

ZOO502 - Animal Physiology and Behavior

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.

Animal Models 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**). Provide insight into the physiological processes of disease

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-3STRUCTURE-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.

Structural Specialization for 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.

Structure-Function Relationships Exist At All Levels of Biological Organization

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.

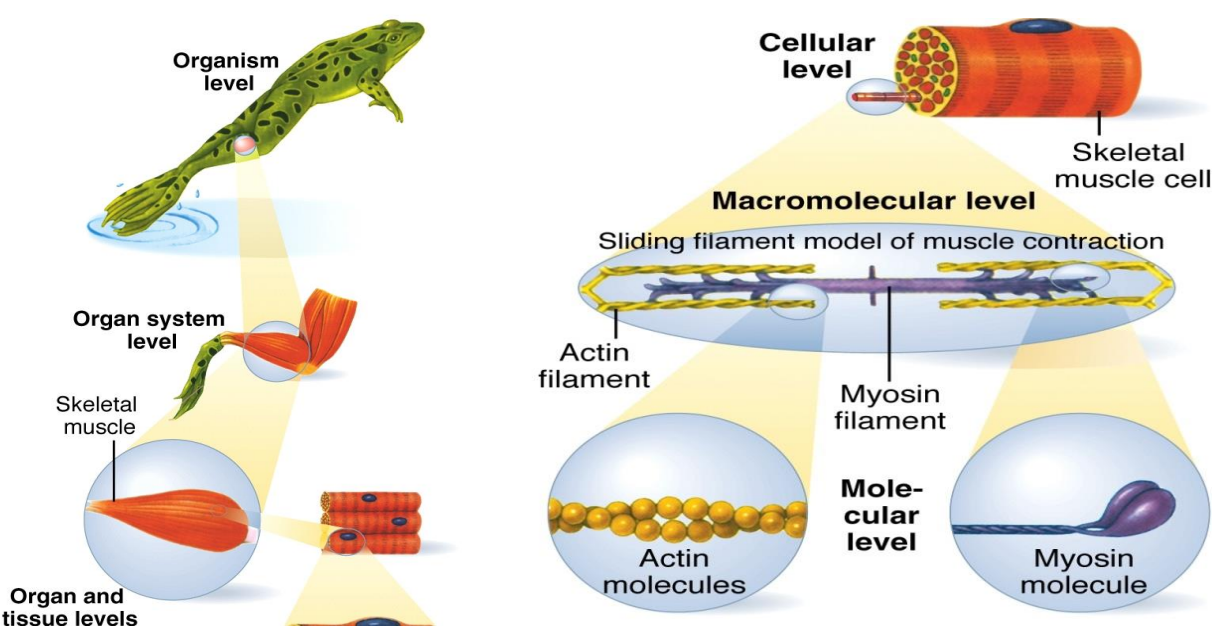
SYSTEM LEVEL: Groups of skeletal muscles form a system that helps to move frog’s limbs.

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:

1. Homeostatic regulation of water
 2. Homeostatic regulation of temperature
 3. Regulation of pH
 4. Regulation of glucose concentration
 5. Regulation of osmotic pressure
 6. Regulation of oxygen level
 7. Regulation of ion conc.
- 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.
 - Homeostasis maintains the temperature of healthy human body near 37°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:

- Variables
- Set point
- Living control systems VS physical control systems
- Three components: Receptors, Control center, effectors

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.

- Temperature control system in air conditioners and water heating geysers VS Endothermic animals
- 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:

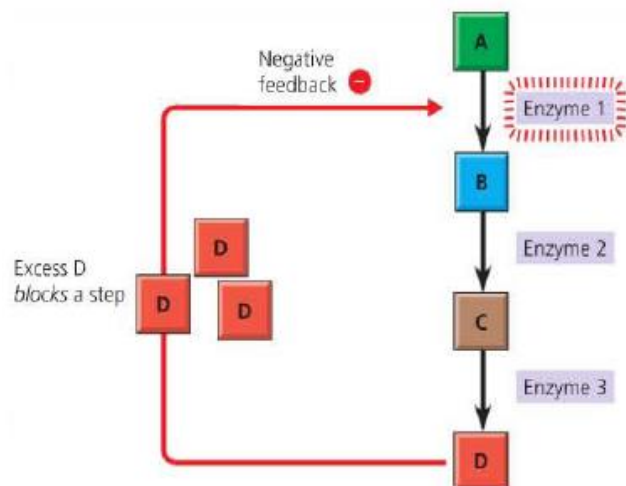
In life, the most common form of regulation encountered is the negative feedback, in which accumulation of an end product works to stop or slow down that process.

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

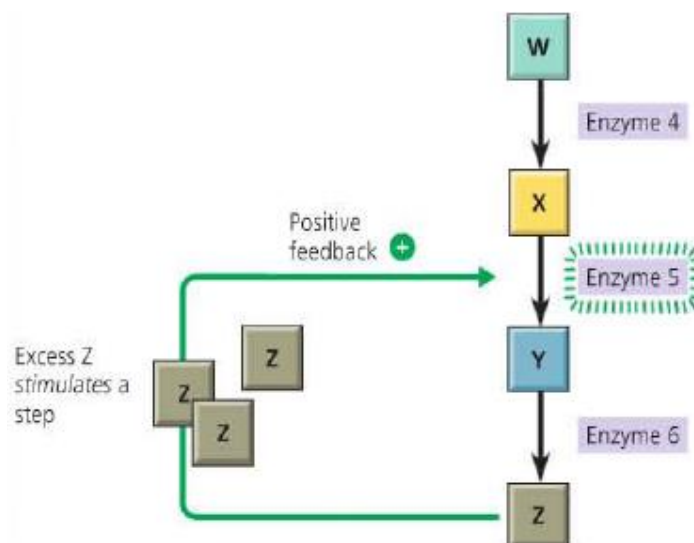
The control of blood sugar (glucose) by insulin is another good example of a negative feedback mechanism.

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.

Conformers

- Animals that conform to external changes
- Are unable to maintain homeostasis for internal conditions

Types

- Osmoconformers
- Oxyconformers
- Thermoconformers

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.

Regulators

- Use internal control mechanisms to regulate internal conditions

- Maintain homeostasis

Types

- Osmoregulators
- Oxyregulators
- Thermoregulators

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

Selective 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.

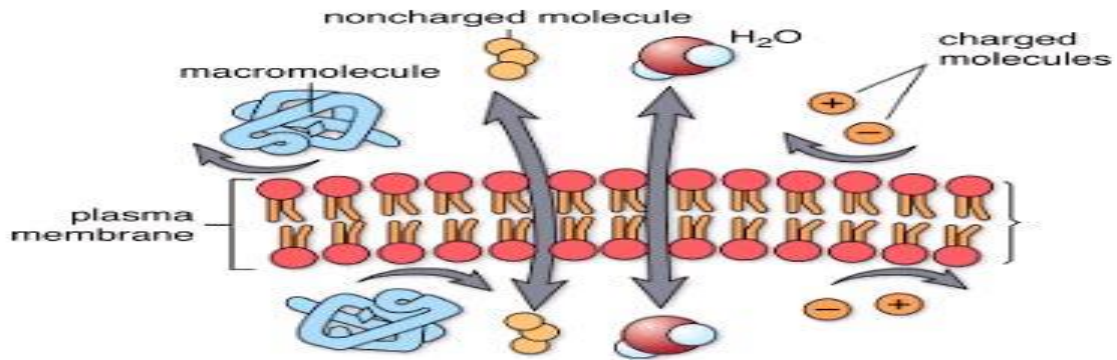
Membrane Permeability For Various Substances

- Varies greatly with type and size of molecules.

Non-Polar, Lipid-Soluble Substances

- Cross passively by dissolving in the lipid bilayer of membrane.
- Rate of penetration depends on lipid solubility and size of molecules.

v



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.

Polar Substances & Ions

- Have difficulty in passing through because of hydrophobic interior of lipid bilayer.

Macromolecules

- Cannot cross plasma membrane due to size.

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.

Permeability can be altered:

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^- .

Permeability can be Altered

- Hormones and some other molecules can alter the permeability to certain substances.
- Hormones react with receptor sites and influence channel size or carrier mechanisms.

Examples

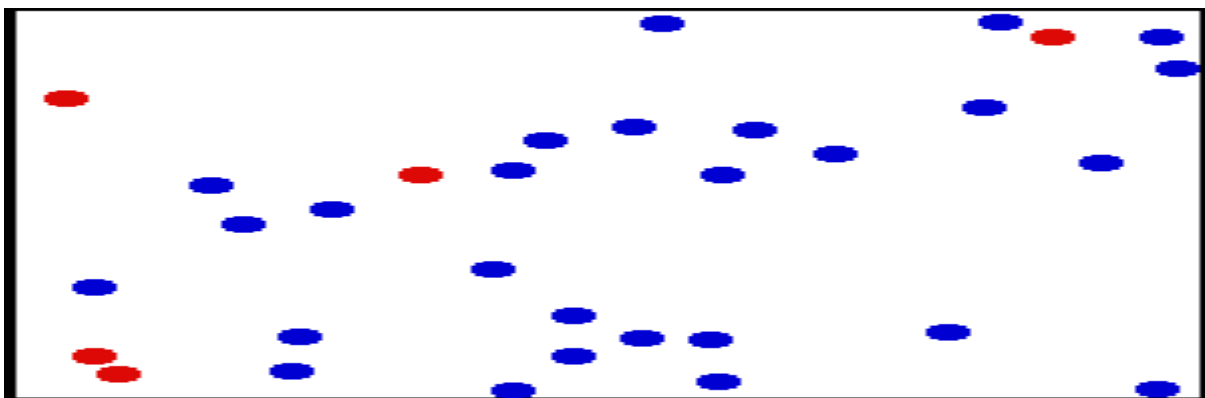
- Antidiuretic hormone can increase water permeability of renal collecting duct in mammals up to 10 times.
- Neurotransmitters induce large increase in permeability to ions by acting on integral membrane proteins in nerve and muscle cells.

TOPIC-9 DIFFUSION AND MEMBRANE FLUX

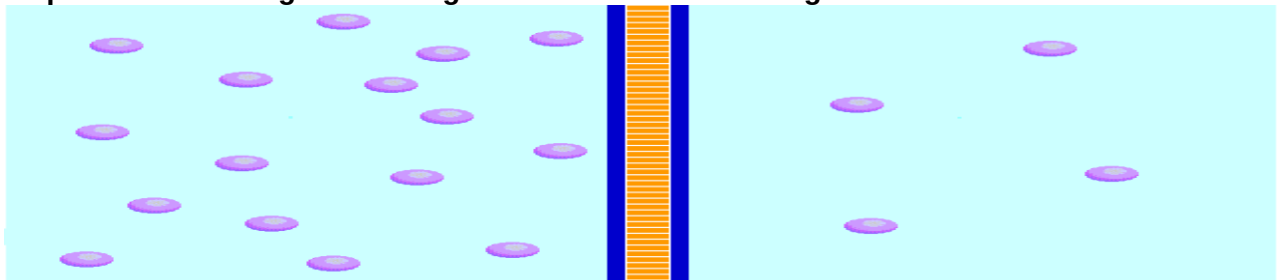
Diffusion:

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”.



Diffusion—Applications

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:

- Example: Diffusion of Oxygen

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.

Diffusion—Mechanism

- Diffusion is a passive transport and occurs without the expense of energy.
- Concentration gradient itself acts as potential energy and drives diffusion.
- Rate of diffusion varies for different molecules due to permeability differences.

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:

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

Where:

- 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.

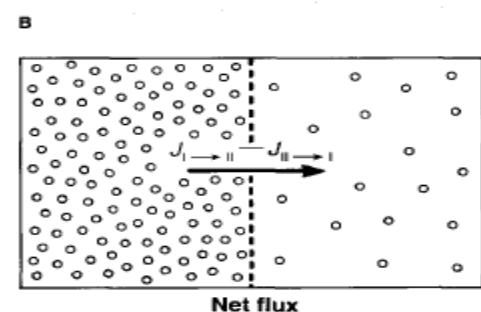
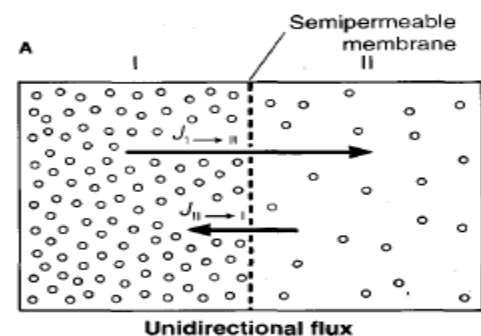
Membrane Flux

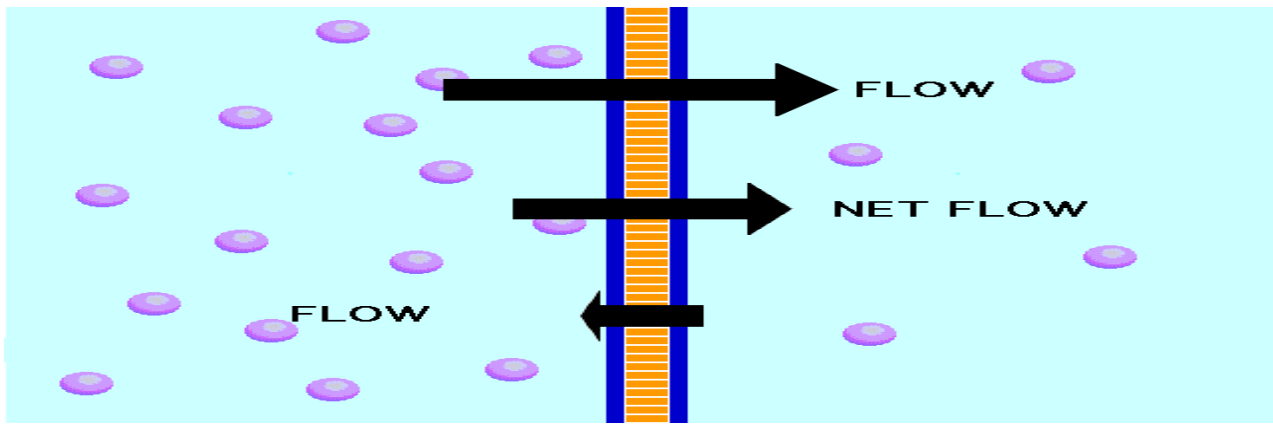
The amount of solute that passes through a unit area of membrane every second in one direction is known as the flux. It is represented by “J”. So,

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

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.

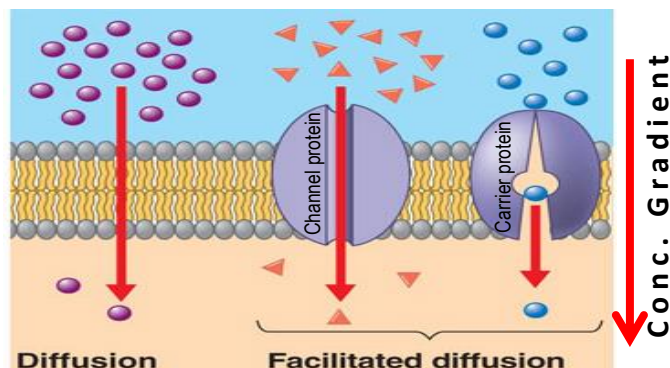




TOPIC-10 DIFFUSION THROUGH MEMBRANE CHANNELS AND CARRIER PROTEINS: THE FACILITATED DIFFUSION

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:

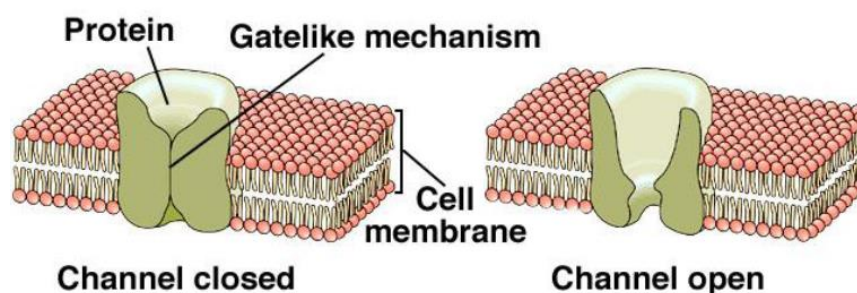
The two types of transport proteins are:

- 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.

Channel Proteins

- Extend across the cell membrane.
- Have water-filled pores: membrane channels.

Membrane Channels

- Allow specific molecule or ion to pass through and cross the membrane.
- Diameter of channels is less than 1.0 nm.
- Can opening and close.
- Opening and closing is regulated.
- Molecules can cross the membrane when these pores are open.

Examples of facilitated diffusion through Channel Proteins:

Channel Proteins: Types

- Water channel proteins
- Ion channel proteins
- Specialized 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:

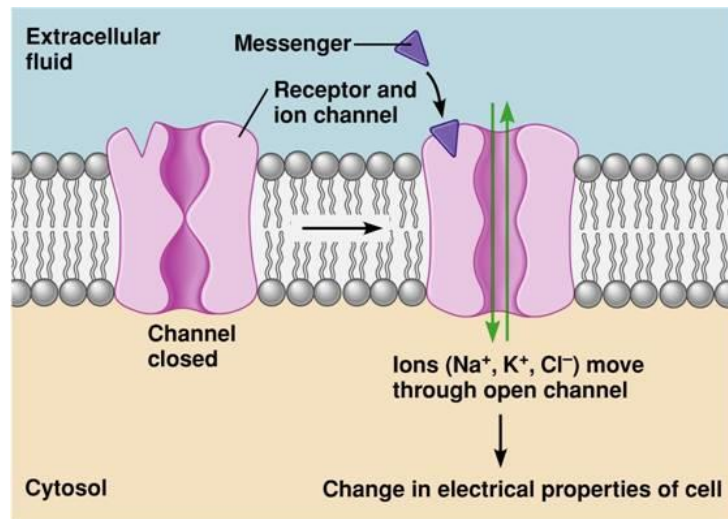
Another group of channel proteins are ion channels, many of which function as gated channels, which open or close in response to a stimulus.

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.

Ion Channel Proteins

- Allow specific ions.
- Gated channels
- Open or close in response to an electrical or chemical stimulus.
- Chemical stimulus is a substance other than that is to be transported. e.g. neurotransmitters for Na^+ gated ion channels.
- Electrical stimulus activates K^+ ion channels



c) Specialized membrane channels:

Many small, uncharged polar molecules, such as CO₂, 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.

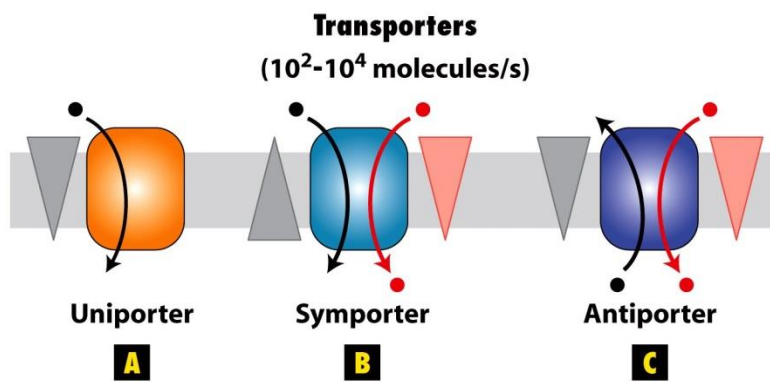
Types of Carrier proteins:

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.
 - Coupled transporters that transfer two solutes in the same direction are called symporters.
 - Coupled transporters that transfer solutes in opposite directions are called antiporters.

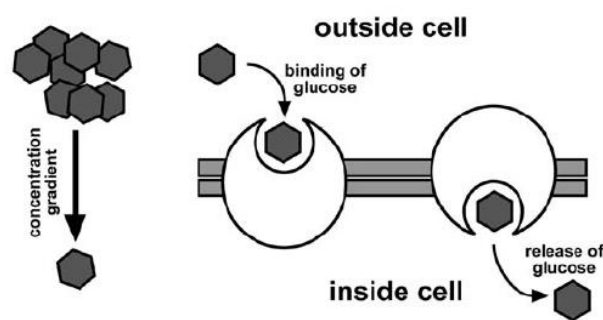
Carrier Proteins–Types

- Exist in many forms in all types of membranes.
- Various functional types:
 - Uniporters
 - Coupled transporters
 - Symporters
 - Antiporters
- Uniporters transport a single solute from one side of the membrane to the other.
- Coupled transporters transfer one solute and simultaneously or sequentially transfer a second solute.
- Symporters are coupled transporters that transfer two solutes in the same direction.
- Antiporters are coupled transporters that transfer two solutes in opposite directions.



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

Discovery

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:

Definition

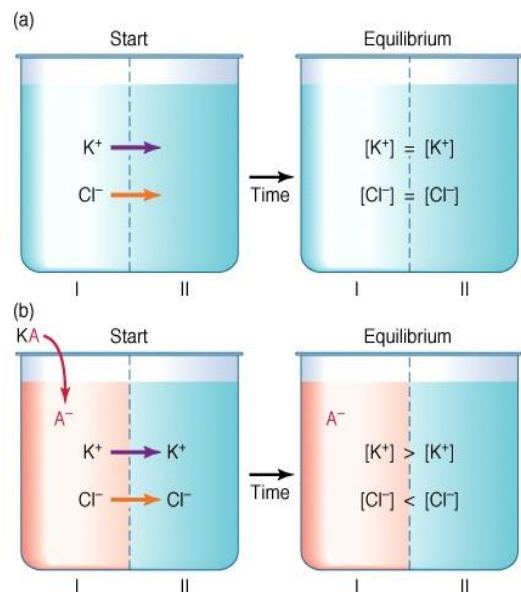
“If diffusible solutes are separated by a membrane that is freely permeable to water and electrolytes but totally impermeable to one species of ion, the diffusible solutes become unequally distributed between the two compartments”.

Example—An Experiment

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 non diffusible 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 non diffusible solute remains high even at equilibrium. This is known as Donnan effect.

Donnan Effect & Living Cells

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.

- This results in potential difference across the membrane.
- Major ions that are unequally distributed are: K^+ , Na^+ , Cl^- and Ca^{2+} .

Examples:

Distribution of 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.

Distribution of 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.

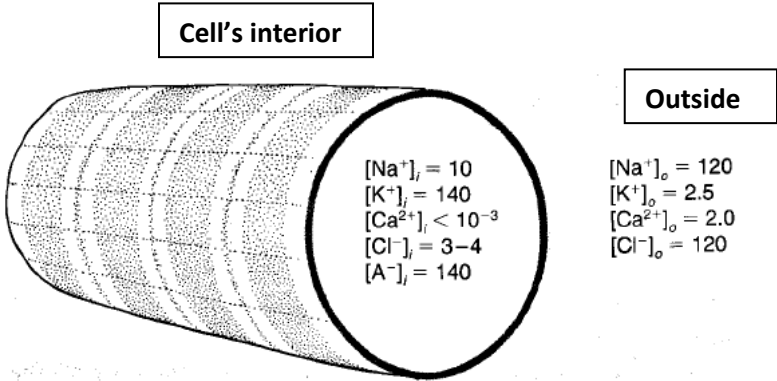
Distribution of Ca^{2+} ions

- 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 cytosol 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.

Active Transport

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.

Membrane Pumps

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

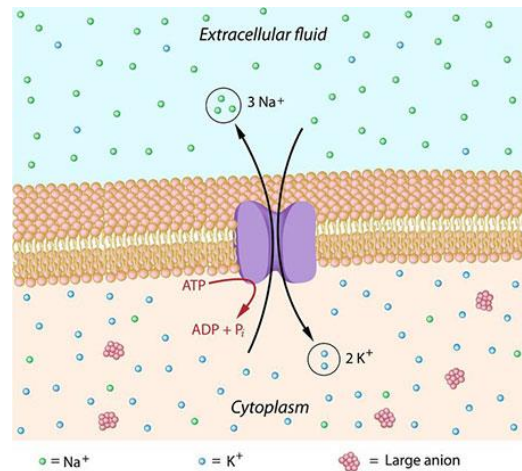
The mechanisms that involve carrier proteins to actively transport substances against a gradient are collectively called membrane pumps.

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.

Role of 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.



Nature & Function of Na⁺/K⁺ Pump

- 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.

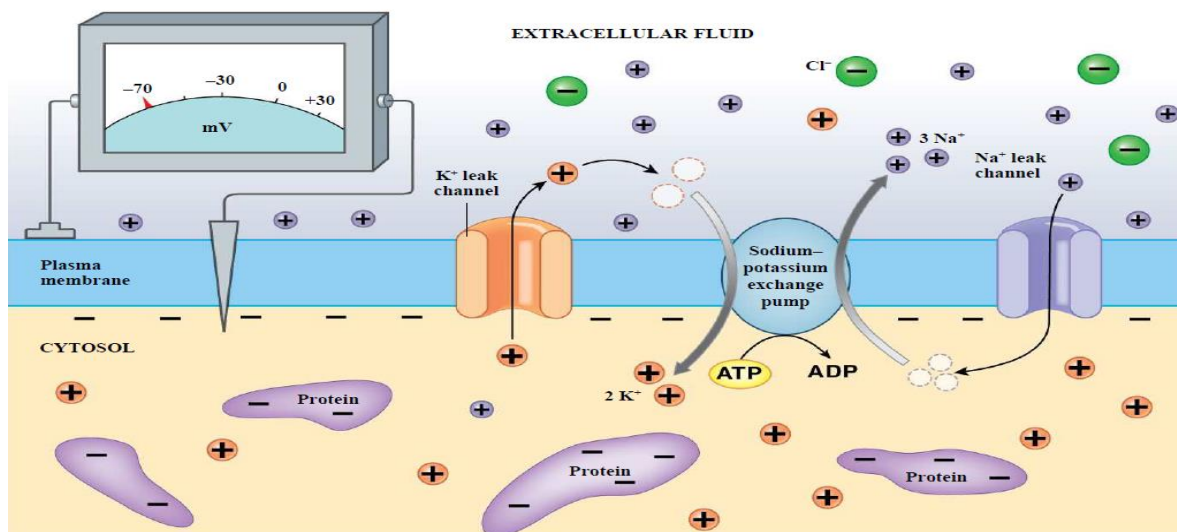
TOPIC-14 MEMBRANE POTENTIAL AND MEMBRANE EXCITATION

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.

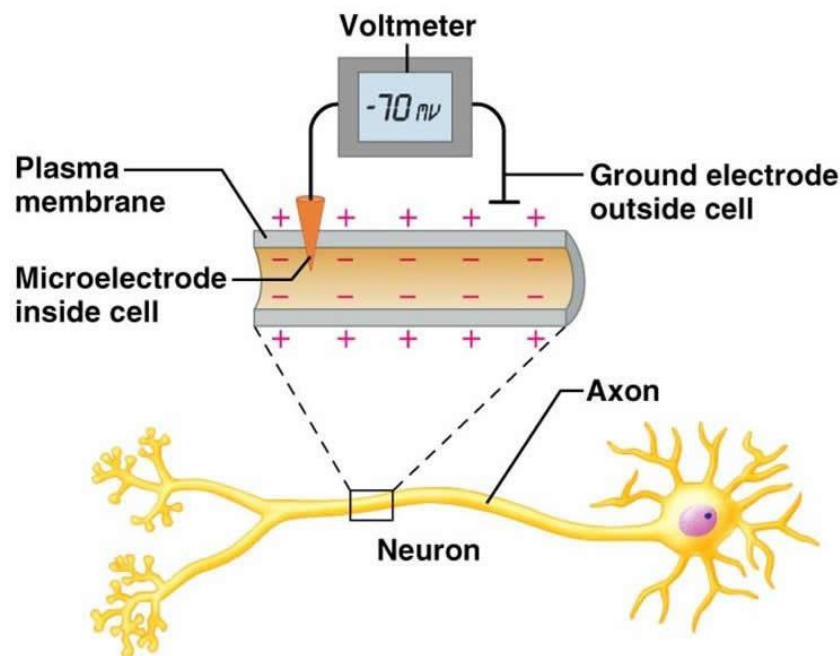
Voltage Clamp Method: Detection and measurement of membrane potentials

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

Ion Channels

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
- Voltage-gated ion selective channels
- Ligand-gated ion channels
- Stimulus-activated ion channels

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.

Voltage-Gated Ion Channels: Types

- 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.

Voltage-Gated Na^+ Channels

- The voltage-gated Na^+ channels are fast-acting channels. They are activated by depolarization and produce rising phase of action potential.

Voltage-Gated Ca^{2+} Channels

- 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

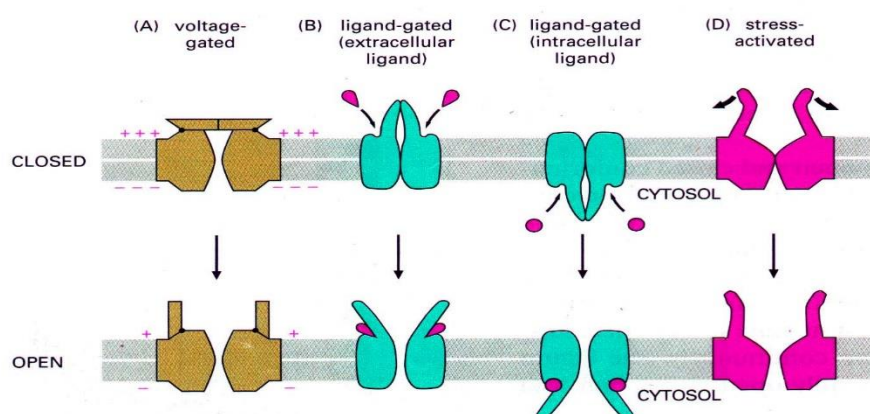
- Voltage-gated K^+ channels are also known as “delayed rectifiers”. They allow potassium ions to flow out of the cell and rapidly repolarize the membrane to terminate an action potential.

Ca^{2+} Activated K^+ Channels

- 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

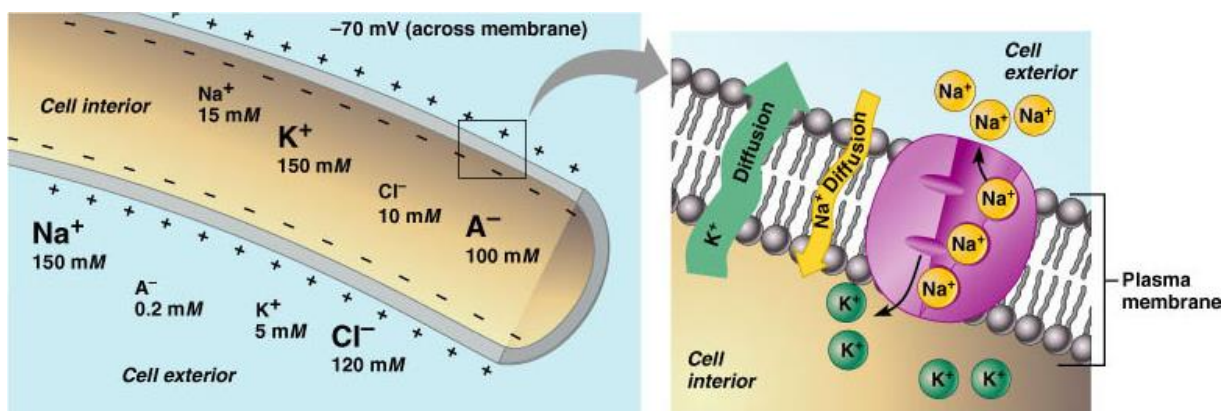
Every cell that is in a non-excited or "resting" state has a potential difference, V_{rest} , across its membrane. The values of V_{rest} vary in different types of cells. Generally the reference value of resting membrane potential in neurons is taken as -70mV, when no impulse is being conducted.

Ions Responsible for RMP

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.

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

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:

- The always open resting K^+ selective channels and voltage-gated Na^+ channels play important role in producing and maintaining the transmembrane potential difference.

Role of K^+ Channels

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.

Role of Na^+ Channels

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.

- Actions potentials are large but brief changes in membrane potential that are propagated along axons without decrement.

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:

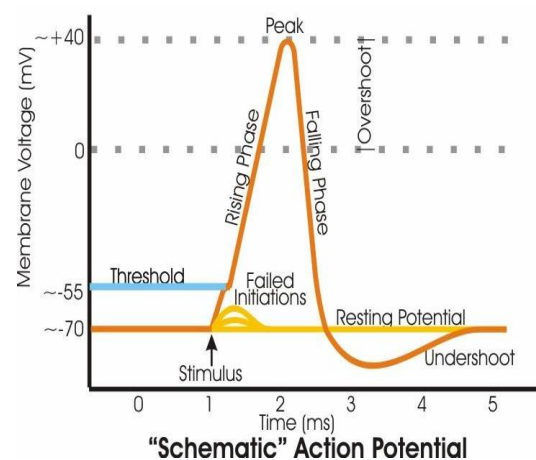
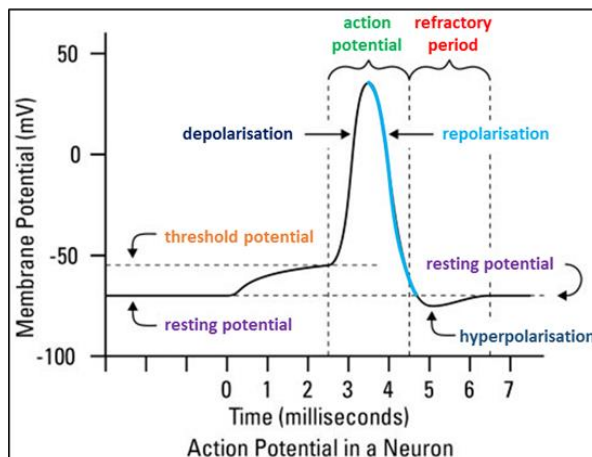
- APs in the nervous system are responsible for every sensation, every memory, every thought—indeed every impulse to act in the environment.
- The action potentials carry information over long distances in nerve and muscle tissues.

- 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)



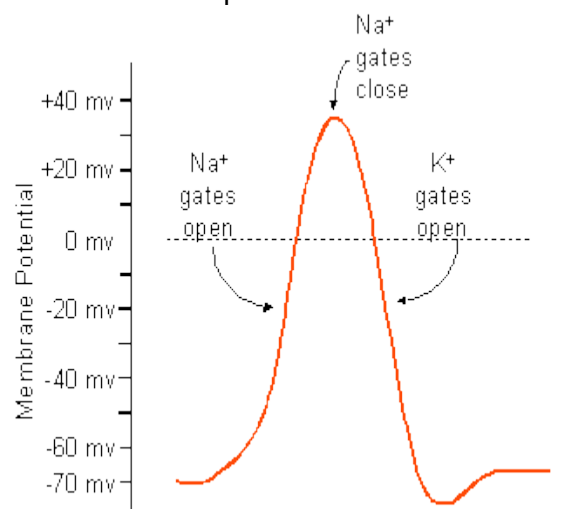
Stimulation

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 $E_{\text{Na}} \sim +55\text{mV}$. 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.

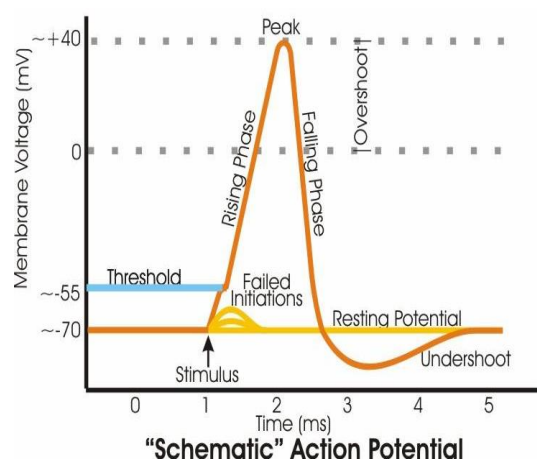
4. **Action potentials are “All-or-None” events**

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. Action potentials propagate along nerve fibers without any reduction in amplitude. The speed of propagation is also constant.

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.

6. 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.

7. Number of Ions Involved in an AP

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)

8. 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.

9. 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.

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.

10. 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.

11. 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.

- Two types:
 - Phasic response
 - Tonic response

Adaptation: Phasic response

The type of adaptation in which neurons adapt rapidly and stop generating more APs after initial one or two APs.

Adaptation: Tonic Response

The type of adaptation in which neurons adapt slowly and fire repetitively to a subthreshold stimulus, but with gradually decreasing frequency.

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

Sodium and Potassium Channels

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.

Unequal Distribution of Ions

The production of an action potential depends on:

Unequal Distribution of Ions

- 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.

Gating of Ion Channels

- 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.

Ionic Currents Through Ion Channels

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

Role of Na^+ and K^+ Channels .

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.

Role of Na^+ and K^+ Channels

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.

Use of Antibodies in Localization of Ion Channels

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

Nature

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

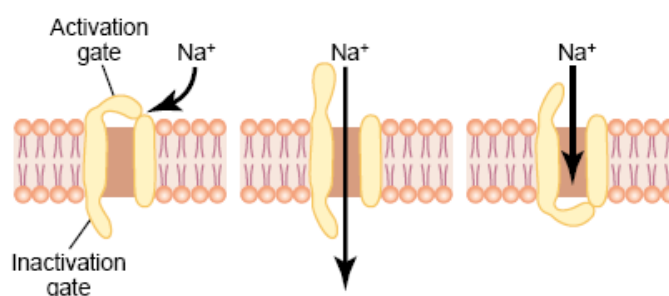
They are activated when a stimulus causes depolarization of membrane. Their opening results in inward flow of Na^+ ions that produce rising phase of action potential.

Channel Gates

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.

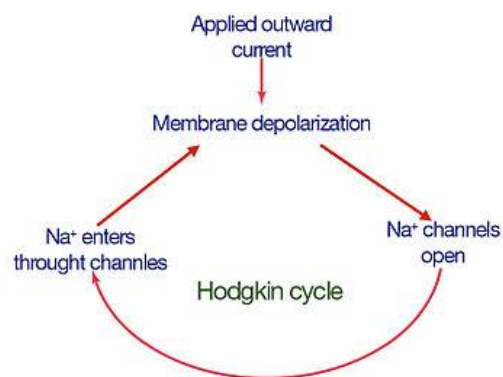
Each channel can pass up to 10^7 (10 million) Na^+ ions per second, providing enough I_{Na} (sodium current) to account for the macroscopic currents that have been measured in various neurons.

Opening and closing of Na^+ channels—the Hodgkin cycle:

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.

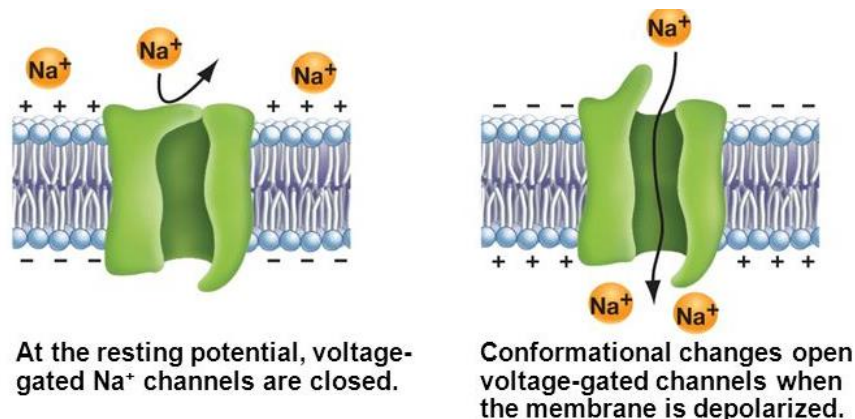
During an AP, Na^+ channels respond to an initial depolarization by opening, allowing Na^+ to enter the cell, which further depolarize the membrane. This depolarization causes more channels to open, allowing still more Na^+ to enter the cell and triggering an explosive, regenerative event. This relationship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



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.

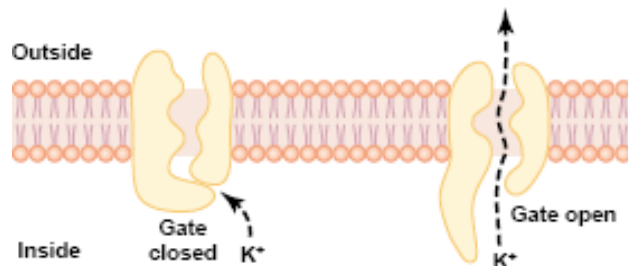
TOPIC-23 VOLTAGE-GATED POTASSIUM (K^+) CHANNELS

Size: Features

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.

Hyperpolarization

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.

Role in 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.

Number of K^+ Channels in Neurons

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

Features

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.

Role of Ca^{2+} ions:

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

NERVE PHYSIOLOGY

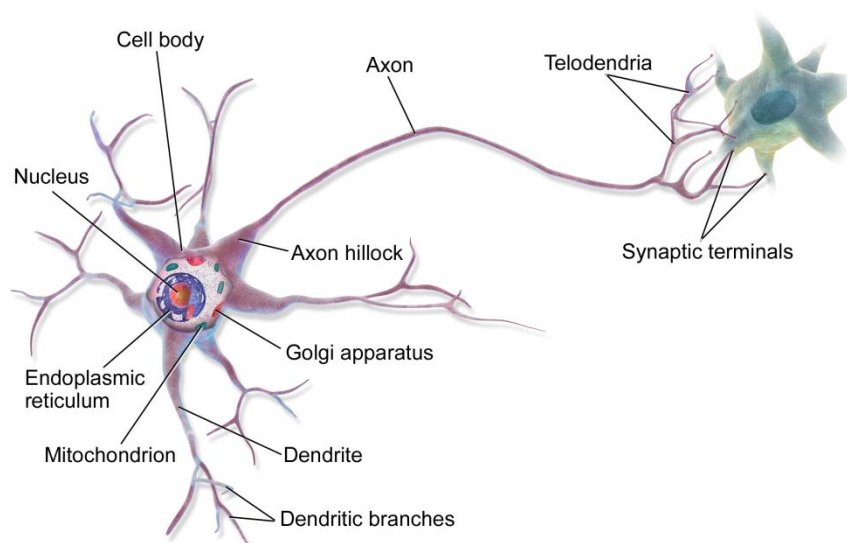
TOPIC-25 STRUCTURAL FEATURES OF NEURON

- 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

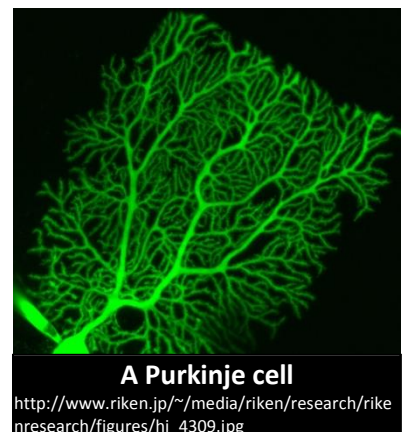
Neurofibrils are delicate threads running from cytoplasm of the nerve cell body into the axon and the dendrites. They are formed by clumping of neurotubules and neurofilaments.

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.



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 axons 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.

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.

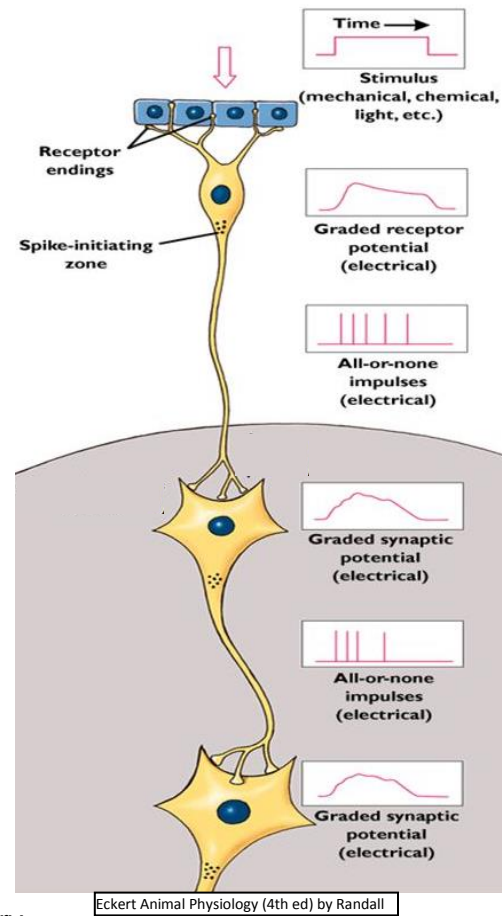
Graded potentials are produced at sensory and postsynaptic membranes where short distance conduction is required.

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.

Regenerative Property of APs

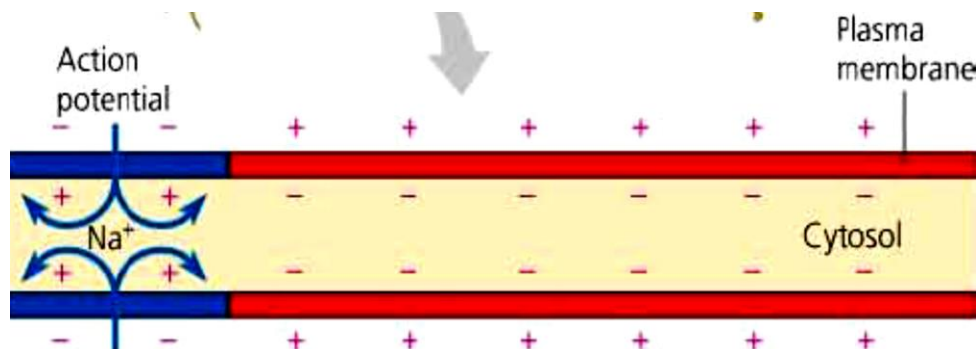
As an action potential occurs over a region of few millimeters only, the events of action potential must regenerate i.e. occur over and over again along the length of an axon.

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:

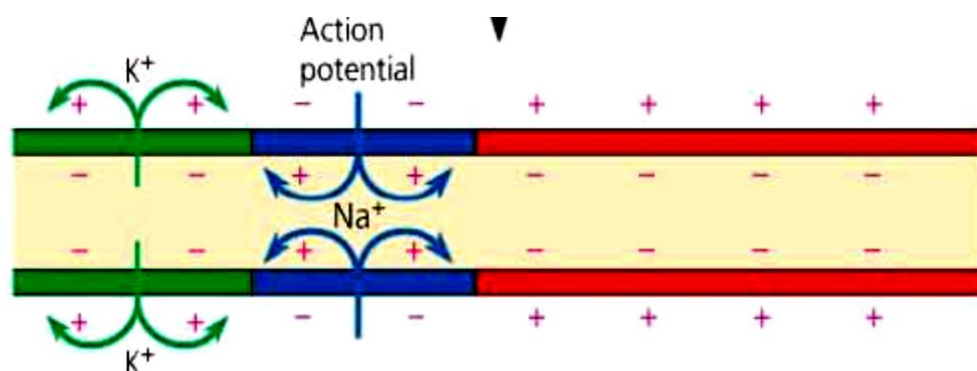
In this process, the action potential elicited at any one point on an excitable membrane, spreads excitation to the adjacent portions of the membrane, resulting in its propagation along the membrane.

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.

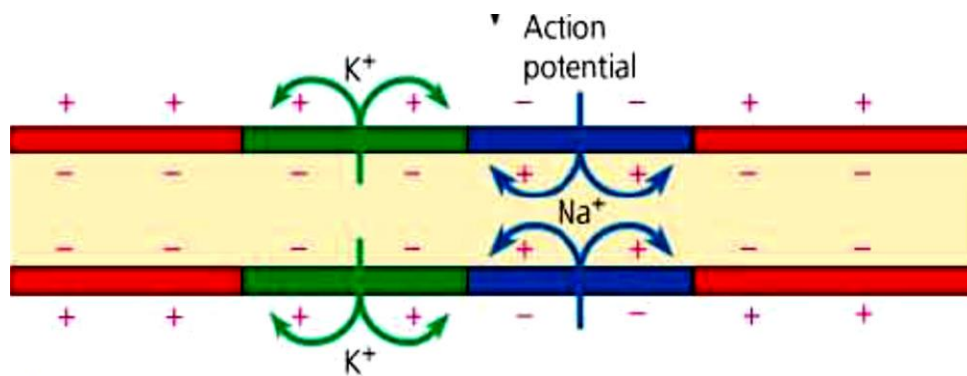


The sodium current in one region, also affects about one to three millimeters of the adjacent neighboring area of axonal membrane. This causes excitation and depolarization in this region too.

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 (2.8×10^8 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

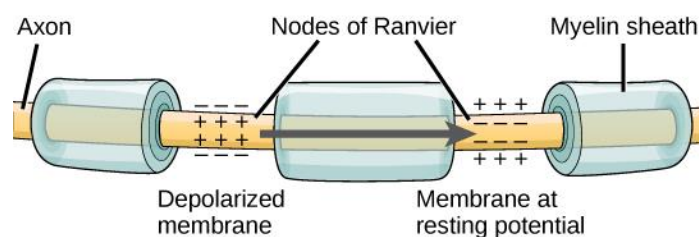
Myelin sheath is deposited around the axon during the course of development.

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

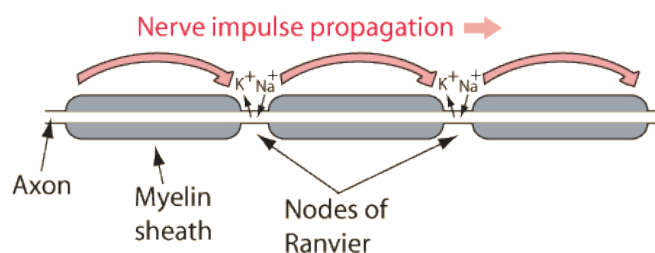
- The insulation provided by the myelin sheath increases the transmembrane resistance to ion flow and decreases the membrane capacitance.
- Both factors enhance the efficiency of longitudinal spread of current, resulting in rapid transmission of nerve impulse.
- In non-myelinated fibers the speed of 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:

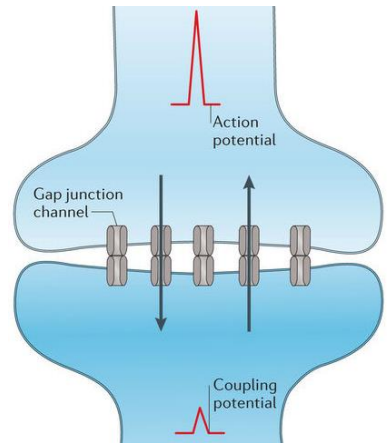
- Electrical synapses
- Chemical synapses

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

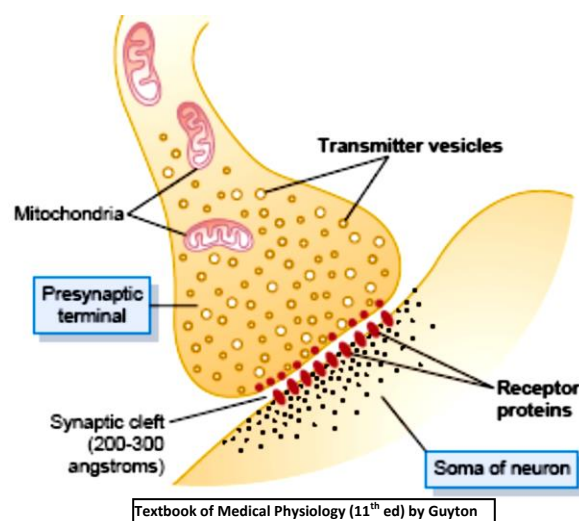
Fast chemical synapses are found in the central nervous system and at the neuromuscular junctions. Although this transmission is called "fast" it is in fact considerably slower than transmission across electrical synapses.

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.



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:

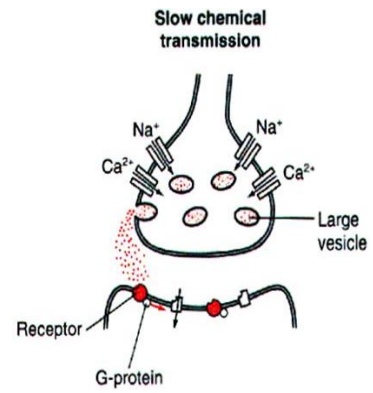
The neurotransmitters involved in slow synaptic transmission are:

- 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.



Mode of Action of slow Neurotransmitters

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

They act through G protein-linked receptors.

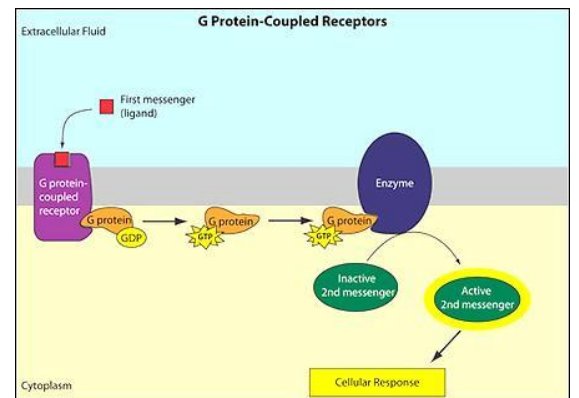
When a neurotransmitter binds to its receptor, the neurotransmitter-receptor complex activates a G protein.

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

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 Ca²⁺ channels, allowing Ca²⁺ 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 Ca²⁺ into the terminal is essential for transmitter release; therefore, when the influx of Ca²⁺ 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.

Excitatory Postsynaptic Current

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^- .

Inhibitory Transmitters

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.

Mechanism of Inhibition

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.

Channel properties vs Neurotransmitters Example: Acetylcholine

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 proteins. 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.

Fast, Direct Neurotransmitters

Types:

1. Fast excitatory synaptic transmitters
2. Fast inhibitory transmitters

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.

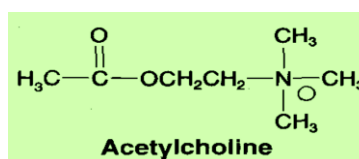
Fast Excitatory Transmitters

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

- Include:
 - Acetylcholine (ACh)
 - Glutamate
 - Aspartate

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.



Cholinergic Neurons

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

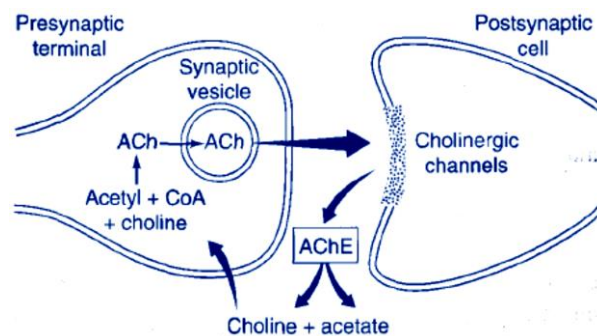
- vertebrate motor neurons
- preganglionic neurons of the vertebrate autonomic nervous system
- postganglionic neurons of the parasympathetic division of the autonomic nervous system
- many neurons of the vertebrate central nervous system
- a number of invertebrate neurons e.g. cells of the molluscan 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.

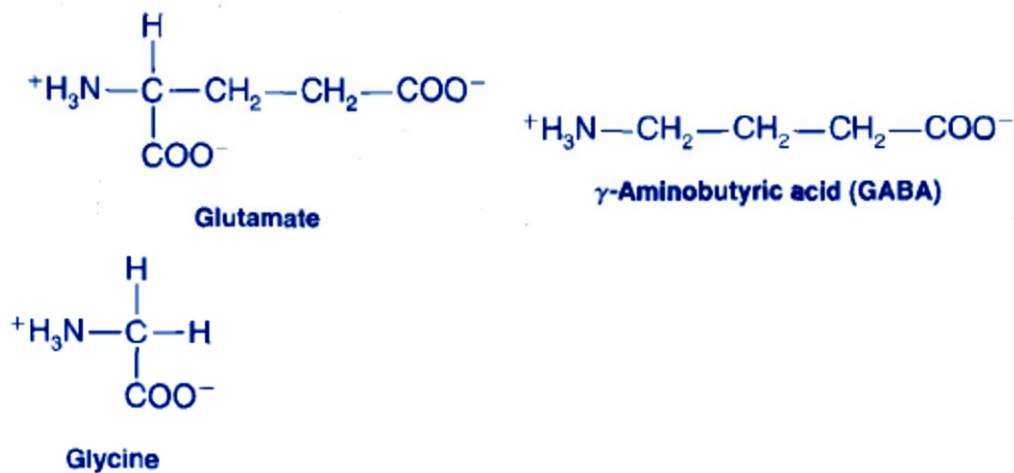
Fast Inhibitory Transmitters

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⁻.



TOPIC-37 Slow, Indirect Neurotransmitters

These neurotransmitters include two major classes:

- Biogenic amines
- Neuropeptides

Biogenic Amines

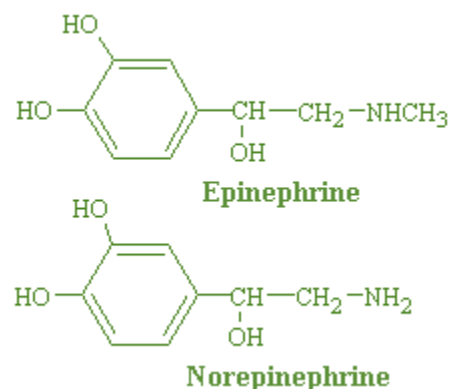
The biogenic amines act through second messengers to produce slow synaptic transmission.

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.



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

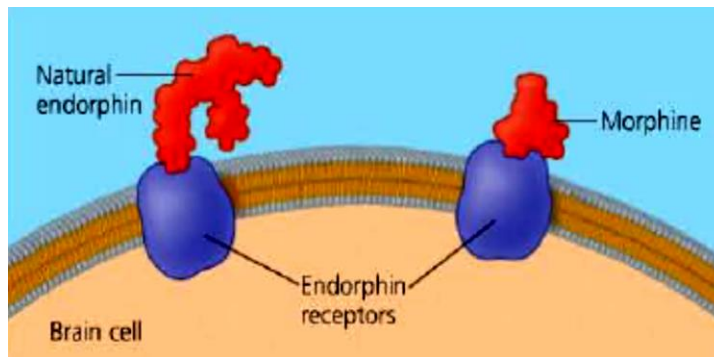
The neuropeptides endorphins and enkephalins are two groups of naturally occurring signaling molecules that are produced within the central nervous system.

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)

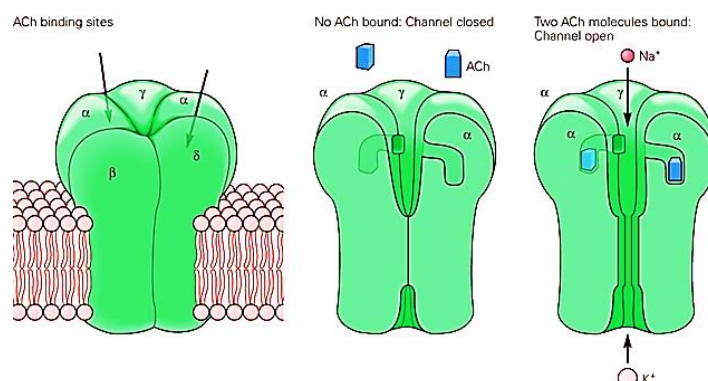
- Most of the knowledge about fast channels has been obtained through the studies of acetylcholine receptors and channels at the vertebrate neuromuscular junction.
- Acetylcholine receptors are of two types: Nicotinic AChRs and Muscarinic AChRs.
- Both receptors consist of two different types of channel 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.

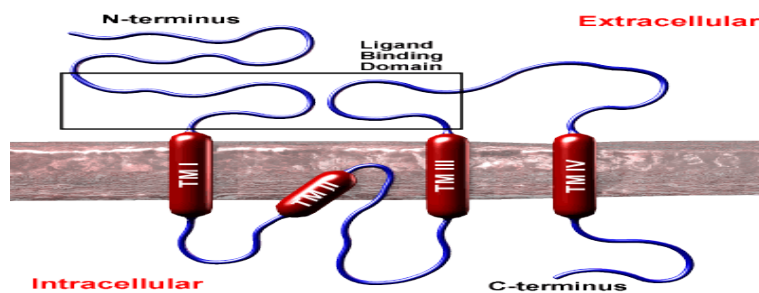
Each type of receptor is expressed in a unique and characteristic pattern within the mammalian brain.

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.



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

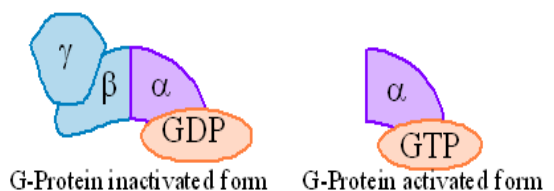
G Protein-Linked Receptors

- 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.



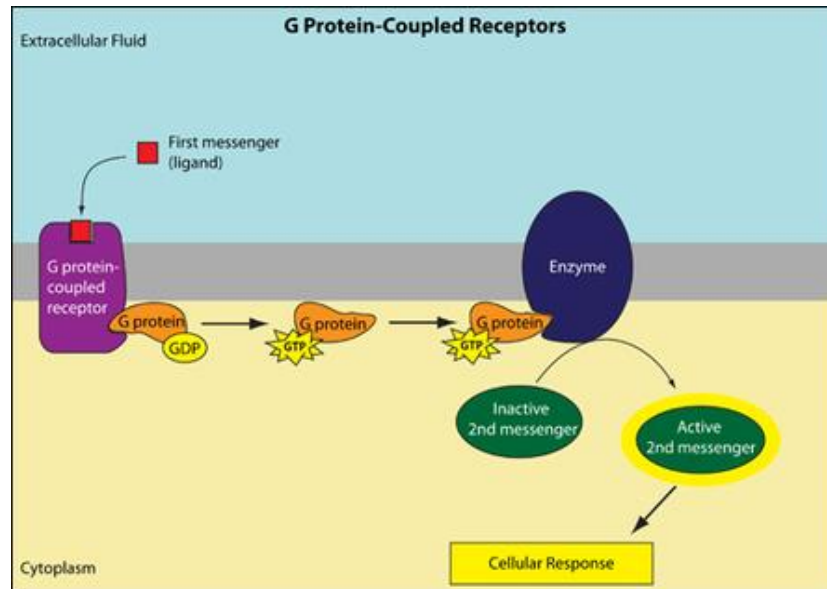
The Receptor Molecules

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. ACh as Slow, Indirect Neurotransmitter

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 Neuromodulators:

- 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.

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, Sensory Organs & Receptor Cells

- Stimulus is an external or internal factor that can provoke response through nervous system.
- Sensory organs receive the info. of the stimulus.
- Sensory organs have receptor cells which are stimulated by stimulus and generate a sensory signal and transmit this signal to the N.S.

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).

Types of Stimuli

Two types:

- **External stimuli**
Stimuli of odor, touch, light, sound and gravitation

- **Internal stimuli**
Stimuli of pain, homeostatic imbalances and blood pressure

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.
- Send this information to the nervous system.

Features of Receptor cells

Have Receptor Molecule

- They have a chemical group or molecule (such as a protein) on the cell surface or in the cell interior that has an affinity for a specific chemical group, molecule, or virus.
- Such molecule or group is known as receptor.

Have Capacity of Stimulus Transduction

- A physical or chemical stimulus received by the receptor cell is converted (transduced) into electrical signals that can travel through the nervous system.

Linked to the Nervous System

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

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:

1. Sense of vision perceived through eyes having photoreceptors
2. Sense of hearing perceived through ears having mechanoreceptors
3. Sense of touch perceived through skin having Meissner’s corpuscles
4. Sense of taste perceived through taste buds in tongue having gustatory receptors
5. 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.

Range Fractionation 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

Definition

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.

Manifestation

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.

Adaptation Example:

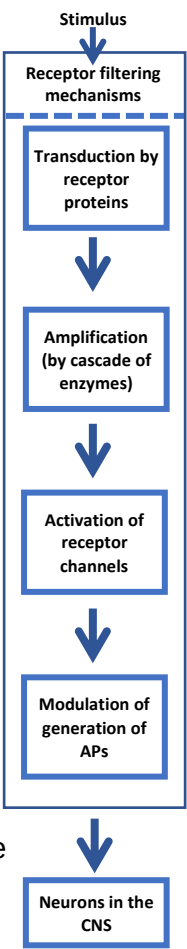
Wearing clothing stimulates touch receptors at all points where our garments touch the skin. But we typically adapt to the touch input from our garments. So we can easily detect any new touch stimuli that impinge on our skin, even at locations covered by our clothing.

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

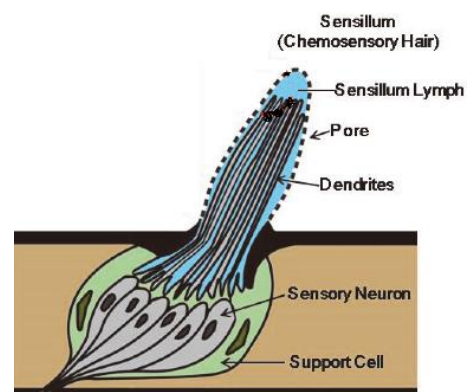
The gustatory (taste) receptors respond to dissolved molecules that come in direct contact with the receptive structure.

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.



http://www.naro.affrc.go.jp/archive/nias/eng/research/h26/links/2015e-7_01.jpg

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

Taste receptors in vertebrates

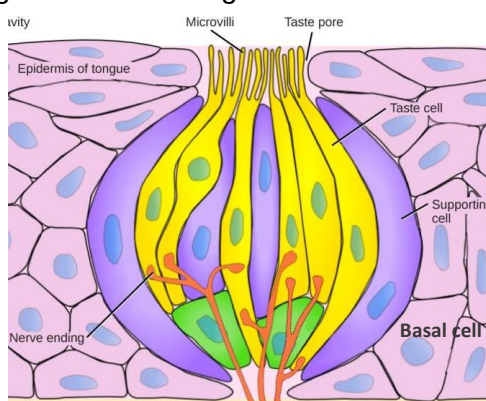
- Many aquatic vertebrates have taste receptors on different locations of the body.

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.



http://philschatz.com/biology-book/resources/Figure_36_03_04.jpg

Taste Receptor Cells

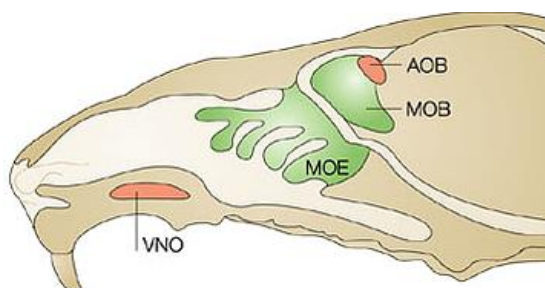
- The outer tips of the taste cells are arranged around a minute taste pore.
- From the tip of each taste cell, several microvilli, or taste hairs, protrude outward into the taste pore to approach the cavity of the mouth.
- These microvilli provide the receptor surface for taste.
- Interwoven around 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
- Vomerinal 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.

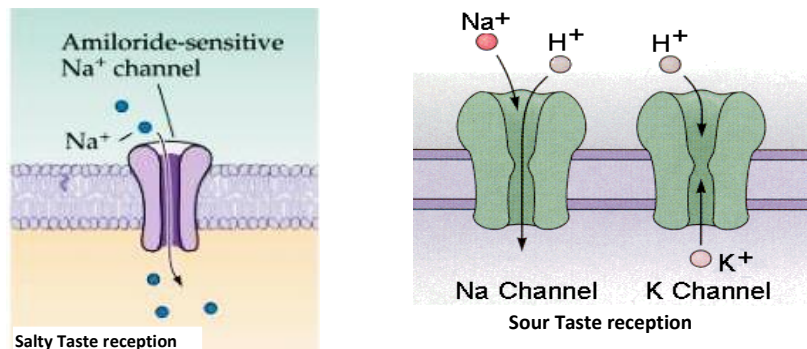
The receptors of sweet, umami, and bitter tastes are G protein-coupled receptors, while the receptors for salty and sour tastes are ion channels.

Mechanisms of Taste Reception

Salty Taste Reception

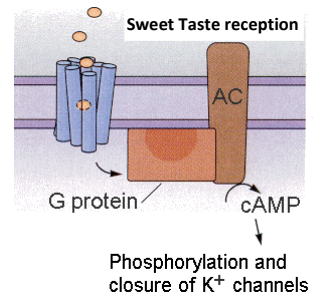
- Salty stimuli such as NaCl, readily dissociate in water into Na⁺ and Cl⁻ ions.
- The Na⁺ ions enter receptors through Na⁺ channels in the membrane to directly depolarize the receptor cell membrane.

- These Na^+ channels are distinctive because they can be blocked by the drug amiloride unlike the voltage-gated Na^+ channels that mediate most APs.



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.

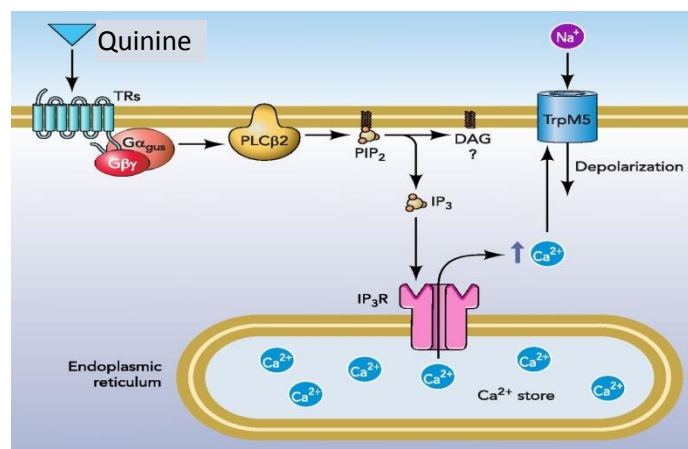


Sweet Taste Reception

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 biphosphate 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.



<http://physiologyonline.physiology.org/content/nips/28/1/51/F1.large.jpg>

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 Ca^{2+} 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

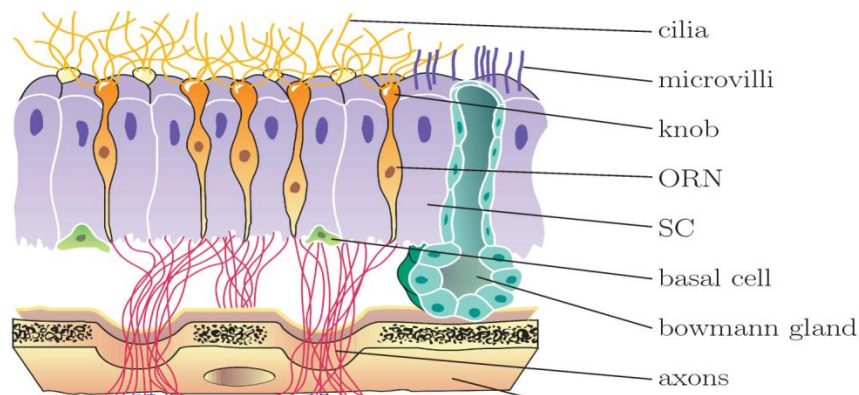
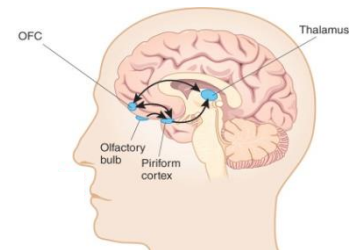
Each receptor subtype for five kinds of taste sensations is connected to a particular set of axons.

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

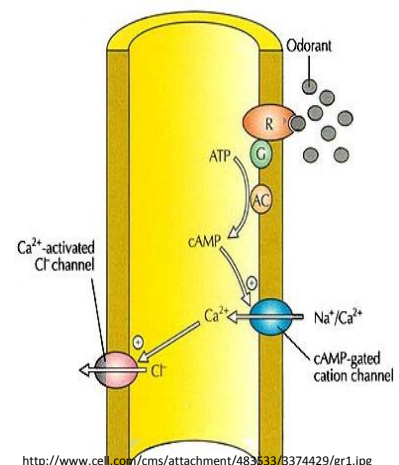
- The olfactory receptors of vertebrates are located inside the nasal cavity.
- The sensory receptor cells involved in olfaction are actually neurons.
- These neurons have long axons. All these axons are packed together in the olfactory nerve. Nerve impulses are sent directly to the olfactory bulb of 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.



<https://chroniclesofxenopuslaevis.files.wordpress.com/2013/09/olfactory1.png>

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.
- 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

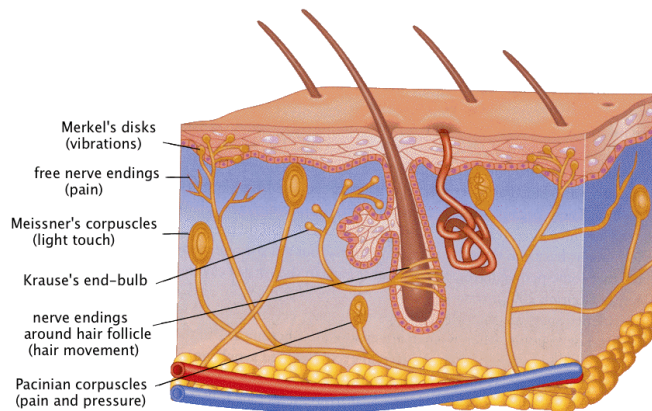
The simplest mechanoreceptors consist of morphologically undifferentiated nerve endings found in the connective tissue of skin.

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.



<http://webpace.ship.edu/cgboer/skinreceptors.gif>

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. Hair cells are ciliary cells.

- Found in several sensory organs of vertebrates.
- They are highly sensitive mechanoreceptors.
- Responsible for transducing mechanical stimuli into electrical signals.

Lateral-line System is Based on Hair Cells. Systems Based on Hair Cells: Examples

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

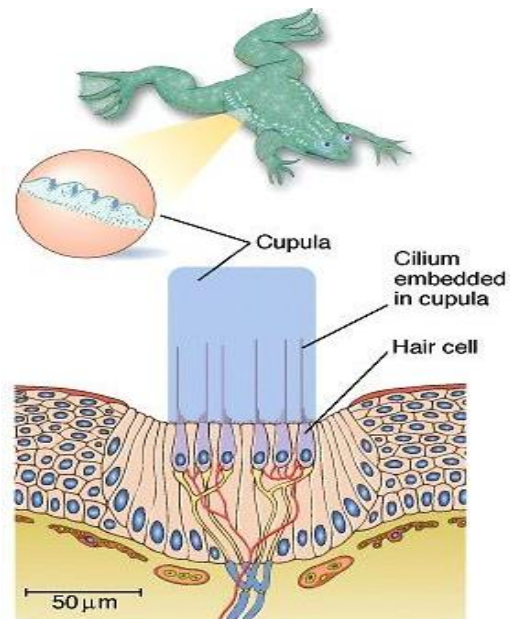
Ear and Vestibular System is Based on Hair Cells

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

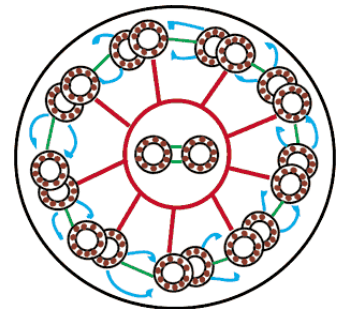


Hair Cells in Lateral-line System

Eckert Animal Physiology (4th ed) by Randall

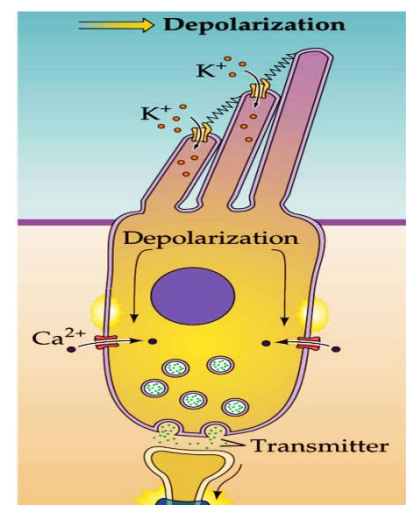
Hair Cell Cilia

- 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

- 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.



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

Topic-55Organs of Equilibrium

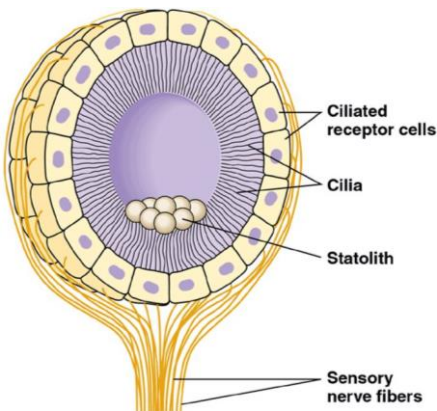
The **organs of equilibrium** detect an animal's position with respect to gravity or its acceleration.

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.



http://slideplayer.com/8936534/27/images/26/Figure+49.21+The+statocyst+of+an+invertebrate.jpg

Working Mechanism of Statocyst

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

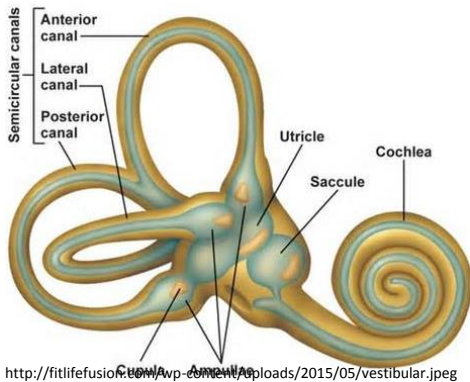
The stimulated receptor cells generate signals that travel to the central nervous system and set up reflex movements of the appendages that bring the body in equilibrium.

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.



http://fitlifefusion.com/wp-content/uploads/2015/05/vestibular.jpeg

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.

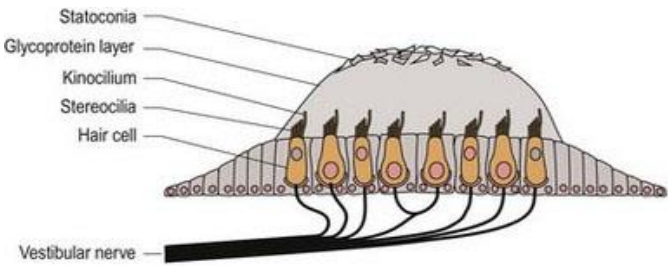
The macula of the utricle lies in the horizontal plane on the inferior surface.

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

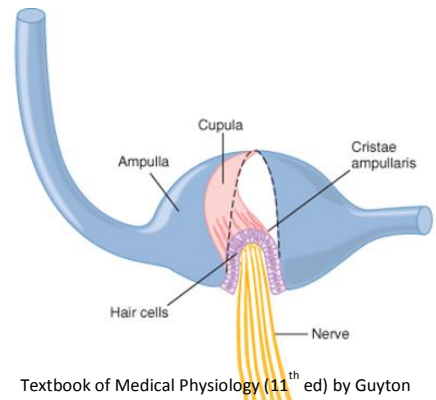
The macula of the saccule is located in the vertical plane.

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



Textbook of Medical Physiology (11th ed) by Guyton

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

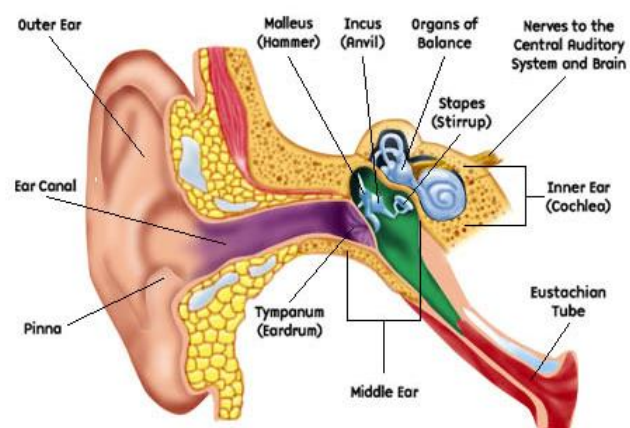
Functional Anatomy of Mammalian Ear

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.

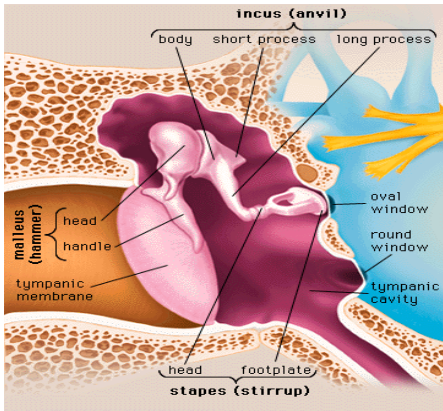
The ear canal acts as a resonator that amplifies sound in particular frequency ranges.

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 cm²) and oval window (0.032 cm²).

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.

Membranous Labyrinth

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:

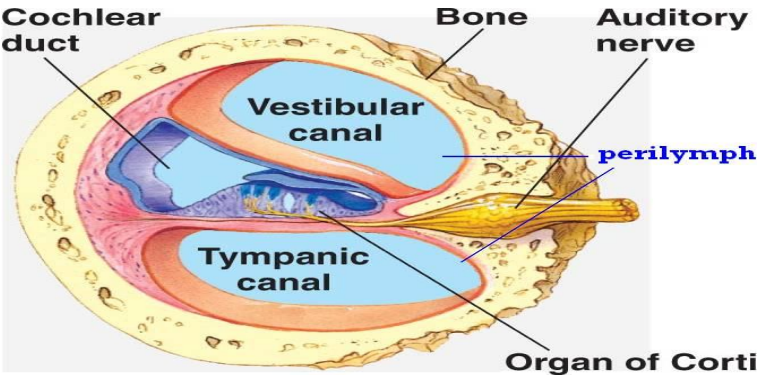
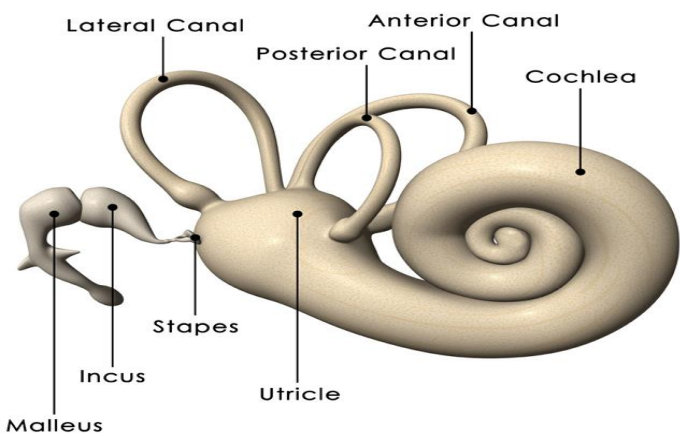
- 1. Upper, scala vestibuli (vestibular duct) filled with perilymph.
- 2. Middle triangular passageway, scala media (cochlear duct), filled with endolymph.
- 3. Lower, scala tympani (tympanic duct), filled with perilymph

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.



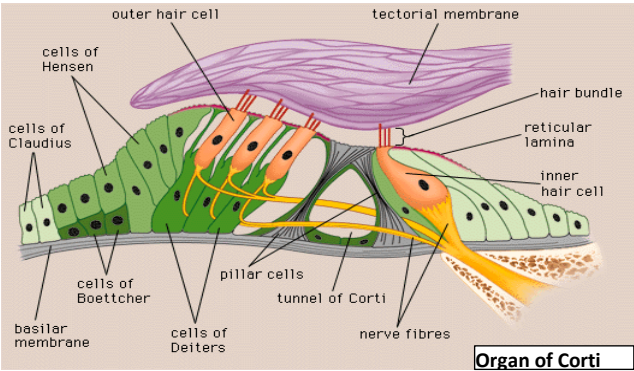
Organ of Corti

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



Hair Cells in Organ of Corti

<https://media1.britannica.com/eb-media/00/14300-004-5FF07709.jpg>

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

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

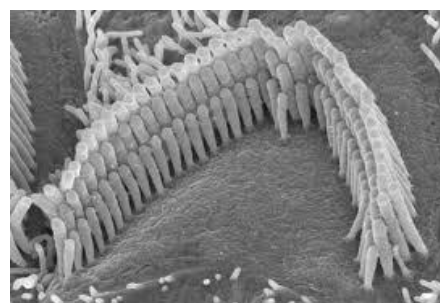
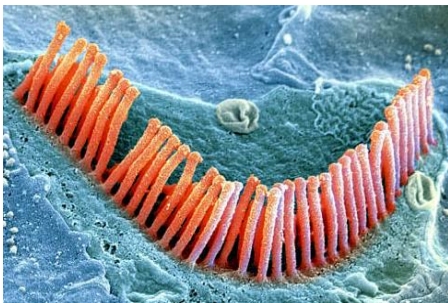
Both types are quite different in their functional anatomy.

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 (tympanic 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 width and stiffness of basilar membrane.
2. Placement of hair cells on the basilar membrane.

1. Variations in Width and Stiffness of Basilar membrane

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).

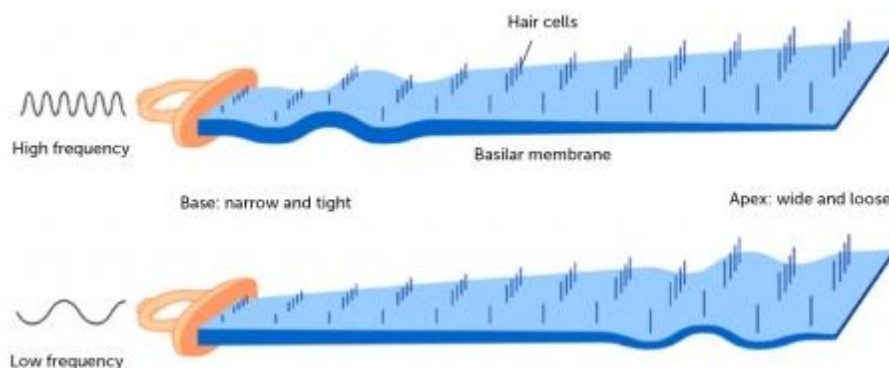
As a result, different frequencies of sound cause different portions of the basilar membrane to vibrate, stimulating particular hair cells and sensory neurons.

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.

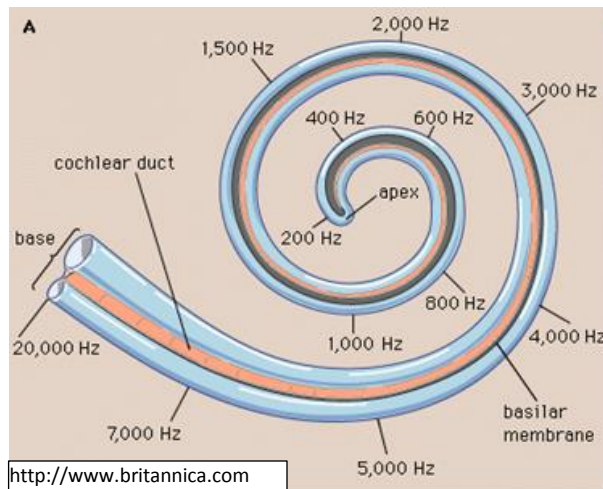
These vibrations travel along the basilar membrane from the base toward its apex causing displacement of the membrane.

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 Electoreception

Electoreception

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

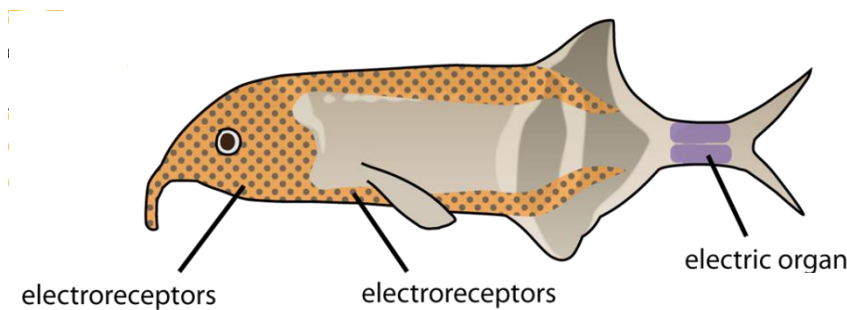
Electoreception is defined as the ability to detect electric fields generated by the animal itself or by other animals in the aquatic environment.

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

Electoreceptors

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

The electoreceptors 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 Electoreception

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

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

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

The electoreceptor 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 Electoreception. Uses of Electoreception

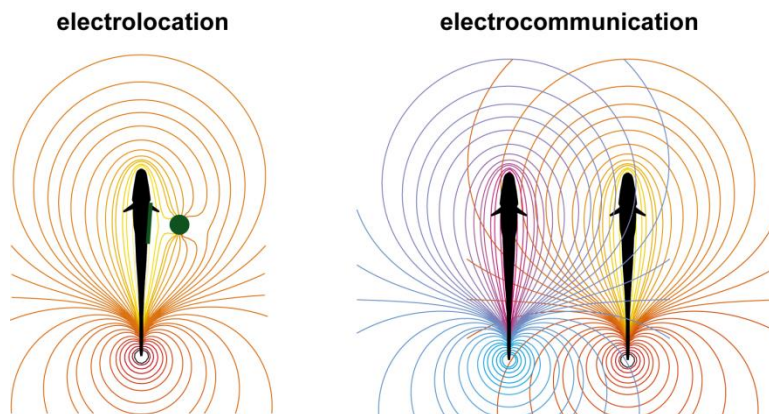
The ability to detect electric fields helps a fish to find mates, capture prey, avoid predators and for orienting towards or away from certain objects.

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.

Electrocommunication

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



Electrolocation

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.

➤ Thermoreceptor Types

Warmth and Cold Receptors

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

- Cold receptors
 - Warmth receptors
- Both types of receptors are quite sensitive and enable humans to detect a change in skin temp. of as little as 0.01°C .

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 A δ 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.

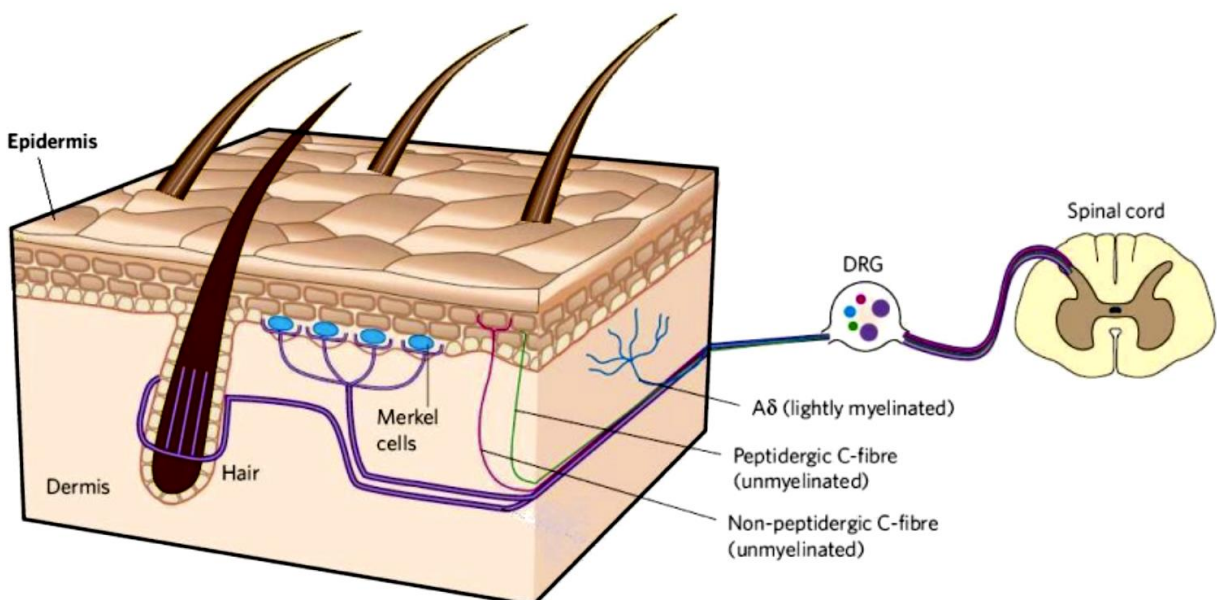
The transduction of temperature in cold receptors is mediated by the TRPA and TRPM while TRPV are involved in warmth reception.

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:

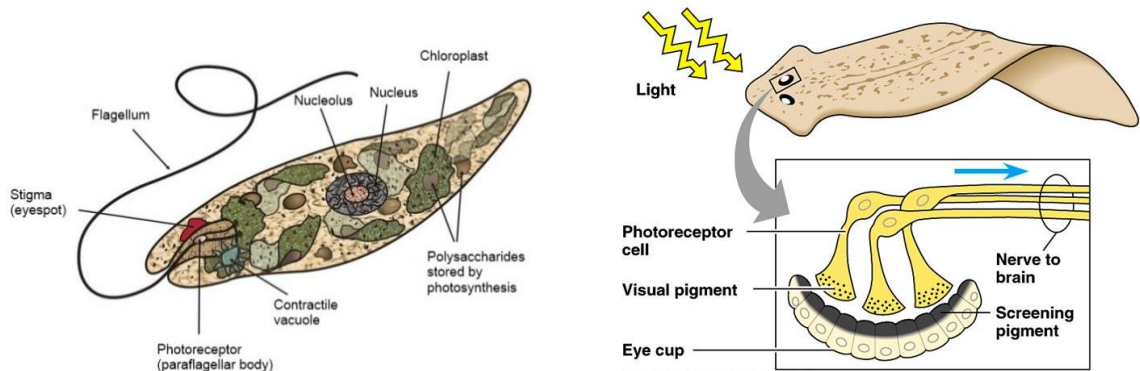
Photoreceptors possess light-sensitive pigments which are carotenoids retinal and 3-dehydroretinal associated with opsin proteins to form rhodopsins.

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.

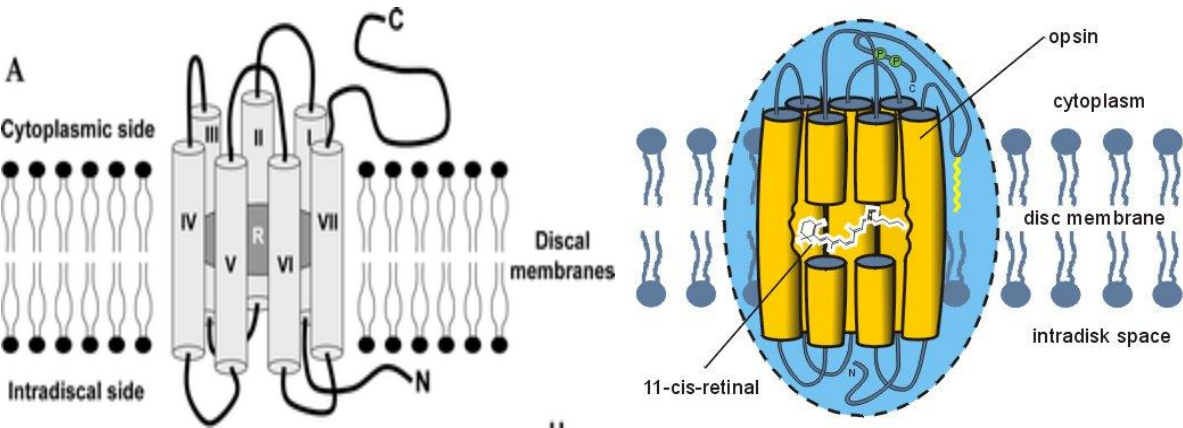
Pigments in Visual Transduction

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.



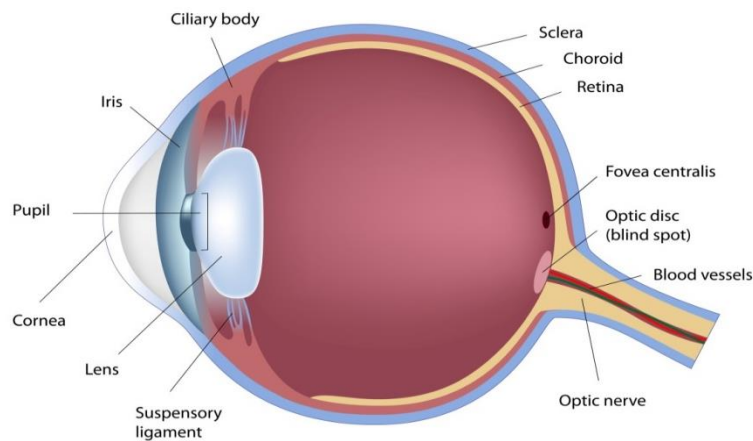
Opsins are coupled to light-absorbing photopigment Retinal to form a functional pigment molecule rhodopsin.

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.

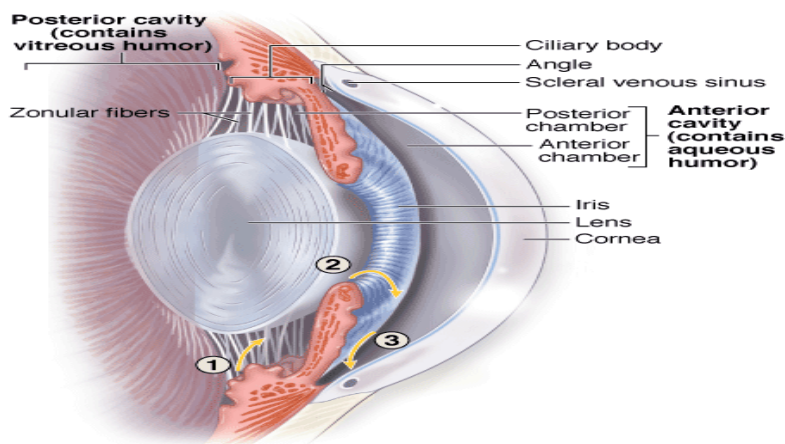
Pupil is dilated in dim light by the contraction of radially oriented muscle fibers. This allows an increased amount of light to enter the eye.

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.



Role of Ciliary muscles

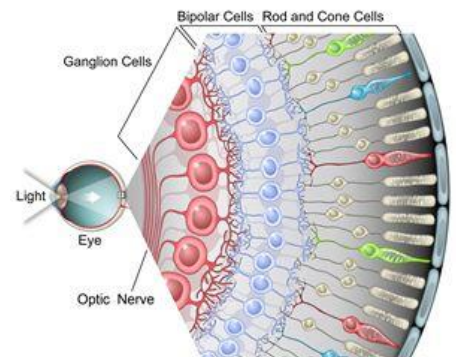
- Ciliary muscles are attached with the fibers of zonula.
- Their contraction and relaxation adjusts the amount of tension exerted on the lens.
- When the ciliary muscles contract, the lens is flattened by elastic tension exerted by the fibers of the zonula, which pull the perimeter of the lens outward. 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.

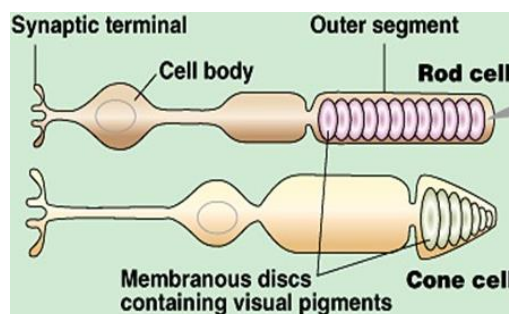


Topic-64 Visual Receptor Cells of Vertebrates

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.

Types of Cones

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. Rods and Cones in Animal Retinas

- 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 mm² central part of retina and has a very high density of cones (about 150,000 cones per mm²) 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.

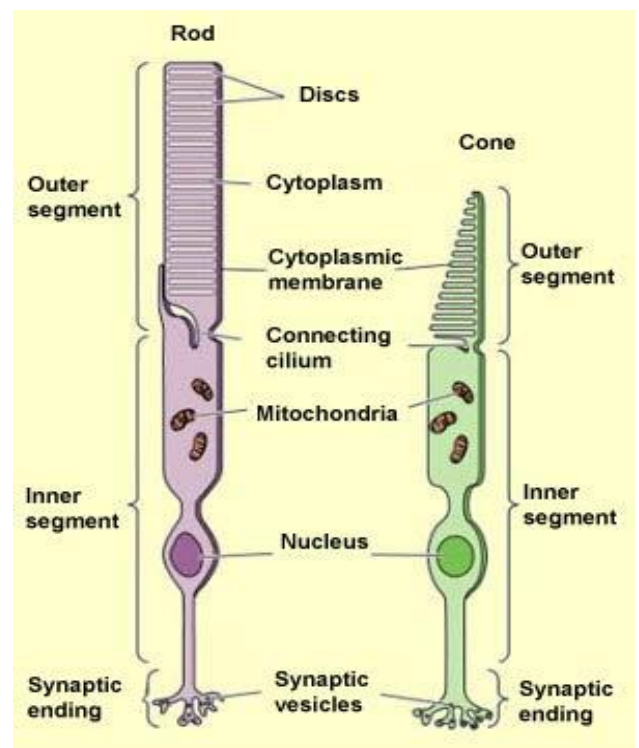
There are as many as 1000 discs in each rod or cone.

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.

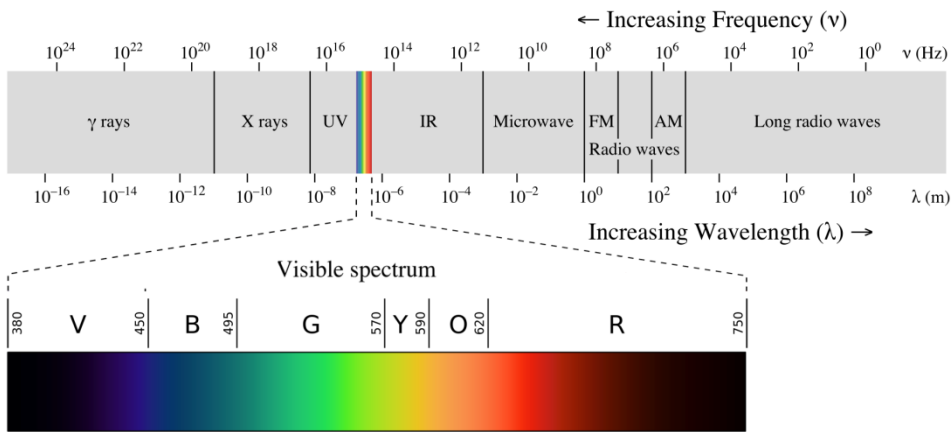
Topic-65 Visual Pigments and Their Photochemistry-I

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 A₁ (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-66 Visual Pigments and Their Photochemistry-II

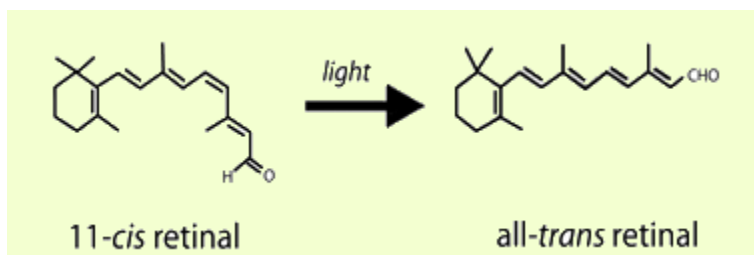
Isomerization of Rohodopsin

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.

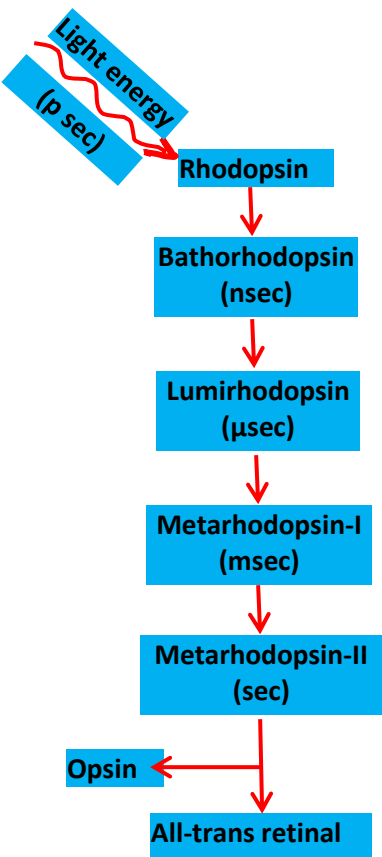
This state of decomposition is the activated state of rhodopsin that results in a series of biochemical activity in the receptor membrane resulting in transduction of light energy captured by rhodopsin into electrical form.

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

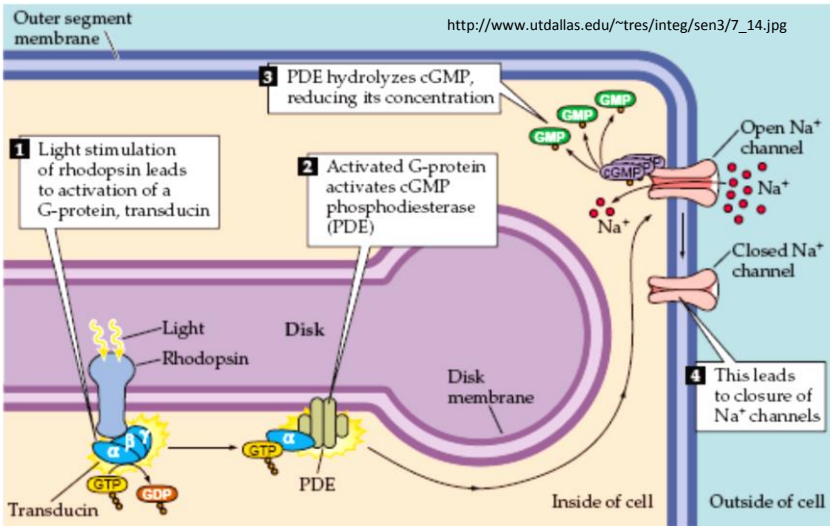
Metarhodopsin II activates a G protein transducin that is associated with the membrane.

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⁺, Mg²⁺ and Ca²⁺. 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-67The 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.

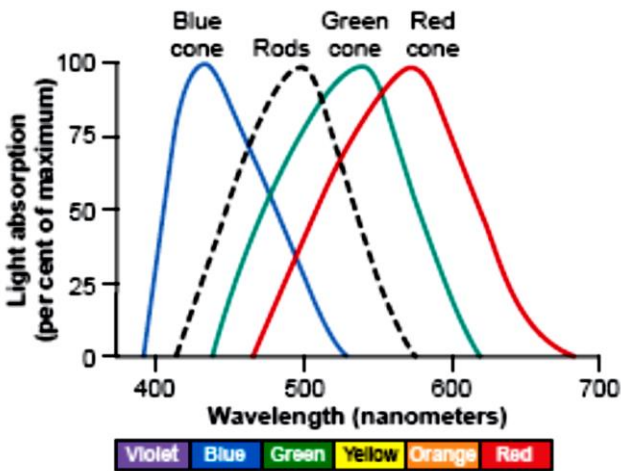
Slight differences in the opsin proteins are sufficient for each photopsin to absorb light optimally at a distinct wavelength.

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.

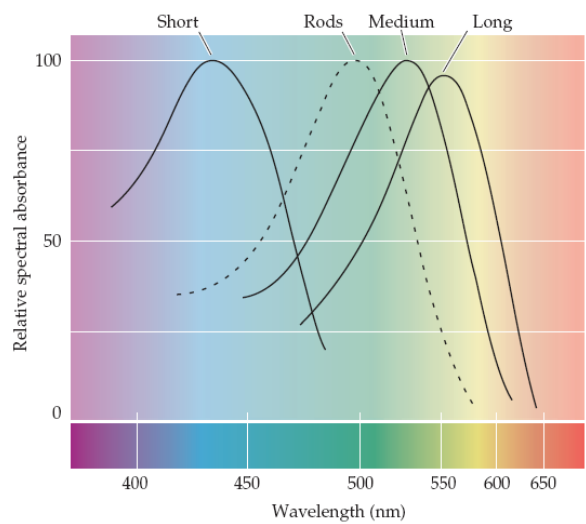
A person missing a single type of color receptive cones is unable to distinguish some colors.

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

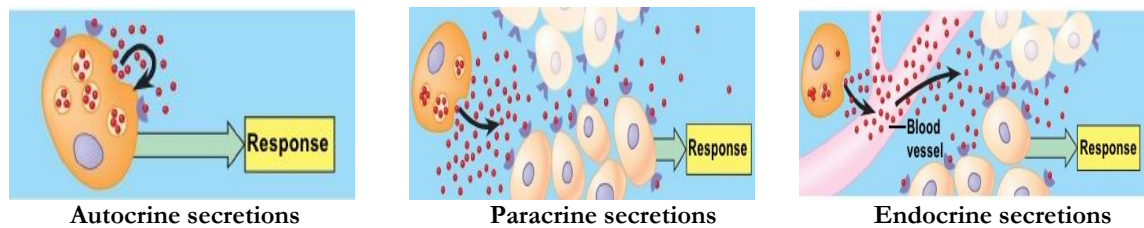
Autocrine Secretions

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.

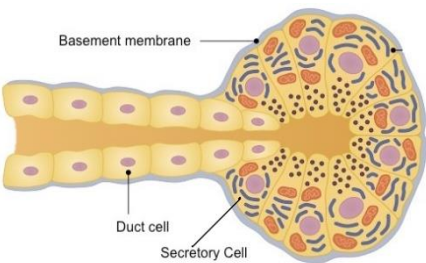


Endocrine Secretions

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.



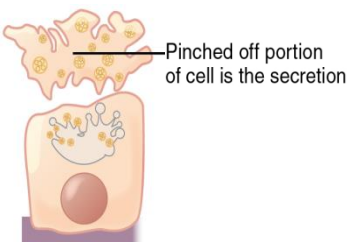
Secretory Mechanisms

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.

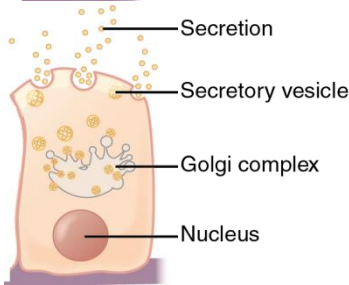


Merocrine Release

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.

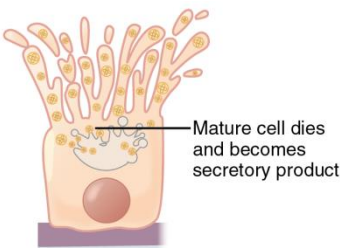
It is the most common method of secretion.

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

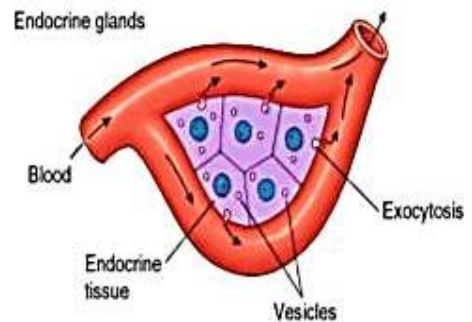
Glands are broadly classified into two types:

- a) Endocrine glands
- b) 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

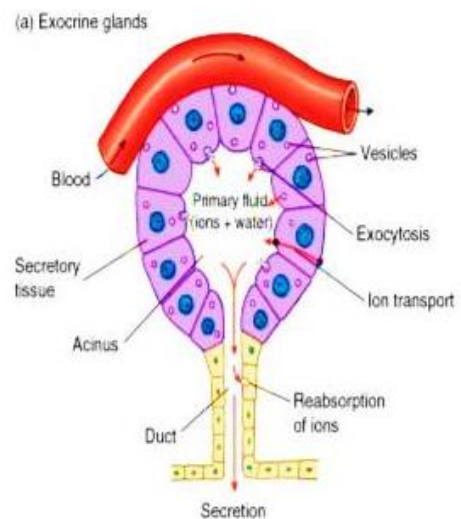
Pituitary, thyroid and adrenal glands.

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 hormone (MSH)	Stimulates melanocytes of the skin increasing 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

Identification of Glands

- Some glands are distinct and easily identifiable.
- However a large number of endocrine tissues are not distinct and are embedded in organs with quite different, nonendocrine functions.

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
 - Hormonal action depend on the type of receptor
- 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.
- 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).

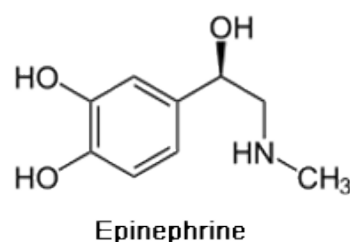
In general, polypeptides with 100 or more amino acids are called proteins, and those with fewer than 100 amino acids are referred to as peptides.

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).

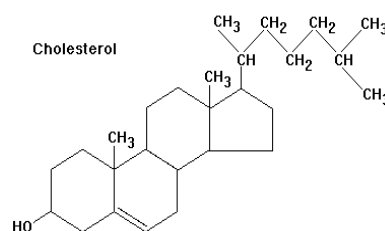
They are small molecules synthesized from a single amino acid tyrosine.



Steroid hormones

Steroid hormones are synthesized from the precursor steroid cholesterol.

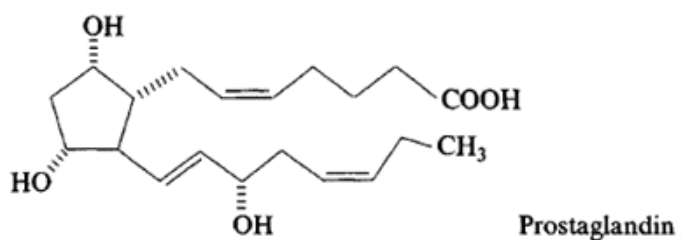
They consist of four fused carbon rings including three cyclohexyl rings and one cyclopentyl ring combined into a single structure.



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.



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.c

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
2. Neurohypophyseal 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:

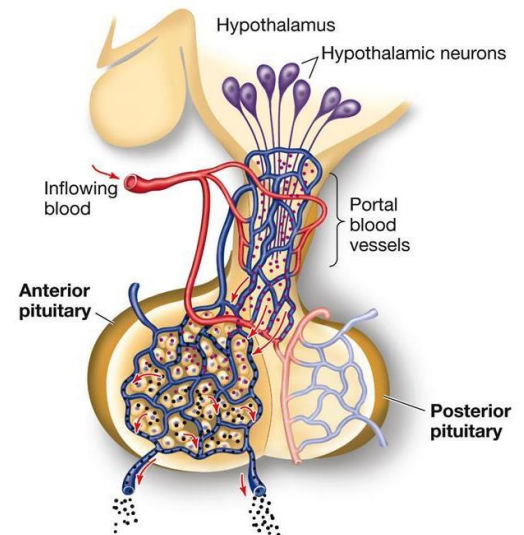
- Hypothalamic releasing hormones (RHs) which stimulate the secretory activity of adenohypophysis (anterior pituitary).
These hormones are:
 - Corticotropin releasing hormone (CRH) that stimulates adrenocorticotrophic hormone (ACTH) release from anterior pituitary
 - GH releasing hormone (GHRH) that 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.

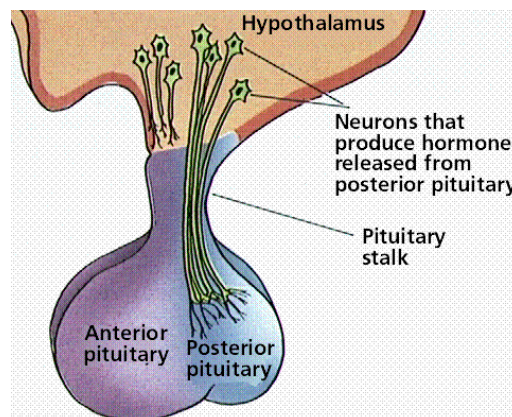
These hormones can produce effects on the anterior pituitary gland in very low concentrations because of close proximity and direct portal connection of hypothalamus and the anterior pituitary gland.



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.



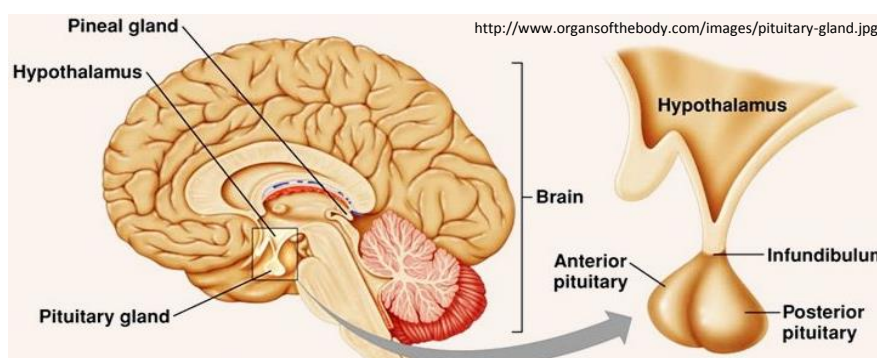
Topic-75 Pituitary Gland and Its Hormones

Pituitary Gland

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 adrenocorticotrophic 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

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. Adrenocorticotrophic hormone (ACTH)
2. Thyroid stimulating hormone (TSH)
3. Luteinizing Hormone (LH)
4. Follicle stimulating hormone (FSH)

Adrenocorticotrophic 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-stimulating hormone (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 somatotrophic 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

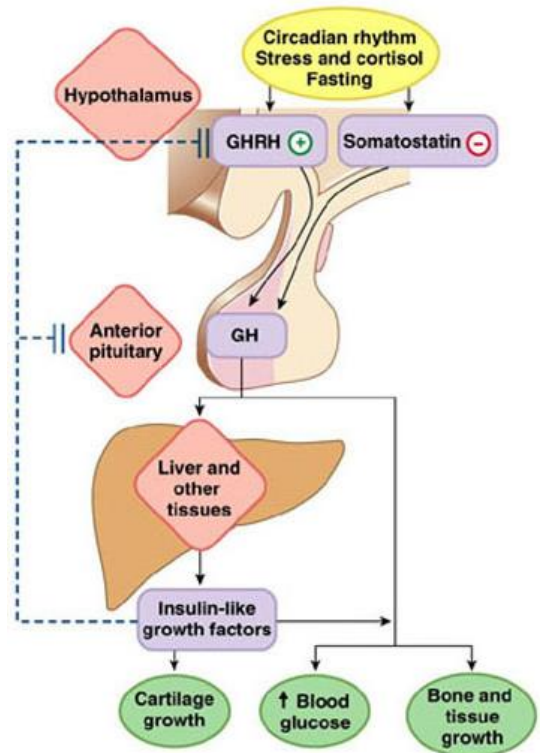
Growth hormone exerts both metabolic and developmental effects.

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 (IGFs) 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

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.

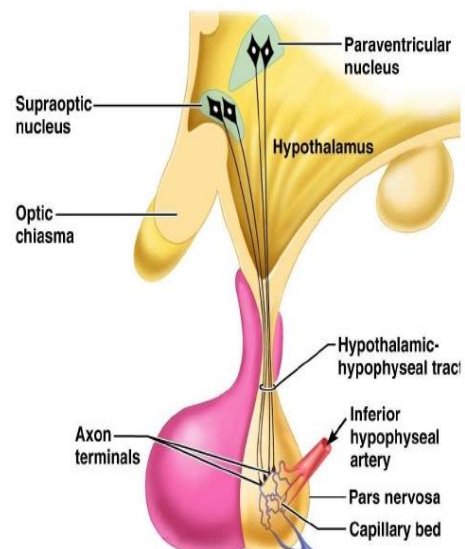
Functions of ADH

- The specialized function of ADH is to help 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.



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Topic-79 Thyroid Gland and Its Hormones

Thyroid Gland

Thyroid gland consists of two lobes on the ventral surface of the trachea.

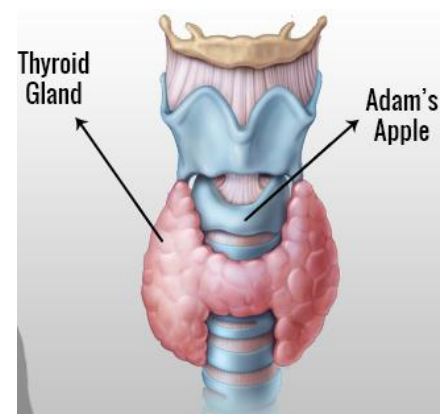
It has two types of glandular cells:

Follicular cells which secrete two hormones:

- ✓ Triiodothyronine (T_3)
- ✓ Tetraiodothyronine (T_4) also known as thyroxine

Parafollicular cells which secrete one hormone:

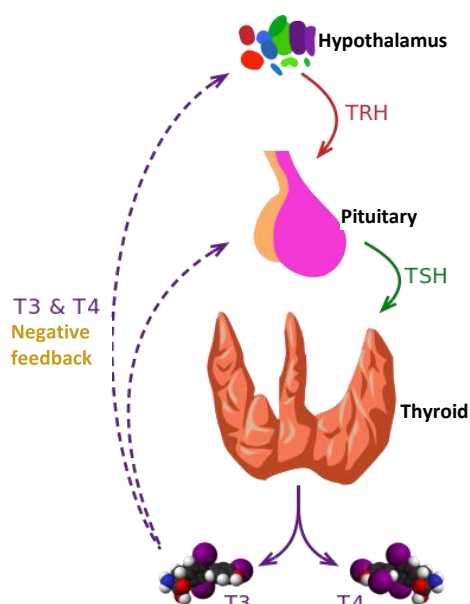
- Calcitonin



Secretion of T₃ and T₄

The secretion of T₄ predominates T₃. However the target cells convert most of T₄ to T₃, 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 T₃ and T₄

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 T₃ and T₄

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 of T₃ & T₄

- 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 of T₃ & T₄

- 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.

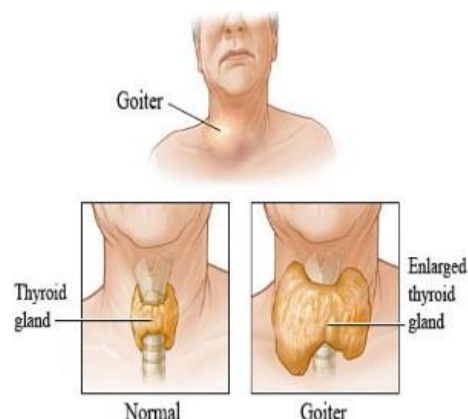
Role of Calcitonin

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

Parathyroid Glands

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.

Parathormone (PTH)

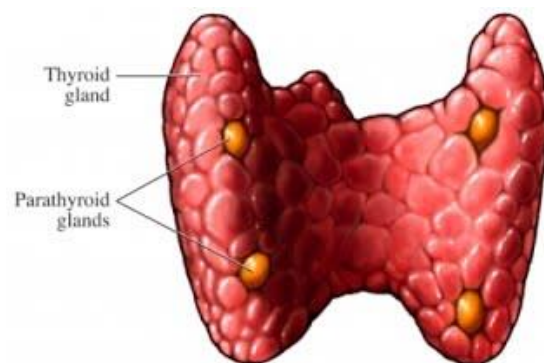
It promotes calcium reabsorption by the kidney tubules to decrease the amount of calcium excreted in the urine.

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 $1\alpha,25$ -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.

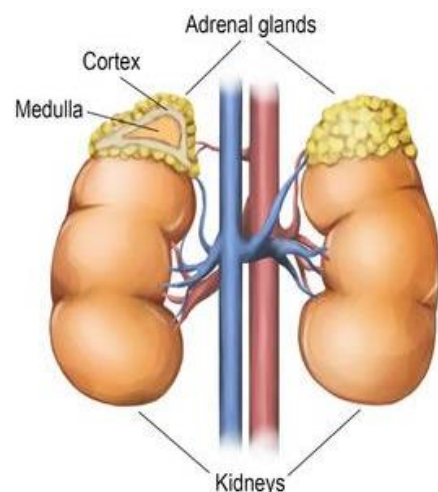
Adrenal Cortex and Medulla

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

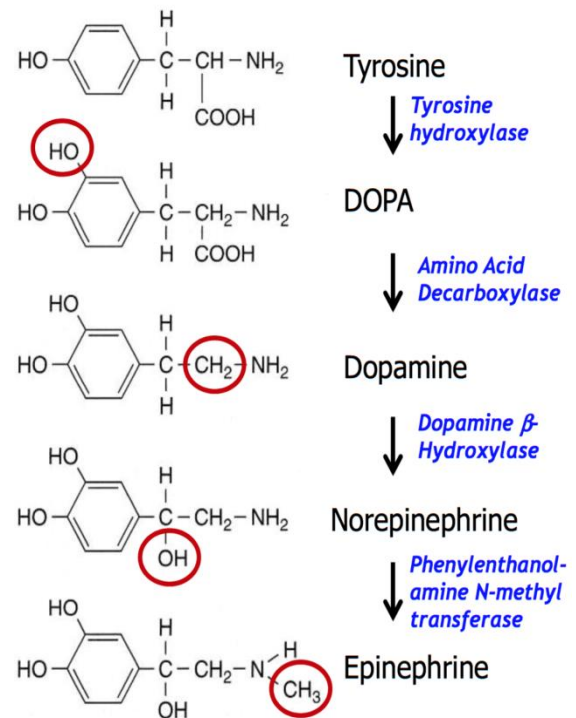
Synthesis of Catecholamines

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. Negative Feedback Controls 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 (InsP₃) pathway, leading to elevation of intracellular InsP₃.
- Elevated InsP₃ 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

Hormones of Adrenal Cortex

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. They have a primary effect on glucose metabolism.
- They are involved in gluconeogenesis under stress, starvation and disease.

Effects of glucocorticoids. Glucocorticoids' Role in Gluconeogenesis

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.

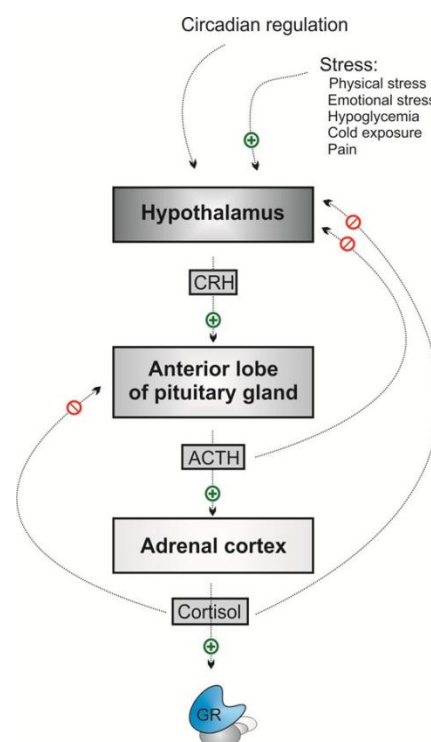
Regulation of Glucocorticoids

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.

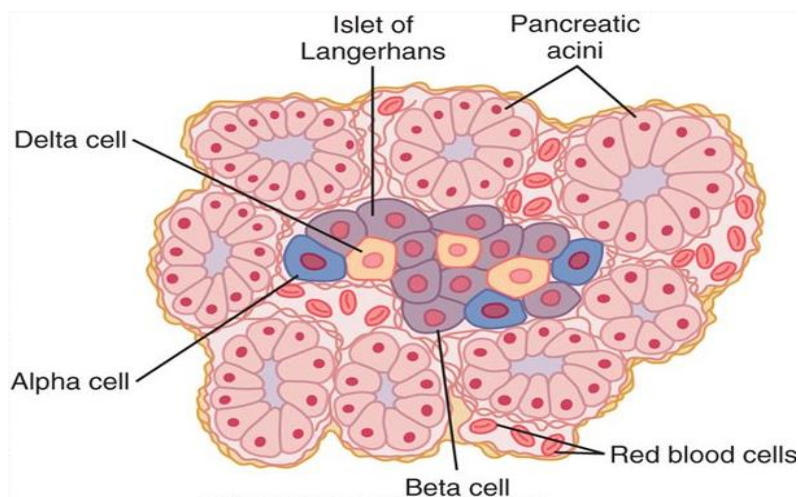
Dehydroepiandrosterone (DHEA): It is the primary precursor of natural estrogens.

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 II 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

Roles of Testes

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:

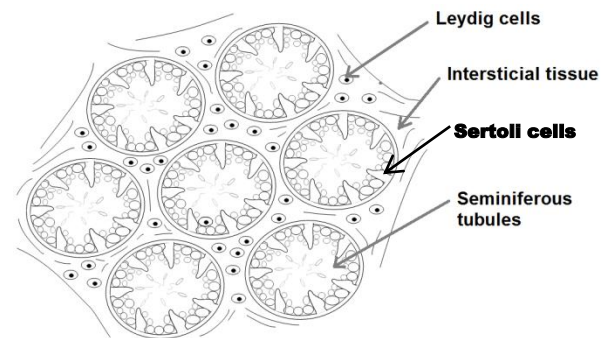
- Seminiferous tubules
- Interstitial Tissue

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

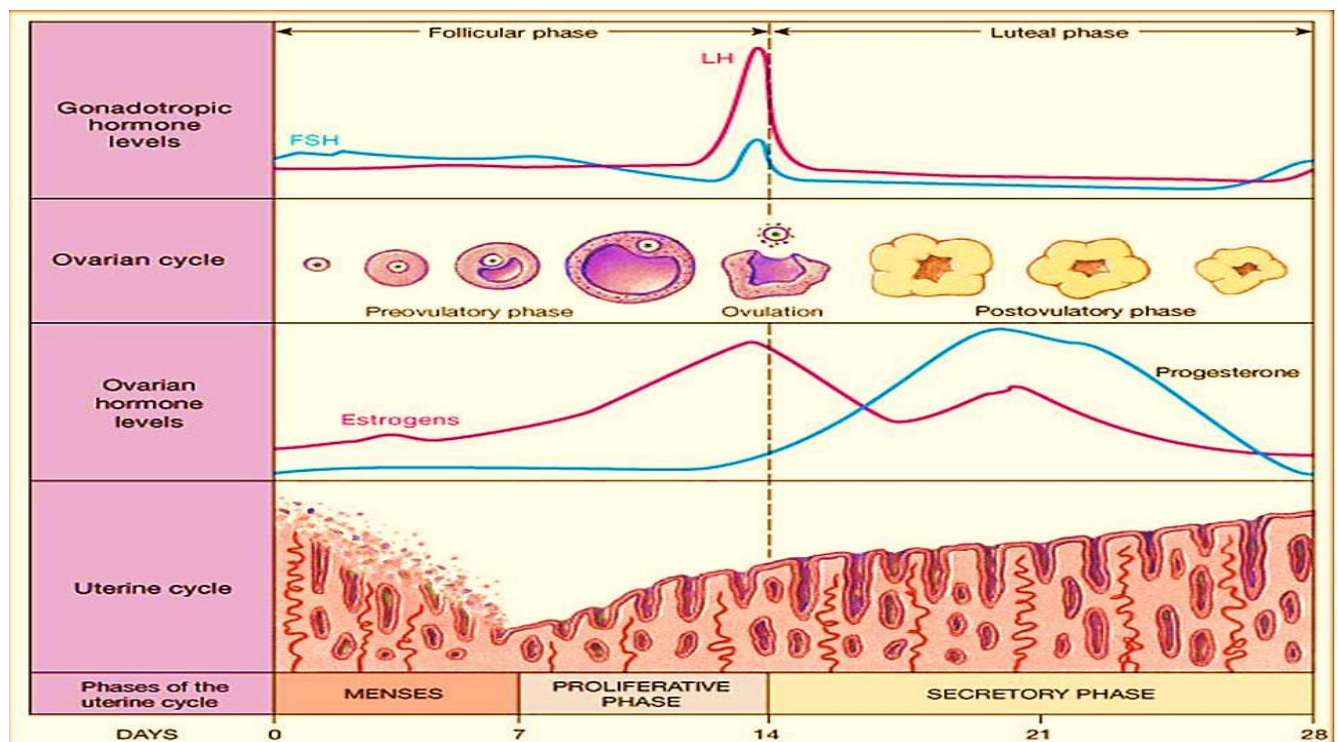
Uterine and Ovarian Cycles

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.

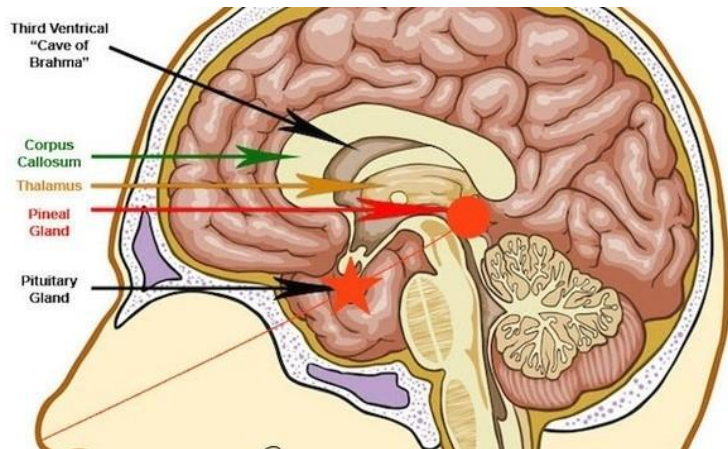
In many other mammals, such as the rat, the corpus luteum, stimulated by prolactin, continues to grow and secrete estrogen and progesterone throughout the gestation period.

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. A Modified Photoreceptor

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.

role 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

Hormones Involved in Metabolism and Development

Several hormones regulate metabolism and affect developmental processes.

These include:

- Insulin
- Glucagon
- Glucocorticoids
- Catecholamines
- Thyroxine
- Growth hormone

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.

Regulation of Water and Ions

- The organs of vertebrates which regulate water and ions are: kidneys, skin, gills, intestine and bone.
- The absorption or excretion of water and ions is regulated through these organs by the coordinated activity of many hormones.

Hormones in Regulation of Water and Ions

- These hormones include:
- Antidiuretic hormone (ADH)
- Aldosterone
- Atrial natriuretic Hormone
- Calcitonin
- Parathormone

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

Regulation of Water and Ions

- As epithelial cells are responsible for the uptake or excretion of water and ions, these hormones act primarily on the epithelial tissues of the organs involved.

Topic-92 Reproductive Hormones

Reproductive Hormones

The reproductive hormones of vertebrates belong to two chemical categories:

- Steroid Sex Hormones
- Peptide Hormones

These hormones:

- Develop primary and secondary sexual characters
- Control and regulate reproductive activities.

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-17 β 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.

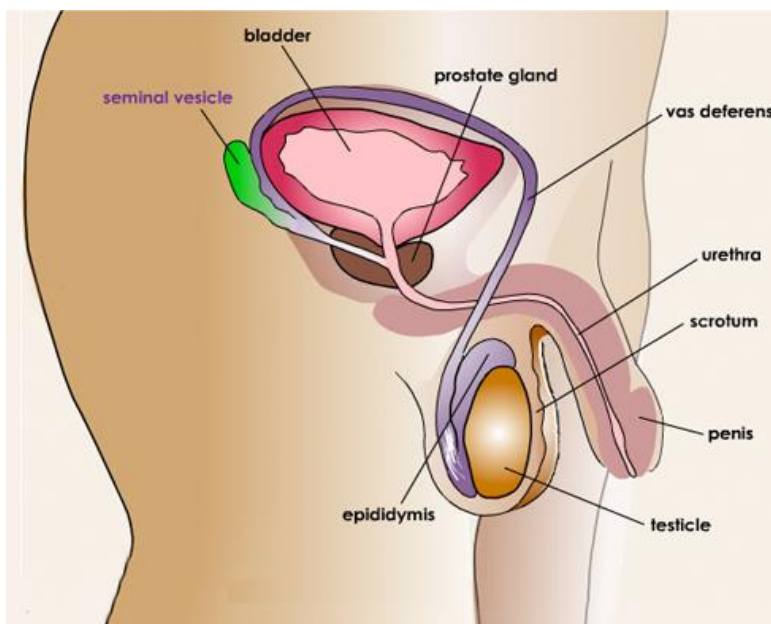
Roles of Androgens in Males

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 Prolactin and Oxytocin

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.

- Oxytocin is specialized in stimulating uterine contractions during parturition (child birth).
- It also stimulates ejection of milk from the mammary glands.

Topic-93 Prostaglandins

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

Feedback Loops

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.

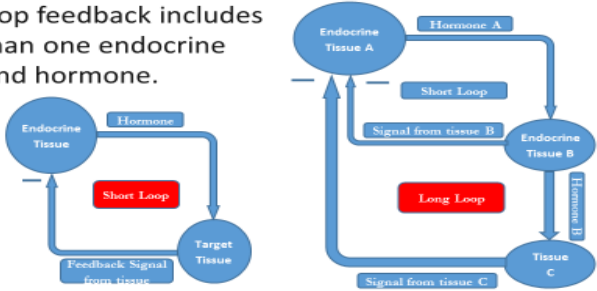
In short-loop feedback, the concentration of the hormone itself, or a byproduct of its activity, acts back directly on the endocrine tissue to reduce secretion, thereby keeping hormone secretion in check.

Long-loop feedback operates on similar principles, but it includes more than one endocrine gland and hormone in the feedback pathway.

Feedback Mechanisms

Loops of Negative Feedback

- ve feedback involves either a short loop or long loop.
- In short-loop, hormone or a byproduct of its activity, acts back directly on the secreting endocrine tissue.
- Long-loop feedback includes more than one endocrine gland and hormone.



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

Phases 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

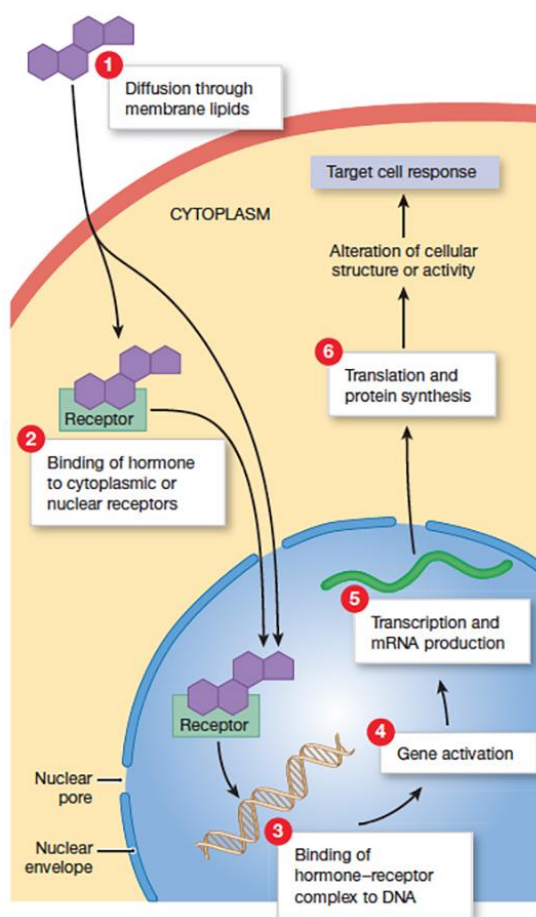
Once these hormones reach their target tissues, they dissociate from their carrier proteins and readily enter the cells by diffusing across the plasma membrane.

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.

Receptors for Lipid-Soluble Hormones

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.

Long-Lasting Effect of Lipid-Soluble Hormones

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

Hormone-Receptor Complex

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 (InsP₃) and diacylglycerol (DAG)
- Ca²⁺ ions and associated calmodulin

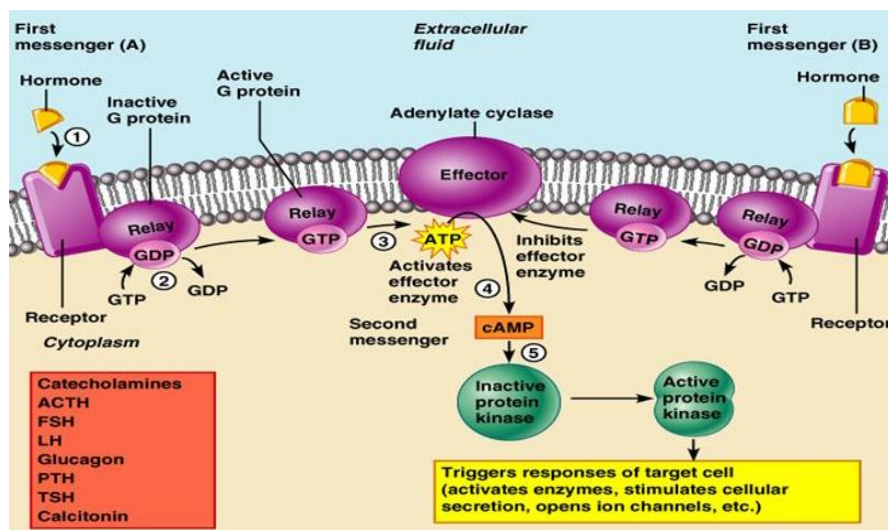
Topic-98 Cyclic Nucleotide Signaling Systems

Cyclic Nucleotide Second Messengers

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.

Differences b/w cGMP and cAMP Pathways

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

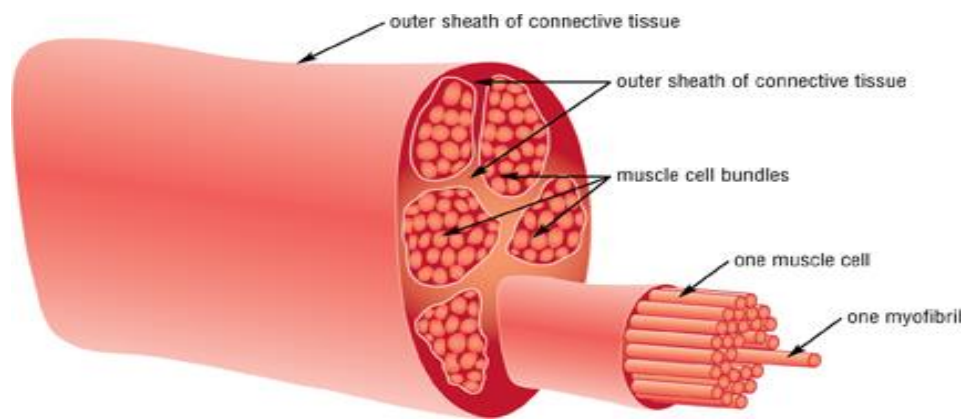
Calcium-calmodulin pathway is used to activate myosin kinase, which acts directly on the myosin of smooth muscle and causes smooth muscle contraction.

Topic-100 The Structure of Muscle

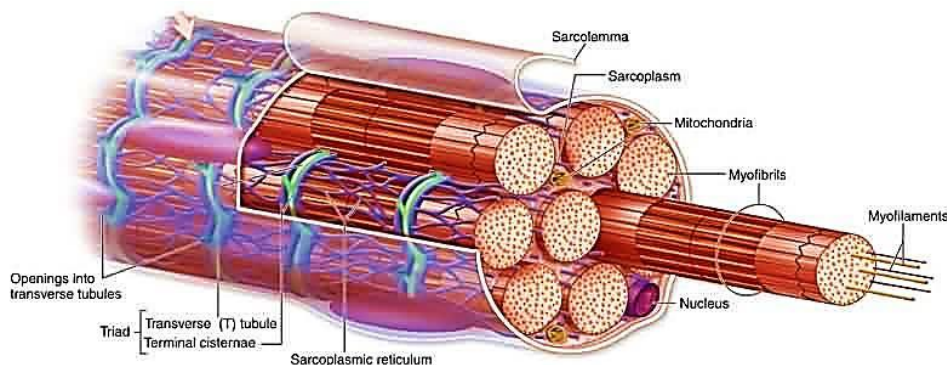
The Muscle Cells (Myofibers)

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.



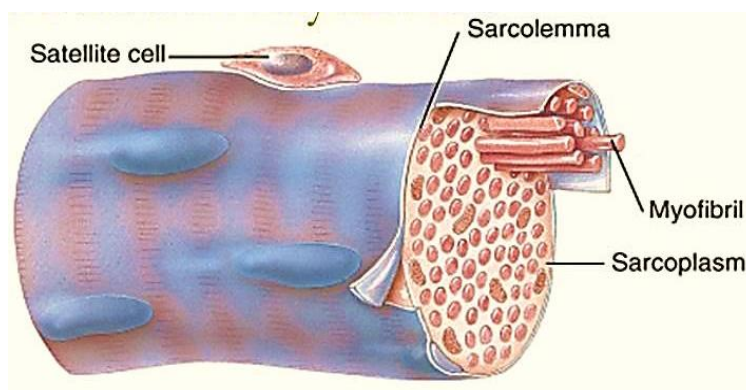
The membrane of the cell is called sarcolemma, its cytoplasm is called sarcoplasm and its endoplasmic reticulum is known as sarcoplasmic reticulum.



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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.

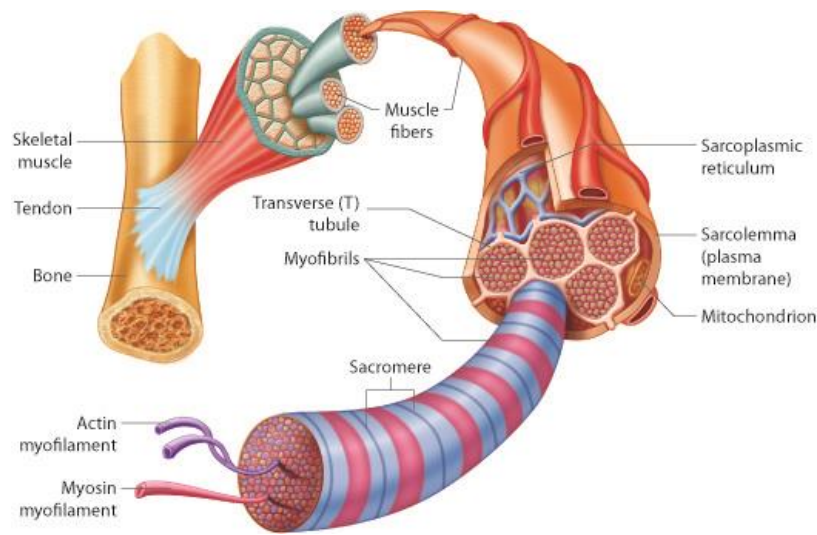


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Myofilaments

Each myofibril is composed of myofilaments. Myofilaments are of two types, thin filaments and thick filaments.

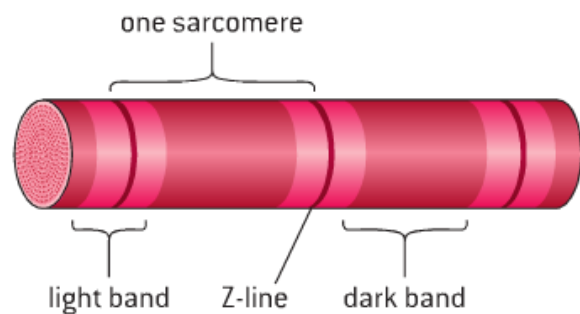
Thin filaments are composed of actin while the thick filaments are composed of myosin molecules.



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.

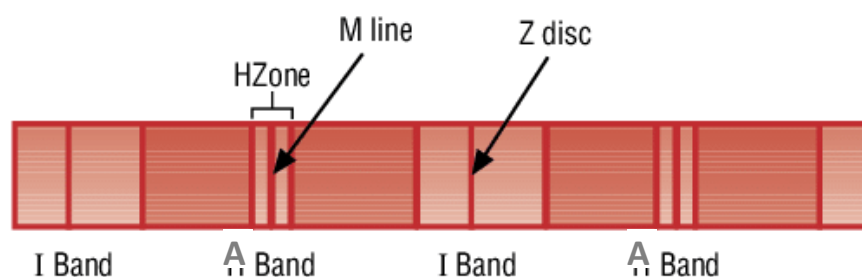


Each repeating unit is called a sarcomere and is the basic functional contractile unit of the muscle.

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.

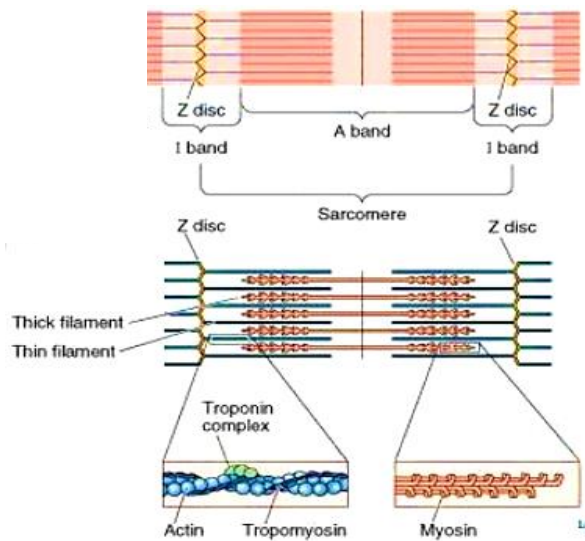


Topic-101 Myofilament Substructure

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.



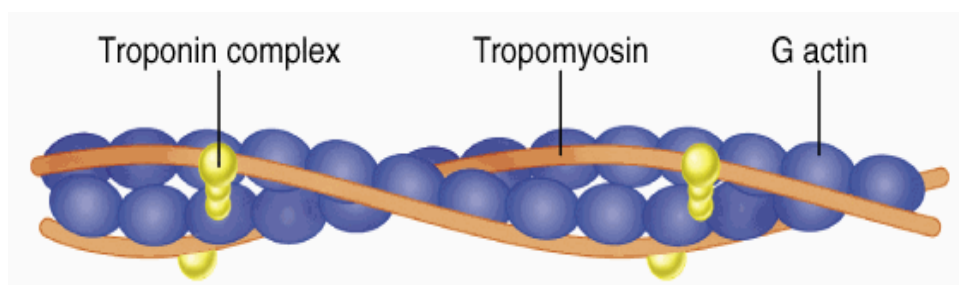
Myosin Molecule

- 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.



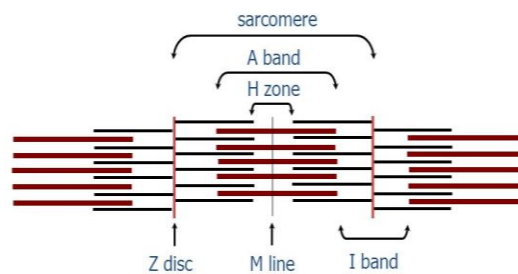
Thin Filaments

- 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.

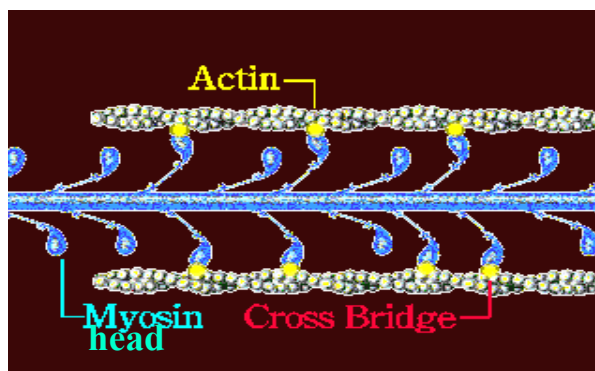
When a muscle contracts, the thin actin filaments actively slide along between the thick myosin filaments and move closer to the center of the sarcomere. As a result, the sarcomere becomes shorter.

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.



<https://kristindockter.wikispaces.com/file/view/HEM21.gif/133853275/HEM21.gif>

- 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.

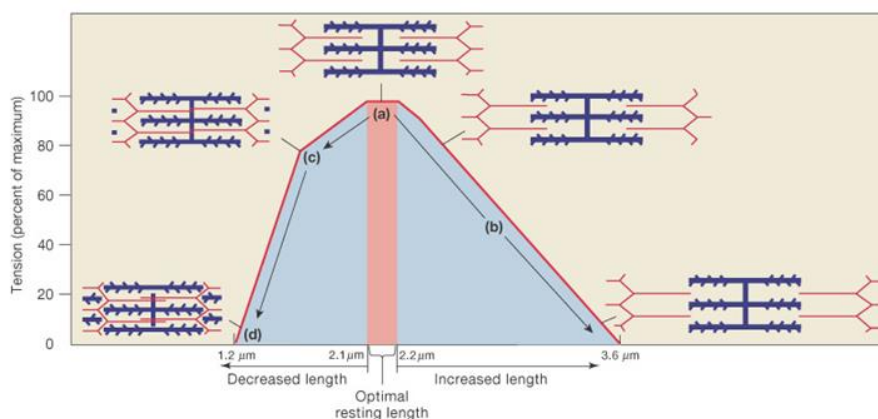
Length-Tension Curve

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 crossbridges.



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. $A + M = AM$

- ATP causes the AM complex to rapidly dissociate into actin and myosin-ATP: **AM + ATP = A + M-ATP**
- The Myosin-ATP complex hydrolyzes to form myosin-ADP-P_i complex.
- **M-ATP → M-ADP-P_i**
- However, ADP and P_i unbind from myosin very slowly.
- **M-ADP-P_i → M + ADP + P_i**

Cyclic Activity of AM Complex

- 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.



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

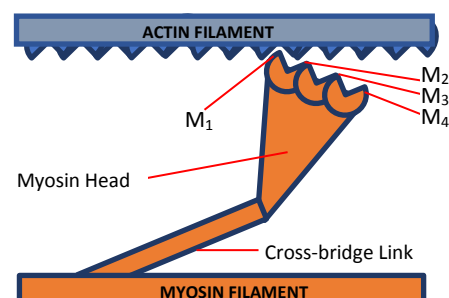
During muscle contraction, myosin heads make cross-bridges with actin filaments that pull the thin filament toward the center of sarcomere. The force for pulling is produced by the partial rotation of myosin heads.

How Rotation is Produced?

The rotation is produced when the four sites M₁ to M₄ 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 rotation of the head is complete, it dissociates from the actin filament and rotates back to its relaxed position.
- Dissociation occurs when Mg²⁺ & ATP bind to head.
- ATP is then hydrolyzed, and myosin head changes conformation.
- Head rebind to a little farther site on the actin filament.

Cyclic Repetition

- Attachment, rotation, and detachment of myosin heads is repeated over and over in cyclic manner, causing filaments to slide past one another in small steps, resulting in sarcomere contraction.

Topic-105 Role of Calcium in Contraction

Role of Calcium in Cross-bridge Attachment

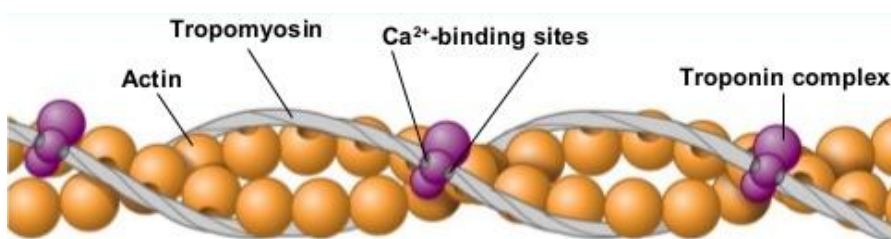
Ca^{2+} plays a crucial role in regulating the contractile activity of muscles as it helps to expose the myosin binding sites of actin. This exposure induces cross bridge formation, necessary for contraction.

Ca^{2+} Acts Through Regulatory Proteins

- Ca^{2+} induces contraction with the help of two regulatory proteins troponin and tropomyosin, associated with actin filaments.
- Troponin
- Tropomyosin
- **Tropomyosin Masks Active Sites of Actin**

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.

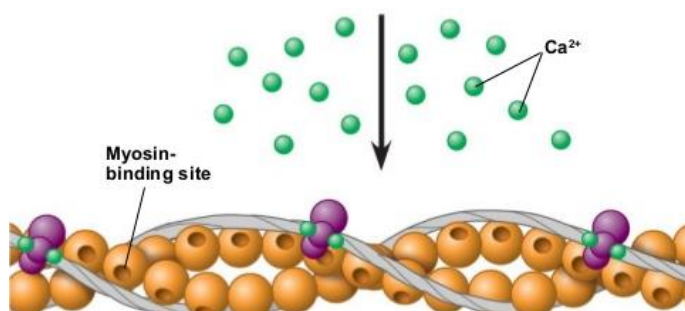
- Troponin complex binds to tropomyosin about every 40 nm along the thin actin filament.



Biology. (8th ed) 2008. By Neil A. Campbell and Jane B. Reece

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.



Ca^{2+} Binding to Troponin Results in Contraction

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.

Release of Acetylcholine

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.

Membrane Excitation

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.

Generation of Action 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 from 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 .

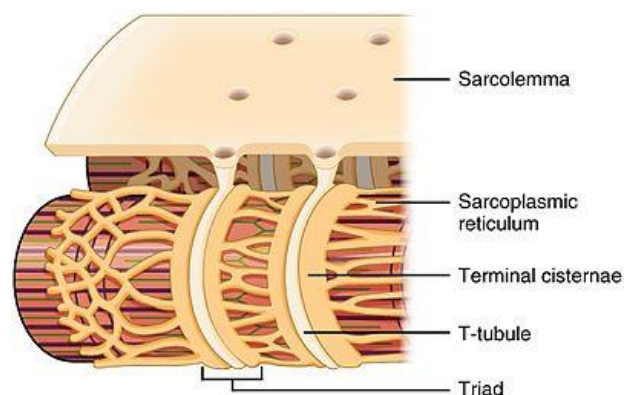
They innervate the cell at the level of Z disk and make branching networks around the perimeter of each myofibril.

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

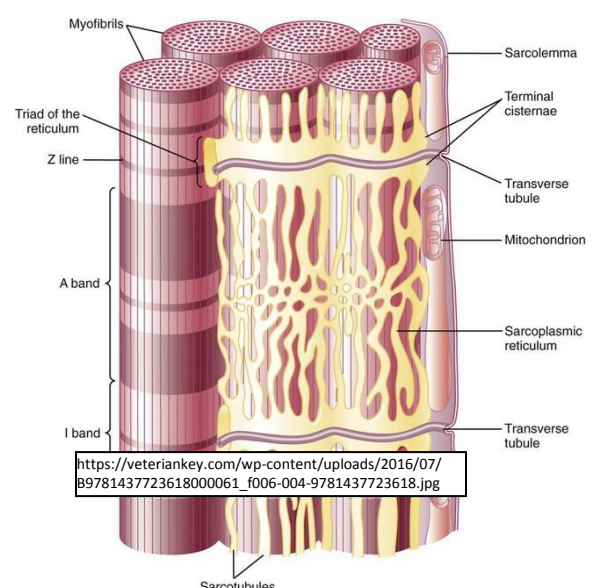
Sarcoplasmic Reticulum

- 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.

Structure of SR

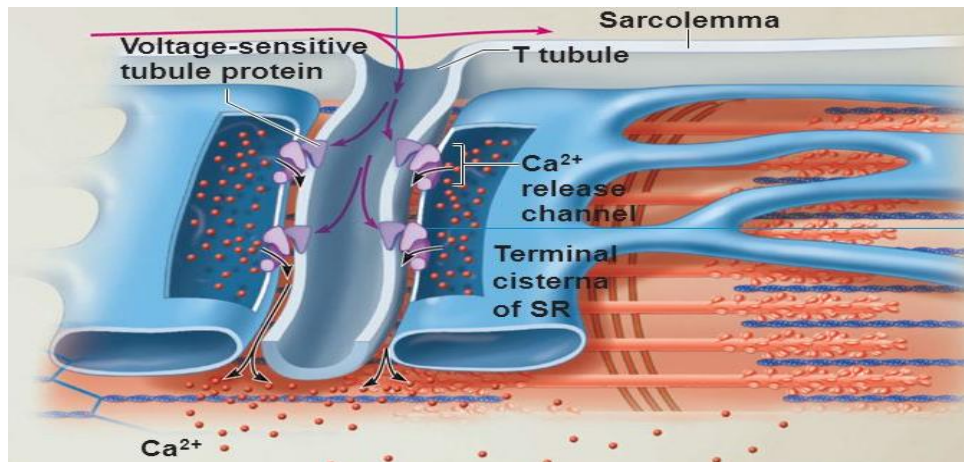
SR is composed of two major parts:

- (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.



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.

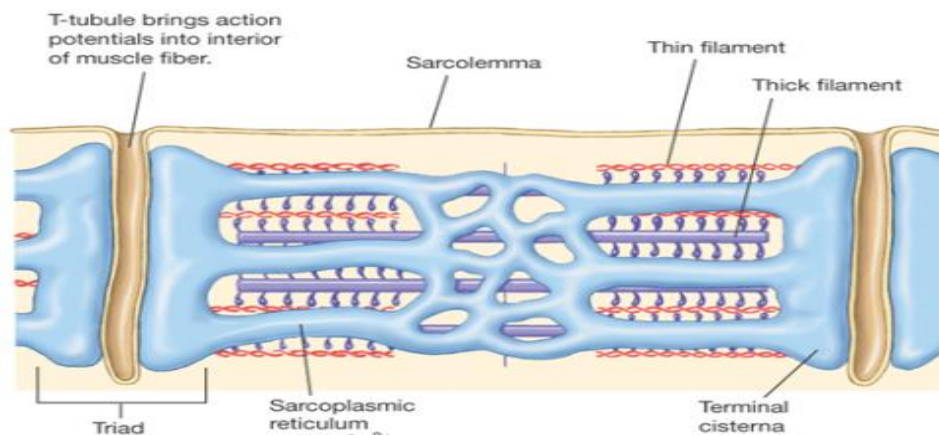
Action potential in T tubules causes opening of calcium channels in the terminal cisternae of SR and large quantities of stored Ca^{2+} ions are released.

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.



http://faculty.pasadena.edu/dkwon/chapt_11/images/image16.png

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+} .

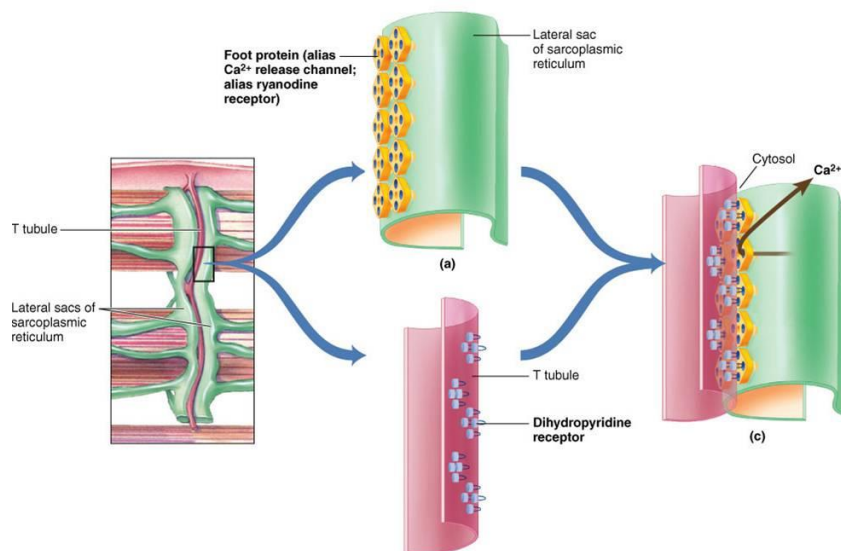
Receptors in Triads and Release of Ca^{2+}

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.

Ryanodine and Dihydropyridine Receptors



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

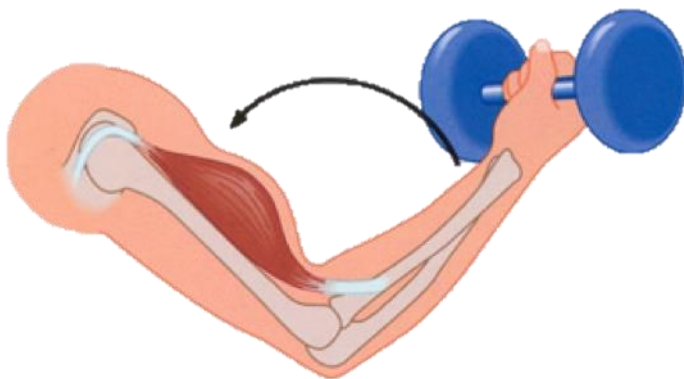
Based on how the length changes, isotonic contractions are further classified into two types:

1. Concentric contractions
2. 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.



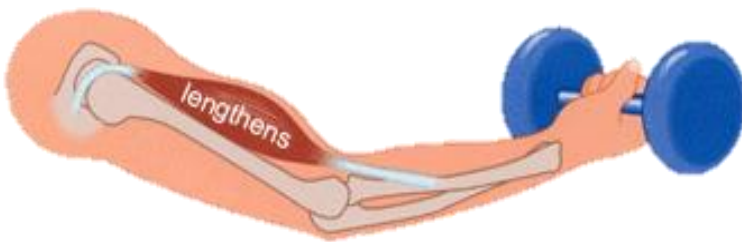
Eccentric Contractions

If the muscle generates tension and the entire muscle lengthens, it is an 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:

1. The latent period, or lag phase
2. The contraction phase
3. 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.

Types of Tetanus

A tetanic contraction can be either unfused (incomplete) or fused (complete).

✓ Unfused Tetanus

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

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.

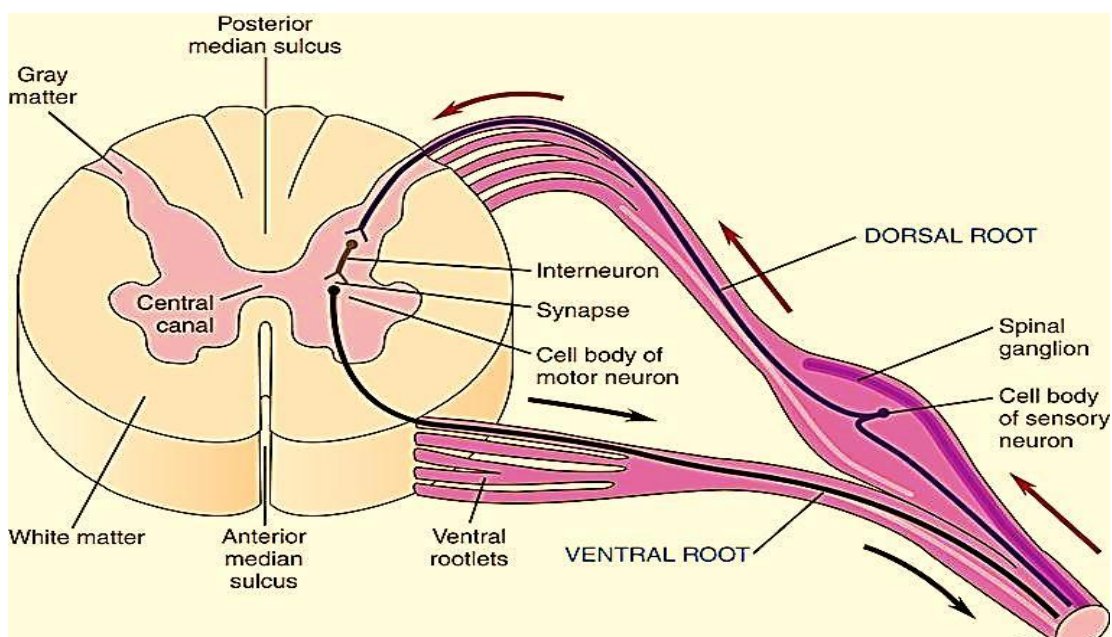
Topic-113 Neural Control of Muscle Contraction

Neural Control of Coordination of Muscle Contraction

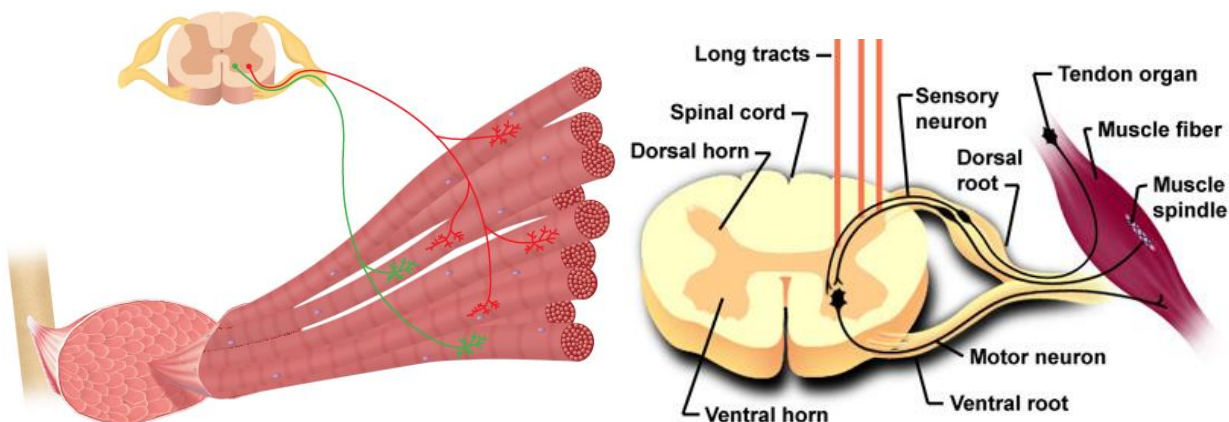
- Effective animal movement requires the contractions of many fibers within a muscle-and of many muscles within the body.
- These contractions need to be correctly timed with respect to one another.
- This coordination is generated within the nervous system which sends neuronal impulses at the neuromuscular 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 α 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.

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^+

Physiological Causes of Muscle Fatigue

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

- ✓ Lever system helps in movement of body parts.
- ✓ Bones, ligaments, and muscles form levers in the body.
- ✓ Muscles apply tension to their points of insertion on bones.
- ✓ Bones, in turn, cause movement.

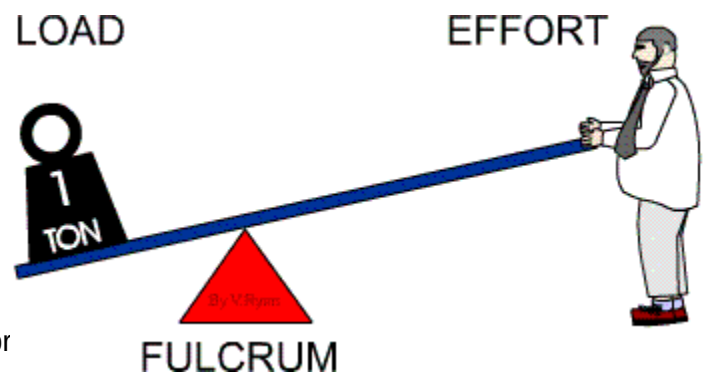
Lever System

- ✓ In physical terms, a lever system has three components:

- ✓ Axis or fulcrum
- ✓ Force or effort
- ✓ Load or resistance

Lever System of the Body

- ✓ In lever system of body:
- ✓ A joint forms the axis
- ✓ Muscles attached to the joint pr
- ✓ Weight or load is moved.



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

Classification depends on:

- Point of muscle insertion
- Its distance from axis (fulcrum)
- Length of the lever arm

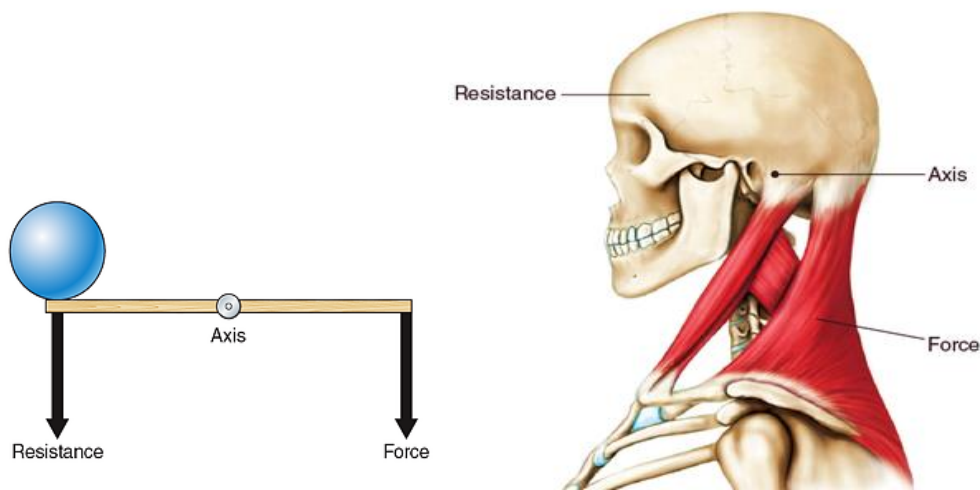
All three types are found in the body, but most levers in the human body are third class.

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.

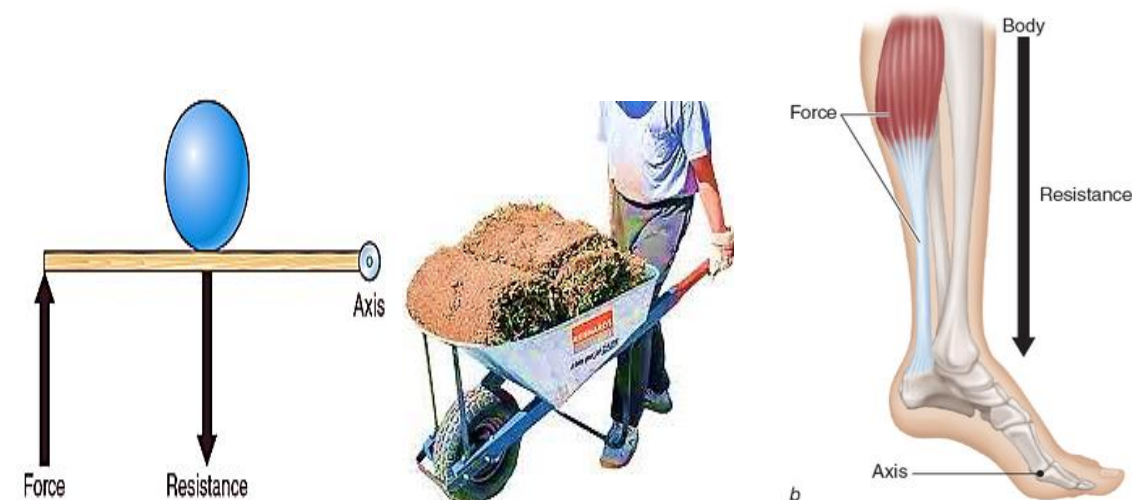


Second-Class Lever

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.

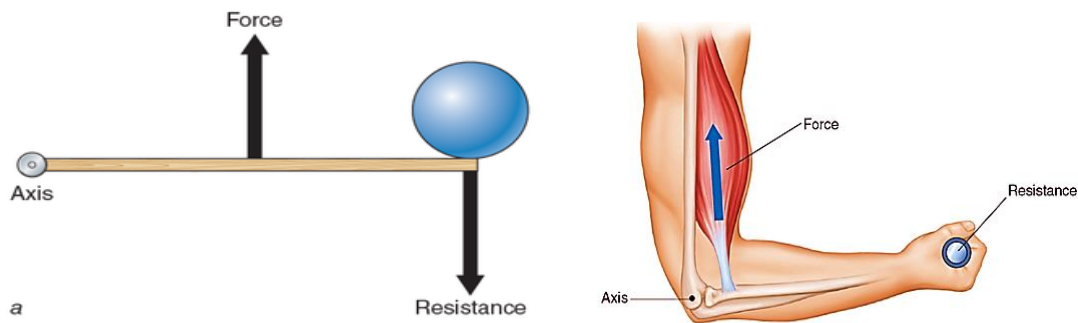


Third-Class Lever

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.

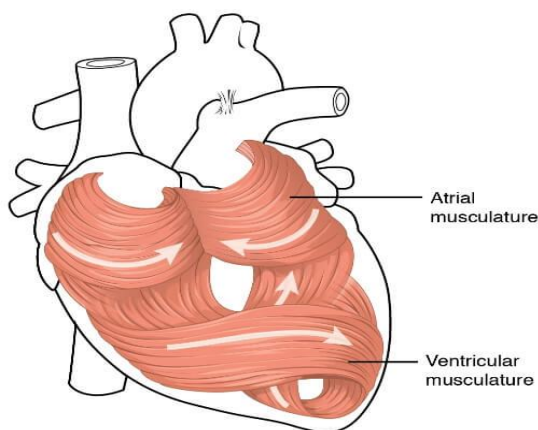


Topic-116 Cardiac Muscles

Cardiac Muscles

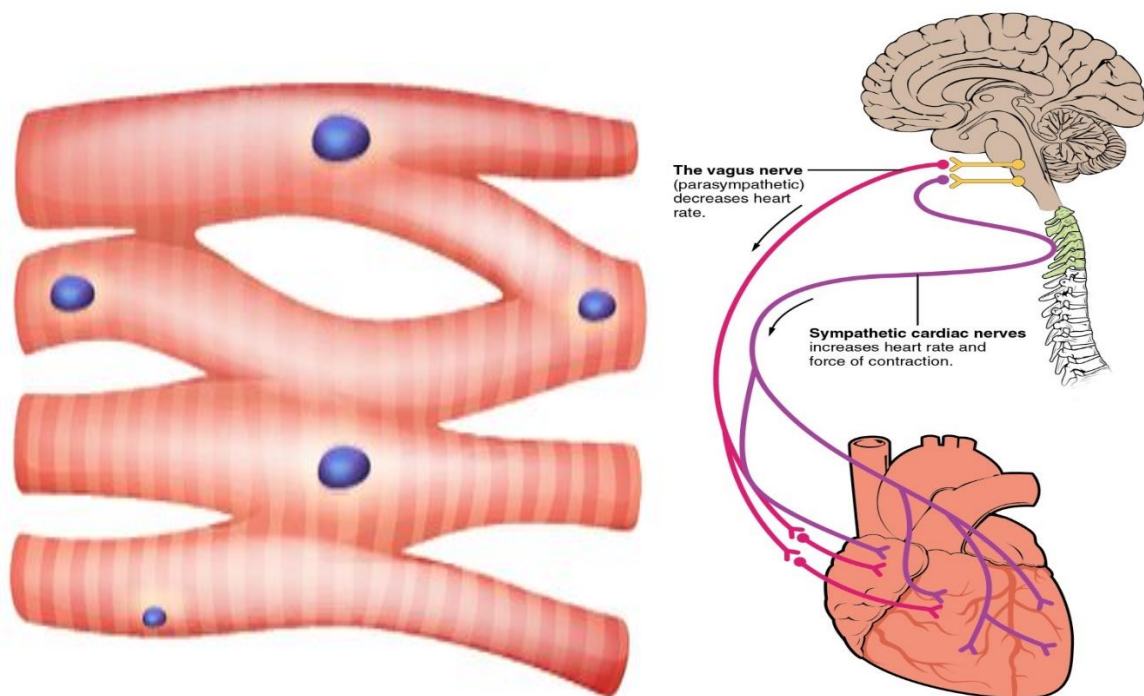
Cardiac muscles are found only in the heart.

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.

Contractile Mechanism of Cardiac Muscles

- 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.

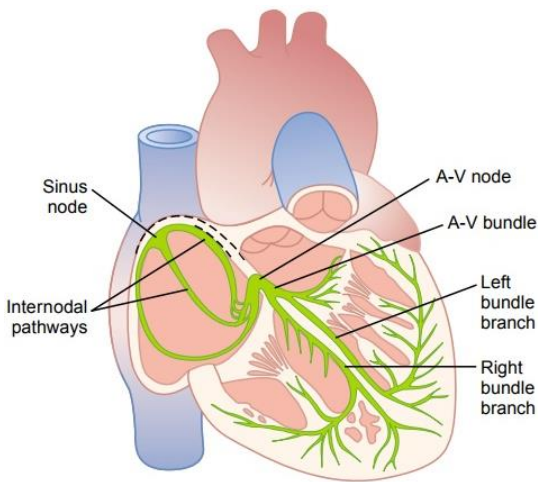
Another special importance of this system is that it allows all portions of the ventricles to contract almost simultaneously. This feature is essential for generating effective pumping pressure in the ventricular chambers.

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.

Pacemaker Types

Two basic types of pacemakers in animals with pumping hearts:

- Neurogenic pacemakers
- Myogenic Pacemakers

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.

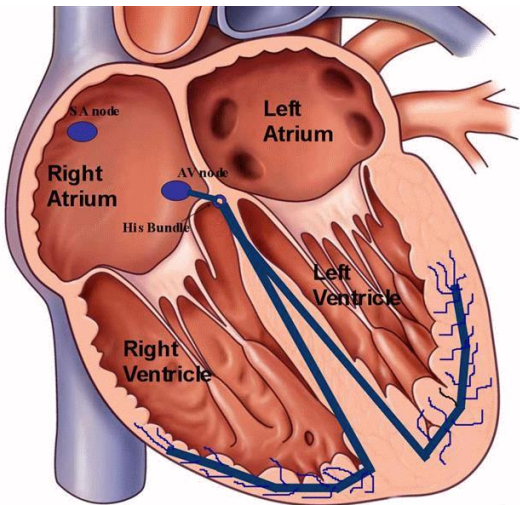
Vertebrate Myogenic Pacemaker

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

- Ability of certain cardiac cells to spontaneously and repetitively generate an electrical impulse without a stimulus from the nervous system.

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.

Pacemaker

- Any cardiac cells that can generate an impulse and can maintain heart rate.
- Include:
 - Sinoatrial node
 - Cells of the AV node
 - Bundle of His
 - Purkinje cells

S-A Node as Pacemaker

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,

Ectopic Pacemakers

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.

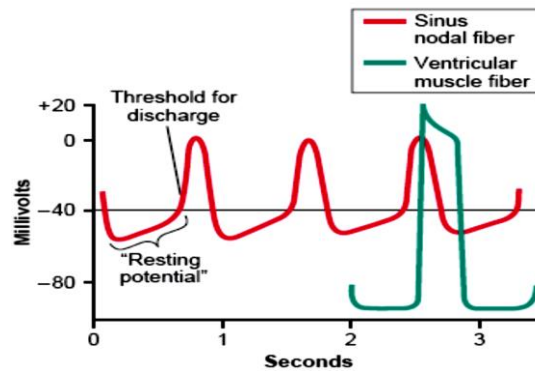
The rhythmic discharge rate of **A-V nodal** fibers is 40 to 60 times per minute, and the **Purkinje fibers** discharge at a rate between 15 and 40 times per minute.

Pacemaker Potentials and Autorhythmicity

Autorhythmicity of Pacemaker: Cause

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.



- Effect:

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

Activity of Ion 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

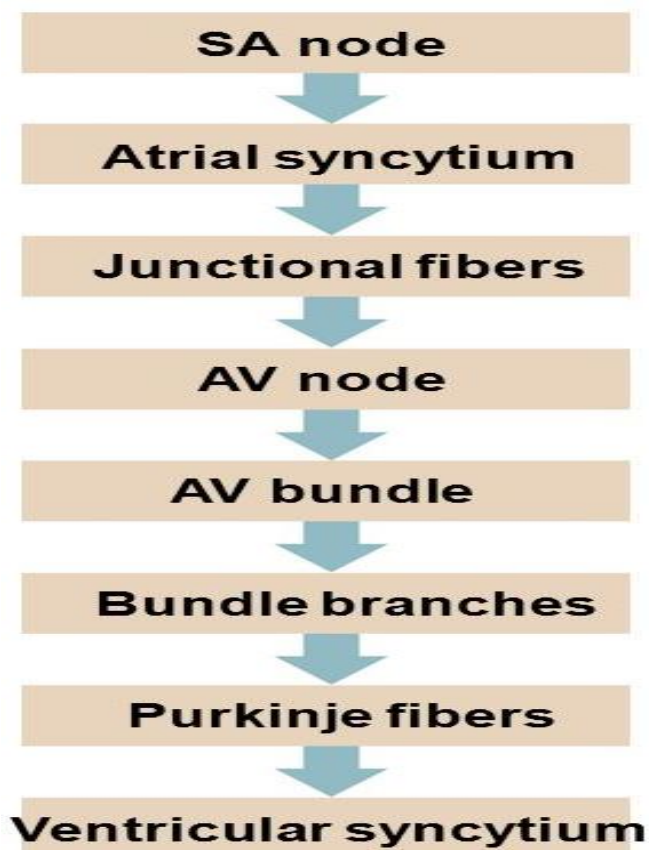
Electrical activity, initiated in the pacemaker region of the heart, spreads over the entire heart from one cell to another because the cells are electrically coupled via membrane gap junctions.

Gap junctions are regions of low resistance between cells and allow current flow from one cell to the next across intercalated disks.

Role of Gap Junctions

- Allow current flow from one cell to the next.
- Pacemaker's electrical activity spreads over the entire heart via gap junctions.

Path of Transmission of Excitation Over the Heart

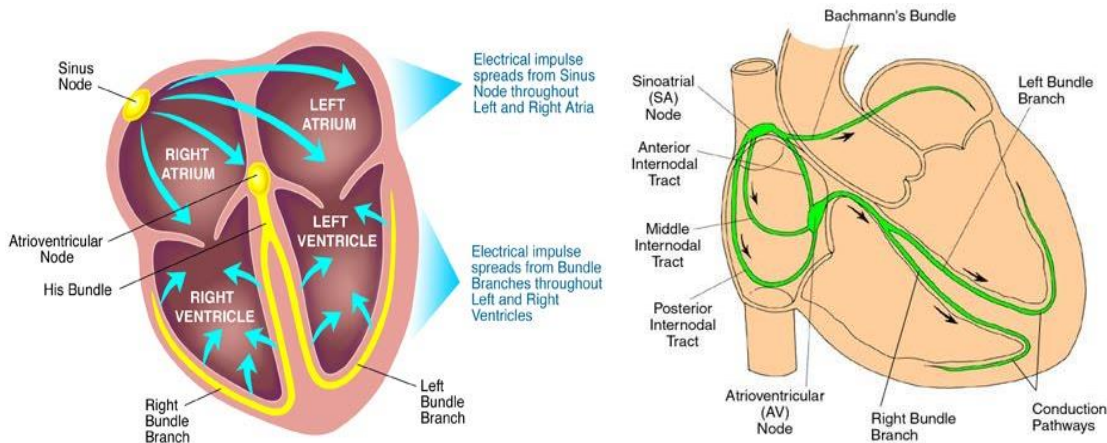


Transmission of Cardiac Impulse Through the Atria

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.



Internodal Pathways

The excitation spreads from the atrial musculature to the atrioventricular node (A-V node) through small junctional fibers that form internodal pathways.

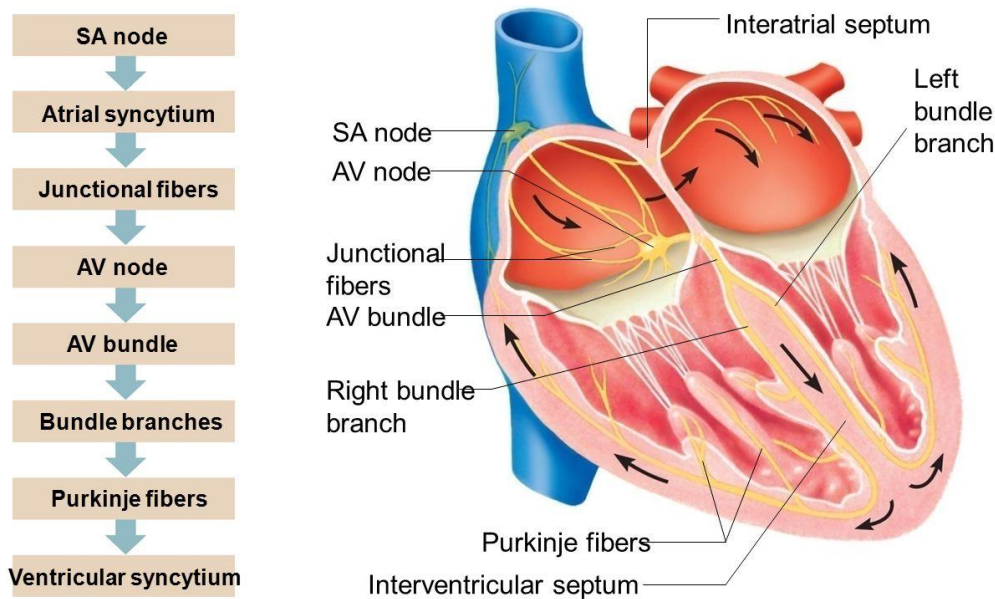
These pathways include:

- 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.



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.

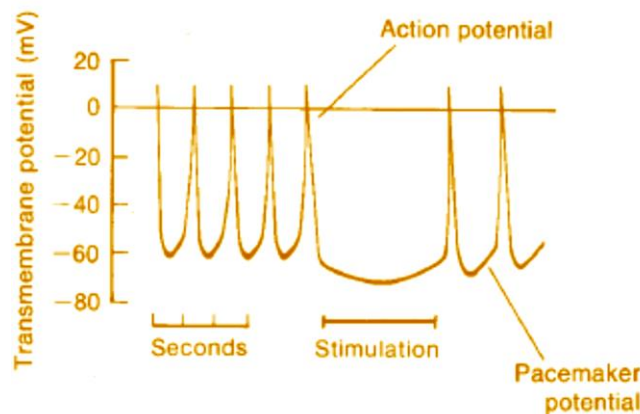
The velocity of transmission through the ventricular muscle mass to the epicardial surfaces is only 0.3 to 0.5 m/sec i.e. one sixth that in the Purkinje fibers.

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.

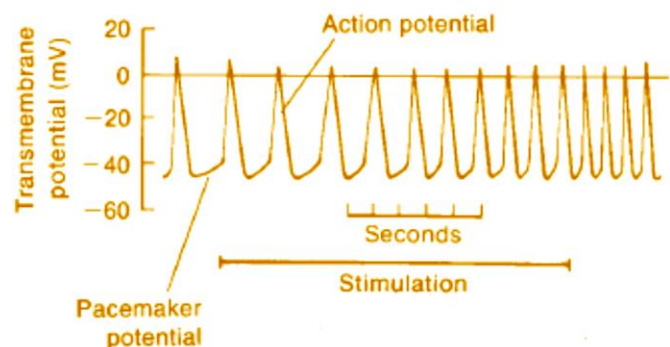
As the heart rate slows, acetylcholine also reduces the velocity of conduction from the atria to the ventricles through the atrioventricular node.

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

• Fluctuations in Pressure and Flow

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. Diastole

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. **Evident Role of Venous Filling Pressure**

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. **Ventricular Contraction**

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. **Ventricular Relaxation**

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

In physics, work is defined as:

- The product of force and distance

$$W = F \times s$$

$$\text{Work} = \text{Force} \times \text{Distance}$$

Work Done by the Heart

- For the heart, work is to move a volume of blood

So, work is equal to:

- Product of volume of blood moved

And

- Pressure required to move it

$$W = V \times P$$

$$\text{Work} = \text{Volume} \times \text{Pressure}$$

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.

Calculating the Work Done by the Heart

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,

Work Done By Right Ventricle

- but the pressures generated in the pulmonary circuit (right ventricle) are much lower. Work done by this ventricle is higher

Work Done By Left Ventricle

- Consequently, the external work done by the right ventricle is much less than that done by the left ventricle. Pressure generated by left ventricle is much higher
- Work done by this ventricle is higher

Topic-127 Electrocardiogram (ECG)

Basis of Electrocardiogram

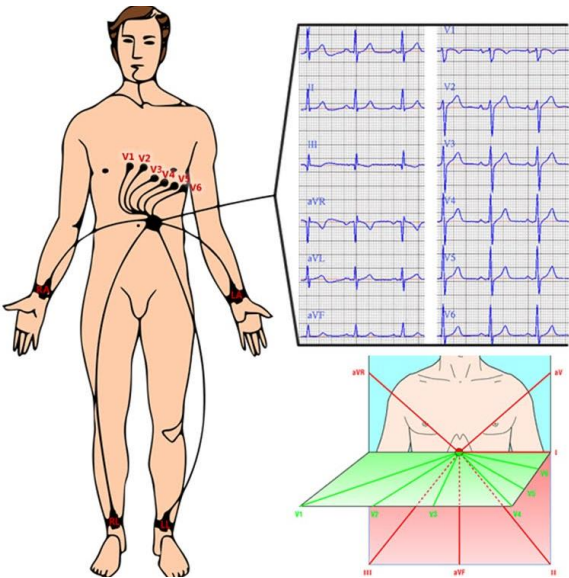
When the cardiac impulses pass through the heart, electrical changes result from depolarization and repolarization of cardiac muscle fibres.

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.

Electrocardiogram

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.

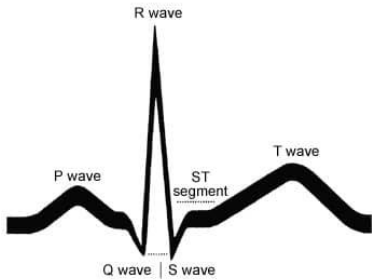
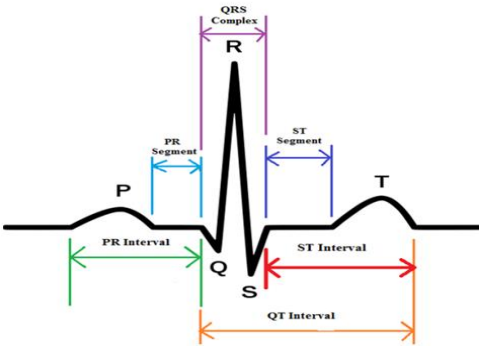
S-T Segment

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.

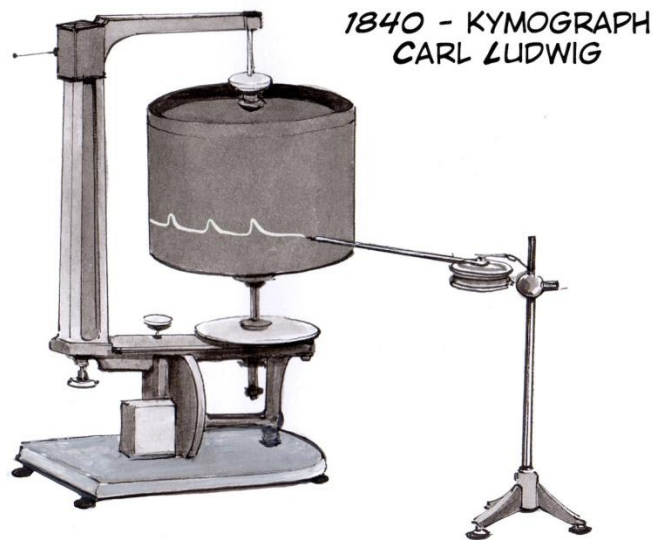
Uses of Kymograph

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.

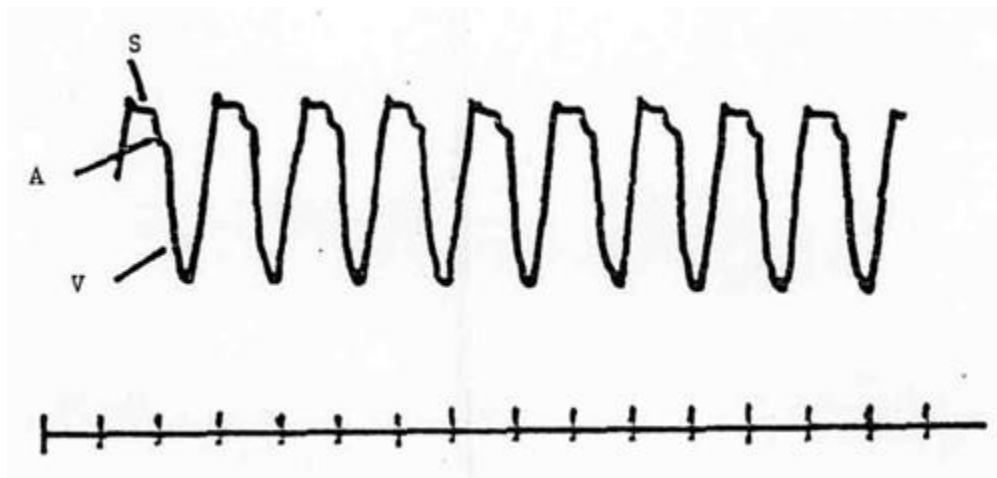
The graphic record generated by the kymograph instrument is commonly translated into a graph, showing changes in pressure or motion on the horizontal x-axis, and time elapsed on the vertical y-axis.

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>)