis. This newly produced heat is rapidly dispersed to other parts of the body by blood flowing through the extensive vasculature of the brown fat tissue.

Topic-227 Endothermy in Cold Environments

Retaining Body Heat in Cold

Endotherms adapted to cold environments have evolved temporary and permanent mechanisms to retain body heat. These mechanisms involve anatomical and physiological features e.g. pelage, plumage, blubber and vasoconstriction.

Role of Pelage and Plumage

Fur and feathers provide heat insulation to mammals and birds respectively.

They lower specific heat conductances by reducing convection and dissipation of body heat by the wind.

The fluffed hairs and feathers trap air which is warmed by body heat, protecting the animal from cold.

The size and thickness of pelage varies in animals with insulation needs arising in face of environmental cold and seasonal variation.

Arctic mammals have very thick pelage, which provides more endurance to cold.

Animals living in the temperate zone exhibit seasonal variations by shedding fur or feathers in summer and growing new bodily cover in winter. This provides thick insulation during the winter, and prevents overheating during the summer.

Role of Blubber

Marine mammals (seals, walruses, sirenians, cetaceans—whales) have thick layers of insulating subcutaneous fat which is known as blubber.

Blubber is a good insulator because it has a lower thermal conductivity.

Fatty tissues are metabolically very inactive and have little blood vascularization. This prevents heat loss through body surface.

Vasoconstriction

An important means of controlling heat loss from the surface is the diversion of blood flow away from the skin.

Vasoconstriction of arterioles leading to the skin keeps warm blood from perfusing cold skin and conserves the heat of the body core.

Topic-228 Countercurrent Heat Exchange Systems

Heat Loss through Extremities

The limbs and extremities (e.g. gills, ears, nose) of endotherms are well vascularized but not massively insulated.

They are also thin and have large surface areas.

So they are major avenues of heat loss.

Reduction of Heat Loss—Countercurrent Exchange System

In many homeothermic animals living in cold climates excessive heat loss from extremities is reduced drastically by countercurrent heat exchange systems. Such systems have been found in cetaceans, seals, wading birds, arctic land mammals and many heterothermic fishes

A countercurrent exchange system is based on the fact that arterial blood, originating in the animal's core, is warm. Conversely, the venous blood returning from peripheral tissues may be very cold.

In the countercurrent exchange systems of appendages, arteries bringing blood towards extremities, pass just parallel to the out-going veins.

As the blood flows from the core and enters the limbs, the warm arterial blood gives up heat to the returning venous blood. So, arterial blood becomes successively cooler as it enters the extremity. By the time it reaches the periphery, this blood is precooled, only a few degrees above the ambient temperature. On reaching the extremity, it causes little heat loss.

Conversely, the returning venous blood becomes warmed by the arterial blood, so it is nearly at core temperature before it enters the core.

Rete Mirabile

Rete mirabile is a highly evolved system of countercurrent heat exchange. In this system, the artery carrying warm blood flowing toward the extremity is completely encased in a circlet of veins carrying cold blood back from the extremity.

Rete mirabile is found widely in homeothermic and heterothermic vertebrates

Advantage of Countercurrent Heat Exchange Systems

This system reduces heat loss into the environment without reducing blood flow, oxygen and nutrients supply.

This is the best alternative arrangement to vasoconstriction that reduces flow of blood to the periphery.

Due to this system, the extremities of cold-climate endotherms are maintained at temperatures that are far below the core temperature and often approach ambient temperature.

Topic-229 Endothermy in Hot Environments

Dissipation of Body Heat from Surface

Endotherms adapted to hot environments have evolved mechanisms to lose body heat.

Heat is always lost from the body surface. It is transferred from core to the surface by circulation. The rate of heat loss to the environment is regulated by the blood vessels supplying blood to the surface.

Heat Windows

Endotherms use various heat windows on their body surface to lose body heat. Opening or shutting these windows occurs by regulating blood flow.

These heat windows permit the loss of heat by radiation, conduction and convection.

Examples of Heat Windows

Ears:

The thin, membranous and lightly furred ears of many mammals with extensively branched blood vessels act as temperature-regulating windows.

Horns

Horns of various mammals (e.g. goats and cattle) are highly vascularized by a network of blood vessels that, under conditions of heat load, vasodilate and act as radiators of heat.

Limbs and Snout

The limbs and snout, having large surface area to volume ratios, are also used as thermal windows for the dissipation of heat by regulation of the rate of blood flow through the arterioles serving the skin of the appendages.

Lightly Furred or Naked Areas on Body

Some mammals living under conditions of intense solar radiation or high temperatures have certain areas of the body surface exceptionally lightly furred or even naked to facilitate heat loss by radiant, evaporative, or conductive means.

Such areas generally include the axilla (armpit), groin, scrotum, and parts of the ventral surface.

Some of these areas, such as the udder and scrotum, carry additional temperature sensors that are used to detect changes in air temperature with minimal interference from the core temperature.

Evaporative Heat Loss

Evaporating water from the surface takes away heat and causes cooling effect. Many vertebrates use sweating or panting to produce evaporative cooling.

Behavioral Mechanisms

Variations in posture or body orientation can increase rate of heat loss.

By adjusting the posture and orientation of body with respect to solar radiation, endothermic animals can adjust the degree to which their thermal windows are open or shut, permitting a change in thermal conductance.

This posturally controlled flexibility in surface insulation permits variability in heat transfer across the surface of endotherms that is independent of surface-to-mass ratio.

Topic-230 Evaporative Cooling

Evaporation of Water

Evaporation of water from the surface causes cooling effect.

For animals, it is the most effective means of removing excess body heat.

Evaporative Cooling by Animals

- Animals with naturally moist skin, such as amphibians, keep a body temperature lower than ambient temperature because of evaporative cooling.
- Certain reptiles, birds and some mammals take available body water (saliva and urine) or water from the environment and spread it on various body surfaces, allowing it to evaporate and take away body heat.
- Some vertebrates use sweating or panting to produce evaporative cooling.

Sweating

- Sweating is a mechanism for evaporative cooling in some mammals having sweat glands in the skin.
- Sweat glands actively extrude water through pores onto the surface of the skin.
- Sweating is under autonomic control.

Panting

- Panting involves use of respiratory system to lose heat by evaporative cooling. It occurs in mammals, birds and some reptiles.
- During panting, mammals inhale through the nose and exhale through the mouth, exposing the tongue and other mouth structures to encourage further water evaporation and therefore heat loss.
- It also involves increase in breathing rate and depth (hyperventilation).
- Heat is carried away in exhalant air because the dimensions of the mouth are such that exhalant air retains the heat absorbed in the lungs.
- In contrast, nasal passages and their vascularization are effective in retaining both water and body heat.

Topic-231 Thermostatic Role of Hypothalamus

A Thermostatic Control System

Body temperature control system of homeothermic endotherms is similar to the mechanized thermostatic control systems. Such a system has a temperature sensor with a set-point temperature, a thermostat and the heating unit.

Endothermic Heat Production

This analogy is especially applicable to endothermic heat production and control in the zone of metabolic regulation, in which heat production increases with decreasing ambient temperature.

Thermostatic Mechanism

The regulation of body temperature, T_b, works along the principles of negative feedback.

Most animals have many temperature sensors in various regions of the body.

Furthermore, to maintain T_b at about T_{set}, homeothermic animals can call on several heat-producing and heat-exchanging mechanisms, so the thermostat controls heat conserving and heat-loss mechanisms as well as heat production.

Temperature Sensors in Body

Mammalian body temperatures can vary widely (as much as 30°C) between the periphery and the body core, with the extremities undergoing far more variation than the core.

Temperature-sensitive neurons and nerve endings exist in the brain, spinal cord, skin and sites in the body core, providing input to thermostatic centers in the brain.

Hypothalamus as Mammalian Thermostat

Mammals may have several thermoregulatory centers, the most important one is located in the hypothalamus and is considered to be the body's "thermostat".

Mammalian hypothalamic thermostat is highly sensitive to temperature.

Cooling the hypothalamus produces an increase in metabolic rate and a rise in Tb, whereas heating it evokes panting and a drop in Tb.

Temperature Sensitive Neurons of Hypothalamus

Highly temperature sensitive neurons are located in the anterior part of the hypothalamic thermostat.

Some of these neurons respond to increased hypothalamic temperature. These neurons activate heat dissipating responses such as vasodilation and sweating.

Other neurons respond when the brain temperature drops below the set-point temperature. They control the activation of heat-conserving responses (e.g., pilomotor) and heat-producing responses (e.g., shivering, nonshivering thermogenesis, brown-fat metabolism).

Topic-232 Thermoregulatory Centers in Non-mammals

Thermoregulatory Centers in Fishes

- Fishes have a temperature-sensitive center in the hypothalamus.
- It senses temperature rise of the body to regulate rate of respiration.
- A rise in temperature leads to an increased rate of metabolism, so need for oxygen is also increased. Fishes have adapted to a temperature-determined adjustment in the rate of respiration.

Thermoregulatory Centers in Reptiles

Reptiles also have a temperature-sensitive center in the hypothalamus.

The reptilian response to cooling of the hypothalamus is to engage in thermophilic (i.e., heat-seeking) behavior, whereas heating of the hypothalamus elicits thermopbobic (i.e., heat-avoiding) behavior.

Thermoregulatory Centers in Birds

Thermostatic control of body temperature in birds is more complex.

The region of the hypothalamus that serves as the thermoregulatory center in mammals is virtually insensitive to temperature changes in birds.

The spinal cord has a site of central temperature sensing in many birds.

Temperature receptors outside the central nervous system send signals to the thermostat in spinal cord, which in turn integrates the input and activates the thermoregulatory effectors.

Topic-233 Fever

Pyrogens

The hypothalamic thermoregulatory center is sensitive to certain chemicals collectively termed as pyrogens (fever-producing substances).

Categories of Pyrogens

There are two general categories of pyrogens, based on their origins.

- Exogenous pyrogens
- Endogenous pyrogens

Exogenous Pyrogens

- Exogenous pyrogens are toxins produced by gram negative bacteria.
- These are heat-stable, high-molecular-weight polysaccharides.
- They are so potent that a mere 10^{-9} g of purified toxin injected into a large mammal causes an elevation of body temperature.

Endogenous Pyrogens

- Endogenous pyrogens arise from animal's own tissues.
- They are heat-labile (heat sensitive) proteins.
- Leukocytes release endogenous pyrogens in response to circulating exogenous pyrogens produced by infectious bacteria.
- Thus, exogenous pyrogens cause a rise in body temperature indirectly by stimulating the release of endogenous pyrogens that act directly on the hypothalamic center.

Fever

The sensitivity of the hypothalamic temperature sensing neurons to pyrogen molecules leads to an elevation in the set point to a higher temperature than normal. As a result, body temperature rises several degrees. This rise in temperature is called as fever.

Significance of Fever

The adaptive significance of endogenous pyrogens and of their production of fever may be related to the bacteriostatic effects of elevated body temperature.

Topic-234 Thermoregulation during Exercise

Muscle Contraction and Heat Generation

For every joule of chemical energy converted into mechanical work during muscle contraction, 3 J of energy is degraded to heat. So, the energy efficiency of muscle contraction is only about 25%.

Exercise Generates Excess heat

Exercise involves muscle contraction. So, extra heat is produced during exercise that is added to the heat produced by basal metabolism. It causes a rise in body temperature above the set-point.

Rise in Body Temperature

To avoid a rise in core temperature, the extra heat generated during exercise is dissipated to the environment simultaneously. However, a rise in temperature does occur during exercise, indicating incomplete removal of the excess heat.

The level to which the core temperature rises in homeotherms is proportional to the rate of muscular work.

During light or moderate exercise in cool environments, body temperature rises to a new level and is regulated at that level as long as the exercise continues. Thus, temperature appears to remain under the control of the body's thermostat.

During heavy exercise, especially in warm environments, the core temperature can rise to high levels as heat-dissipating mechanisms are not able to balance heat production.

Elevations of 4 to 5 Celsius degrees in core temperature are commonly observed in human beings after strenuous, sustained running and in race horses, greyhounds, and sled dogs after racing.

Dissipation of Excess Heat

The rise in T_b is kept small by the high sensitivity of the feedback control of heat-dissipating mechanisms.

For example, a small increase in Tb above the set-point temperature produces a strong and steep increase in the rate of sweating. The effectiveness of evaporative heat loss is affected by humidity of the surrounding air-the higher the humidity, the less effective the heat loss.

Topic-235 Dormant States: Sleep and Torpor

Dormancy

Dormancy is a general term for reduced body activities, including reduced metabolic rate.

Dormancy can be classified based on its duration, ability for arousal and decrease in body temperature.

Dormancy includes: sleep, torpor, hibernation, winter sleep, and estivation.

All these forms of dormancy are related to physiological processes.

Sleep

Sleep is a naturally recurring state of mind and body, characterized by altered consciousness, decreased ability to react to stimuli, inhibition of nearly all voluntary muscles, and reduced interactions with surroundings

Sleep has been the most thoroughly investigated form of dormancy because it is also found in humans.

The time course and extent of sleep varies greatly among animals, e.g.

- Seals resting on ice sleep for only a few minutes at a time.
- Human beings and many other mammals sleep for hours at a time.
- Many of the big carnivores (e.g., lions and tigers) sleep for as long as 20 hours a day, especially after a meal.

Triggers of Sleep

There may be a variety of triggers of sleep.

In mammals, certain sleep-inducing substances build up in extracellular fluids of the central nervous system during wakefulness. Their concentration induces sleep.

The Sleep Process

Sleep process has been divided into two phases:

- Slow wave sleep (deep sleep)
- Rapid eye movement (REM) sleep

Slow Wave Sleep

In mammals, slow wave sleep is associated with:

- A drop in body temperature
- A drop in hypothalamic temperature sensitivity
- Changes in respiratory and cardiovascular reflexes

Rapid-Eye-Movement (REM) Sleep

A smaller portion of total sleep time associated with desynchronized and fast brain waves, eye movements, loss of muscle tone and suspension of homeostasis.

Hypothalamic temperature control is under suspension.

Torpor

Small endotherms can not maintain their high rates of metabolic rates when they are not feeding during periods of inactivity.

During those periods, some of these animals enter a state of torpor, in which body temperature and metabolic rate decrease.

The lower basal metabolism lowers the rate of conversion of energy stores into body heat.

Thus, it is generally advantageous to allow body temperature to decrease during periods of nonfeeding and inactivity.

As the animal comes out of torpor and becomes active, it undergoes a burst of metabolic activity, through shivering or oxidation of brown-fat and its body temperature rises.

Daily torpor is practiced by many terrestrial birds.

The hummingbird is a classic example, allowing its body temperature to fall from a daytime level of about 40°C to a nighttime level as low as 13°C.

Several species of small mammals also undergo torpor (e.g., shrews).

Topic-236 Hibernation, Winter Sleep and Estivation

Hibernation

During the winter, various endotherms go into hibernation that may last for weeks or months.

Hibernation is a time of decreased metabolism and lowered body temperature as well as the heart and breathing rates.

The set point of a hibernator's thermoregulatory center drops to about 20° C, but thermoregulation is not suspended.

True hibernation occurs in some small mammals belonging to orders, Rodentia (ground squirrels), Insectivora (shrews), and Chiroptera (bats).

Preparation for Hibernation

Hibernation occurs only in those mammals which can store sufficient energy reserves to survive the periods of nonfeeding.

Hibernating animals prepare for hibernation by building up fat reserves and growing long winter pelts.

All hibernating animals have brown fat.

Decreasing day length stimulates both increased fat deposition and fur growth.

Arousal from Hibernation

The rate of arousal from hibernation is often much higher than the rate of entry into hibernation. For example in ground squirrel, the transition to the dormant state is completed within 12 to 18 hours, whereas arousal requires less than 3 hours.

Arousal depends on rapid heating initiated by intensive oxidation of brown fat, accompanied by shivering. This leads to a large surge in metabolic rate and rise in body temperature.

Many hibernators arouse periodically (as often as once a week or as infrequently as every 4-6 weeks) to empty their bladders and defecate.

Winter Sleep

Winter sleep is a state of prolonged inactivity in winter that occurs in some larger mammals such as badgers, bears, opossums, raccoons, and skunks.

Body temperatures do not drop substantially (drops only a few degrees), and sleeping animals can wake and become active very quickly. As the body temperature remains near normal, this is not called hibernation.

Large energy reserves sustain these mammals through periods of winter inactivity.

Estivation

Aestivation is a period of inactivity in some animals to withstand extended hot and dry periods.

The animal enters a burrow as its environment begins to dry.

It generally does not eat or drink, its metabolism becomes slow and becomes inactive.

The animal emerges from estivation when moisture returns in environment.

Aestivation is common in many invertebrates (especially mollusks), lung fishes, reptiles, and amphibians.

Animal Behavior

Topic-237 Animal Behavior: Basics

Animal Behavior

The sum of responses made by an animal to the external and internal stimuli is called behavior.

Behavior is based on physiological systems and processes of the animal.

Ethology

The scientific study of animal behavior in their natural environment is called as ethology.

Examples of Behavior

The behaviors may be as simple as moving towards or away from light to the complex behaviors e.g.

- Territory defense
- Courtship and mating
- Liking, disliking and fighting or caring
- Migration and navigation
- Building hives, nests or dens
- Producing voices or songs
- Recognition and communication
- Procuring food
- Learning and memorizing

Behavior is Subject to Natural Selection

Most of the animal behaviors are essential for survival and reproduction.

So the development of behavior has remained subject to substantial natural selection.

Natural selection contributed to the anatomical development of nervous system as well as enhancing the physiological features that contributed to the evolution of complex behavioral patterns.

Objectives of Ethology

1. Understanding the stimuli that elicit behavior.
2. Understanding the physiological mechanisms that mediate the response.
3. Understanding how an animal's experience during growth and development influence the response.
4. Understanding how the behavior aids in survival and reproduction.
5. Understanding the behavior's evolutionary history.

Topic-238 Scientific Approaches to Study Animal Behavior

Behavioral scientists have taken two complementary approaches to understand animal behavior.

1. Neuroethological approach
2. Ethological approach

Neuroethological Approach

The neuroethological approach involves bringing the animal into the laboratory and observing its behavior in a very simplified set of well-defined circumstances.

Simplified Set of Circumstances

In the laboratory:

- there are no predators
- the number and sex of conspecifics (members of the same species) are controlled by the experimenter
- there are unusual lights, smells and sounds
- the animal is often limited to a relatively small and confined space

Study of Behavior with Neuroethological Approach

- The neuroethological approach focuses on the study of neuronal responses generated during the manifestation of an animal's behavior.
- In some cases, the nervous system of animal is exposed surgically to allow the experimenter to record from neurons while behavior is going on.
- Studies under these reduced conditions are useful for obtaining answers to many questions about behavior.
- However, the results from such experiments can be difficult to translate into an understanding of how animals deal with challenges in their everyday lives in natural environment.

Ethological Approach

- The ethological approach is to go into the field and observe the animal's behavior in its natural environment.
- Observing animals in their normal state is an ancient practice.
- However, for a physiologist, these natural conditions raise severe problems that differ from those created by laboratory conditions.
- While observing an animal in its natural setting, it is impossible to record activity from the animal's nervous system that is involved in producing behavior.

Topic-239 Neurosensory Basis of Behavior

Role of Nervous System in Behavior

Nervous system plays an essential role for the human and other animal's behaviors.

The behavior of an organism is manifested in response to the stimuli from the environment. The stimuli act as sensory input for the nervous system. In response to the sensory input, nervous system produces motor output that controls the contraction of muscles.

All behavioral acts are generated by this motor output of the nervous system.

Complexity of Behaviors

Some of these input-output relations are simple and predictable reflexes. Other kinds of behavior are highly dependent on information stored from past experience, and therefore are less predictable to an observer.

Neuronal Networks Underlie All Behaviors

The hardware underlying all behavior is composed of neuronal networks i.e. interconnecting circuits of neurons.

Lower animals with simple behavioral patterns have simple neural network.

The neural circuitry is more complex in animals with a centralized nervous system.

As the interneurons of the CNS increase, the behavioral potential of animal also increases.

Higher animals with complex CNS have developed the ability to learn from experience and to associate combinations of stimuli.

The complex behaviors, learning and memory have neurophysiological basis, rooted in the vast array of neural circuitry lying between the afferent sensory pathways and efferent motor pathways.

Topic-240 Neuronal Plasticity

Although the basic architecture of the nervous system is established during embryonic development, the behavioral patterns can modify with experience. This capacity of nervous system to change with experience is known as neuronal plasticity.

Neuronal plasticity is of premier importance for the survival of any organism.

Examples of Neural Plasticity

- Learning, memory and development of motor skills and habits.
- Neural plasticity lies behind human intelligence.
- The ability of all higher animals to respond to stimuli in diverse ways, different from fixed and programmed reflexes.
- Behavioral plasticity, virtually demonstrated by all animals.

Mechanism of Neuronal Plasticity

Much of the reshaping of the nervous system occurs at synapses.

The mechanisms that underlie synaptic plasticity are currently the subject of many experiments.

Modifying Synapses—Synaptic Plasticity

Synaptic plasticity may takes place as a result of developmental events over the course of a lifetime.

Synaptic connections that are established in embryos are later refined into adult patterns.

Later, changes in synaptic strengths result in learning and memory at mature synapses.

Changes in mature synapses involved in learning and memory depend on a retrograde (reverse) signal that is sent from the postsynaptic neuron to the presynaptic neuron.

Mechanisms of Synaptic Plasticity

Change in mature synapses i.e. synaptic plasticity occurs by two types of mechanisms:

(1) Presynaptic mechanisms:
Involve changes in the functioning of presynaptic terminals.
For example, a change in the amount of transmitter released from presynaptic terminals.

(2) Postsynaptic Mechanisms:
Involve changes in the postsynaptic neurons.
For example a change in the postsynaptic apparatus that results in altered amplitude of depolarizations.

Topic-241 Inborn, Innate or Instinctive Behaviors

Inborn, Innate or Instinctive Behaviors

The inborn or innate behaviors are developmentally fixed particular complex behaviors exhibited by most members of a species.

These behaviors are built-in part of the nervous system at the time of birth or develop at an appropriate point in maturation.

Such behaviors are also known as instinctive behaviors which are different from reflexes, which are simple responses of an organism to a specific stimulus.

Genetic Basis of Instinctive Behaviors

Innate behaviors are closely controlled by genes with little or no environmental influence.

The responses to particular stimuli or situations are determined by neural programmes which are encoded by the hereditary material. These programmes contain information for anatomical and physiological organization of the nervous system.

Exhibition of Instinctive Behaviors

Innate behaviors do not have to be learned or practiced.

They are performed in a reasonably complete form even when they are exhibited first time by the individual, without prior exposure or experience.

The innate behaviors can often be modified through experience but only to a limited extent.

Examples

- A human new born will turn to suckle when brought near the mother's breasts.
- Sea turtles, newly hatched on a beach, will automatically move toward the ocean.
- A marsupial climbs into its mother's pouch upon being born.
- Animal fighting, animal courtship behaviors, internal escape functions and building of nests are also instinctive behaviors.

Importance of Innate Behaviors

Innate behaviors usually involve basic life functions that are important in the survival.

They are especially important for those animals that have short life spans and poorly developed nervous coordination.

Innate Behaviors in Higher Animals

The role of instincts in determining the behavior of animals varies from species to species.

In animals with more complex neural systems, there is greater role of cerebral cortex and social learning, so instincts play a lesser role.

Topic-242 Fixed Action Patterns

Fixed action patterns are a type of instinctive behaviors that are relatively fixed within the species and, once triggered, inevitably run to completion.

They consist of a sequence of unlearned acts that is essentially unchangeable and, once initiated, is usually carried to completion.

Fixed action patterns are triggered in response to external cues known as sign stimuli or key stimuli.

The key stimuli are also called as releasers, because they appear to release a prepatterned behavioral response within an animal.

Example

A classic example of a sign stimulus and fixed action pattern is observed in the male three-spined stickleback fish.

Male sticklebacks have red bellies. A male attacks other males with red bellies, coming to their nesting territories, perceiving them as invaders.

A male stickleback will not attack a fish lacking red coloration but will behave aggressively and attack even unrealistic models and objects having areas of red color on the underside.

So red underside is a sign stimulus for the male sticklebacks and aggressive attacking behavior is the fixed action pattern.

Properties of Fixed Action Patterns

1. They are not simple reflexes. They are relatively complex motor acts, each consisting of a specific temporal sequence of components.
2. They are typically elicited by specific key stimuli rather than by general stimuli.
3. Fixed action patterns have all-or-none property i.e. if the stimulus is removed after the animal's response has initiated, the behavior continues to completion. It means that the key stimulus is required to turn the pattern on; but, once begun, it plays out independently of further stimulation.
4. The stimulus threshold for fixed action patterns may have quite large variation. It varies with the state of the animal. For example, if an animal has copulated once to an arousing stimulus, it cannot be induced to copulate again without intense stimulation.
5. All members of a species perform a given fixed action pattern nearly identically.
6. Fixed action patterns are inherited genetically. They are exhibited in a recognizable form even by the members that have had no prior experience with the key stimuli.

Topic-243 Animal Orientation, Kinesis and Taxis

Animal Orientation

Orientation is the ability of an animal to determine its position in space and move predictably with respect to specific stimuli.

The best examples of animal orientation are observed in response to gravity. A human who has fell down on ground orients himself by standing up. Some animals orient themselves towards the incoming light. Other examples include acoustic and olfactory orientations.

Sensory Motor Basis of Orientation

Animal orientation is a complex process that requires the integration of sensory input and the coordination of motor output.

It includes receiving information through the sensory receptor neurons, processing and correlating it in the central nervous system and forming a response through the muscles that cause the body of animal to move.

Types of Orienting Movements

1. Kinesis
2. taxis

Kinesis

Kinesis is a change in activity or turning rate in response to a change in location.

For example, sow bugs (terrestrial crustaceans) exhibit a kinesis in response to variation in humidity. They become more active in dry areas and less active in humid areas. They do not move toward or away from specific conditions, but their increased movement under dry conditions makes it more likely that they will leave a dry area and encounter a moist area, where they survive better.

Taxis

A taxis is an oriented movement toward (positive taxis) or away (negative taxis) from some stimulus.

For example, trout and many other river fishes automatically swim or orient themselves in an upstream direction (toward the current). This taxis keeps the fish from being swept away and keeps it facing the direction from which food will come.

Cockroaches move away from the stimulus of light, which is called negative phototaxis.

An animal that turns toward the light is said to exhibit positive phototaxis.

Topic-244 Animal Navigation and Migration

Migration is a regular, long-distance change in location. It involves animal navigation over long distances through unfamiliar territories and environments they have not previously encountered.

Many animals seasonally migrate in response to various environmental stimuli involving seasonal droughts or harsh weather conditions of summer and winter.

Migratory behavior is observed in a wide variety of birds, fishes, butterflies, grey whales and many other animals.

Cues Used in Migration and Navigation

The navigational abilities of animals rely on several different sensory cues that guide in orientation and finding their way to the destination.

Many of these cues are difficult to detect and study as they are generally unavailable to human beings.

During navigation, animals may use:

- Sun compass
- Celestial cues
- Earth's magnetic field
- Visual, auditory and olfactory cues

Sun Compass

Many migrating animals track their position relative to the sun.

The sun's position relative to Earth changes throughout the day.

Animals adjust for these changes by means of a circadian clock, an internal mechanism that maintains a 24-hour activity rhythm or cycle.

Celestial Cues

Nocturnal navigators can use the North Star, which has a constant position in the night sky.

Earth's Magnetic Field

Many long-distance migrants, e.g. birds and fishes, navigate by sensing their position relative to Earth's magnetic field.

Visual, Auditory and Olfactory Cues

Many birds also use particular landmarks, odors, sounds, and additional visual cues such as the plane of polarized light to find their way to reach their destination.

Topic-245 Behavioral Rhythms

Biological Clocks

Animals respond rhythmically to cyclic fluctuations in their environment like changes in seasons and daily light and dark periods. The rhythmic behaviors of animals are controlled by the biological clocks which regulate the daily and seasonal cyclic activities of animals. These clocks have a molecular genetic basis as genes for keeping time sense have been identified in many animals including human beings.

These biological clocks may be:

- Circadian clocks
- Circannual clocks
- Lunar clocks

These clocks are influenced by dark and light periods and lunar cycles.

Circadian Clock and Circadian Rhythms

The most important biological clock is the circadian clock that regulates and coordinates daily behavioral activities of all animals.

The output of this clock is a circadian rhythm that is exhibited as a daily cycle of rest and activity.

The clock is normally synchronized with the light and dark cycles of the environment. However it can also maintain rhythmic activity under constant environment conditions, such as during hibernation.

Circannual Rhythms

Some behaviors, such as hibernation, migration and reproduction, reflect biological rhythms linked to the yearly cycle of seasons are called circannual rhythms.

A circannual rhythm spans events that repeat on a 12 month basis corresponding to the tilt of earth's spin axis resulting in seasonal changes.

Circannual rhythms influence the animal physiology by changing the periods of day light and darkness as well as temperature in the environment.

Lunar Cycles and Tidal Rhythms

The lunar cycles are controlled by the phase of the moon whose gravitation pull determines the timing of tidal rhythms in marine environments.

The courtship and reproductive behaviors of many marine animals are linked to the timing of the new and full moon.

Timing the behavior to the lunar cycle links their reproduction to the times of greatest tidal movement.

The tides disperse larvae to deeper waters, where they complete early development in relatively safer environment.

Topic-246 Animal Signals and Communication

Animal Signals

A stimulus transmitted from one animal to another is called a signal.

The signals may be visual, chemical, tactile, or auditory.

Animal Communication

The transmission and reception of signals constitute animal communication.

Animal communication is an essential element of interactions between individuals.

The communication patterns are correlated with the signals and result in:

- Visual communication
- Olfactory communication
- Tactile communication
- Auditory communication

The form of communication used to transmit information is closely related to an animal's lifestyle and environment. For example, in nocturnal terrestrial mammals visual displays are relatively ineffective. Instead, these species use olfactory and auditory signals, which work as well in the dark as in the light. In contrast, the diurnal (active mainly in daytime) animals communicate primarily by visual and auditory signals.

Examples of Animal Communication

1. Courtship Behavior of Drosophila

Courtship behavior in fruit fly *Drosophila melanogaster* constitutes a stimulus-response chain, in which the response to each stimulus is itself the stimulus for the next behavior.

- The courtship begins with a male identifying and orienting toward a female of the same species.
- When the male sees the female, he relies on visual communication.
- In addition, the male's sense of smell, or olfactory system, detects chemicals released into the air by the female. This is an example of chemical communication.
- Having recognized the female, the male approaches and taps the female with a foreleg. This touching is the tactile communication.
- Now the male extends and vibrates his wing, producing a specific courtship song. This singing is an example of auditory communication, informs the female that the male is of the same species.

If all of these forms of communication are successful, the female will become receptive and allow the male to attempt copulation.

2. Communication for Information Transfer

The information content of animal communication varies considerably.

One remarkable example is the symbolic language by which honeybees share information about the location of food sources.

A honeybee which finds a food source returns to its hive quickly becomes the center of attention for other bees, called followers. If the food source is close to the hive (less than 50 m away), the returning bee moves in tight circles while waggling its abdomen from side to side. This behavior, called the "round dance;' motivates the follower bees to leave the hive and search for nearby food.

When the source of food is farther from the nest, the returning bee instead performs a "waggle dance." This dance, consisting of a half-circle swing in one direction, a straight run, and a half-circle swing in the other direction, communicates to the follower bees both the direction and distance of the food source from the hive.

Topic-247 Pheromones and Chemical Communication

Many animals communicate by releasing chemical substances called pheromones.

Pheromones are:

- Chemical messengers with particular odors
- Released to the environment
- Spreads through air
- Effective at remarkably low concentrations
- Detected by the olfactory receptors of the receiving animal
- Affect the behavior of individuals of the same species

Chemical communication is well developed in insects, fishes, salamanders and mammals.

Roles of Pheromones

1. **Recognize members of species:**
    - Unicellular organisms recognize members of their own species.
    - Many insects identify members of their colony through chemical communication.
2. **Reproductive Roles:**
    - Pheromones may attract members of opposite sex for breeding.
    - They induce courtship behaviors in the members of a species
    - Pheromones have adaptive value for successful external fertilization. In many aquatic invertebrates and fishes, spawning by one individual triggers spawning in other individuals of the population because pheromones are liberated along with the gametes. These pheromones induce spawning in other individuals.
3. **Territorial behaviors:**
    - Many male mammals mark their territories with pheromones to warn other males of their occupied area.
4. **Insect's Social Order**
    - In a honeybee colony, pheromones produced by queen maintain hive's complex social order.
5. **Alarm Calls**
    - Members of some species produce pheromones on getting injured to warn other members of presence of danger.
6. **Repel Predators**
    - Pheromones also are used to repel predators.
    - A common example is the foul-smelling musk that makes skunks unpalatable to their enemies.

Advantages of Pheromones as Chemical Signal

The chemical signals:

1. Usually provide a simple message that can last for hours or days
2. Are equally effective during night or day
3. May be transported over long distances by air
4. Take relatively little energy to produce

Disadvantages of Chemical Signals

Chemical signals are slow to act and cannot be changed quickly.

Topic-248 Genes & Environment in Behavior Development

Interaction of Genetic & Environmental Factors

- In past, the scientists have debated whether the behavior of an animal is due to genes (nature) or to environment (nurture).
- It is now known that animal behavior is governed by complex interactions between genetic and environmental factors.
- Although the inherited DNA sequence of an individual provides instructions for the development of behavior, the expression of genes is influenced by many factors.

Environmental Factors in Behavior Development

These include:

- Environment of the fertilized egg
- Animal's diet
- Animals social interactions
- Environmental conditions surrounding the animal

Environment's Effect on Behavioral Gene Expression

Scientists have used a number of methods to determine the extent of environmental effects on the expression of genes determining an animal's behavior.

1. **Cross-fostering study**

In this method, the young of one species are placed in the care of adults from another species.

The extent to which the offspring's behavior changes in such a situation is one measure of how the social and physical environment influences behavior.

The males of certain mouse species have behavioral differences that are well suited for cross-fostering studies.

2. **Twin Studies**

For humans, the influence of genetics and environment on behavior can be explored by a twin study.

In such a study, researchers compare the behavior of identical twins raised apart with those raised in the same household.

The results of twin studies carried out for human behavioral disorders, such as schizophrenia, anxiety disorders, and alcoholism have revealed that in different environments the expression of disorder varies between 20 to 80 % in separate environmental conditions.

Both environment and genetics therefore contribute significantly to the behaviors that characterize these disorders in humans.

Topic-249 Habituation and Imprinting

Learning Behaviors

Most behaviors are variable with experience. Such behaviors are known as learning behaviors. Habituation and imprinting are two of the many examples of learning behaviors.

Habituation

Habituation is one of the simplest forms of learning.

In habituation, an animal learns to ignore a repeated, irrelevant stimulus.

It is defined as a loss of responsiveness to stimuli that convey little or no new information.

Example

Many mammals and birds recognize alarm calls of members of their species.

However, if these calls prove fake repetitively, they stop responding (the "cry-wolf" effect).

An example of learning by habituation is observed in squirrels.

When one squirrel feels threatened, the others hear its signal and go to the nearest refuge.

However if the signal comes from an individual who has caused many false alarms, its signal is ignored.

Significance

By habituation to unimportant stimuli, an animal conserves energy and time that are better spent on other important functions.

Imprinting

Imprinting is the formation of a long-lasting behavioral attachment to a particular individual or object at a specific stage in life.

It is a type of learning in which a very young animal fixes its attention on the first object with which it has visual, auditory or tactile experience and thereafter follows that object.

Sensitive or Critical Period

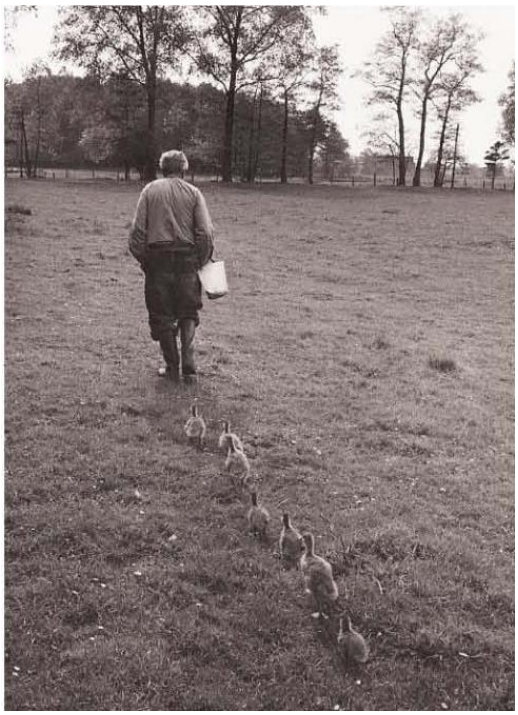
Imprinting usually forms only during a specific sensitive period, also called a critical period, a limited developmental phase when certain behaviors can be learned.

During the sensitive period, the young imprint on their parent and learn the basic behaviors of their species, while the parent learns to recognize its offspring.

Examples

Among gulls, the sensitive period for a parent to bond with its young lasts one to two days. If bonding does not occur, the parent will not care for the infant, leading to death for the offspring.

Another example comes from the classic experiment of Konard Lorenz who conducted experiments with geese. He made the goslings to imprint on him. These goslings followed him as though he was their mother.



Topic-250 Spatial Learning and Cognitive Maps

Spatial Learning

Every natural environment shows some spatial variation, e.g. in the locations of nest sites, hazards, food, and prospective mates. Consequently, an organism's fitness may be enhanced by the capacity for spatial learning, the establishment of a memory that reflects the environment's spatial structure.

Example

The behavior of a female digger wasp, which nests in small burrows dug into sand mounds. When a wasp lefts her nest to go hunting, she covers the entrance with sand. Upon her return, she flies directly to her hidden nest, despite the presence of hundreds of other burrows in the area. The wasp locates her nest by learning its position relative to visible landmarks, or location indicators.

This visual learning of object maps is proved by experimentally disturbing the landmarks that confuses the wasp.

Cognitive Maps

Some animals guide their activity by a cognitive map, a representation in the nervous system of the spatial relationships between objects in an animal's surroundings. Rather than relying solely on moving from landmark to landmark, animals using cognitive maps can navigate more flexibly and efficiently by relating landmark positions to one another.

Example

The Clark's nutcracker birds store thousands of pine seeds in fall at thousands of hiding places called caches, distributed over an area as large as 35 km^2. During the winter, the birds relocate many of their caches.

By experimentally varying the distance between landmarks, researchers demonstrated that birds can identify the halfway point between landmarks. Such behavior suggests that nutcrackers employ an abstract geometric rule, which we can approximate as "Seed caches are found halfway between particular landmarks". Such rules are a fundamental property of cognitive maps and reduce the amount of detail required to remember an object's location.

Topic-251 Associative Learning

A learning that involves making associations between experiences.

Example

If a white-footed mouse bites a brightly colored caterpillar that tastes bad, the mouse avoids attacking insects of similar appearance in future.

The ability to associate one environmental feature (such as a color) with another (such as a foul taste) is called associative learning.

Types of Associative learning

Associative learning can be divided into two types:

- Classical conditioning
- Operant conditioning

Classical Conditioning

In classical conditioning, an arbitrary stimulus becomes associated with a particular outcome.

Example

Russian physiologist Ivan Pavlov carried out early experiments in classical conditioning, demonstrating that if he always rang a bell just before feeding a dog, the dog would eventually salivate at the bell's sound alone, in anticipation of food.

Operant Conditioning

In operant conditioning, also called trial-and-error learning, an animal learns to associate one of its own behaviors with a reward or punishment and then tends to repeat or avoid that behavior.

Example

A predator may learn to avoid certain kinds of potential prey if they are associated with painful experiences.

Similarly, an animal may repeat an action that has resulted in a surprise finding of food. For example, in a classic experiment, a rat was trained through repeated trials to obtain food by pressing a lever.

Topic-252 Cognition and Problem Solving

Cognition

Cognition is the process of intellect, represented by awareness, understanding, reasoning, recalling memories and judgments.

It is the most complex form of learning.

Cognition is exhibited characteristically by primates. Many mammals, cephalopods and insects also exhibit cognition.

Problem Solving

Problem solving is a cognitive activity of devising a method to proceed from one state to another in the face of apparent obstacles.

Problem solving capacity of an animal depends on the information processing ability of a nervous system.

Examples

If a chimpanzee is placed in a room with several boxes on the floor and a banana hung high out of reach, the chimp can “size up" the situation and stack the boxes, enabling it to reach the food.

Such problem solving behavior is highly developed in some mammals, especially primates and dolphins.

Notable examples have also been observed in some bird species, especially ravens, crows, and jays.

Many animals learn to solve problems by observing the behavior of other individuals. Young wild chimpanzees, for example, learn how to crack oil palm nuts with two stones by copying experienced chimpanzees.

Topic-253 Foraging Behavior

Foraging Behavior

The behavior that includes all activities of an animal related to search, recognize and capture food items is called foraging behavior.

Foraging Choices for Animals

Foraging behavior of animals includes the following choices:

1. What items should be included in the diet?
2. If food occurs in patches, what path should an animal take between patches, and how should it locate new patches of food?
3. If the food in a patch is depleted, when should the animal depart from that location and seek another patch of food?

Hummingbirds and various species of bees that visit clumps of flowers to obtain nectar must make each of these decisions.

Owls that forage for small rodents in different habitats, including fields and forests, must make similar decisions.

Evolution of Foraging Behavior

As nutrition is essential for an animal's survival and reproductive success, natural selection has operated to refine behaviors that enhance the efficiency of feeding.

Example

The fruit fly (*Drosophila melanogaster*) provides an example of simple genetic variation that explains the evolution of foraging behavior.

Variation in a gene called *forager* (*for*) dictates the food search behavior of fruit fly larvae.

The larvae carrying the for^R ("Rover") allele travel nearly twice as far while feeding as larvae with the for^s ("sitter") allele.

Experiments revealed that the enzyme encoded by the *forager* locus is involved in signal transduction pathways and is more active in for^R than in for^s larvae.

These results indicate that changes in processing of environmental information can substantially alter behavior.

Topic-254 Foraging Model: Risk and Reward Balance

Gains and Costs of Foraging

There are energy gains and costs in finding and consuming food:

- Energy gain from food
- Energy expenditure in foraging
- Risk of predation while foraging

Optimal Foraging Model

Behavioral ecologists apply a model of cost-benefit analysis to study the foraging strategies of animals.

This model concludes that animal foraging behaviors reflect a compromise between competing selective pressures i.e. the benefits of nutrition and the costs of obtaining food.

Optimal Energy Expenditure

This model analyzes the energy needed to search food, energy needed to pursue and handle food and energy required to digest the food.

For an animal, the energy gain from a given food item must exceed the energy costs.

According to the optimal foraging model, natural selection favors a foraging behavior that minimizes the costs of foraging and maximizes the benefits.

Balancing Risk and Reward

One of the most significant potential costs to a forager is risk of predation.

Maximizing energy gain and minimizing energy costs are of little benefit if the behavior makes the forager a likely meal for a predator.

Animal's foraging behaviors reflect more safety from predation risk and not the hunger for more food gain.

Topic-255 Mating Behaviors and Systems

Mating Behavior

Mating behaviors of animal species evolved through sexual selection, a form of natural selection.

Mating behavior enhances reproductive success of a species.

Mate Choice

The mating behavior involves mate choice. Mate choice includes:

- Seeking or attracting mates
- Choosing among potential mates
- Competing for mates

Mating Systems

Mating systems of different species vary.

They are of three types:

- Monogamous mating system
- Polygamous mating system
- Promiscuous mating system

Monogamous Mating Systems

- In monogamous relationship, one male mates with one female during a breeding season.
- The mates usually remain together for a longer period.
- Monogamy is rare in most animal groups. It is specifically found in groups exhibiting nesting behaviors and parental care.
- In birds it is most frequent as more than 90% are monogamous.
- In a few bird species such as swans and geese, partners are chosen for life and often remain together throughout the year.
- In others, seasonal monogamy is more common

Polygamous Mating Systems

In polygamous system, an individual of one sex mates with several of the other.

Polygamous relationships are of two types:

- Polygynous Systems
- Polyandrous Systems

Polygynous Systems

- Polygynous systems involve an exclusive relationship of one male with two or more females
- Polygynous species are generally dimorphic, with males being showier and often larger than females

Polyandrous Systems

- In polyandrous systems, one female has an exclusive relationship with two or more males.
- Polyandrous species are also dimorphic with females generally more ornamented and larger than males.

Promiscuous Mating System

- In this system, a member of one sex within the social group mates with any member of the opposite sex.
- This system involves no strong pair-bonds or lasting relationships.
- Among promiscuous species, males and females are often so much alike morphologically that they may be difficult or impossible to distinguish based on external characteristics.

Topic-256 Parental Care

Parental Care

- Parental care caters the needs of the newborn and young offspring.
- It is more evolved in animals whose newborns and young cannot care for their selves.
- So, it has been an important factor in the evolution of mating systems.

Parental Care in Birds

Birds present an excellent example of parental care.

- Most newly hatched birds cannot care for themselves.
- They require a large, continuous food supply that is difficult for a single parent to meet.
- To enhance the chances of viability of offspring, most birds are monogamous.
- The male stays with and helps its mate till the offspring are able to fulfill their own needs.

Parental Care in Mammals

- In mammals, lactating female nourishes the young and is involved in most of the caring behaviors. Males usually play no role in raising the young.
- In some mammalian species, such as lions, males protect the females and young. In such species a male or small group of males takes care of many females at once in a harem.

Polygyny When no Parental Care

- Mammals and birds whose young ones can feed and care for themselves almost immediately after hatching, males do not stay with their partner.
- Males of these species can maximize their reproductive success by seeking other mates.
- Therefore, polygyny is relatively common in such animals.

Male Parental Care: Certainty of Paternity

Certainty of paternity is an important factor influencing mating behavior and parental care of males.

Certainty of maternity of young born to or eggs laid by a female is not doubtful. However, certainty of paternity is relatively low in most species, even within a monogamous relationship.

Male parental care is found in very few species of birds and mammals. In such species, males engage in behaviors that appear to increase their certainty of paternity. These behaviors include guarding females, removing any sperm from the female reproductive tract before copulation, and introducing large quantities of sperm to displace the sperm of other males.

Topic-257 Sexual Selection and Mate Choice

Sexual Selection

Sexual selection among the members of a species can take the form of:

- Intersexual selection
- Intrasexual selection

Intersexual Selection

Intersexual selection involves mate choice.

In this selection, members of one sex choose mates on the basis of particular characteristics of other sex, such as appearance, color or courtship songs.

Intersexual selection has led to sexual dimorphism in secondary sexual characteristics, such as the ornate plumage of birds, or the antlers of deer, or the manes of lions.

Such selective characters correlate in general with the mate's health and vitality.

Purpose of mate choice is to choose a healthy partner that is likely to enhance the reproductive success.

Mate choice patterns vary among species. In some, females make choice for their mates while in others, males make selections among the available pool of females.

Intrasexual Selection

Intrasexual selection involves competition between members of the same sex for access to members of the opposite sex.

Intrasexual selection usually occurs between males and may take the form of male-to-male combat or fight.

Such species or individuals have developed better weapons for competition e.g. horns, antlers etc.

There are two main types of competition over females, scramble and contest competition.

Scramble involves a race to get to the female first and grab her. Male body size and vigor contributes to success.

Contest is a more typical form of competition where the male with the best fighting technique, largest body size or the largest weapons will win the female.

Topic-258 Social Behaviors

Social behaviors consist of a set of interactions among individuals of the same species.

Sociality in Animals

- A wide range of sociality occurs among animals.
- Some animals rarely interact with one another. Such animals are called asocial animals e.g. mosquitoes and polar bears.
- Social animals live together in large groups or form tightly knit colonies.

Examples of Social Animals

- Ants and termites
- Bees and wasps
- Many birds
- Wilderbeests
- Wolves and Lions
- Monkeys and gorillas
- Humans

Characters of Social Behaviors

- Most social behaviors are based on cooperation, competition, conflict, exchange, or coercion or sacrifice.
- Most social animals often cooperate with one another to conduct many tasks.
- Many social behaviors are adaptive and increase animal's fitness and reproductive success.
- Animals in groups show joint aggregation against predators.
- Many social behaviors are agonistic and based on competition. Such behaviors are selfish and individuals benefit at the expense of others
- Even in the absence of agonistic behavior, most adaptations that benefit one individual may indirectly harm others.

  For example, superior foraging ability of one individual may leave less food for others.

- Some behaviors are altruistic or unselfish in which an animal favors other at the expense of its own benefits.

Topic-259 Social Behavior: Living in Groups

Animal populations are often organized into groups.

Groups may be:

- Simple aggregation of individuals
- Complex animal societies

Aggregation

- An aggregation is any form of gathering of animals or the process of coming together.
- There is minimal interaction between members of an aggregation.
- For example, several Drosophila flies living on a piece of rotting fruit.

Animal Societies

- A stable group of individuals of the same species that maintains a close-knit cooperative social relationship is called animal society.
- This association typically has complex social organization and extends beyond the level of mating and taking care of young.
- Such societies are observable both in invertebrates and vertebrates.

Advantages of Social Grouping

- Belonging to a group gives protection against predators.
- Group members may warn each other about an intruder.
- Cooperative hunting and search of food increases the feeding efficiency.
- Social huddling in cold weather protects its members from harsh environment.
- Members of a social groups help each other in finding mate and rearing of young.
- Many insects have developed social grouping. These social groups have division of labor. Specific individuals perform specialized tasks of defense, food procurement and feeding of young.

Disadvantages of Social Groupings

- Competition for resources (food, mates) develops between members of a social group.
- Diseases and parasites spread more rapidly in a group of animals.
- They interfere each other for reproduction and rearing of young.
- Large congregations of animals are more susceptible to predation. During attacks, large groups have difficulty seeking hiding places.

Topic-260 Agonistic Behaviors

Agonistic Behavior

- Agonistic behaviors are confrontation behaviors involving aggression, threat displays, attacks and fights between animals.
- Agonistic behaviours are seen in many animal species because resources including food, shelter, and mates are often limited.
- These behaviors are usually used only to intimidate the enemies and are rarely lethal
- Agnostic behaviors seem to be antisocial but these are necessary to maintain social order.

Types of Agonistic Behaviors

Agnostic behaviors are important in the maintenance of territories and dominance hierarchies. So they are of two types:

- Territorial Behaviors
- Dominance hierarchies

1. Territorial Behaviors

Territorial ownership and defense is an important aspect of sociality in animal populations e.g. insects, crustaceans, fishes, amphibians, lizards, birds, and mammals, including humans.

A territory is a fixed area in which an animal spends most of its time and defends it from intruders of the same species.

Purposes of Territorial Behaviors

Territorial behavior has multiple purposes:

Breeding place: Many male birds and mammals occupy a breeding territory. The male actively defends his area against other males. He attracts a female in his territory and performs courtship and mating without interference.

Food source: Some animals occupy territories that contain abundant food supply.

Shelter: Purpose of some territories is to provide shelter to the animal from predators and unfavorable climate.

2. Dominance Hierarchies

Dominance hierarchies exist in many vertebrate groups.

- The organization of group of animals in such a way that some members of the group have greater access to resources like food or mates than others is called dominance hierarchies.

- Some animals are present near the top of the order. They have first choice of resources.
- The animals present near the bottom do not get sufficient resources.

Topic-261 Altruism

Definition

Altruism is a selfless behavior in which an individual endangers his own survival or sacrifices some of its own reproductive potential to benefit another individual.

Evolutionary Basis

Altruism is an innate trait developed through the process of evolution in many animal species particularly in species with complex social structures e.g. primates, some other mammals and insects. However, there are wide individual variations in tendencies toward altruism.

Negates Darwinism Fitness Principle

Altruism is a different kind of social behavior which has been hard to explain within the framework of Darwinism and natural selection because it reduces the fitness of the altruist.

Significance of Altruism

- In ethology, the costs and benefits of a behavior are measured in terms of reproductive fitness, or expected number of offspring.
- So by behaving altruistically, an organism reduces the number of offspring it is likely to produce itself. However, by sacrificing its own favors to save others, it indirectly boosts the would-be number of offspring that other members of species are likely to produce.

Examples of Altruism

- A belding's ground squirrel that sees a predator gives a high-pitched alarm call that alerts unaware individuals to retreat to their burrows. The squirrel that warns others becomes conspicuous and increases the risk of being killed by the predator. Similar behaviors are observed in crows and monkeys.
- In social insect colonies (ants, wasps, bees and termites), sterile workers devote their whole lives to caring for the queen, constructing and protecting the nest, foraging for food, and tending the larvae. Such behaviour is maximally altruistic
- Similarly, worker bees sting intruders. This behavior helps defend the hive but results in the death of those workers.
- Vampire bats regurgitate blood and donate it to other members of their group who have failed to feed that night, ensuring they do not starve.

Topic-262 Kin Selection and Inclusive Fitness

Kin Selection

Kin selection is an altruistic evolutionary strategy that favors the reproductive success of an organism's close relatives, even at a cost of organism's own survival and reproduction.

Kin selection is an instance of inclusive fitness, which combines the number of offspring produced by an individual itself and the number of individuals it can ensure by supporting other close relatives (siblings).

William Hamilton proposed the idea of kin (relatives) selection to explain how selection acting on related animals can affect the fitness of an individual.

Through kin selection, a gene carried by a particular individual passes to the next generation through a related individual.

The fitness of an individual is based on the genes it passes on as well as on those common genes that its relatives pass on.

For kin selection to be effective, the individuals of a group must be able to identify their relatives. This is the reason that it is found in animals with advanced social structures i.e. primates and social insects.

The altruistic kin selection behavior is most readily apparent in the act of parents sacrificing for their offspring. When parents sacrifice their own well-being to produce and aid offspring, this actually increases the fitness of the parents because it maximizes their genetic representation in the population.

Inclusive Fitness

Inclusive fitness is the measure of fitness of whole group of members of a species which may not be close relatives.

An organism's inclusive fitness is determined by its personal fitness, plus its weighted effects on the fitness of every other individual in the population. The weights are determined by the coefficient of relationship.

It is favored by natural selection that acts to maximize the fitness of group of individuals in the population, rather than thinking in terms of selfish genes trying to maximize their future representation in the gene-pool.

Helping behavior of individuals of a species for those who are not their close relatives is an example of inclusive behavior.

Topic-263 Reciprocal Altruism

Reciprocal Altruism

- Some animals occasionally behave altruistically toward others who are not relatives.
- A baboon may help an unrelated companion in a fight, or a wolf may offer food to another wolf even though they share no kinship.
- Such behavior can be adaptive if the aided individual returns the favor in future.
- This sort of exchange of aid is called reciprocal altruism.
- Reciprocal altruism is limited largely to species with social groups stable enough that individuals have many chances to exchange aid (e.g. chimpanzees, humans).
- It generally occurs when individuals are likely to meet again.

Cheating

- Reciprocal altruism is also associated with negative consequences if favors are not returned to individuals who had been helpful in the past.
- Such a pattern of behavior that does not reciprocate favors is referred to as "cheating" by behavioral ecologists.
- It occurs as cheating may benefit the cheater substantially.

Game Theory and Tit for Tat Strategy

- Game theory explains how reciprocal altruism dominates over cheating behavior. It involves a behavioral strategy called tit for tat.
- In the tit-for-tat strategy, an individual treats another in the same way it was treated the last time they met.
- Individuals adopting this behavior are always altruistic, or cooperative, on the first encounter with another individual and will remain so as long as their altruism is reciprocated.
- When their cooperation is not reciprocated, individuals employing tit for tat will retaliate immediately but return to cooperative behavior as soon as the other individual becomes cooperative.
- The tit for tat strategy has been used to explain the few apparently reciprocal altruistic interactions observed in animals-ranging from blood sharing between nonrelated vampire bats to social grooming in primates.

Topic-264 Social Learning

Social Learning

The type of learning that involves observing and copying others behavior is called social learning.

Example: young chimpanzees learn to crack palm nuts by copying the behavior of more experienced individuals.

Social Learning and Culture

Social learning forms the roots of culture. Culture is defined as a system of information transfer through social learning or teaching that influences the behavior of individuals in a population.

Cultural transfer of information can alter behavioral phenotypes and thereby influence the fitness of individuals.

Culture based changes in phenotype occur on a much shorter time scale than changes resulting from natural selection.

Social Learning Behaviors

Social learning behaviors are prevalent in animal kingdom, specially vertebrates.

Types:

- Copying behaviors
- Fine-tuned social learning

Copying Behaviors: Mate-Choice Copying

Mate-choice copying is a form of social learning behavior in which individuals in a population copy the mate choice of others.

In mate choice copy, an individual is attracted to a mate that is also attractive to most other individuals of opposite sex.

This behavior has been demonstrated in several fish and bird species.

Fine-tuned Social Learning

Fine-tuned learning with experience in humans is well known. A human baby starts to learn expressive words and accents that modify and improve with age.

Studies on vervet monkeys have demonstrated fine-tuned learning in animals.

Fine-Tuned Learning of Alarm Calls

Vervet monkeys produce a complex set of alarm calls. Their repertoire of calls includes giving distinct alarm calls for predators like leopards, eagles or snakes.

When a vervet sees a leopard, it gives a loud barking sound. When it sees an eagle, it gives a short double-syllabled cough. The alarm call for a snake is a “chutter”.

Upon hearing a particular alarm call, other vervets behave in an appropriate way: They run up a tree on hearing the alarm for a leopard. Look up on hearing the alarm for an eagle. Look down on hearing the alarm for a snake.

Infant vervet monkeys give alarm calls, but in a relatively undiscriminating way. For example, they give the "eagle" alarm on seeing any bird, including harmless birds. With age, the monkeys improve their accuracy. Infants learn how to give the right call by observing other members of the group and receiving social confirmation of correct calls from learned members.

Topic-265 Evolution and Human Culture

Genetic Basis of Human Culture

Human culture and certain social behaviors are due to expression of genes that have been perpetuated by natural selection. So, human culture is related to Darwinian evolutionary theory.

However, an irrational interpretation of the genetic and evolutionary basis of human behavior may be misleading. It may be used to justify the status quo in human society, thus rationalizing social injustices and animal behaviors of human.

Plasticity of Human Behavior

Actually, the evolutionary explanation of human behavior does not make human behavior a rigid genetic model.

Just as the anatomical features of individuals vary extensively, so do the inherent behaviors.

Just like environment intervenes in the phenotypic expression of a genotype for physical traits, it is more significantly involved in the expression of behavioral traits.

As human have greater capacity for learning, human behavior is probably more plastic than that of any other animal.

Control of Instinctive Behavior by Culture

In the human cultural history, humans have built up a diversity of structured societies with institutionalized governments, laws, cultural values, and religions.

These institutions define what behavior is acceptable and what is not. Many of the instinctive behaviors that might enhance an individual's Darwinian fitness are considered unacceptable by law and are prohibited.

Perhaps these are the social and cultural institutions that make human behavior distinct and controlled than that of other animal societies.