JFII JLO FITNESS INSTITUTE OF INDIA

Level 5
Weight Management & Exercise Specialist

Registered to Certify in Sports Fitness Education and Skilled Development Program

JFII

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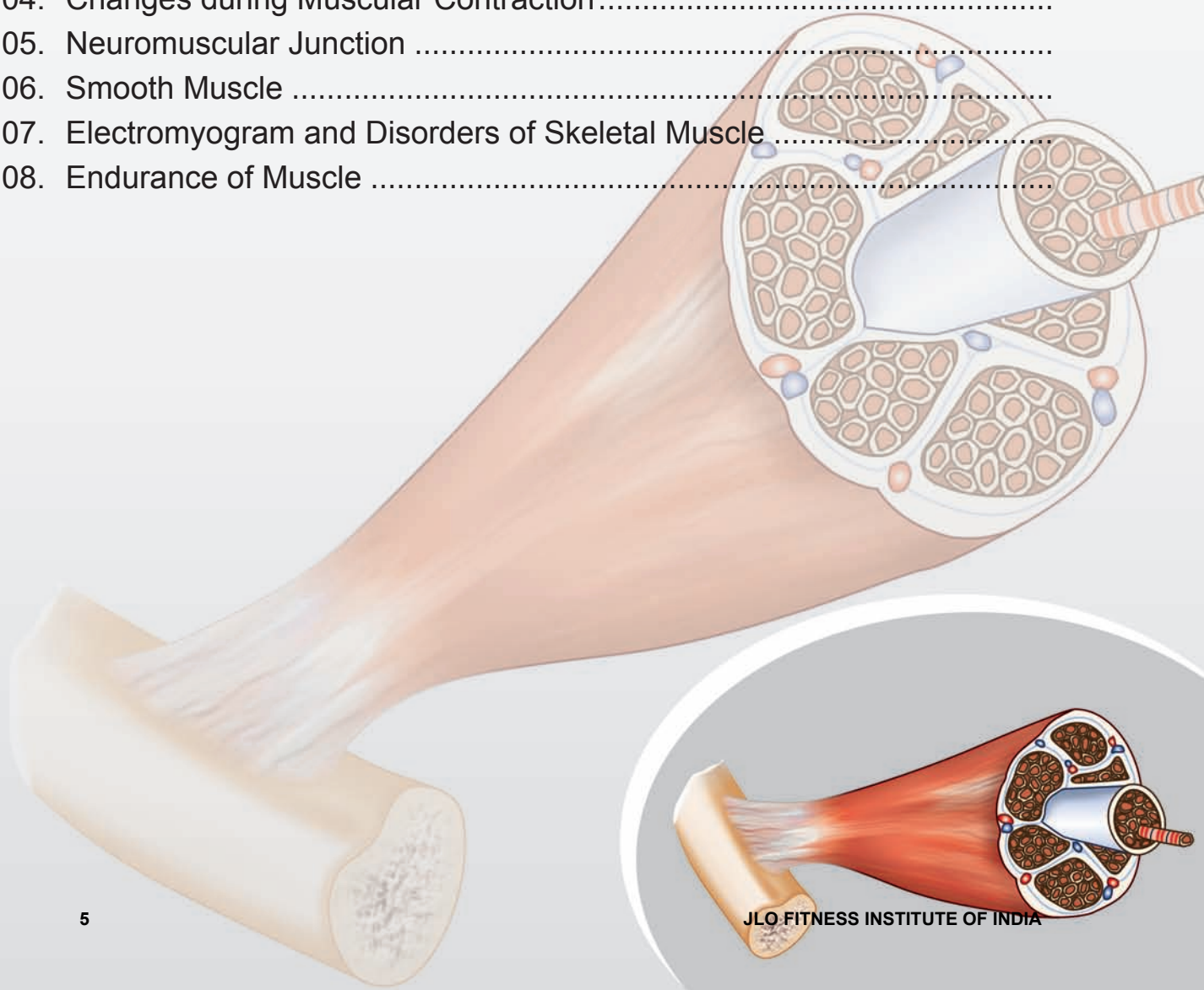
Dedicated to my students, who are to my spirits what ATP is to my cells;

Level 5 Contents

GENERAL TOPICS

LEVEL 5

1 Muscle Physiology



Chapter 1

Classification of Muscles

- DEPENDING UPON STRIATIONS
- DEPENDING UPON CONTROL
- DEPENDING UPON SITUATION

Human body has more than 600 muscles. Muscles perform many useful functions and help us in doing everything in day-to-day life. Muscles are classified by three different methods, based on different factors:

I. Depending upon the presence or absence of striations
II. Depending upon the control
III. Depending upon the situation.

DEPENDING UPON STRIATIONS

Depending upon the presence or absence of cross striations, the muscles are divided into two groups:

1. Striated muscle
2. Non-striated muscle.

1. *Striated Muscle*

Striated muscle is the muscle which has a large number of cross-striations (transverse lines). Skeletal muscle and cardiac muscle belong to this category.

2. *Non-striated Muscle*

Muscle which does not have cross-striations is called non-striated muscle. It is also called plain muscle or smooth muscle. It is found in the wall of the visceral organs.

DEPENDING UPON CONTROL

Depending upon control, the muscles are classified into two types:

1. Voluntary muscle
2. Involuntary muscle.

1. *Voluntary Muscle*

Voluntary muscle is the muscle that is controlled by the will. Skeletal muscles are the voluntary muscles. These muscles are innervated by somatic nerves.

2. *Involuntary Muscle*

Muscle that cannot be controlled by the will is called involuntary muscle. Cardiac muscle and smooth muscle are involuntary muscles. These muscles are innervated by autonomic nerves.

DEPENDING UPON SITUATION

Depending upon situation, the muscles are classified into three types:

1. Skeletal muscle
2. Cardiac muscle
3. Smooth muscle.

Features of these muscles are given in Table 28.1.

1. *Skeletal Muscle*

Skeletal muscle is situated in association with bones forming the skeletal system. The skeletal muscles form 40% to 50% of body mass and are voluntary and striated. These muscles are supplied by somatic nerves.

TABLE 28.1: Features of skeletal, cardiac and smooth muscle fibers

Features	Skeletal muscle	Cardiac muscle	Smooth muscle
Location	In association with bones	In the heart	In the visceral organs
Shape	Cylindrical and unbranched	Branched	Spindle-shaped, unbranched
Length	1 cm to 4 cm	80 µ to 100 µ	50 µ to 200 µ
Diameter	10 µ to 100 µ	15 µ to 20 µ	2 µ to 5 µ
Number of nucleus	More than one	One	One
Cross-striations	Present	Present	Absent
Myofibrils	Present	Present	Absent
Sarcomere	Present	Present	Absent
Troponin	Present	Present	Absent
Sarcotubular system	Well developed	Well developed	Poorly developed
'T' tubules	Long and thin	Short and broad	Absent
Depolarization	Upon stimulation	Spontaneous	Spontaneous
Fatigue	Possible	Not possible	Not possible
Summation	Possible	Not possible	Possible
Tetanus	Possible	Not possible	Possible
Resting membrane potential	Stable	Stable	Unstable
For trigger of contraction, calcium binds with	Troponin	Troponin	Calmodulin
Source of calcium	Sarcoplasmic reticulum	Sarcoplasmic reticulum	Extracellular
Speed of contraction	Fast	Intermediate	Slow
Neuromuscular junction	Well defined	Not well defined	Not well defined
Action	Voluntary action	Involuntary action	Involuntary action
Control	Only neurogenic	Myogenic	Neurogenic and myogenic
Nerve supply	Somatic nerves	Autonomic nerves	Autonomic nerves

Fibers of the skeletal muscles are arranged in parallel. In most of the skeletal muscles, muscle fibers are attached to tendons on either end. Skeletal muscles are anchored to the bones by the tendons.

2. *Cardiac Muscle*

Cardiac muscle forms the musculature of the heart. These muscles are striated and involuntary. Cardiac muscles are supplied by autonomic nerve fibers.

3. *Smooth Muscle*

Smooth muscle is situated in association with viscera. It is also called visceral muscle. It is different from skeletal and cardiac muscles because of the absence of cross-striations, hence the name smooth muscle. Smooth muscle is supplied by autonomic nerve fibers. Smooth muscles form the main contractile units of wall of the various visceral organs.

Chapter 2

Structure of Skeletal Muscle

- MUSCLE MASS
- MUSCLE FIBER
- MYOFIBRIL
  - MICROSCOPIC STRUCTURE
- SARCOMERE
  - ELECTRON MICROSCOPIC STUDY
- CONTRACTILE ELEMENTS (PROTEINS) OF MUSCLE
  - MYOSIN MOLECULE
  - ACTIN MOLECULE
  - TROPOMYOSIN
  - TROPONIN
- OTHER PROTEINS OF THE MUSCLE
- SARCOTUBULAR SYSTEM
  - STRUCTURES
  - FUNCTIONS
- COMPOSITION OF MUSCLE

MUSCLE MASS

Muscle mass or muscle tissue is made up of a large number of individual **muscle cells** or **myocytes.** The muscle cells are commonly called muscle fibers because these cells are long and slender in appearance. Skeletal muscle fibers are multinucleated and are arranged parallel to one another with some connective tissue in between (Fig. 29.1).

Muscle mass is separated from the neighboring tissues by a thick fibrous tissue layer known as **fascia.** Beneath the fascia, muscle is covered by a connective tissue sheath called **epimysium.** In the muscle, the muscle fibers are arranged in various groups called bundles or **fasciculi.** Connective tissue sheath that covers each fasciculus is called **perimysium.** Each muscle fiber is covered by a connective tissue layer called the **endomysium** (Fig. 29.2).

MUSCLE FIBER

Each muscle cell or muscle fiber is cylindrical in shape. Average length of the fiber is 3 cm. It varies between 1 cm and 4 cm, depending upon the length of the muscle. The diameter of the muscle fiber varies from 10 µ to 100 µ. The diameter varies in a single muscle.

Muscle fibers are attached to a tough cord of connective tissue called **tendon.** Tendon is in turn attached to the bone. Tendon of some muscles is thin, flat and stretched but tough. Such type of tendon is called **aponeurosis.**

Each muscle fiber is enclosed by a cell membrane called plasma membrane, that lies beneath the endomysium. It is also called **sarcolemma** (Fig. 29.3). Cytoplasm of the muscle is known as **sarcoplasm.**

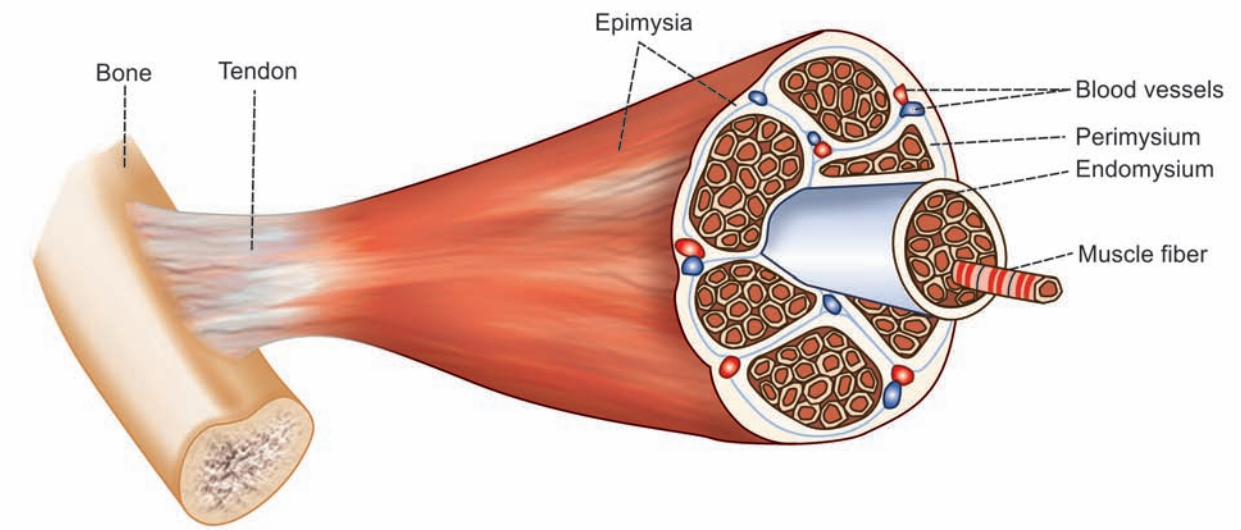


FIGURE 29.1: Structure of a skeletal muscle

Structures embedded within the sarcoplasm are:

1. Nuclei
2. Myofibril
3. Golgi apparatus
4. Mitochondria
5. Sarcoplasmic reticulum
6. Ribosomes
7. Glycogen droplets
8. Occasional lipid droplets.

Each muscle fiber has got one or more nuclei. In long muscle fibers, many nuclei are seen. Nuclei are oval or elongated and situated just beneath the sarcolemma. Usually in other cells, the nucleus is in the interior of the cell.

All the organelles of muscle fiber have the same functions as those of other cells.

■ MYOFIBRIL

Myofibrils or myofibrillae are the fine parallel filaments present in sarcoplasm of the muscle cell. Myofibrils run through the entire length of the muscle fiber.

In the cross-section of a muscle fiber, the myofibrils appear like small distinct dots within the sarcoplasm. Diameter of the myofibril is 0.2 to 2 µ. The length of a myofibril varies between 1 cm and 4 cm, depending upon the length of the muscle fiber (Table 29.1).

In some muscle fibers, some of the myofibrils are arranged in groups called **Cohnheim's areas** or fields.

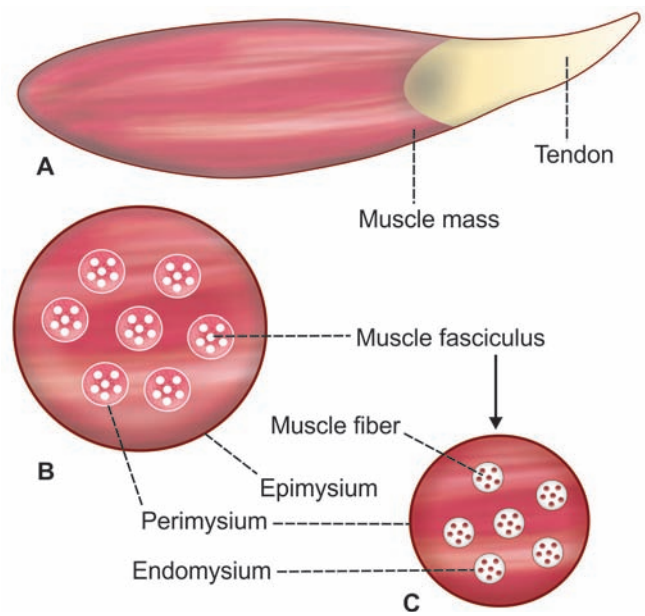


FIGURE 29.2: Diagram showing. **A.** Skeletal muscle mass; **B.** Cross-section of muscle; **C.** One muscle fasciculus.

■ MICROSCOPIC STRUCTURE OF A MYOFIBRIL

Light microscopic studies show that, each myofibril consists of a number of two alternating bands which are also called the sections, segments or disks. These bands are formed by muscle proteins.

The two bands are:

1. Light band or 'I' band.
2. Dark band or 'A' band.

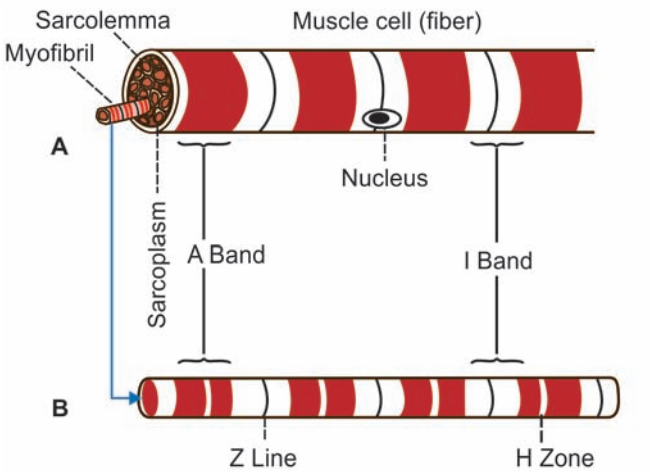


FIGURE 29.3: A. One muscle cell; **B.** One myofibril.

Light Band or 'I' Band

Light band is called 'I' **(isotropic)** band because it is isotropic to **polarized light.** When polarized light is passed through the muscle fiber at this area, light rays are refracted at the same angle.

Dark Band or 'A' Band

Dark band is called 'A' **(anisotropic)** band because it is anisotropic to polarized light. When polarized light is passed through the muscle fiber at this area, the light rays are refracted at different directions (An = not; iso = it; trops = turning). Dark band is also called **'Q' disk** (Querscheibe = cross disk).

In an intact muscle fiber, 'I' band and 'A' band of the adjacent myofibrils are placed side-by-side. It gives the appearance of characteristic cross-striations in the muscle fiber.

I band is divided into two portions, by means of a narrow and dark line called **'Z' line** or **'Z' disk** (in German, zwischenscheibe = between disks). The 'Z' line is formed by a protein disk, which does not permit passage of light. The portion of myofibril in between two 'Z' lines is called sarcomere.

TABLE 29.1: Dimensions of structures in skeletal muscle

Structure	Length	Diameter
Muscle fiber	1 cm to 4 cm	10 µ to 100 µ
Myofibril	1 cm to 4 cm	0.2 µ to 2 µ
Actin filament	1 µ	20 Å
Myosin filament	1.5 µ	115 Å

■ SARCOMERE

Definition

Sarcomere is defined as the structural and functional unit of a skeletal muscle. It is also called the basic contractile unit of the muscle.

Extent

Each sarcomere extends between two 'Z' lines of myofibril. Thus, each myofibril contains many sarcomeres arranged in series throughout its length. When the muscle is in relaxed state, the average length of each sarcomere is 2 to 3 µ.

Components

Each myofibril consists of an alternate dark 'A' band and light 'I' band (Fig. 29.4). In the middle of 'A' band, there is a light area called **'H' zone** (H = hell = light – in German, H = Henson – discoverer). In the middle of 'H' zone lies the middle part of myosin filament. This is called **'M' line** (in German-mittel = middle). 'M' line is formed by myosin binding proteins.

■ ELECTRON MICROSCOPIC STUDY OF SARCOMERE

Electron microscopic studies reveal that the sarcomere consists of many thread-like structures called **myofilaments.**

Myofilaments are of two types:

1. Actin filaments
2. Myosin filaments.

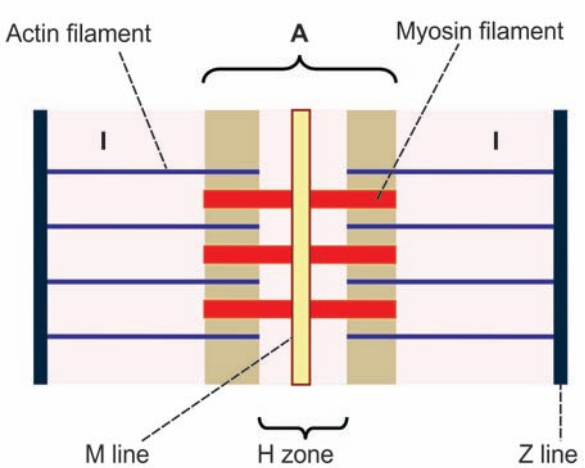


FIGURE 29.4: Sarcomere. A = A band, I = I band.

Actin Filaments

Actin filaments are the thin filaments with a diameter of 20 Å and a length of 1 µ. These filaments extend from either side of the 'Z' lines, run across 'I' band and enter into 'A' band up to 'H' zone.

Myosin Filaments

Myosin filaments are thick filaments with a diameter of 115 Å and a length of 1.5 µ. These filaments are situated in 'A' band.

Cross-bridges

Some lateral processes (projections) called cross-bridges arise from each myosin filament. These bridges have enlarged structures called myosin heads at their tips. Myosin heads attach themselves to actin filaments. These heads pull the actin filaments during contraction of the muscle, by means of a mechanism called sliding mechanism or ratchet mechanism.

During the contraction of the muscle, the actin filaments glide down between the myosin filaments towards the center of 'H' zone and approach the corresponding actin filaments from the next 'Z' line (Fig. 29.5). The 'Z' lines also approach the ends of myosin filaments, so that the 'H' zone and 'I' bands are shortened during contraction of the muscle. During the relaxation of the muscle, the actin filaments and 'Z' lines come back to the original position.

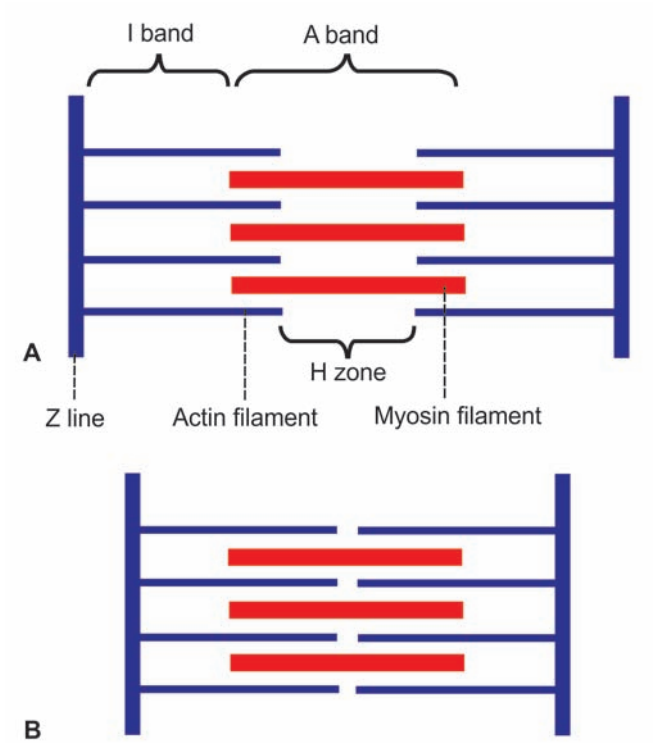


FIGURE 29.5: Sarcomere in resting muscle **A.** Contracted muscle; **B.** During contraction; Z lines come close, H zone and I band are reduced and no change in A band.

■ CONTRACTILE ELEMENTS (PROTEINS) OF MUSCLE

Myosin filaments are formed by myosin molecules. Actin filaments are formed by three types of proteins called actin, tropomyosin and troponin. These four proteins together constitute the contractile proteins or the contractile elements of the muscle.

■ MYOSIN MOLECULE

Each myosin filament consists of about 200 myosin molecules. Though about 18 classes of myosin are identified, only myosin II is present in the sarcomere.

Myosin II is a globulin with a molecular weight of 480,000. Each myosin molecule is made up of 6 polypeptide chains, of which two are heavy chains and four are light chains (Fig. 29.5). Molecular weight of each heavy chain is 200,000 (2 × 200,000 = 400,000). Molecular weight of each light chain is 20,000 (4 × 20,000 = 80,000). Thus, total molecular weight of each myosin molecule is 480,000 (400,000 + 80,000).

Portions of Myosin Molecule

Each myosin molecule has two portions:

1. Tail portion
2. Head portion.

Tail portion of myosin molecule

It is made up of two heavy chains, which twist around each other in the form of a double helix (Fig. 29.6).

Head portion of myosin molecule

At one end of the double helix, both the heavy chains turn away in opposite directions and form the globular head portion. Thus the head portion has two parts. Two light chains are attached to each part of the head portion of myosin molecule (Fig. 29.6).

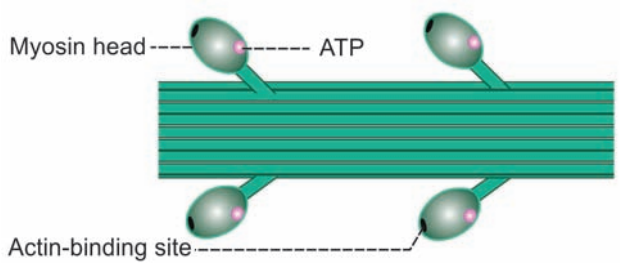


FIGURE 29.6: Diagram showing myosin filament. ATP = Adenosine triphosphate.

Each myosin head has two attachment sites. One site is for actin filament and the other one is for one ATP molecule (Fig. 29.7). Myosin head is absent in the central part of myosin filament, i.e. in the 'H' zone.

■ ACTIN MOLECULE

Actin molecules are the major constituents of the thin actin filaments. Each actin molecule is called **F-actin** and it is the polymer of a small protein known as **G-actin.** There are about 300 to 400 actin molecules in each actin filament. The molecular weight of each molecule is 42,000. The actin molecules in the actin filament are also arranged in the form of a double helix.

Each F-actin molecule has an active site to which the myosin head is attached (Fig. 29.8).

■ TROPOMYOSIN

About 40 to 60 tropomyosin molecules are situated along the double helix strand of actin filament. Each tropomyosin molecule has the molecular weight of 70,000. In relaxed condition of the muscle, the tropomyosin molecules cover all the active sites of F-actin molecules.

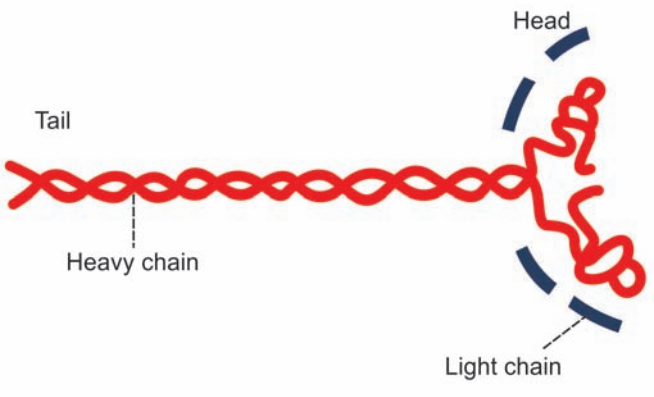


FIGURE 29.7: Myosin molecule formed by two heavy chains and four light chains of polypeptides

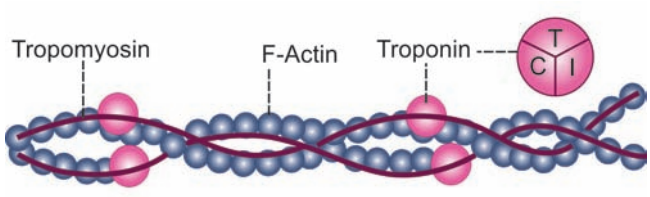


FIGURE 29.8: Part of actin filament. Troponin has three subunits, T, C and I.

■ TROPONIN

It is formed by three subunits:

1. Troponin I, which is attached to F-actin
2. Troponin T, which is attached to tropomyosin
3. Troponin C, which is attached to calcium ions.

■ OTHER PROTEINS OF THE MUSCLE

In addition to the contractile proteins, the sarcomere contains several other proteins such as:

1. **Actinin,** which attaches actin filament to 'Z' line.
2. **Desmin,** which binds 'Z' line with sarcolemma.
3. **Nebulin,** which runs in close association with and parallel to actin filaments.
4. **Titin,** a large protein connecting 'M' line and 'Z' line. Each titin molecule forms **scaffolding** (framework) for sarcomere and provides elasticity to the muscle.

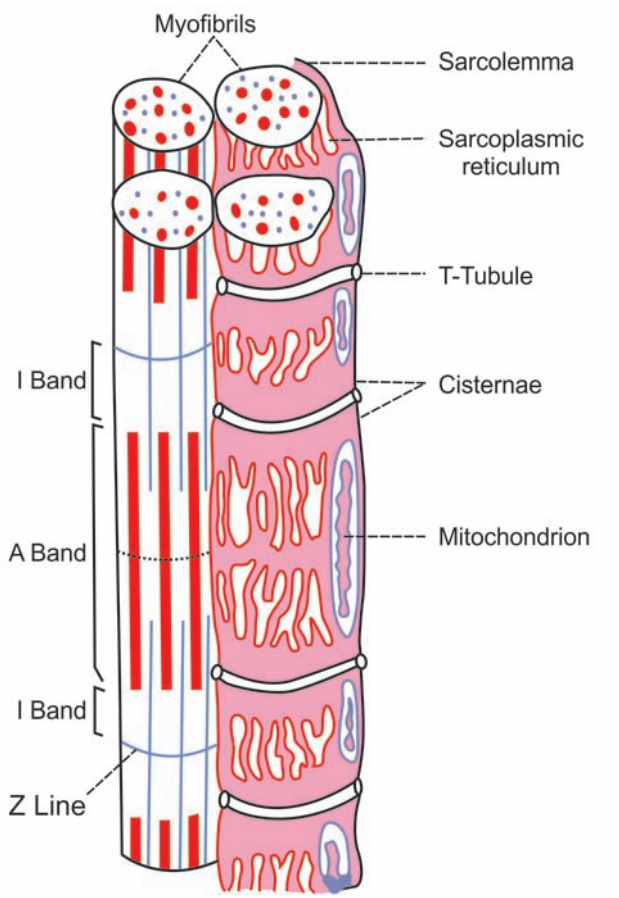


FIGURE 29.9: Diagram showing the relation between sarcotubular system and parts of sarcomere. Only few myofilaments are shown in the myofibril drawn on the right side of the diagram.

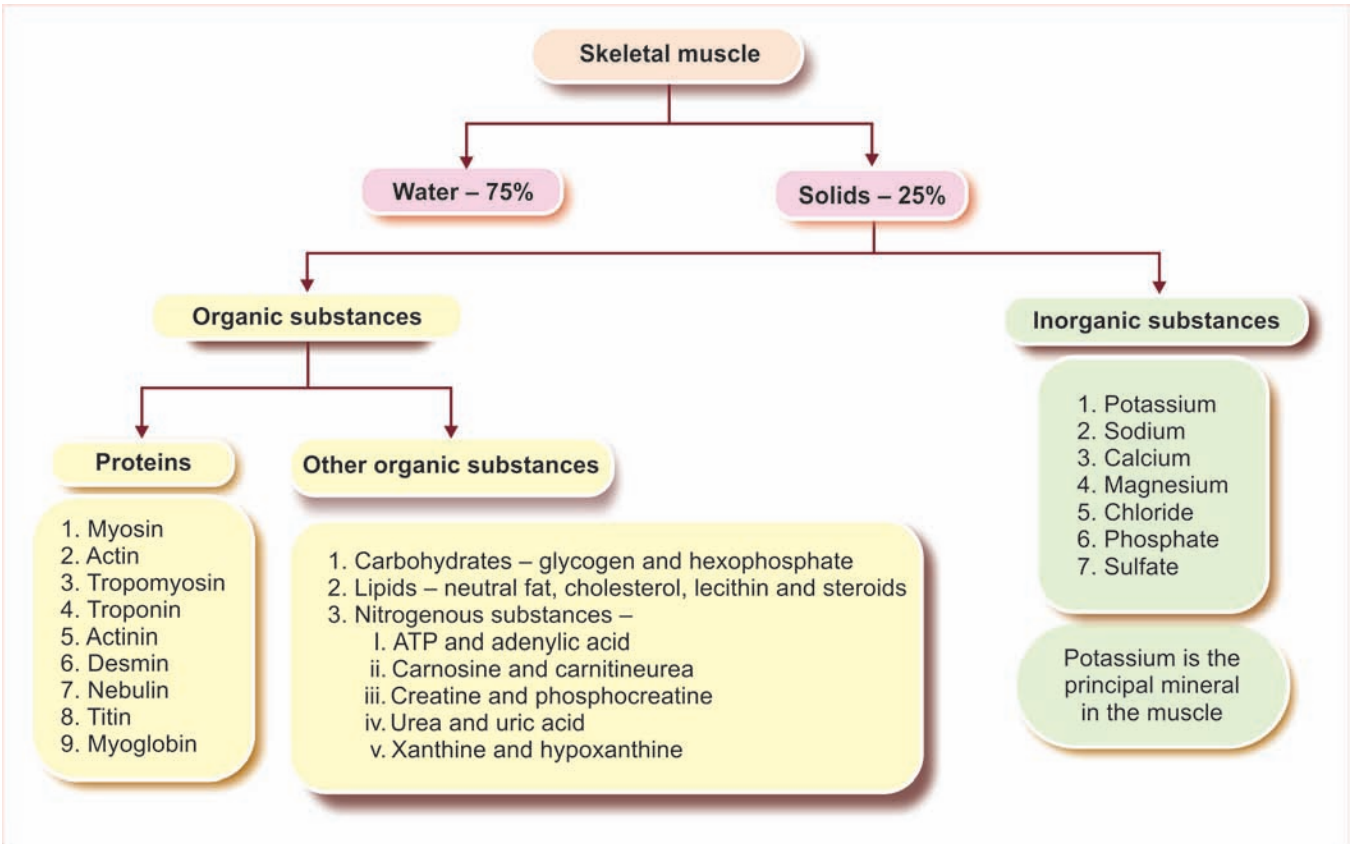


FIGURE 29.10: Composition of skeletal muscle

When the muscle is stretched, the titin unfolds itself. However, if the stretching is more, it offers resistance and protects the sarcomere from overstretching.

5. **Dystrophin,** a rod-shaped large protein that connects actin filament to **dystroglycan.** Dystroglycan is a transmembrane protein, present in the sarcolemma. Dystrophin and dystroglycan form dystrophin-dystroglycan or dystrophin-glycoprotein complex.

■ SARCOTUBULAR SYSTEM

Sarcotubular system is a system of membranous structures in the form of vesicles and tubules in the sarcoplasm of the muscle fiber. It surrounds the myofibrils embedded in the sarcoplasm (Fig. 29.9).

■ STRUCTURES CONSTITUTING THE SARCOTUBULAR SYSTEM

Sarcotubular system is formed mainly by two types of structures:

1. T-tubules
2. L-tubules or sarcoplasmic reticulum.

T-Tubules

T-tubules or transverse tubules are narrow tubules formed by the invagination of the sarcolemma. These tubules penetrate all the way from one side of the muscle fiber to an another side. That is, these tubules penetrate the muscle cell through and through. Because of their origin from sarcolemma, the T-tubules open to the exterior of the muscle cell. Therefore, the ECF runs through their lumen.

L-Tubules or Sarcoplasmic Reticulum

L-tubules or longitudinal tubules are the closed tubules that run in long axis of the muscle fiber, forming **sarcoplasmic reticulum.** These tubules form a closed tubular system around each myofibril and do not open to exterior like T-tubules.

L-tubules correspond to the endoplasmic reticulum of other cells. At regular intervals, throughout the length of the myofibrils, the L-tubules dilate to form a pair of lateral sacs called terminal **cisternae.** Each pair of terminal cisternae is in close contact with T-tubule. The T-tubule along with the cisternae on either side is called the triad of skeletal muscle.

In human skeletal muscle, the triads are situated at the junction between 'A' band and 'I' band. Calcium ions are stored in L-tubule and the amount of calcium ions is more in cisternae.

■ FUNCTIONS OF SARCOTUBULAR SYSTEM

Function of T-Tubules

T-tubules are responsible for rapid transmission of impulse in the form of action potential from sarcolemma to the myofibrils. When muscle is stimulated, the action potential develops in sarcolemma and spreads through it. Since T-tubules are the continuation of sarcolemma, the action potential passes through them and reaches the interior of the muscle fiber rapidly.

Function of L-Tubules

L-tubules store a large quantity of calcium ions. When action potential reaches the cisternae of L-tubule, the calcium ions are released into the sarcoplasm. Calcium ions trigger the processes involved in contraction of the muscle. The process by which the calcium ions cause contraction of muscle is called excitation-contraction coupling.

■ COMPOSITION OF MUSCLE

Skeletal muscle is formed by 75% of water and 25% of solids. Solids are 20% of proteins and 5% of organic substances other than proteins and inorganic substances (Fig. 29.10).

Among the proteins, the first eight proteins are already described in this chapter. **Myoglobin** is present in sarcoplasm. It is also called myohemoglobin. Its function is similar to that of hemoglobin, that is, to carry oxygen. It is a conjugated protein with a molecular weight of 17,000.

Properties of Skeletal Muscle

Chapter 3

EXCITABILITY

DEFINITIONS

Excitability

Excitability is defined as the reaction or response of a tissue to irritation or stimulatiosn. It is a physicochemical change.

Stimulus

Stimulus is the change in environment. It is defined as an agent or influence or act, which causes the response in an excitable tissue.

TYPES OF STIMULUS

Stimuli, which can excite the tissue are of four types :

1. Mechanical stimulus (pinching)
2. Electrical stimulus (electric shock)
3. Thermal stimulus (applying heated glass rod or ice piece)
4. Chemical stimulus (applying chemical substances like acids).

Electrical stimulus is commonly used for experimental purposes because of the following reasons:

i. It can be handled easily
ii. Intensity (strength) of stimulus can be easily adjusted
iii. Duration of stimulus can be easily adjusted
iv. Stimulus can be applied to limited (small) area on the tissues
v. Damage caused to tissues is nil or least.

QUALITIES OF STIMULUS

To excite a tissue, the stimulus must possess two characters:

1. Intensity or strength
2. Duration.

1. *Intensity*

Intensity or strength of a stimulus is of five types:

i. Subminimal stimulus
ii. Minimal stimulus
iii. Submaximal stimulus
iv. Maximal stimulus
v. Supramaximal stimulus.

Stimulus whose strength (or voltage) is sufficient to excite the tissue is called threshold or liminal or minimal stimulus. Other details are given under the heading 'Factors affecting force of contraction' in this chapter.

2. *Duration*

Whatever may be the strength of the stimulus, it must be applied for a minimum duration to excite the tissue. However, the duration of a stimulus depends upon the strength of the stimulus. For a weak stimulus, the duration is longer and for a stronger stimulus, the duration is shorter. The relationship between the strength and duration of stimulus is demonstrated by means of excitability curve or strength-duration curve.

■ EXCITABILITY CURVE OR STRENGTH-DURATION CURVE

Excitability curve is the graph that demonstrates the exact relationship between the strength and the duration of a stimulus. So, it is also called the strength-duration curve (Fig. 30.1).

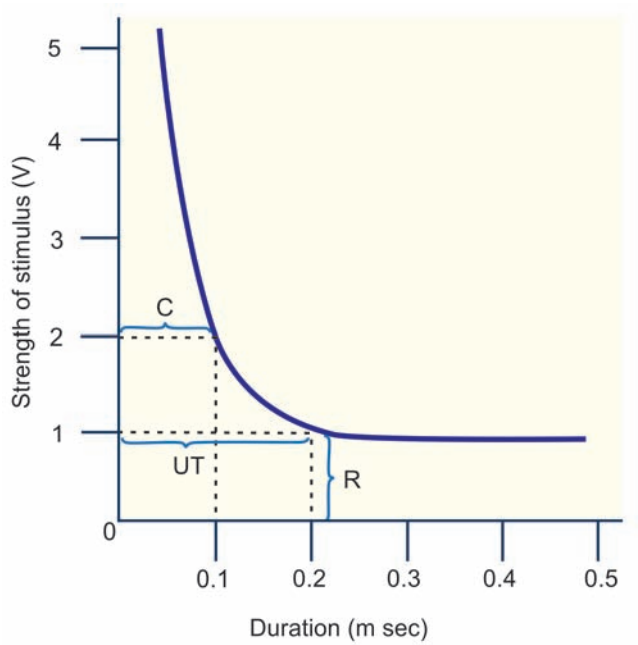


FIGURE 30.1: Strength–duration curve. R = Rheobase, UT = Utilization time, C = Chronaxie.

Method to Obtain the Curve

In this curve, the strength of the stimulus is plotted (in volts) vertically and the duration (in milliseconds) horizontally.

To start with, a stimulus with higher strength or voltage (4 or 5 volt) is applied. The minimum duration, taken by the stimulus with particular strength to excite the tissue is noted. The strength and duration are plotted in the graph. Then, the strength of the stimulus is decreased and the duration is determined. Like this, the voltage is decreased gradually and the duration is determined every time. All the results are plotted and the curve is obtained.

Characteristic Features of the Curve

The shape of the curve is similar in almost all the excitable tissues. Following are the important points to be observed in the excitability curve:

1. Rheobase
2. Utilization time
3. Chronaxie.

1. *Rheobase*

Rheobase is the minimum strength (voltage) of stimulus, which can excite the tissue. The voltage below this cannot excite the tissue, whatever may be the duration of the stimulus.

2. *Utilization Time*

Utilization time is the minimum time required for rheobasic strength of stimulus (threshold strength) to excite the tissue.

3. *Chronaxie*

Chronaxie is the minimum time required for a stimulus with double the rheobasic strength (voltage) to excite the tissue.

Importance of chronaxie

Measurement of chronaxie determines the excitability of the tissues. It is used to compare the excitability in different tissues. Longer the chronaxie, lesser is the excitability.

Normal chronaxie

In human skeletal muscles : 0.08 to 0.32 milliseconds.
In frog skeletal muscle : 3 milliseconds.

Variations in chronaxie

Chronaxie is:

1. Ten times more in skeletal muscles of infants than in the skeletal muscles of adults

2. Shorter in red muscles than in pale muscles
3. Shorter in **warm-blooded (homeothermic)** animals than in **cold-blooded (poikilothermic)** animals
4. Shortened during increased temperature and prolonged during cold temperature
5. Longer in paralyzed muscles than in normal muscle
6. Prolonged gradually during progressive neural diseases.

■ CONTRACTILITY

Contractility is the response of the muscle to a stimulus. Contraction is defined as the internal events of muscle with change in either length or tension of the muscle fibers.

■ TYPES OF CONTRACTION

Muscular contraction is classified into two types based on change in the length of muscle fibers or tension of the muscle:

1. Isotonic contraction
2. Isometric contraction.

1. *Isotonic Contraction*

Isotonic contraction is the type of muscular contraction in which the tension remains the same and the length of the muscle fiber is altered (iso = same: tonic = tension).

Example: Simple flexion of arm, where shortening of muscle fibers occurs but the tension does not change.

2. *Isometric Contraction*

Isometric contraction is the type of muscular contraction in which the length of muscle fibers remains the same and the tension is increased.

Example: Pulling any heavy object when muscles become stiff and strained with increased tension but the length does not change.

■ SIMPLE MUSCLE CONTRACTION OR TWITCH OR CURVE

The contractile property of the muscle is studied by using **gastrocnemius-sciatic preparation** from frog. It is also called muscle-nerve preparation.

When the stimulus with threshold strength is applied, the muscle contracts and then relaxes. These activities are recorded graphically by using suitable instruments. The contraction is recorded as upward deflection from the base line. And, relaxation is recorded as downward deflection back to the base line (Fig. 30.2).

Simple contraction of the muscle is called simple muscle twitch and the graphical recording of this is called simple muscle curve.

Important Points in Simple Muscle Curve

Four points are to be observed in simple muscle curve:

1. Point of stimulus (PS): The time when the stimulus is applied.
2. Point of contraction (PC): The time when muscle begins to contract.
3. Point of maximum contraction (PMC): The point up to which the muscle contracts. It also indicates the beginning of relaxation of the muscle.
4. Point of maximum relaxation (PMR): The point when muscle relaxes completely.

Periods of Simple Muscle Curve

All the four points mentioned above divide the entire simple muscle curve into three periods:

1. Latent period (LP)
2. Contraction period (CP)
3. Relaxation period (RP).

1. *Latent period*

Latent period is the time interval between the point of stimulus and point of contraction. The muscle does not show any mechanical activity during this period.

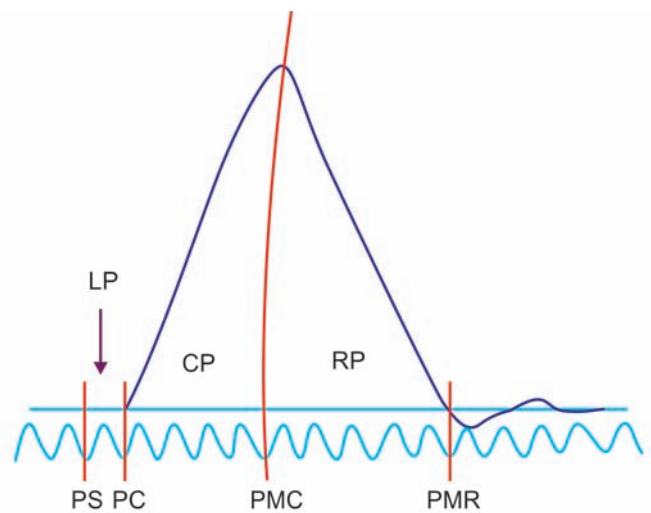


FIGURE 30-2: Isotonic simple muscle curve
PS = Point of stimulus
PC = Point of contraction
PMC = Point of maximum contraction
PMR = Point of maximum relaxation
LP = Latent period (0.01 sec)
CP = Contraction period (0.04 sec)
RP = Relaxation period (0.05 sec)

2. *Contraction period*

Contraction period is the interval between point of contraction and point of maximum contraction. Muscle contracts during this period.

3. *Relaxation period*

Relaxation period is the interval between point of maximum contraction and point of maximum relaxation. The muscle relaxes during this period.

Duration of different periods in a typical simple muscle curve:

Latent period	:	0.01 second
Contraction period	:	0.04 second
Relaxation period	:	0.05 second
Total twitch period	:	0.10 second

Contraction period is always shorter than relaxation period. It is because, the contraction is an active process and relaxation is a passive process.

Causes of Latent Period

1. Latent period is the time taken by the impulse to travel along the nerve from place of stimulation to muscle.
2. It is the time taken for the onset of initial chemical changes in the muscle.
3. It is due to the delay in the conduction of impulse at the neuromuscular junction.
4. It is due to the resistance offered by viscosity of the muscle.
5. It is also due to the inertia of the recording instrument.

Variations in Latent Period

Latent period is not constant. It varies even in physiological conditions. It decreases in high temperature. It increases in low temperature, during fatigue and with increase in weight.

■ CONTRACTION TIME – RED MUSCLE AND PALE MUSCLE

Contraction time or total twitch period varies from species to species. It is less in homeothermic animals than in poikilothermic animals. In the same animal, it varies in different groups of muscles.

Based on contraction time, the skeletal muscles are classified into two types:

1. Red muscles
2. Pale muscles.

Similarly, depending upon contraction time and myosin ATPase activity the muscle fibers are also divided into two types:

1. Type I fibers or slow fibers or slow twitch fibers, which have small diameter.
2. Type II fibers or fast fibers or fast twitch fibers, which have large diameter.

Most of the skeletal muscles in human beings contain both the types of fibers.

Red Muscles

Muscles, which contain large quantity of myoglobin are called red muscles. These muscles are also called **slow muscles** or slow twitch muscles. Red muscles have large number of type I fibers. The contraction time is longer in this type of muscles.

Example: Back muscles and gastrocnemius muscles.

Pale Muscles

Muscles, which contain less quantity of myoglobin are called pale muscles or white muscles. These muscles are also called **fast muscles** or fast twitch muscles. Pale muscles have large number of type II fibers. Contraction time is shorter in this type of muscles.

Examples: Hand muscles and ocular muscles.

Characteristic features of red and pale muscles are given in Table 30.1.

■ FACTORS AFFECTING FORCE OF CONTRACTION

Force of contraction of the skeletal muscle is affected by the following factors:

1. Strength of stimulus
2. Number of stimulus
3. Temperature
4. Load.

1. *Effect of Strength of Stimulus*

When the muscle is stimulated by stimuli with different strength (voltage of current), the force of contraction also differs.

Types of strength of stimulus

Strength of stimulus is of five types:

i. *Subminimal or subliminal stimulus:* It is less than minimal strength and does not produce any response in the muscle if applied once.

TABLE 30.1: Features of red and pale muscles

	Red (slow) muscle	Pale (fast) muscle
1.	Type I fibers are more	Type II fibers are more
2.	Myoglobin content is high. So, it is red	Myoglobin content is less. So, it is pale
3.	Sarcoplasmic reticulum is less extensive	Sarcoplasmic reticulum is more extensive
4.	Blood vessels are more extensive	Blood vessels are less extensive
5.	Mitochondria are more in number	Mitochondria are less in number
6.	Response is slow with long latent period	Response is rapid with short latent period
7.	Contraction is less powerful	Contraction is more powerful
8.	This muscle is involved in prolonged and continued activity as it undergoes sustained contraction	This muscle is not involved in prolonged and continued activity as it relaxes immediately
9.	Fatigue occurs slowly	Fatigue occurs quickly
10.	Depends upon cellular respiration for ATP production	Depends upon glycolysis for ATP production

ii. *Minimal stimulus, threshold stimulus or liminal stimulus:* It is the least strength of stimulus at which minimum force of contraction is produced.
iii. *Submaximal stimulus:* It is more than minimal and less than maximal strength of stimulus. It produces more force of contraction than minimal stimulus.
iv. *Maximal stimulus:* It produces almost the maximum force of contraction.
v. *Supramaximal stimulus:* It produces the maximum force of contraction. Beyond this, the force of contraction cannot be increased.

2. *Effect of Number of Stimulus*

Contractility of the muscle varies, depending upon the number of stimuli. If a single stimulus is applied, muscle contracts once (simple muscle twitch). Two or more than two (multiple) stimuli produce two different effects.

Effects of two successive stimuli

When two stimuli are applied successively to a muscle, three different effects are noticed depending upon the interval between the two stimuli (Fig. 30.3):

i. Beneficial effect
ii. Superposition or wave summation
iii. Summation effect.

i. *Beneficial Effect*

When two successive stimuli are applied to the muscle in such a way that the second stimulus falls after the relaxation period of the first curve, two separate curves are obtained and the force of second contraction is greater than that of first one. This is called beneficial effect.

Cause for beneficial effect

During first contraction, the temperature increases. It decreases the viscosity of muscle. So, the force of second contraction is more.

ii. *Superposition*

While applying two successive stimuli, if the second stimulus falls during relaxation period of first twitch, two curves are obtained. However, the first curve is superimposed by the second curve. This is called superposition or superimposition or **incomplete summation.** Here also, the second curve is bigger than the first curve because of beneficial effect.

iii. *Summation*

If second stimulus is applied during contraction period, or during second half of latent period, the two contractions are summed up and a single curve is obtained. This is called summation curve or complete summation curve.

Summation curve is different from the simple muscle curve because, the amplitude of the summation curve is greater than that of simple muscle curve. This is due to the summation of two contractions to give rise to one single curve. Base of the summation curve is also broader than that of the simple muscle curve.

Effects of multiple stimuli

In a muscle-nerve preparation, the multiple stimuli cause two types of effects depending upon the frequency of stimuli:

i. Fatigue
ii. Tetanus.

i. *Fatigue*

Definition

Fatigue is defined as the decrease in muscular activity due to repeated stimuli. When stimuli are applied repeatedly, after some time, the muscle does not show any response to the stimulus. This condition is called fatigue.

Fatigue curve

When the effect of repeated stimuli is recorded continuously, the amplitude of first two or three contractions increases. It is due to the beneficial effect. Afterwards, the force of contraction decreases gradually. It is shown by gradual decrease in the amplitude of the curves. All the periods are gradually prolonged. Just before fatigue occurs, the muscle does not relax completely. It remains in a partially contracted state. This state is called **contracture** or **contraction remainder** (Fig. 30.4).

Causes for fatigue

a. Exhaustion of acetylcholine in motor endplate
b. Accumulation of metabolites like lactic acid and phosphoric acid
c. Lack of nutrients like glycogen
d. Lack of oxygen.

Site (seat) of fatigue

In the muscle-nerve preparation of frog, neuromuscular junction is the first seat of fatigue. It is proved by direct stimulation of fatigued muscle. Fatigued muscle gives response if stimulated directly. However, the force of contraction is less and the contraction is very slow. Second seat of fatigue is the muscle. And the nerve cannot be fatigued.

In the intact body, the sites of fatigue are in the following order:

a. Betz (pyramidal) cells in cerebral cortex
b. Anterior gray horn cells (motor neurons) of spinal cord
c. Neuromuscular junction
d. Muscle.

Recovery of the muscle after fatigue

Fatigue is a reversible phenomenon. Fatigued muscle recovers (Fig. 30.5) if given rest and nutrition. For this, the muscle is washed with saline.

Causes of recovery

a. Removal of metabolites
b. Formation of acetylcholine at the neuromuscular junction
c. Re-establishment of normal polarized state of the muscle
d. Availability of nutrients
e. Availability of oxygen.

The recovered muscle differs from the fresh resting muscle by having acid reaction. The fresh resting muscle is alkaline. But the muscle, recovered from fatigue is acidic. So it relaxes slowly.

In the intact body, all the processes involved in recovery are achieved by circulation itself. In human beings, fatigue is recorded by using Mosso's ergograph.

ii. *Tetanus*

Definition

Tetanus is defined as the sustained contraction of muscle due to repeated stimuli with high frequency. When the multiple stimuli are applied at a higher frequency in such a way that the successive stimuli fall during contraction period of previous twitch, the muscle remains in state of tetanus. It relaxes only after the stoppage of stimulus or when the muscle is fatigued.

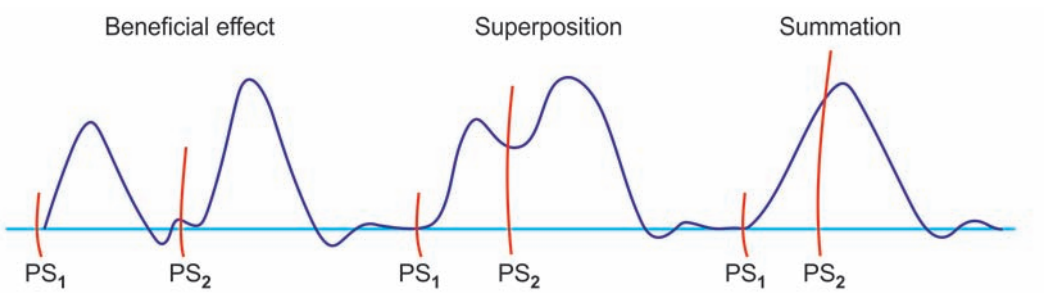


FIGURE 30.3: Effects of two successive stimuli. PS_1 = Point of first stimulus, PS_2 = Point of second stimulus.

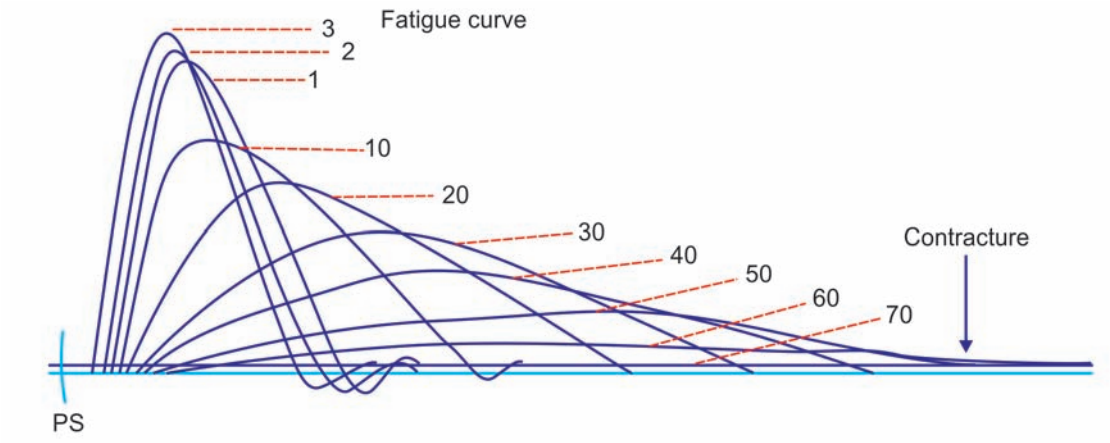


FIGURE 30.4: Fatigue curve. PS = Point of stimulus.

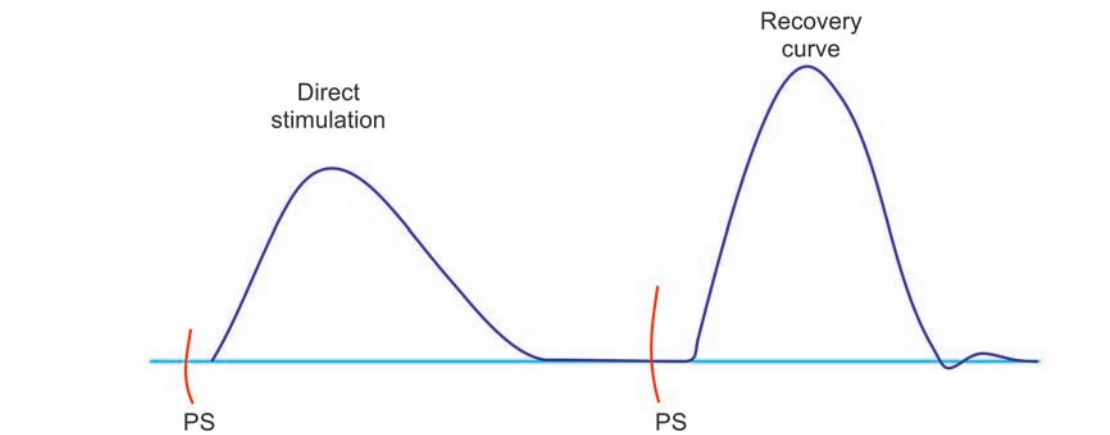


FIGURE 30.5: Recovery curve. PS = Point of stimulus.

Tetanus and genesis of tetanus curves

Genesis of tetanus and tetanus in frog's muscle is recorded by using the instrument called vibrating interruptor. It is used to adjust the frequency of stimuli as 5, 10, 15, 20, 25, 30 and 35/second. While increasing the frequency, fusion of contractions increases every time and finally complete tetanus occurs (Fig. 30.6). Nowadays, electronic stimulator is used. By using this instrument, the stimuli with different strength and frequency are obtained.

When the frequency of stimuli is not sufficient to cause tetanus, the fusion of contractions is not complete. It is called incomplete tetanus or clonus.

Frequency of stimuli necessary to cause tetanus and clonus

In frog gastrocnemius-sciatic preparation, the frequency of stimuli required to cause tetanus is 40/second and for clonus it is 35/second.

In gastrocnemius muscle of human being, the frequency required to cause tetanus is 60/second. And for clonus, the frequency of stimuli necessary is 55/second.

Pathological Tetanus

Sustained contraction of muscle due to repeated stimuli of high frequency is usually called **physiological tetanus.** It is distinct from pathological tetanus, which refers to the spastic contraction of the different muscle groups in pathological conditions. This disease is caused by bacillus ***Clostridium tetani*** found in the soil, dust and manure. The bacillus enters the body through a cut, wound or puncture caused by objects like metal pieces, metal nails, pins, wood splinters, etc.

This disease affects the nervous system and its common features are **muscle spasm** and **paralysis.** The first appearing symptom is the spasm of the jaw

muscles resulting in locking of jaw. Therefore, tetanus is also called **lockjaw disease.** The manifestations of tetanus are due to a toxin secreted by the bacteria. If timely treatment is not provided, the condition becomes serious and it may even lead to death.

Treppe or Staircase Phenomenon

Treppe or staircase phenomenon is the gradual increase in force of contraction of muscle when it is stimulated repeatedly with a maximal strength at a low frequency. It is due to beneficial effect. Treppe is distinct from summation of contractions and tetanus.

3. *Effect of Variations in Temperature*

If the temperature of muscle is altered, the force of contraction is also affected (Fig. 30.7).

Warm temperature

At warm temperature of about 40°C, the force of muscle contraction increases and all the periods are shortened because of the following reasons:

i. Excitability of muscle increases
ii. Chemical processes involved in muscular contraction are accelerated
iii. Viscosity of muscle decreases.

Cold temperature

At cold temperature of about 10°C, the force of contraction decreases and all the periods are prolonged because of the following reasons:

i. Excitability of muscle decreases
ii. Chemical processes are slowed or delayed
iii. Viscosity of the muscle increases.

High or hot temperature – Heat rigor

At high temperature above 60°C, the muscle develops heat rigor. Rigor refers to shortening and stiffening of muscle fibers. Heat rigor is the rigor that occurs due to increased temperature. It is an irreversible phenomenon.

Cause of heat rigor is the coagulation of muscle proteins, actin and myosin.

Other types of rigors

i. *Cold rigor:* Due to the exposure to severe cold. It is a reversible phenomenon.
ii. *Calcium rigor:* Due to increased calcium content. It is also reversible.
iii. *Rigor mortis:* Develops after death.

Rigor mortis

Rigor mortis refers to a condition of the body after death, which is characterized by stiffness of muscles and joints (Latin word 'rigor' means stiff). It occurs due to stoppage of aerobic respiration, which causes changes in the muscles.

Cause of rigor mortis

Soon after death, the cell membrane becomes highly permeable to calcium. So a large number of calcium ions

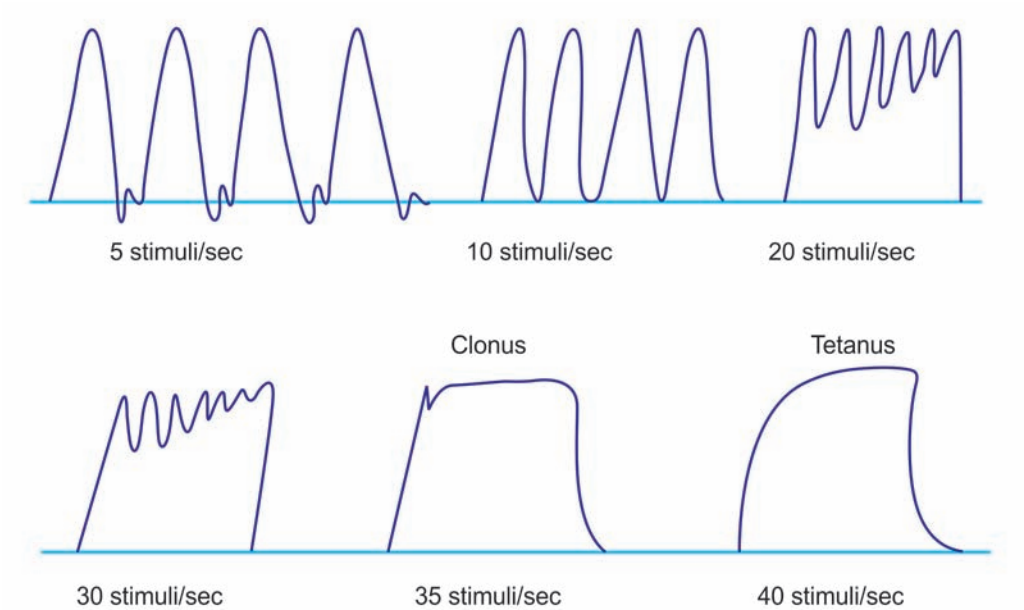


FIGURE 30.6: Genesis of tetanus and tetanus curves

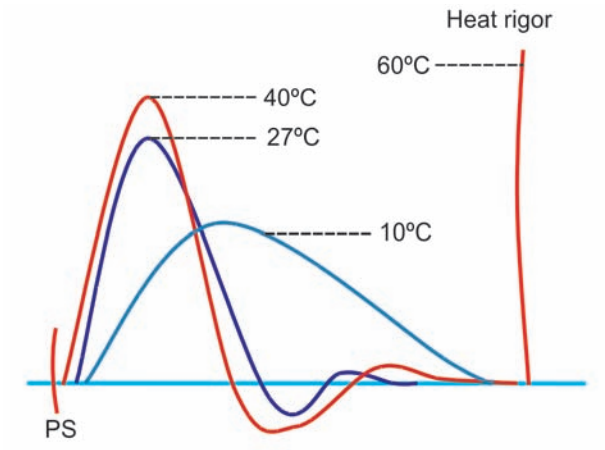


FIGURE 30.7: Effects of variations of temperature

enters the muscle fibers and promotes the formation of actomyosin complex resulting in contraction of the muscles.

Few hours after death, all the muscles of body undergo severe contraction and become rigid. The joints also become stiff and locked.

Normally for relaxation, the muscle needs to drive out the calcium, which requires ATP. But during continuous muscular contraction and other cellular processes after death, the ATP molecules are completely exhausted. New ATP molecules cannot be produced because of lack of oxygen. So in the absence of ATP, the muscles remain in contracted state until the onset of decomposition.

Medicolegal importance of rigor mortis

Rigor mortis is useful in determining the time of death. Onset of stiffness starts between 10 minutes and 3 hours after death depending upon condition of the body and environmental temperature at the time of death. If the body is active or the environmental temperature is high at the time of death, the stiffness sets in quickly.

The stiffness develops first in facial muscles and then spreads to other muscles. The maximum stiffness occurs around 12 to 24 hours after death. The stiffness of muscles and joints continues for 1 to 3 days.

Afterwards, the decomposition of the general tissues starts. Now the lysosomal intracellular hydrolytic enzymes like **cathepsins** and **calpains** are released. These enzymes hydrolyze the muscle proteins, actin and myosin resulting in breakdown of actomyosin complex. It relieves the stiffness of the muscles. This process is known as **resolution of rigor.**

4. *Effect of Load*

Load acting on muscle is of two types:

i. After load
ii. Free load.

After load

After load is the load, that acts on the muscle after the beginning of muscular contraction. Example of after load is lifting any object from the ground. The load acts on muscles of arm only after lifting the object off the ground, i.e. only after beginning of the muscular contraction.

Free load

Free load is the load, which acts on the muscle freely, even before the onset of contraction of the muscle. It is otherwise called fore load. Example of free load is filling water from a tap by holding the bucket in hand.

Free load Vs after load

Free load is more beneficial (advantageous) since force of contraction and work done by the muscles are greater in free-loaded condition than in after-loaded condition. It is because, in free-loaded condition, the muscle fibers are stretched and the initial length of muscle fibers is increased. It facilitates the force of contraction. This is in accordance with Frank-Starling law.

Frank-Starling law

Frank-Starling law states that the force of contraction is directly proportional to the initial length of muscle fibers within physiological limits.

Experiment to prove Frank-Starling law

Frank-Starling law can be proved by using the muscle-nerve preparation of frog. First, one simple muscle curve is recorded with 10 g weight in after-loaded condition of the muscle (Fig. 30.8). Then, many contractions are recorded by increasing the weight everytime, until the muscle fails to lift the weight or till the curve becomes almost flat near the base line. The work done by the muscle is calculated for every weight (Fig. 30.9).

Effects of increasing the weight in after-loaded condition are:

i. Force of contraction decreases gradually
ii. Latent period prolongs
iii. Contraction and relaxation periods shorten (Fig. 30.8).

Afterwards, the muscle (with weight added for last contraction) in after-loaded condition, is brought to the free-loaded condition and stimulated. Now, the muscle

contracts and a curve is recorded. The work done by the muscle is calculated.

Work done in free-loaded condition is more than in after-loaded condition. This proves Frank-Starling law, i.e. the force of contraction is directly proportional to the initial length of muscle fiber.

Work done by the muscle

Work done is calculated by the formula:

Work done = W × h

Where, W = Weight lifted by the muscle

h = Height up to which the weight is lifted

'h' is determined by the formula

$$h = \frac{l \times H}{L}$$

This formula is derived as follows:

$$\Delta ABC = \Delta DEC$$

$$\frac{BC}{EC} = \frac{AB}{DE} \text{ or } \frac{L}{l} = \frac{H}{h}$$

$$h \times L = l \times H$$

$$h = \frac{l \times H}{L}$$

L = Length between fulcrum and writing point

l = Length between fulcrum and point where weight is added

H = Height of the curve

h = Height up to which the weight is lifted

So work done by the muscle =

$$W \times \frac{l \times H}{L} \text{ g cm}$$

Work done is expressed as ergs or g cm.

Optimum load

Optimum load is the load at which the work done by the muscle is maximum.

■ LENGTH-TENSION RELATIONSHIP

Tension or force developed in the muscle during resting condition and during contraction varies with the length of the muscle.

Tension developed in the muscle during resting condition is known as **passive tension.** Tension developed in the muscle during isometric contraction is called **total tension.**

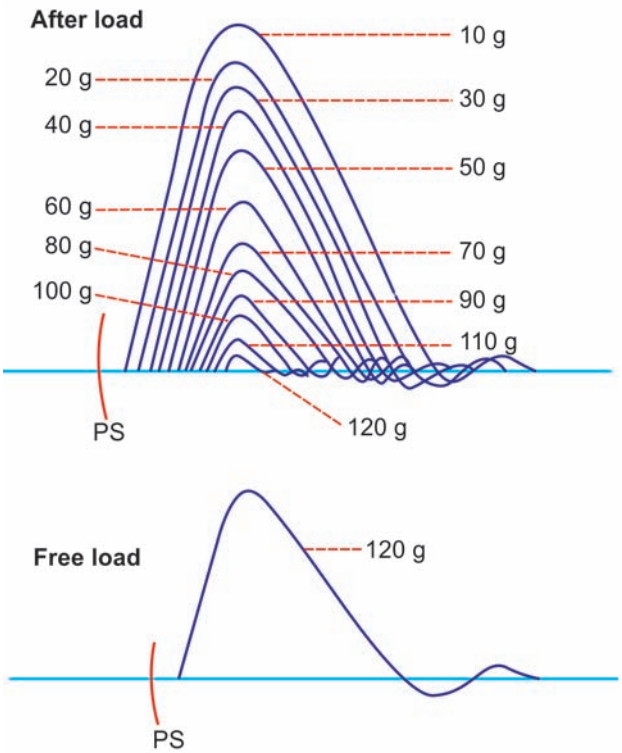


FIGURE 30.8: Effect of after load and free load. PS = Point of stimulus. In free-loaded condition, the force of contraction is greater than in after-loaded condition with the same weight.

Active Tension

Difference between the passive tension and total tension at a particular length of the muscle is called **active tension.** Active tension is considered as the real tension that is generated in the muscle during contractile process. It can be determined by the length-tension curve.

Length-Tension Curve

Length-tension curve is the curve that determines the relationship between length of muscle fibers and the tension developed by the muscle. It is also called **length-force curve.** The curve is obtained by using frog gastrocnemius-sciatic preparation. Muscle is attached to micrometer on one end and to a force transducer on other end. Muscle is not allowed to shorten because of its attachment on both the ends (Fig. 30.10).

A micrometer is used to set length of the muscle fibers. Force transducer is connected to a polygraph. Polygraph is used to measure the tension developed by the muscle during isometric contraction.

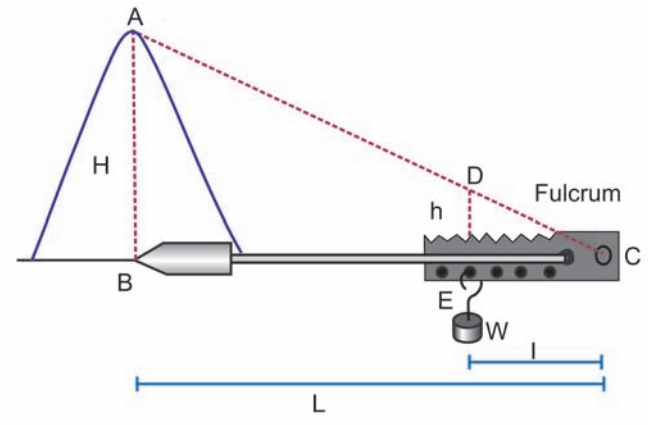


FIGURE 30.9: Work done by the muscle

L = Length between fulcrum and writing point
l = Length between fulcrum and point where weight is added
H = Height of the curve
h = Height up to which the weight is lifted
W = Weight

To begin with, the minimum length of the muscle is set by using the micrometer. The passive tension is determined by using force transducer. Then the muscle is stimulated and total tension is determined. From these two values the active tension is calculated. Then the length of muscle is increased gradually. At every length, both passive tension and total tension are determined followed by calculation of active tension. All the values of active tension at different lengths are plotted to obtain the length-tension curve (Fig. 30.11). From the curve the resting length is determined.

Resting Length

Resting length is the length of the muscle at which the active tension is maximum. Active tension is proportional to the length of the muscle up to resting length. Beyond resting length, the active tension decreases.

Tension Vs Overlap of Myofilaments

Length-tension relationship is explained on the basis of sliding of actin filaments over the myosin filaments during muscular contraction. The active tension is proportional to overlap between actin and myosin filaments in the sarcomere and the number of cross bridges formed between actin and myosin filaments. When the length of the muscle is less than the resting length, there is increase in the overlap between the actin and myosin filaments and the number of cross bridges. The active tension gradually increases up to the resting length. During stretching of the muscle beyond resting length, there is reduction in the overlap between the actin and myosin filaments and the number of cross bridges. And the active tension starts declining beyond resting length.

■ REFRACTORY PERIOD

Refractory period is the period at which the muscle does not show any response to a stimulus. It is because already one action potential is in progress in the muscle during this period. The muscle is unexcitable to further stimulation until it is repolarized.

Refractory period is of two types.

1. Absolute refractory period
2. Relative refractory period

1. *Absolute Refractory Period*

Absolute refractory period is the period during which the muscle does not show any response at all, whatever may be the strength of stimulus.

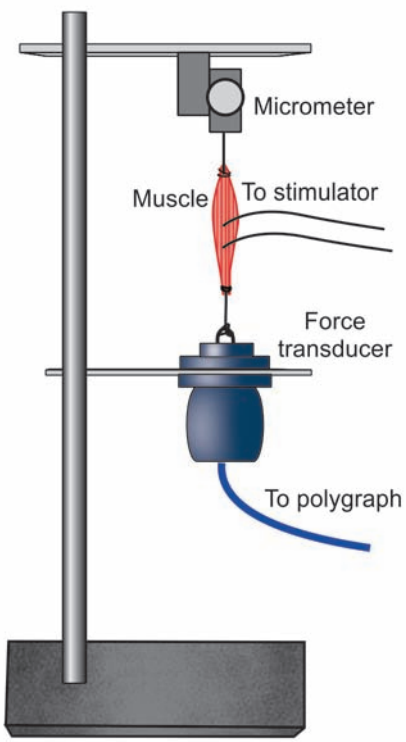


FIGURE 30.10: Experimental setup to measure the tension developed in the muscle

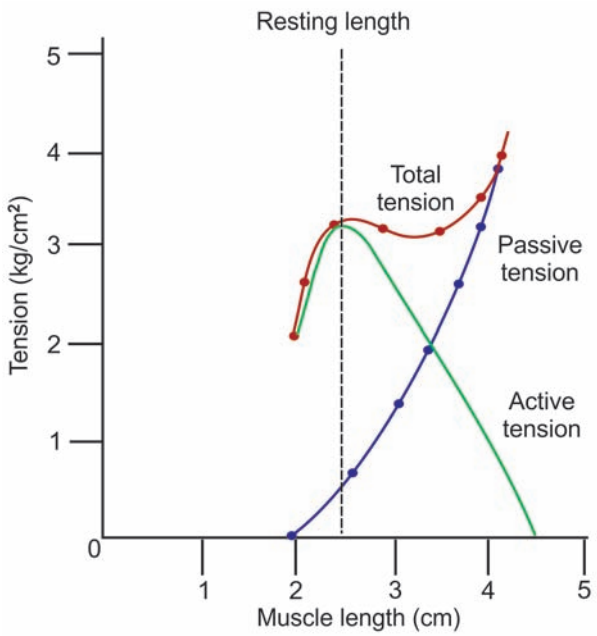


FIGURE 30.11: Length-tension curve

2. *Relative Refractory Period*

Relative refractory period is the period, during which the muscle shows some response if the strength of stimulus is increased to maximum.

Refractory Period in Skeletal Muscle

In skeletal muscle, whole of the latent period is refractory period. The absolute refractory period falls during first half of latent period (0.005 sec). And, relative refractory period extends during second half of latent period (0.005 sec). Totally, it is 0.01 sec.

Refractory Period in Cardiac Muscle

In cardiac muscle, absolute refractory period extends throughout contraction period (0.27 sec). And, relative refractory period extends during first half of relaxation period (about 0.26 sec). Totally it is about 0.53 sec. Thus, the refractory period in cardiac muscle is very long compared to that of skeletal muscle.

Significance of long refractory period in cardiac muscle

Because of the long refractory period, cardiac muscle does not show:

i. Complete summation of contractions
ii. Fatigue
iii. Tetanus.

■ MUSCLE TONE

■ DEFINITION

Muscle tone is defined as continuous and partial contraction of the muscles with certain degree of vigor and tension. More details on muscle tone are given in .

■ MAINTENANCE OF MUSCLE TONE

In Skeletal Muscle

Maintenance of tone in skeletal muscle is neurogenic. It is due to continuous discharge of impulses from gamma motor neurons in anterior gray horn of spinal cord. The gamma motor neurons in spinal cord are controlled by higher centers in brain.

In Cardiac Muscle

In cardiac muscle, maintenance of tone is purely myogenic, i.e. the muscles themselves control the tone. The tone is not under nervous control in cardiac muscle.

In Smooth Muscle

In smooth muscle, tone is myogenic. It depends upon calcium level and number of cross bridges.

■ APPLIED PHYSIOLOGY – ABNORMALITIES OF MUSCLE TONE

Abnormalities of muscle tone are:

1. Hypertonia
2. Hypotonia
3. Myotonia.

Changes during Muscular Contraction

Chapter 4

INTRODUCTION

The muscle contracts when it is stimulated. Contraction of the muscle is a physical or mechanical event. In addition, several other changes occur in the muscle.

Changes taking place during muscular contraction:

1. Electrical changes
2. Physical changes
3. Histological (molecular) changes
4. Chemical changes
5. Thermal changes.

ELECTRICAL CHANGES DURING MUSCULAR CONTRACTION

Electrical events occur in the muscle during resting condition as well as active conditions. Electrical potential in the muscle during resting condition is called resting membrane potential.

Electrical changes that occur in active conditions, i.e. when the muscle is stimulated are together called action potential.

Electrical potentials in a muscle (or any living tissue) are measured by using a cathode ray oscilloscope or computerized polygraph.

RESTING MEMBRANE POTENTIAL

Resting membrane potential is defined as the electrical potential difference (voltage) across the cell membrane (between inside and outside of the cell) under resting condition.

It is also called membrane potential, transmembrane potential, transmembrane potential difference or transmembrane potential gradient.

When two electrodes are connected to a cathode ray oscilloscope through a suitable amplifier and placed over the surface of the muscle fiber, there is no potential difference, i.e. there is zero potential difference. But, if one of the electrodes is inserted into the interior of muscle fiber, potential difference is observed across the sarcolemma (cell membrane). There is negativity inside and positivity outside the muscle fiber. This potential difference is constant and is called resting membrane potential. The condition of the muscle during resting membrane potential is called **polarized state.** In human skeletal muscle, the resting membrane potential is –90 mV.

Ionic Basis of Resting Membrane Potential

Development and maintenance of resting membrane potential in a muscle fiber or a neuron are carried out by movement of ions, which produce ionic imbalance across the cell membrane. This results in the development of more positivity outside and more negativity inside the cell.

Ionic imbalance is produced by two factors:

1. Sodium-potassium pump
2. Selective permeability of cell membrane.

1. *Sodium-potassium pump*

Sodium and potassium ions are actively transported in opposite directions across the cell membrane by means of an electrogenic pump called sodium-potassium pump. It moves three sodium ions out of the cell and two potassium ions inside the cell by using energy from ATP. Since more positive ions (cations) are pumped outside than inside, a net deficit of positive ions occurs inside the cell. It leads to negativity inside and positivity outside the cell (Fig. 31.1). More details of this pump are given in Chapter 3.

2. *Selective permeability of cell membrane*

Permeability of cell membrane depends largely on the transport channels. The transport channels are selective for the movement of some specific ions. Their permeability to these ions also varies. Most of the channels are **gated channels** and the specific ions can move across the membrane only when these gated channels are opened.

Two types of channels are involved:

i. Channels for major anions like proteins
ii. Leak channels.

i. *Channels for major anions (negatively charged substances) like proteins*

Channels for some of the negatively charged large substances such as proteins, organic phosphate and sulfate compounds are absent or closed. So, such substances remain inside the cell and play a major role in the development and maintenance of negativity inside the cell (resting membrane potential).

ii. *Leak channels*

Leak channels are the passive channels, which maintain the resting membrane potential by allowing movement of positive ions (Na^+ and K^+) across the cell membrane.

Three important ions, sodium, chloride and potassium are unequally distributed across the cell membrane. Na^+ and Cl^- are more outside and K^+ is more inside.

Since, Cl^- channels are mostly closed in resting conditions Cl^- are retained outside the cell. Thus, only the positive ions, Na^+ and K^+ can move across the cell membrane.

Na^+ is actively transported (against the concentration gradient) out of cell and K^+ is actively transported (against the concentration gradient) into the cell. However, because of concentration gradient, Na^+ diffuses back into the cell through Na^+ leak channels and K^+ diffuses out of the cell through K^+ leak channels.

In resting conditions, almost all the K^+ leak channels are opened but most of the Na^+ leak channels are closed. Because of this, K^+, which are transported actively into the cell, can diffuse back out of the cell in an attempt to maintain the **concentration equilibrium.** But among the Na+, which are transported actively out of the cell, only a small amount can diffuse back into the cell. That means, in resting conditions, the passive K^+ efflux is much greater than the passive Na^+ influx. It helps in establishing and maintaining the resting membrane potential.

After establishment of the resting membrane potential (i.e. inside negativity and outside positivity), the efflux of K^+ stops in spite of concentration gradient.

It is because of two reasons:

i. Positivity outside the cell repels positive K+ and prevents further efflux of these ions
ii. Negativity inside the cell attracts positive K+ and prevents further leakage of these ions outside.

Importance of intracellular potassium ions

Concentration of K^+ inside the cell is about 140 mEq/L. It is almost equal to that of Na^+ outside. The high concentration of K^+ inside the cell is essential to check the negativity. Normally, the negativity (resting membrane potential) inside the muscle fiber is –90 mV and in a nerve fiber, it is –70 mV. It is because of the presence of negatively charged proteins, organic phosphates and sulfates, which cannot move out normally. Suppose if the K^+ is not present or decreased, the negativity increases

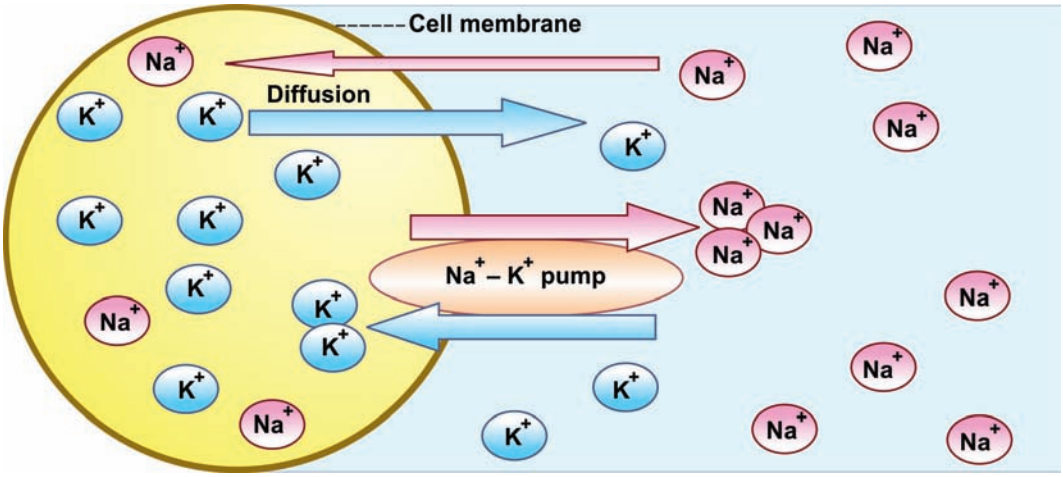


FIGURE 31.1: Development of resting membrane potential by sodium-potassium (Na^+-K^+) pump and diffusion of ions. Na^+-K^+ pump actively pumps three Na^+ outside and two K^+ into the cell. However, the diffusion of K^+ out of the cell is many times greater than the diffusion of Na^+ inside the cell because many of the K^+ leak channels are opened and many of the Na^+ leak channels are closed.

beyond –120 mV, which is called hyperpolarization. At this stage, the development of action potential is either delayed or does not occur.

■ ACTION POTENTIAL

Action potential is defined as a series of electrical changes that occur in the membrane potential when the muscle or nerve is stimulated.

Action potential occurs in two phases:

1. Depolarization
2. Repolarization.

Depolarization

Depolarization is the initial phase of action potential in which inside of the muscle becomes positive and outside becomes negative. That is, the polarized state (resting membrane potential) is abolished resulting in depolarization.

Repolarization

Repolarization is the phase of action potential in which the muscle reverses back to the resting membrane potential. That is, within a short time after depolarization the inside of muscle becomes negative and outside becomes positive. So, the polarized state of the muscle is re-established.

Properties of Action Potential

Properties of action potential are listed in Table 31.1.

■ ACTION POTENTIAL CURVE

Action potential curve is the graphical registration of electrical activity that occurs in an excitable tissue such as muscle after stimulation. It shows three major parts:

1. Latent period
2. Depolarization
3. Repolarization.

Resting membrane potential in skeletal muscle is –90 mV and it is recorded as a straight baseline (Fig. 31.2).

1. *Latent Period*

Latent period is the period when no change occurs in the electrical potential immediately after applying the stimulus. It is a very short period with duration of 0.5 to 1 millisecond.

Stimulus artifact

When a stimulus is applied, there is a slight irregular deflection of baseline for a very short period. This is called stimulus artifact. The artifact occurs because of the disturbance in the muscle due to leakage of current from stimulating electrode to the recording electrode. The stimulus artifact is followed by latent period.

2. *Depolarization*

Depolarization starts after the latent period. Initially, it is very slow and the muscle is depolarized for about 15 mV.

Firing level and depolarization

After the initial slow depolarization for 15 mV (up to –75 mV), the rate of depolarization increases suddenly. The point at which, the depolarization increases suddenly is called firing level.

Overshoot

From firing level, the curve reaches **isoelectric potential (zero potential)** rapidly and then shoots up (overshoots) beyond the zero potential **(isoelectric base)** up to +55 mV. It is called overshoot.

3. *Repolarization*

When depolarization is completed (+55 mV), the repolarization starts. Initially, the repolarization occurs rapidly and then it becomes slow.

Spike potential

Rapid rise in depolarization and the rapid fall in repolarization are together called spike potential. It lasts for 0.4 millisecond.

After depolarization or negative after potential

Rapid fall in repolarization is followed by a slow re-polarization. It is called after depolarization or negative after potential. Its duration is 2 to 4 milliseconds.

After hyperpolarization or positive after potential

After reaching the resting level (–90 mV), it becomes more negative beyond resting level. This is called after hyperpolarization or positive after potential. This lasts for more than 50 milliseconds. After this, the normal resting membrane potential is restored slowly.

Ionic Basis of Action Potential

Voltage gated Na^+ channels and the voltage gated K^+ channels play important role in the development of action potential.

During the onset of depolarization, voltage gated sodium channels open and there is slow influx of Na^+. When depolarization reaches 7 to 10 mV, the voltage gated Na^+ channels start opening at a faster rate. It is called Na^+ channel activation. When the firing level is reached, the influx of Na^+ is very great and it leads to overshoot.

But the Na^+ transport is short lived. It is because of rapid inactivation of Na^+ channels. Thus, the Na^+ channels open and close quickly. At the same time, the K^+ channels start opening. This leads to efflux of K^+ out of the cell, causing repolarization.

Unlike the Na^+ channels, the K^+ channels remain open for longer duration. These channels remain opened for few more milliseconds after completion of repolarization. It causes efflux of more number of K^+ producing more negativity inside. It is the cause for hyperpolarization.

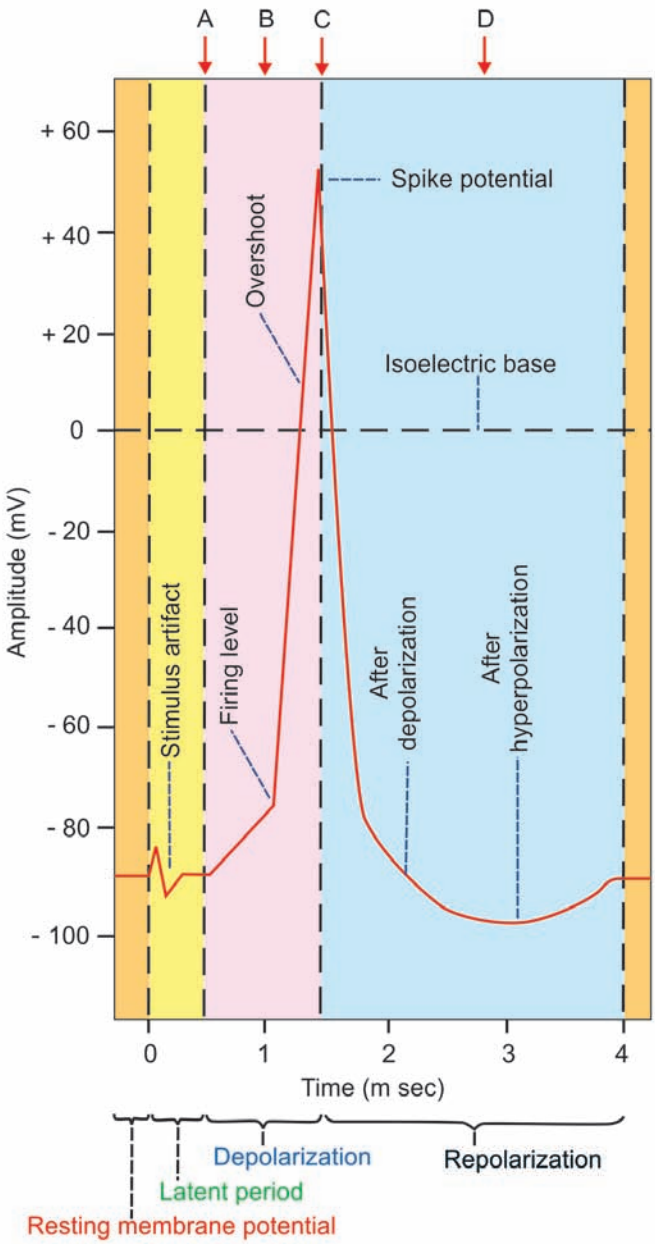


FIGURE 31.2: Action potential in a skeletal muscle
A = Opening of few Na^+ channels
B = Opening of many Na^+ channels
C = Closure of Na^+ channels and opening of K^+ channels
D = Closure of K^+ channels

■ MONOPHASIC, BIPHASIC AND COMPOUND ACTION POTENTIALS

Monophasic Action Potential

Monophasic action potential is the series of electrical changes that occur in a stimulated muscle or nerve fiber, which is recorded by placing one electrode on its surface and the other inside. It is characterized by a positive deflection. The action potential in the muscle discussed above belongs to this category.

Biphasic Action Potential

Biphasic or diphasic action potential is the series of electrical changes in a stimulated muscle or nerve fiber, which is recorded by placing both the recording electrodes on the surface of the muscle or nerve fiber. It is characterized by a positive deflection followed by an isoelectric pause and a negative deflection.

Recording of biphasic action potential

Biphasic action potential is recorded by extracellular electrodes, i.e. by placing both the recording electrodes on the surface of a nerve fiber or muscle. Figure 31.3 explains the biphasic action potential in an axon.

Sequence of events of biphasic action potential:

1. In resting state before stimulation, the potential difference between the two electrodes is zero. So the recording shows a baseline (Fig. 31.3A).
2. When the axon is stimulated at one end, the action potential (impulse) is generated and it travels towards the other end of an axon by passing through the recording electrodes. When the impulse reaches first electrode, the membrane under this electrode becomes depolarized (outside negative) but the membrane under second electrode is still in polarized state (outside positive). By convention, this is graphically recorded as an upward deflection (Fig. 31.3B).
3. When the impulse crosses and travels away from the first electrode, the membrane under this electrode is repolarized. Later when the impulse just travels in between the two electrodes (before reaching the second electrode) the potential difference between both the electrode falls to zero and the baseline is recorded (Fig. 31.3C)
4. When the impulse reaches the second electrode, the membrane under this electrode is depolarized (outside negative) and a negative deflection is recorded (Fig. 31.3D).
5. When the impulse travels away from second electrode, the membrane under this gets repolarized. Once again the potential difference between the two electrodes becomes zero and the graph shows the baseline (Fig. 31.3E). Since this recording shows both positive and negative components it is called biphasic action potential.

Effect of crushing or local anesthetics

When a small portion of axon between the two electrodes is affected by crushing or local anesthetics, the action potential cannot travel through this part of the axon. So, while recording the potential only a single deflection (monophasic) action potential is recorded (Fig. 31.4).

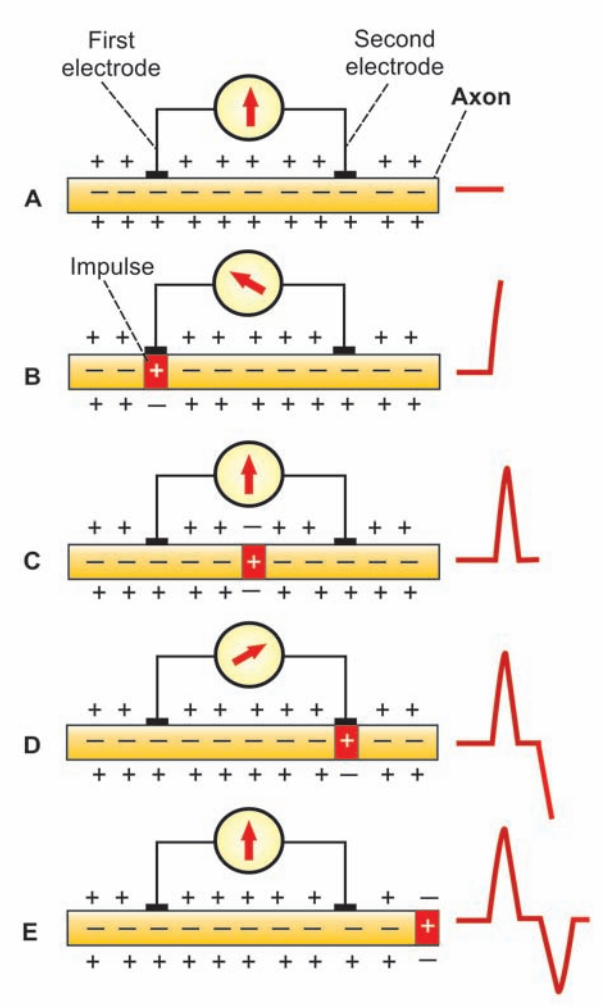


FIGURE 31.3: Biphasic action potential in an axon recorded by placing both the electrodes outside the axon
A = Resting state – zero potential
B = Depolarization of membrane under first electrode
C = Repolarization of membrane under first electrode followed by zero potential
D = Depolarization of membrane under second electrode
E = Repolarization of membrane under second electrode

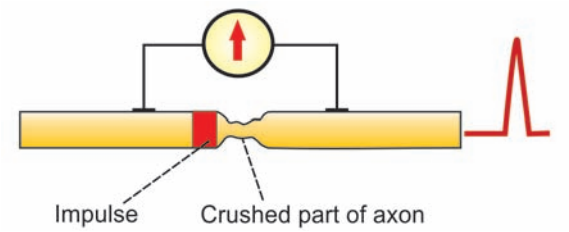


FIGURE 31.4: Monophasic action potential in a crushed axon

Compound Action Potential

Compound action potential (CAP) is the algebraic summation of all the action potentials produced by all the nerve fibers. Each nerve is made up of thousands of axons. While stimulating the whole nerve, all the nerve fibers are activated and produce action potential. The compound action potential is obtained by recording all the action potentials simultaneously.

■ GRADED POTENTIAL

Graded potential is a mild local change in the membrane potential that develops in receptors, synapse or neuromuscular junction when stimulated. It is also called graded membrane potential, graded depolarization or local potential. It is non-propagative and characterized by mild depolarization or **hyperpolarization.** Graded potential is distinct from the action potential and the properties of these two potentials are given in table 31.1.

In most of the cases, the graded potential is responsible for the generation of action potential. However, in some cases the graded potential hyperpolarizes the membrane potential (more negativity than resting membrane potential) and inhibits the generation of action potential (as in inhibitory synapses:.

Different Graded potentials

1. End plate potential in neuromuscular junction
2. Electronic potential in nerve fibers
3. Receptor potential
4. Excitatory postsynaptic potential
5. Inhibitory postsynaptic potential.

■ PATCH-CLAMP TECHNIQUE

Patch-clamp technique or patch clamping is the method to measure the ion currents across the biological membranes. This advanced technique in modern electrophysiology was established by Erwin Neher in 1992. Patch clamp is modified as voltage clamp to study the ion currents across the membrane of neuron.

TABLE 31.1: Properties of action potential and graded potential

Action Potential	Graded potential
Propagative	Non-propagative
Long-distance signal	Short-distance signal
Both depolarization and repolarization	Only depolarization or hyperpolarization
Obeys all-or-none law	Does not obey all-or-none law
Summation is not possible	Summation is possible
Has refractory period	No refractory period

Procedure

Patch-clamp experiments use mostly the cultured cells. The cells isolated from the body are placed in dishes containing culture media and kept in an incubator.

Probing a single cell

The dish with tissue culture cells is mounted on a microscope. A micropipette with an opening of about 0.5 µ is also mounted by means of a pipette holder. The pipette is filled with saline solution. An electrode is fitted to the pipette and connected to a recording device called patch-clamp amplifier. The micropipette is pressed firmly against the membrane of an intact cell. A gentle suction applied to the inside of the pipette forms a tight seal of giga ohms (GΩ) resistance between the membrane and the pipette.

This patch (minute part) of the cell membrane under the pipette is studied by means of various approaches called patch-clamp configurations (Fig. 31.5).

Patch-clamp Con igurations

1. *Cell-attached patch*

The cell is left intact with its membrane. This allows measurement of current flow through ion channel or channels under the micropipette (Fig. 31.5 A).

2. *Inside-out patch*

From the cell-attached configuration, the pipette is gently pulled away from the cell. It causes the detachment of a small portion of membrane from the cell. The external surface of the membrane patch faces pipette solution. But internal surface of the membrane patch is exposed out hence the name inside-out patch (Fig. 31.5 B).

Pipette with membrane patch is inserted into a container with free solution. Concentration of ions can

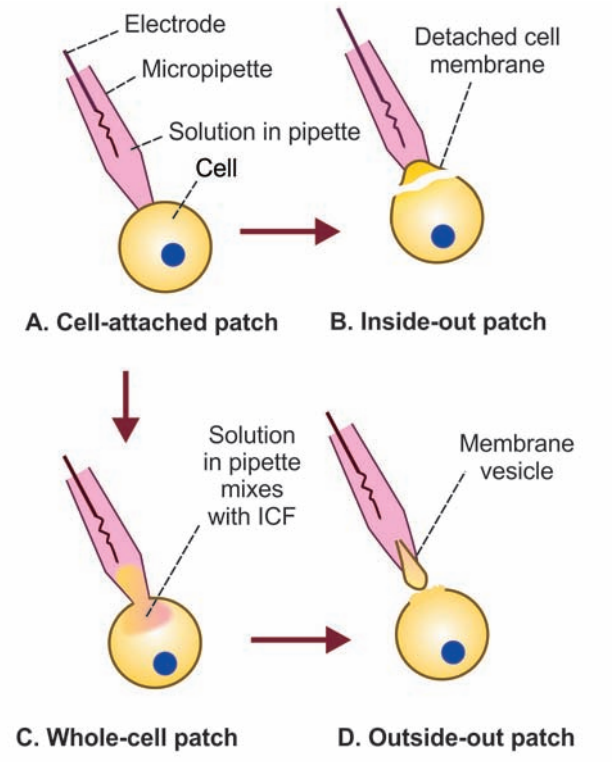


FIGURE 31.5: Patch-clamp configurations

be altered in the free solution. It is used to study the effect of alterations in the ion concentrations on the ion channels.

3. *Whole-cell patch*

From the cell-attached configuration, further suction is applied to the inside of the pipette. It causes rupture of the membrane and the pipette solution starts mixing with intracellular fluid. When the mixing is complete, the equilibrium is obtained between the pipette solution and the intracellular fluid (Fig. 31.5 C).

Whole-cell patch is used to record the current flow through all the ion channels in the cell. The cellular activity also can be studied directly.

4. *Outside-out patch*

From the whole-cell configuration the pipette is gently pulled away from the cell. A portion of membrane is torn away from the cell. Immediately, the free ends of the torn membrane fuse and reseal forming a membrane vesicle at tip of the pipette. The pipette solution enters the membrane vesicle and forms the intracellular fluid. The vesicle is placed inside a bath solution, which forms the extracellular environment (Fig. 31.5D).

This patch is used to study the effect of changes in the extracellular environment on the ion channels. It also helps to study the effects of neurotransmitters and compounds like ozone, G-protein regulators, etc. on the ion channels.

PHYSICAL CHANGES DURING MUSCULAR CONTRACTION

Physical change, which takes place during muscular contraction, is the change in length of the muscle fibers or change in tension developed in the muscle. Depending upon this, the muscular contraction is classified into two types namely isotonic contraction and isometric contraction (refer previous chapter).

HISTOLOGICAL CHANGES DURING MUSCULAR CONTRACTION

ACTOMYOSIN COMPLEX

In relaxed state of the muscle, the thin actin filaments from opposite ends of sarcomere are away from each other leaving a broad 'H' zone.

During contraction of the muscle, actin (thin) filaments glide over myosin (thick) filaments and form actomyosin complex.

MOLECULAR BASIS OF MUSCULAR CONTRACTION

Molecular mechanism is responsible for formation of actomyosin complex that results in muscular contraction. It includes three stages:

1. Excitation-contraction coupling.
2. Role of troponin and tropomyosin.
3. Sliding mechanism.

1. *Excitation-contraction Coupling*

Excitation-contraction coupling is the process that occurs in between the excitation and contraction of the muscle. This process involves series of activities, which are responsible for the contraction of excited muscle.

Stages of excitation-contraction coupling

When a muscle is excited (stimulated) by the impulses passing through motor nerve and neuromuscular junction, action potential is generated in the muscle fiber.

Action potential spreads over sarcolemma and also into the muscle fiber through the 'T' tubules. The 'T' tubules are responsible for the rapid spread of action potential into the muscle fiber. When the action potential reaches the cisternae of 'L' tubules, these cisternae are excited. Now, the calcium ions stored in the cisternae are released into the sarcoplasm (Fig. 31.6). The calcium ions from the sarcoplasm move towards the actin filaments to produce the contraction.

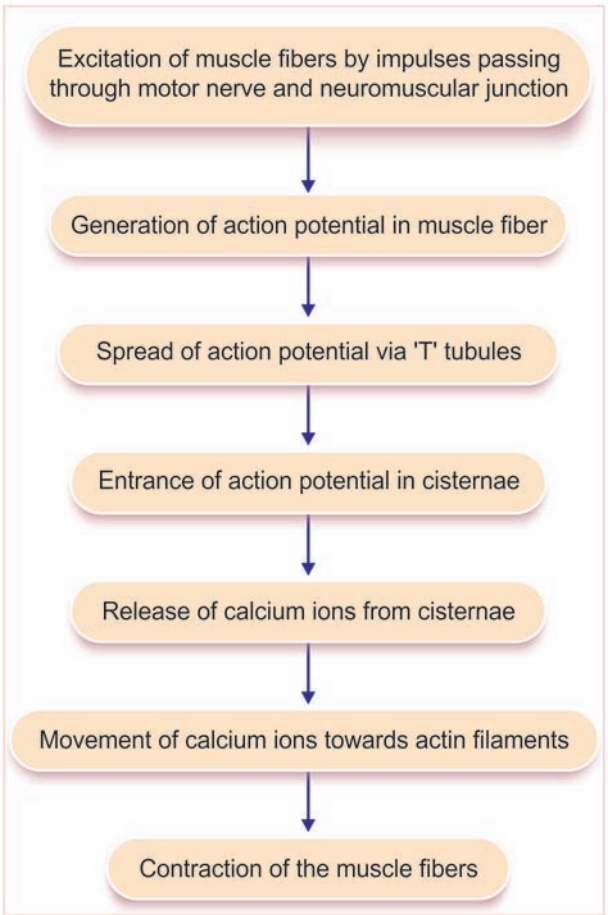


FIGURE 31.6: Excitation-contraction coupling

Thus, the calcium ion forms the link or coupling material between the excitation and the contraction of muscle. Hence, the calcium ions are said to form the basis of excitation-contraction coupling.

2. *Role of Troponin and Tropomyosin*

Normally, the head of myosin molecules has a strong tendency to get attached with active site of F actin. However, in relaxed condition, the active site of F actin is covered by the tropomyosin. Therefore, the myosin head cannot combine with actin molecule.

Large number of calcium ions, which are released from 'L' tubules during the excitation of the muscle, bind with troponin C. The loading of troponin C with calcium ions produces some change in the position of troponin molecule. It in turn, pulls tropomyosin molecule away from F actin. Due to the movement of tropomyosin, the active site of F actin is uncovered and exposed. Immediately the head of myosin gets attached to the actin.

3. *Sliding Mechanism and Formation of Actomyosin Complex – Sliding Theory*

Sliding theory explains how the actin filaments slide over myosin filaments and form the actomyosin complex during muscular contraction. It is also called **ratchet theory** or **walk along theory.**

Each cross bridge from the myosin filaments has got three components namely, a hinge, an arm and a head.

After binding with active site of F actin, the myosin head is tilted towards the arm so that the actin filament is dragged along with it (Fig. 31.7). This tilting of head is called power stroke. After tilting, the head immediately breaks away from the active site and returns to the original position. Now, it combines with a new active site on the actin molecule. And, tilting movement occurs again. Thus, the head of cross bridge bends back and forth and pulls the actin filament towards the center of sarcomere. In this way, all the actin filaments of both the ends of sarcomere are pulled. So, the actin filaments of

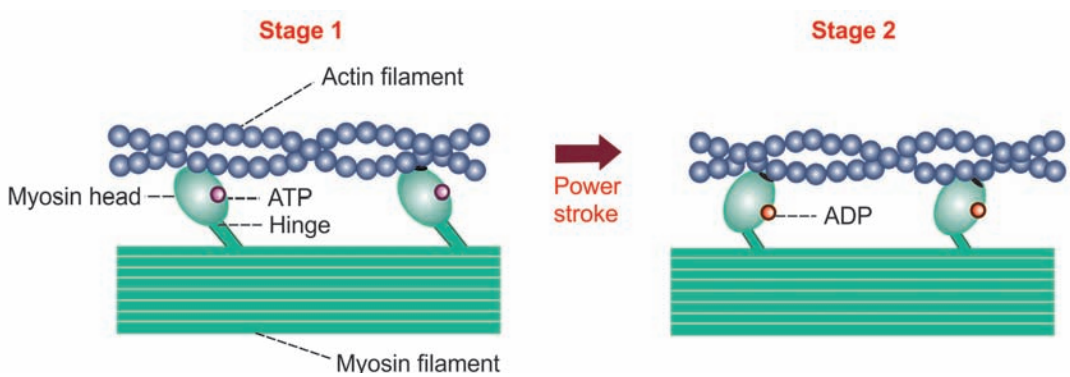


FIGURE 31.7: Diagram showing power stroke by myosin head.
Stage 1: Myosin head binds with actin; Stage 2: Tilting of myosin head (power stroke) drags the actin filament.

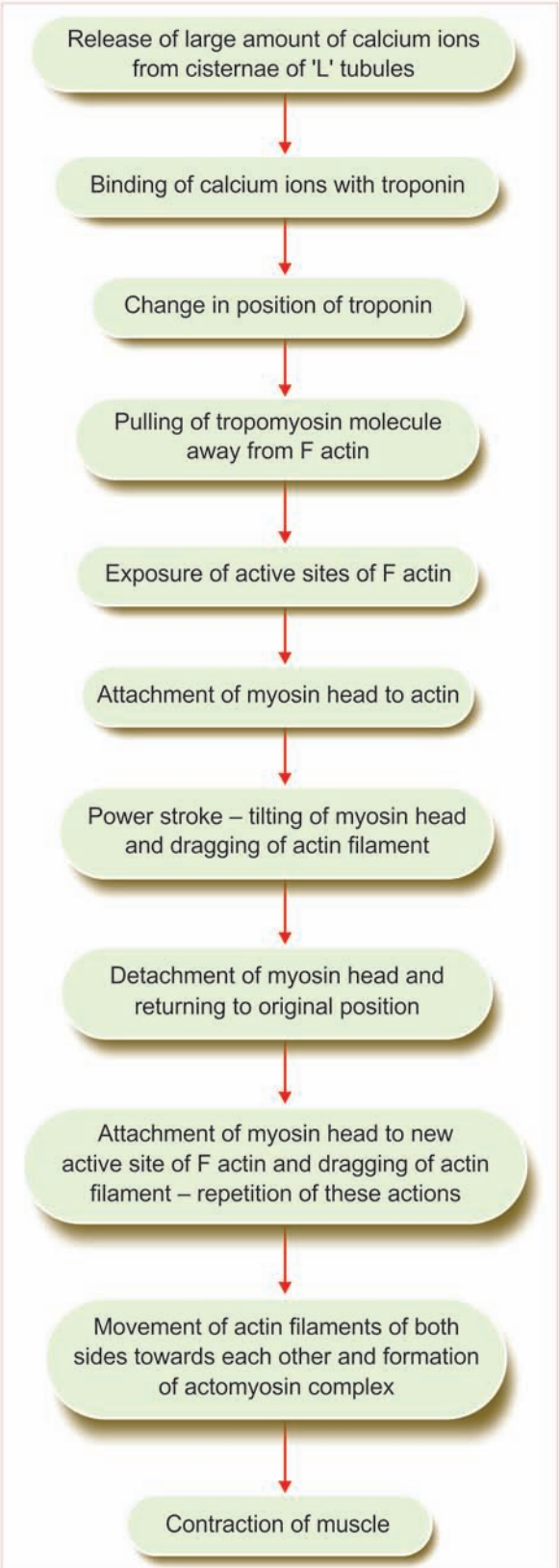


FIGURE 31.8: Sliding mechanism

opposite sides overlap and form actomyosin complex. Formation of actomyosin complex results in contraction of the muscle.

When the muscle shortens further, the actin filaments from opposite ends of the sarcomere approach each other. So, the 'H' zone becomes narrow. And, the two 'Z' lines come closer with reduction in length of the sarcomere. However, the length of 'A' band is not altered. But, the length of 'I' band decreases.

When the muscular contraction becomes severe, the actin filaments from opposite ends overlap and the 'H' zone disappears.

Changes in sarcomere during muscular contraction

Thus, changes that take place in sarcomere during muscular contraction are:

1. Length of all the sarcomeres decreases as the 'Z' lines come close to each other
2. Length of the 'I' band decreases since the actin filaments from opposite side overlap
3. 'H' zone either decreases or disappears
4. Length of 'A' band remains the same.

Summary of sequence of events during muscular contraction is given in Figure 31.8.

Energy for Muscular Contraction

Energy for movement of myosin head (power stroke) is obtained by breakdown of adenosine triphosphate (ATP) into adenosine diphosphate (ADP) and inorganic phosphate (Pi).

Head of myosin has a site for ATP. Actually the head itself can act as the enzyme ATPase and catalyze the breakdown of ATP. Even before the onset of contraction, an ATP molecule binds with myosin head.

When tropomyosin moves to expose the active sites, the head is attached to the active site. Now ATPase cleaves ATP into ADP and Pi, which remains in head itself. The energy released during this process is utilized for contraction.

When head is tilted, the ADP and Pi are released and a new ATP molecule binds with head. This process is repeated until the muscular contraction is completed.

Relaxation of the Muscle

Relaxation of the muscle occurs when the calcium ions are pumped back into the L tubules. When calcium ions enter the L tubules, calcium content in sarcoplasm decreases leading to the release of calcium ions from the troponin. It causes detachment of myosin from actin followed by relaxation of the muscle (Fig. 31.9). The detachment of myosin from actin obtains energy from breakdown of ATP. Thus, the chemical process of

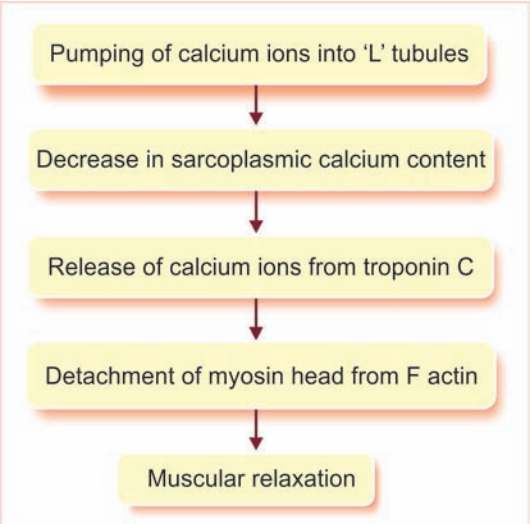


FIGURE 31.9: Sequence of events during muscular relaxation

muscular relaxation is an active process although the physical process is said to be passive.

Molecular Motors

Along with other proteins and some enzymes, actin and myosin form the molecular motors, which are involved in movements. Refer Chapter 3 for details.

■ CHEMICAL CHANGES DURING MUSCULAR CONTRACTION

■ LIBERATION OF ENERGY

Energy necessary for muscular contraction is liberated during the processes of breakdown and resynthesis of ATP.

Breakdown of ATP

During muscular contraction, the supply of energy is from the breakdown of ATP. This is broken into ADP and inorganic phosphate (Pi) and energy is liberated.

$$ATP \rightarrow ADP + Pi$$
$$\downarrow$$
$$Energy$$

Energy liberated by breakdown of ATP is responsible for the following activities during muscular contraction:

1. Spread of action potential into the muscle
2. Liberation of calcium ions from cisternae of 'L' tubules into the sarcoplasm
3. Movements of myosin head
4. Sliding mechanism.

Energy liberated during ATP breakdown is sufficient for maintaining full contraction of the muscle for a short duration of less than one second.

Resynthesis of ATP

Adenosine diphosphate, which is formed during ATP breakdown, is immediately utilized for the resynthesis of ATP. But, for the resynthesis of ATP, the ADP cannot combine with Pi. It should combine with a high-energy phosphate radical. There are two sources from which the high-energy phosphate is obtained namely, creatine phosphate and carbohydrate metabolism.

Resynthesis of ATP from creatine phosphate

Immediate supply of **high-energy phosphate** radical is from the creatine phosphate (CP). Plenty of CP is available in resting muscle. In the presence of the enzyme creatine phosphotransferase, high-energy phosphate is released from creatine phosphate. The reaction is called **Lohmann's reaction.**

$$ADP + CP \rightarrow ATP + Creatine$$

Energy produced in this reaction is sufficient to maintain muscular contraction only for few seconds. Creatine should be resynthesized into creatine phosphate and this requires the presence of high-energy phosphate. So, the required amount of high-energy phosphate radicals is provided by the carbohydrate metabolism in the muscle.

Resynthesis of ATP by carbohydrate metabolism

Carbohydrate metabolism starts with catabolic reactions of glycogen in the muscle. In resting muscle, an adequate amount of glycogen is stored in sarcoplasm.

Each molecule of glycogen undergoes catabolism, to produce ATP. The energy liberated during the catabolism of glycogen can cause muscular contraction for a longer period. The first stage of catabolism of glycogen is via glycolysis. It is called **glycolytic pathway** or **Embden-Meyerhof pathway** (Fig. 31.10).

Glycolysis

Each glycogen molecule is converted into 2 pyruvic acid molecules. Only small amount of ATP (2 molecules) is synthesized in this pathway.

This pathway has 10 steps. Each step is catalyzed by one or two enzymes as shown in Figure 31.10.

During glycolysis, 4 hydrogen atoms are released which are also utilized for formation of additional molecules of ATP. Formation of ATP by the utilization of hydrogen is explained later.

Further changes in pyruvic acid depend upon the availability of oxygen. In the absence of oxygen, the

pyruvic acid is converted into lactic acid that enters the **Cori cycle.** It is known as **anerobic glycolysis.** If oxygen is available, the pyruvic acid enters into **Krebs cycle.** It is known as **aerobic glycolysis.**

Cori cycle

Lactic acid is transported to liver where it is converted into glycogen and stored there. If necessary, glycogen breaks into glucose, which is carried by blood to muscle. Here, the glucose is converted into glycogen, which enters the Embden-Meyerhof pathway (Figs 31.11 and 31.12).

Krebs cycle

Krebs cycle is otherwise known as **tricarboxylic acid cycle** (TCA cycle) or **citric acid cycle.** A greater amount of energy is liberated through this cycle. The pyruvic acid derived from glycolysis is taken into mitochondria where it is converted into acetyl coenzyme A with release of 4 hydrogen atoms. The acetyl coenzyme A enters the Krebs cycle.

Krebs cycle is a series of reactions by which acetyl coenzyme A is degraded in various steps to form carbon dioxide and hydrogen atoms. All these reactions occur in the matrix of mitochondrion. During Krebs cycle, 2 molecules of ATP and 16 atoms of hydrogen are released. Hydrogen atoms are also utilized for the formation of ATP (see below).

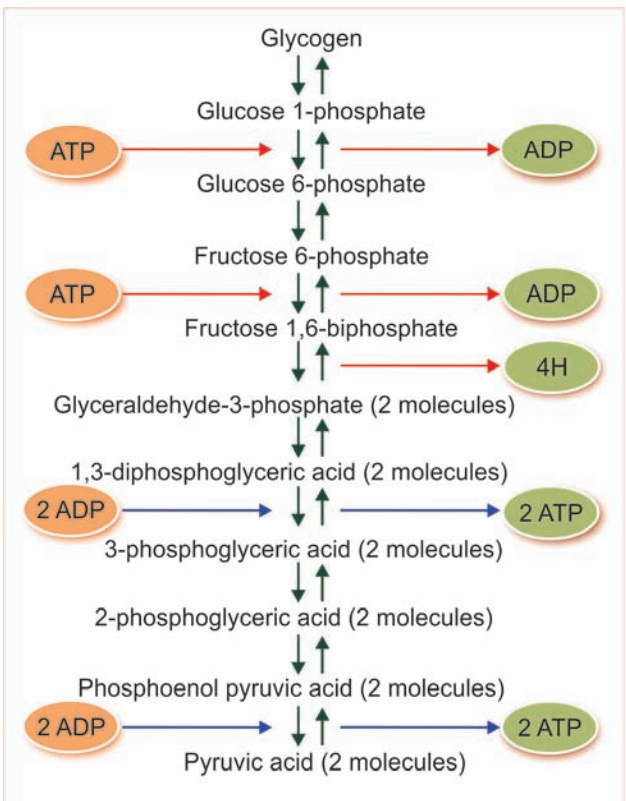


FIGURE 31.10: Glycolysis/Embden-Meyerhof pathway
Number of ATP molecules formed in this pathway:
Total ATP formed = 4 molecules
Loss of ATP during phosphorylation = 2 molecules
Net ATP formed during glycolysis = 2 molecules

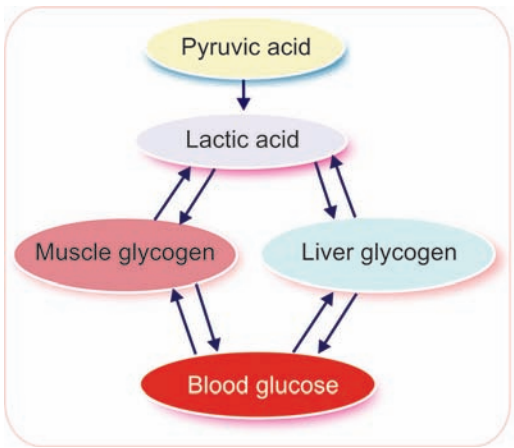


FIGURE 31.11: Cori cycle

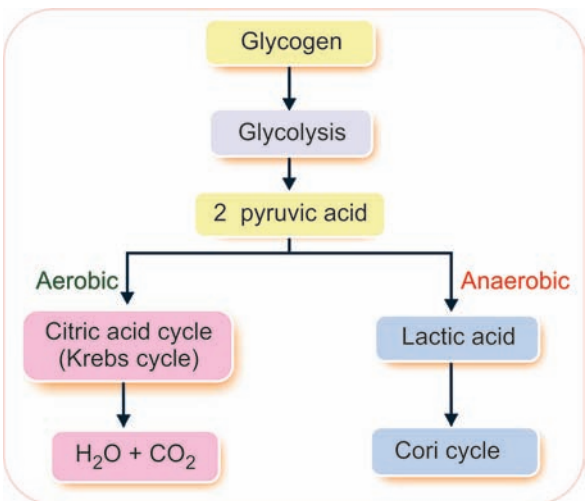


FIGURE 31.12: Schematic diagram showing carbohydrate metabolism in muscle

Significance of Hydrogen Atoms Released during Carbohydrate Metabolism

Altogether 24 hydrogen atoms are released during glycolysis and Krebs cycle:

- 4H : During breakdown of glycogen into pyruvic acid
- 4H : During formation of acetyl coenzyme A from pyruvic acid
- 16H : During degradation of acetyl coenzyme A in Krebs cycle.

Hydrogen atoms are released in the form of two pockets into intracellular fluid and it is catalyzed by the enzyme dehydrogenase. Once released, 20 hydrogen atoms combine with nicotinamide adenine dinucleotide (NAD), which acts as hydrogen carrier. NAD transfers the hydrogen atoms to the cytochrome system where oxidative phosphorylation takes place. Oxidative phosphorylation is the process during which the ATP molecules are formed by utilizing hydrogen atoms.

For every 2 hydrogen atoms 3 molecules of ATP are formed. So, from 20 hydrogen atoms 30 molecules of ATP are formed. Remaining 4 hydrogen atoms enter the oxidative phosphorylation processes directly without combining with NAD. Only 2 ATP molecules are formed for every 2 hydrogen atoms. So, 4 hydrogen atoms give rise to 4 ATP molecules. Thus, 34 ATP molecules are formed from the hydrogen atoms released during glycolysis and Krebs cycle.

Summary of Resynthesis of ATP during Carbohydrate Metabolism

A total of 38 ATP molecules are formed during breakdown of each glycogen molecule in the muscle as summarized below:

During glycolysis	:	2 molecules of ATP
During Krebs cycle	:	2 molecules of ATP
By utilization of hydrogen	:	34 molecules of ATP
Total	:	38 molecules of ATP

■ CHANGES IN pH DURING MUSCULAR CONTRACTION

Reaction and the pH of muscle are altered in different stages of muscular contraction.

In Resting Condition

During resting condition, the reaction of muscle is alkaline with a pH of 7.3.

During Onset of Contraction

At the beginning of the muscular contraction, the reaction becomes acidic. The acidity is due to dephosphorylation of ATP into ADP and Pi.

During Later Part of Contraction

During the later part of contraction, the muscle becomes alkaline. It is due to the resynthesis of ATP from CP.

At the End of Contraction

At the end of contraction, the muscle becomes once again acidic. This acidity is due to the formation of pyruvic acid and/or lactic acid.

■ THERMAL CHANGES DURING MUSCULAR CONTRACTION

During muscular contraction, heat is produced. Not all the heat is liberated at a time. It is released in different stages:

1. Resting heat
2. Initial heat
3. Recovery heat.

■ RESTING HEAT

Heat produced in the muscle at rest is called the resting heat. It is due to the basal metabolic process in the muscle.

■ INITIAL HEAT

During muscular activity, heat production occurs in three stages:

i. Heat of activation
ii. Heat of shortening
iii. Heat of relaxation.

i. *Heat of Activation*

Heat of activation is the heat produced before the actual shortening of the muscle fibers. Most of this heat is produced during the release of calcium ions from 'L' tubules. It is also called **maintenance heat.**

ii. *Heat of Shortening*

Heat of shortening is the heat produced during contraction of muscle. The heat is produced due to various structural changes in the muscle fiber like movements of cross bridges and myosin heads and breakdown of glycogen.

iii. *Heat of Relaxation*

Heat released during relaxation of the muscle is known as the heat of relaxation. In fact, it is the heat produced during the contraction of muscle due to breakdown of ATP molecule. It is released when the muscle lengthens during relaxation.

■ RECOVERY HEAT

Recovery heat is the heat produced in the muscle after the end of activities. After the end of muscular activities, some amount of heat is produced due to the chemical processes involved in resynthesis of chemical substances broken down during contraction.

Chapter 5

Neuromuscular Junction

DEFINITION AND STRUCTURE

DEFINITION

Neuromuscular junction is the junction between terminal branch of the nerve fiber and muscle fiber.

STRUCTURE

Skeletal muscle fibers are innervated by the motor nerve fibers. Each nerve fiber (axon) divides into many terminal branches. Each terminal branch innervates one muscle fiber through the neuromuscular junction (Fig. 32.1).

Axon Terminal and Motor Endplate

Terminal branch of nerve fiber is called axon terminal. When the axon comes close to muscle fiber, it loses the myelin sheath. So, the axis cylinder is exposed. This portion of the axis cylinder is expanded like a bulb, which is called motor endplate.

Axon terminal contains **mitochondria** and **synaptic vesicles.** Synaptic vesicles contain the neurotransmitter

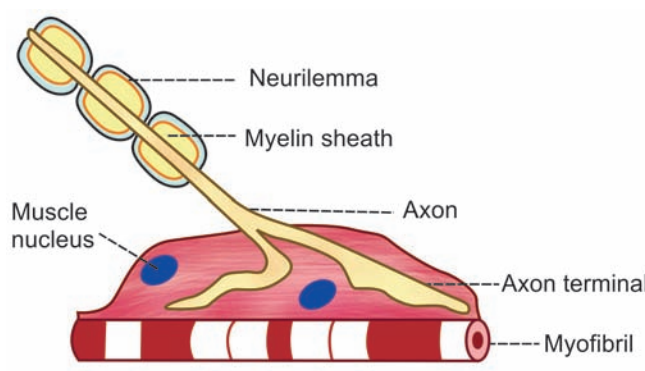


FIGURE 32.1: Longitudinal section of neuromuscular junction

substance, acetylcholine (Ach). The Ach is synthesized by mitochondria present in the axon terminal and stored in the vesicles. Mitochondria contain ATP, which is the source of energy for the synthesis of acetylcholine.

Synaptic Trough or Gutter

Motor endplate invaginates inside the muscle fiber and forms a depression, which is known as **synaptic trough** or **synaptic gutter.** The membrane of the muscle fiber below the motor endplate is thickened.

Synaptic Cleft

Membrane of the nerve ending is called the **presynaptic membrane.** Membrane of the muscle fiber is called **postsynaptic membrane.** Space between these two membranes is called **synaptic cleft.**

Synaptic cleft contains **basal lamina.** It is a thin layer of spongy reticular matrix through which, the extracellular fluid diffuses. An enzyme called acetylcholinesterase (AchE) is attached to the matrix of basal lamina, in large quantities.

Subneural Clefts

Postsynaptic membrane is the membrane of the muscle fiber. It is thrown into numerous folds called **subneural clefts.** Postsynaptic membrane contains the receptors called nicotinic **acetylcholine receptors** (Fig. 32.2).

■ NEUROMUSCULAR TRANSMISSION

Definition

Neuromuscular transmission is defined as the transfer of information from motor nerve ending to the muscle fiber through neuromuscular junction. It is the mechanism by which the motor nerve impulses initiate muscle contraction.

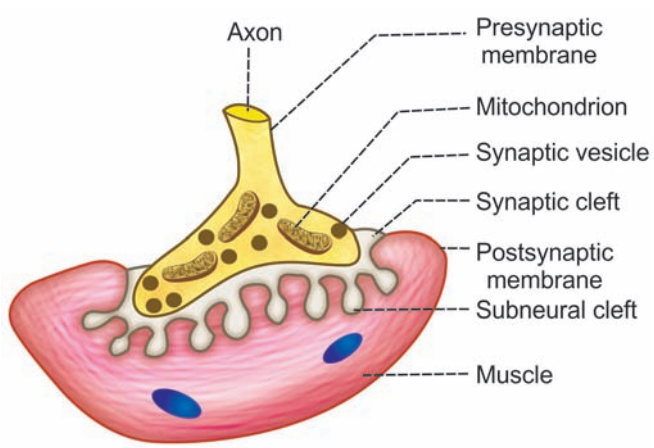


FIGURE 32.2: Structure of neuromuscular junction

Events of Neuromuscular Transmission

A series of events take place in the neuromuscular junction during this process (Fig. 32.3). The events are:

1. Release of acetylcholine
2. Action of acetylcholine
3. Development of endplate potential
4. Development of miniature endplate potential
5. Destruction of acetylcholine.

■ 1. RELEASE OF ACETYLCHOLINE

When action potential reaches axon terminal, it opens the voltage-gated calcium channels in the membrane of axon terminal. Calcium ions from extracellular fluid (ECF) enter the axon terminal. These cause bursting of the vesicles by forcing the synaptic vesicles move and fuse with presynaptic membrane. Now, acetylcholine is released from the ruptured vesicles. By **exocytosis,** acetylcholine diffuses through the presynaptic membrane and enters the synaptic cleft.

Each vesicle contains about 10,000 acetylcholine molecules. And, at a time, about 300 vesicles open and release acetylcholine.

■ 2. ACTION OF ACETYLCHOLINE

After entering the synaptic cleft, acetylcholine molecules bind with nicotinic receptors present in the postsynaptic membrane and form acetylcholine-receptor complex. It increases the permeability of postsynaptic membrane for sodium by opening the ligand-gated sodium channels. Now, sodium ions from ECF enter the neuromuscular junction through these channels. And there, sodium ions alter the resting membrane potential and develops the electrical potential called the endplate potential.

■ 3. DEVELOPMENT OF ENDPLATE POTENTIAL

Endplate potential is the change in resting membrane potential when an impulse reaches the neuromuscular junction. Resting membrane potential at neuromuscular junction is –90 mV. When sodium ions enter inside, slight depolarization occurs up to –60 mV, which is called endplate potential.

Properties of Endplate Potential

Endplate potential is a graded potential and it is not action potential. Refer Table 31.1 for the properties of graded potential.

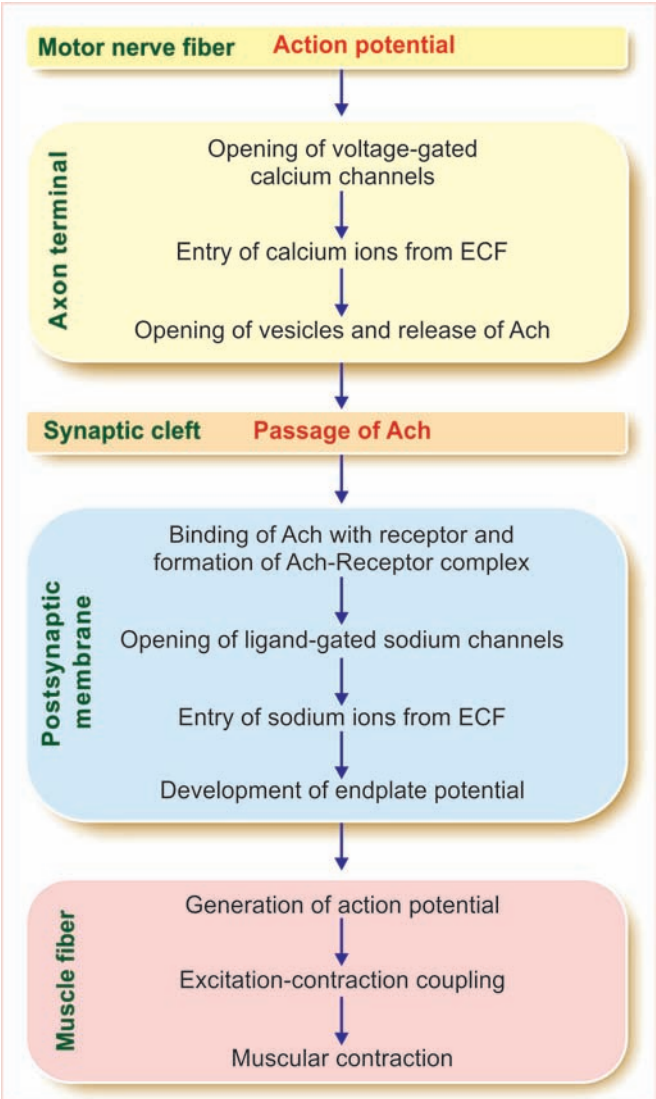


FIGURE 32.3: Sequence of events during neuromuscular transmission. Ach = Acetylcholine, ECF = Extracellular fluid.

Significance of Endplate Potential

Endplate potential is non-propagative. But it causes the development of action potential in the muscle fiber.

■ 4. DEVELOPMENT OF MINIATURE ENDPLATE POTENTIAL

Miniature endplate potential is a weak endplate potential in neuromuscular junction that is developed by the release of a small quantity of acetylcholine from axon terminal. And, each quantum of this neurotransmitter produces a weak miniature endplate potential. The amplitude of this potential is only up to 0.5 mV.

Miniature endplate potential cannot produce action potential in the muscle. When more and more quanta of acetylcholine are released continuously, the miniature endplate potentials are added together and finally produce endplate potential resulting in action potential in the muscle.

■ 5. DESTRUCTION OF ACETYLCHOLINE

Acetylcholine released into the synaptic cleft is destroyed very quickly, within one millisecond by the enzyme, acetylcholinesterase. However, the acetylcholine is so potent, that even this short duration of 1 millisecond is sufficient to excite the muscle fiber. Rapid destruction of acetylcholine has got some important functional significance. It prevents the repeated excitation of the muscle fiber and allows the muscle to relax.

Reuptake Process

Reuptake is a process in neuromuscular junction, by which a degraded product of neurotransmitter re-enters the presynaptic axon terminal where it is reused. Acetylcholinesterase splits (degrades) acetylcholine into inactive choline and acetate. Choline is taken back into axon terminal from synaptic cleft by reuptake process. There, it is reused in synaptic vesicle to form new acetylcholine molecule.

■ NEUROMUSCULAR BLOCKERS

Neuromuscular blockers are the drugs, which prevent transmission of impulses from nerve fiber to the muscle fiber through the neuromuscular junctions. These drugs are used widely during surgery and trauma care. Neuromuscular blockers used during anesthesia relax the skeletal muscles and induce paralysis so that surgery can be conducted with less complication.

Following are important neuromuscular blockers, which are commonly used in clinics and research.

1. *Curare*

Curare prevents the neuromuscular transmission by combining with acetylcholine receptors. So, the acetylcholine cannot combine with the receptors. And, the endplate potential cannot develop. Since curare blocks the neuromuscular transmission by acting on the acetylcholine receptors, it is called receptor blocker.

2. *Bungarotoxin*

Bungarotoxin is a toxin from the venom of deadly snakes. It affects the neuromuscular transmission by blocking the acetylcholine receptors.

3. *Succinylcholine and Carbamylcholine*

These drugs block the neuromuscular transmission by acting like acetylcholine and keeping the muscle in a depolarized state. But, these drugs are not destroyed by cholinesterase. So, the muscle remains in a depolarized state for a long time.

4. *Botulinum Toxin*

Botulinum toxin is derived from the bacteria *Clostridium botulinum*. It prevents release of acetylcholine from axon terminal into the neuromuscular junction.

■ DRUGS STIMULATING NEUROMUSCULAR JUNCTION

Neuromuscular junction can be stimulated by some drugs like neostigmine, physostigmine and diisopropyl fluorophosphate. These drugs inactivate the enzyme, acetylcholinesterase. So, the acetylcholine is not hydrolyzed. It leads to repeated stimulation and continuous contraction of the muscle.

■ MOTOR UNIT

■ DEFINITION

Single motor neuron, its axon terminals and the muscle fibers innervated by it are together called motor unit. Each motor neuron activates a group of muscle fibers through the axon terminals. Stimulation of a motor neuron causes contraction of all the muscle fibers innervated by that neuron.

■ NUMBER OF MUSCLE FIBERS IN MOTOR UNIT

Number of muscle fiber in each motor unit varies. The motor units of the muscles concerned with fine, graded and precise movements have smaller number of muscle fibers.

For example,

Laryngeal muscles : 2 to 3 muscle fibers per motor unit
Pharyngeal muscles : 2 to 6 muscle fibers per motor unit
Ocular muscles : 3 to 6 muscle fibers per motor unit

Muscles concerned with crude or coarse movements have motor units with large number of muscle fibers. There are about 120 to 165 muscle fibers in each motor unit in these muscles. Examples are the muscles of leg and back.

■ RECRUITMENT OF MOTOR UNITS

While stimulating the muscle with weak strength, only a few motor units are involved. When the strength of stimulus is increased, many motor units are put into action. So, the force of contraction increases. The process by which more and more motor units are put into action is called recruitment of motor unit. Thus, the graded response in the muscle is directly proportional to the number of motor units activated.

Activation of motor units can be studied by electromyography.

■ APPLIED PHYSIOLOGY – DISORDERS OF NEUROMUSCULAR JUNCTION

■ MYASTHENIA GRAVIS

Myasthenia gravis is an autoimmune disorder of neuromuscular junction caused by antibodies to cholinergic receptors.

■ EATON-LAMBERT SYNDROME

Eaton-Lambert syndrome is also an autoimmune disorder of neuromuscular junction. It is caused by antibodies to calcium channels in axon terminal.

Chapter 6

Smooth Muscle

- DISTRIBUTION
- FUNCTIONS
- STRUCTURE
- TYPES
- ELECTRICAL ACTIVITY IN SINGLE-UNIT SMOOTH MUSCLE
- ELECTRICAL ACTIVITY IN MULTIUNIT SMOOTH MUSCLE
- CONTRACTILE PROCESS
- NEUROMUSCULAR JUNCTION
- CONTROL OF SMOOTH MUSCLE

DISTRIBUTION OF SMOOTH MUSCLE

Smooth muscles are **non-striated** (plain) and involuntary muscles. These muscles are present in almost all the organs in the form of sheets, bundles or sheaths around other tissues. Smooth muscles form the major contractile tissues of various organs.

Structures in which smooth muscle fibers are present:

1. Wall of organs like esophagus, stomach and intestine in the gastrointestinal tract
2. Ducts of digestive glands
3. Trachea, bronchial tube and alveolar ducts of respiratory tract
4. Ureter, urinary bladder and urethra in excretory system
5. Wall of the blood vessels in circulatory system
6. Arrector pilorum of skin
7. Mammary glands, uterus, genital ducts, prostate gland and scrotum in the reproductive system
8. Iris and ciliary body of the eye.

FUNCTIONS OF SMOOTH MUSCLE

Smooth muscles are concerned with very important functions in different parts of the body.

IN CARDIOVASCULAR SYSTEM

Smooth muscle fibers around the blood vessels regulate blood pressure and blood flow through different organs and regions of the body.

IN RESPIRATORY SYSTEM

Contraction and relaxation of smooth muscle fibers of the air passage alter the diameter of air passage and regulate the inflow and outflow of air.

IN DIGESTIVE SYSTEM

Smooth muscle fibers in digestive tract help in movement of food substances, mixing of food substance with digestive juices, absorption of digested material and elimination of unwanted substances. Sphincters along the digestive tract regulate the flow of materials.

IN RENAL SYSTEM

Smooth muscle fibers in renal blood vessels regulate renal blood flow and glomerular filtration. Smooth muscles in the ureters propel urine from kidneys to urinary bladder through ureters. Smooth muscles present in urinary bladder help voiding urine to the exterior.

■ IN REPRODUCTIVE SYSTEM

In males, smooth muscle fibers facilitate the movement of sperms and secretions from accessory glands along the reproductive tract. In females, these muscles accelerate the movement of sperms through genital tract after sexual act, movement of ovum into uterus through fallopian tube, expulsion of menstrual fluid and delivery of the baby.

■ STRUCTURE OF SMOOTH MUSCLE

Smooth muscle fibers are **fusiform** or elongated cells. These fibers are generally very small, measuring 2 to 5 microns in diameter and 50 to 200 microns in length. Nucleus is single and elongated and it is centrally placed. Normally, two or more nucleoli are present in the nucleus (Fig. 33.1).

Myofibrils and Sarcomere

Well-defined myofibrils and sarcomere are absent in smooth muscles. So the alternate dark and light bands are absent. Absence of dark and light bands gives the non-striated appearance to the smooth muscle.

Myofilaments and Contractile Proteins

Contractile proteins in smooth muscle fiber are actin, myosin and tropomyosin. But troponin or troponin-like substance is absent.

Thick and thin filaments are present in smooth muscle. However, these filaments are not arranged in orderly fashion as in skeletal muscle. Thick filaments are formed by myosin molecules and are scattered in sarcoplasm. These thick filaments contain more number of cross bridges than in skeletal muscle. Thin filaments are formed by actin and tropomyosin molecules.

Dense Bodies

Dense bodies are the special structures of smooth muscle fibers to which the actin and tropomyosin molecules of thin filaments are attached. The dense bodies are scattered all over the sarcoplasm in the network of intermediate filaments, which is formed by the protein **desmin.** Some of the dense bodies are firmly attached with sarcolemma. The anchoring of the dense bodies, intermediate filaments and thin filaments make the smooth muscle fiber shorten when sliding occurs between thick and thin filaments.

Another interesting feature is that the dense bodies are not arranged in straight line. Because of this, smooth muscle fibers twist like corkscrew during contraction. Adjacent smooth muscle fibers are bound together at

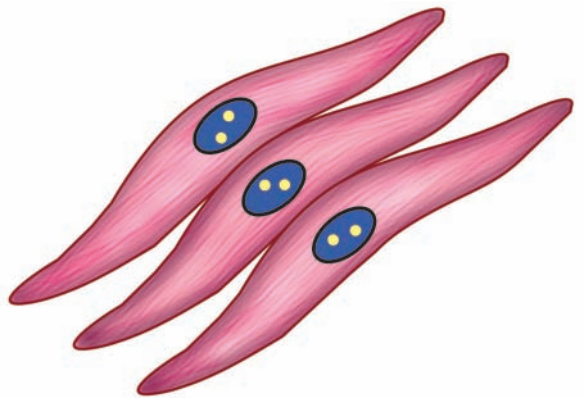


FIGURE 33.1: Smooth muscle fibers

dense bodies. It helps to transmit the contraction from one cell to another throughout the tissue.

Covering and Tendons

Smooth muscle fibers are covered by connective tissue. But the tendons and aponeurosis are absent.

Sarcotubular System

Sarcotubular system in smooth muscle fibers is in the form of network. 'T' tubules are absent and 'L' tubules are poorly developed (see Table 28.1).

■ TYPES OF SMOOTH MUSCLE FIBERS

Smooth muscle fibers are of two types:

1. Single-unit or visceral smooth muscle fibers
2. Multiunit smooth muscle fibers.

■ SINGLE-UNIT OR VISCERAL SMOOTH MUSCLE FIBERS

Single-unit smooth muscle fibers are the fibers with interconnecting gap junctions. The gap junctions allow rapid spread of action potential throughout the tissue so that all the muscle fibers show synchronous contraction as a single unit. Single unit smooth muscle fibers are also called **visceral smooth muscle fibers.**

Features of single-unit smooth muscle fibers:

1. Muscle fibers are arranged in sheets or bundles
2. Cell membrane of adjacent fibers fuses at many points to form gap junctions. Through the gap junctions, ions move freely from one cell to the other. Thus a **functional syncytium** is developed. The syncytium contracts as a single unit. In this way, the visceral smooth muscle resembles cardiac muscle more than the skeletal muscle.

Distribution of Single-unit Smooth Muscle Fibers

Visceral smooth muscle fibers are in the walls of the organs such as gastrointestinal organs, uterus, ureters, respiratory tract, etc.

■ MULTIUNIT SMOOTH MUSCLE FIBERS

Multiunit smooth muscle fibers are the muscle fibers without **interconnecting gap junctions.** These smooth muscle fibers resemble the skeletal muscle fibers in many ways.

Features of multiunit smooth muscle fibers:

1. Muscle fibers are individual fibers
2. Each muscle fiber is innervated by a single nerve ending
3. Each muscle fiber has got an outer membrane made up of glycoprotein, which helps to insulate and separate the muscle fibers from one another
4. Control of these muscle fibers is mainly by nerve signals
5. These smooth muscle fibers do not exhibit spontaneous contractions.

Distribution of Multiunit Smooth Muscle Fibers

Multiunit muscle fibers are in ciliary muscles of the eye, iris of the eye, **nictitating membrane** (in cat), **arrector pili** and smooth muscles of the blood vessels and urinary bladder.

■ ELECTRICAL ACTIVITY IN SINGLE-UNIT SMOOTH MUSCLE

Usually 30 to 40 smooth muscle fibers are simultaneously depolarized, which leads to development of self-propagating action potential. It is possible because of gap junctions and syncytial arrangements of single-unit smooth muscles.

■ RESTING MEMBRANE POTENTIAL

Resting membrane potential in visceral smooth muscle is very **unstable** and ranges between –50 and –75 mV. Sometimes, it reaches the low level of –25 mV.

■ CAUSE FOR UNSTABLE RESTING MEMBRANE POTENTIAL – SLOW-WAVE POTENTIAL

The unstable resting membrane potential is caused by the appearance of some wave-like fluctuations called slow waves. The slow waves occur in a rhythmic fashion at a frequency of 4 to 10 per minute with the amplitude of 10 to 15 mV (Fig. 33.2). The cause of the slow-wave rhythm is not known. It is suggested that it may be due to the rhythmic modulations in the activities of sodium-potassium pump. The slow wave is not action potential and it cannot cause contraction of the muscle. But it initiates the action potential (see below).

■ ACTION POTENTIAL

Three types of action potential occur in visceral smooth muscle fibers:

1. Spike potential
2. Spike potential initiated by slow-wave rhythm
3. Action potential with plateau.

1. *Spike Potential*

Spike potential in visceral smooth muscle appears similar to that of skeletal muscle. However, it is different from the spike potential in skeletal muscles in many ways. In smooth muscle, the average duration of spike potential varies between 30 and 50 milliseconds. Its amplitude is very low and it does not reach the isoelectric base. Sometimes, the spike potential rises above the isoelectric base (overshoot). The spike potential is due to nervous and other stimuli and it leads to contraction of the muscle.

2. *Spike Potential Initiated by Slow-wave Rhythm*

Sometimes the slow-wave rhythm of resting membrane potential initiates the spike potentials, which lead to contraction of the muscle. The spike potentials appear rhythmically at a rate of about one or two spikes at the peak of each slow wave. The spike potentials initiated by the slow-wave rhythm cause rhythmic contractions of smooth muscles. This type of potentials appears mostly in smooth muscles, which are self-excitatory and contract themselves without any external stimuli. So, the spike potentials initiated by slow-wave rhythm are otherwise called **pacemaker waves.** The smooth muscles showing rhythmic contractions are present in some of the visceral organs such as intestine.

3. *Action Potential with Plateau*

This type of action potential starts with rapid depolarization as in the case of skeletal muscle. But, repolarization does not occur immediately. The muscle remains depolarized for long periods of about 100 to 1,000 milliseconds. This type of action potential is responsible for sustained contraction of smooth muscle fibers. After the long depolarized state, slow repolarization occurs.

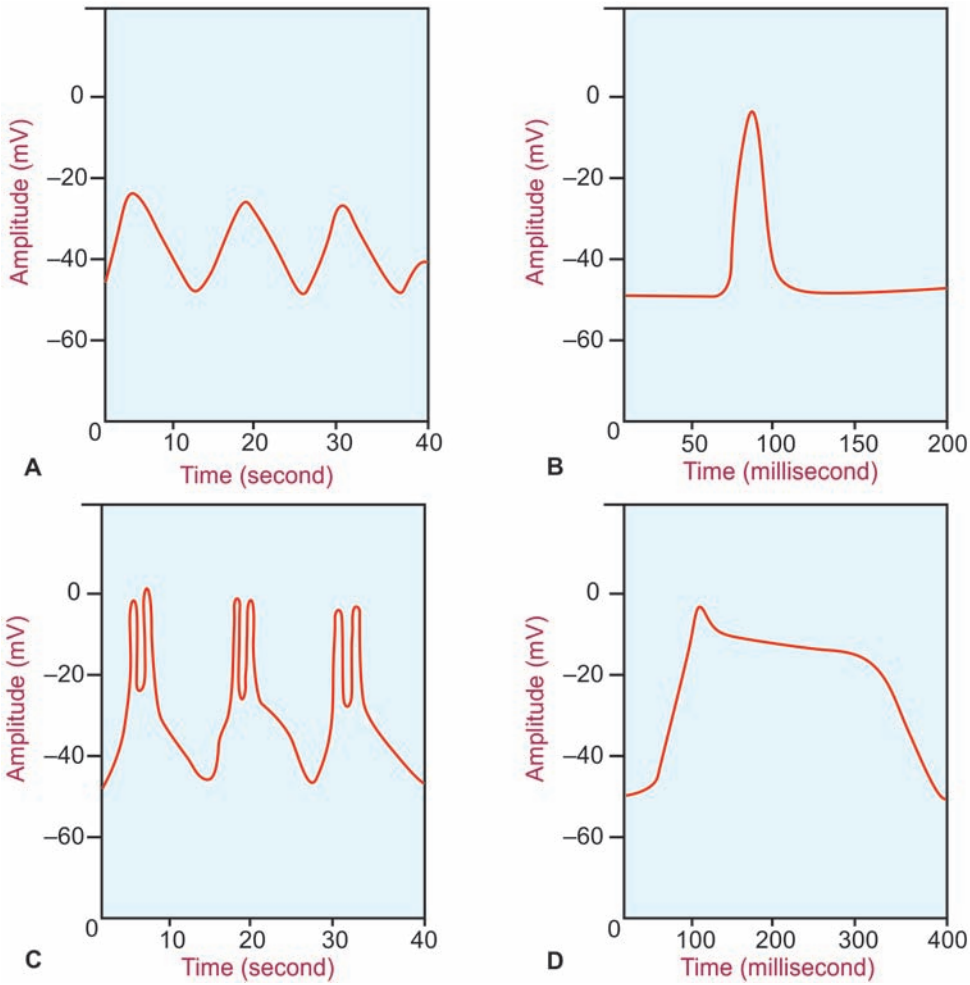


FIGURE 33.2: Electrical activities in smooth muscle
A = Slow-wave rhythm of resting membrane potential
B = Spike potential
C = Spike potential initiated by slow wave rhythm
D = Action potential with plateau

■ TONIC CONTRACTION OF SMOOTH MUSCLE WITHOUT ACTION POTENTIAL

Smooth muscles of some visceral organs maintain a state of partial contraction called **tonus** or **tone.** It is due to the tonic contraction of the muscle that occurs without any action potential or any stimulus. Sometimes, the tonic contraction occurs due to the action of some hormones.

■ IONIC BASIS OF ACTION POTENTIAL

The important difference between action potential in skeletal muscle and smooth muscle lies in the ionic basis of depolarization. In skeletal muscle, the depolarization occurs due to opening of sodium channels and entry of sodium ions from extracellular fluid into the muscle fiber. But in smooth muscle, the depolarization is due to entry of calcium ions rather than sodium ions. Unlike the fast sodium channels, the calcium channels open and close slowly. It is responsible for the prolonged action potential with plateau in smooth muscles. The calcium ions play an important role during the contraction of the muscle.

■ ELECTRICAL ACTIVITY IN MULTIUNIT SMOOTH MUSCLE

Electrical activity in multiunit smooth muscle is different from that in the single unit smooth muscle. Electrical changes leading to contraction of multiunit smooth

muscle are triggered by nervous stimuli. Nerve endings secrete the neurotransmitters like acetylcholine and noradrenaline. Neurotransmitters depolarize the membrane of smooth muscle fiber slightly leading to contraction. The action potential does not develop. This type of depolarization is called **local depolarization** or **excitatory junctional potential** (EJP). This local depolarization travels throughout the entire smooth muscle fiber and causes contraction. Local depolarization is developed because the multiunit smooth muscle fibers are too small to develop action potential.

CONTRACTILE PROCESS IN SMOOTH MUSCLE

Compared to skeletal muscles, in smooth muscles, the contraction and relaxation processes are slow. The latent period is also long. Thus, the total twitch period is very long and it is about 1 to 3 seconds. In skeletal muscle, the total twitch period is 0.1 sec.

MOLECULAR BASIS OF SMOOTH MUSCLE CONTRACTION

The process of excitation and contraction is very slow in smooth muscles because of poor development of 'L' tubules (sarcoplasmic reticulum). So, the calcium ions, which are responsible for excitation-contraction coupling, must be obtained from the extracellular fluid. It makes the process of excitation-contraction coupling slow.

Calcium-calmodulin Complex

Stimulation of ATPase activity of myosin in smooth muscle is different from that in the skeletal muscle. In smooth muscle, the myosin has to be phosphorylated for the activation of myosin ATPase.

Phosphorylation of myosin occurs in the following manner:

1. Calcium, which enters the sarcoplasm from the extracellular fluid combines with a protein called calmodulin and forms calcium-calmodulin complex (Fig. 33.3)
2. It activates calmodulin-dependent myosin light chain kinase
3. This enzyme in turn causes phosphorylation of myosin followed by activation of myosin ATPase
4. Now, the sliding of actin filaments starts.

Phosphorylated myosin gets attached to the actin molecule for longer period. It is called **latch-bridge mechanism** and it is responsible for the sustained contraction of the muscle with expenditure of little energy.

Relaxation of the muscle occurs due to dissociation of calcium-calmodulin complex.

Length-Tension Relationship – Plasticity

Plasticity is the adaptability of smooth muscle fibers to a wide range of lengths. If the smooth muscle fiber is stretched, it adapts to this new length and contracts when stimulated. Because of this property, tension produced in the muscle fiber is not directly proportional to resting length of the muscle fiber. In other words, Starling's law is not applicable to smooth muscle. Starling's law is applicable in skeletal and cardiac muscles and the tension or force of contraction is directly proportional to initial length of fibers in these muscles.

The property of plasticity in smooth muscle fibers is especially important in digestive organs such as stomach, which undergo remarkable changes in volume.

In spite of plasticity, smooth muscle fibers contract powerfully like the skeletal muscle fibers. Smooth muscle fibers also show sustained tetanic contractions like skeletal muscle fibers.

NEUROMUSCULAR JUNCTION IN SMOOTH MUSCLE

Well-defined neuromuscular junctions are absent in smooth muscle. The nerve fibers (axons) do not end in the

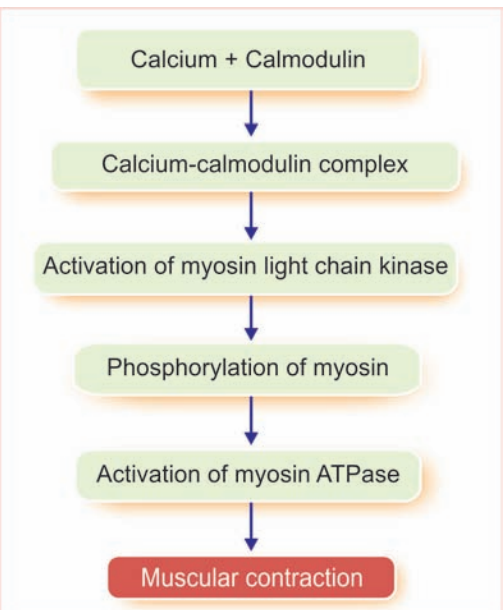


FIGURE 33.3: Molecular basis of smooth muscle contraction

form of endplate. Instead, these nerve fibers end on smooth muscle fibers in three different ways:

1. Nerve fibers diffuse on the sheet of smooth muscle fibers without making any direct contact with the muscle. The diffused nerve fibers form diffuse junctions, which contain neurotransmitters. Neurotransmitters are released into the matrix, which coats the smooth muscle fiber. From here the neurotransmitters enter the muscle fibers
2. In some smooth muscle fibers, the axon terminal ends in the form of many **varicosities.** The varicosities have vesicles, which contain the neurotransmitter. Neurotransmitter is released from varicosities through their wall into the muscle fiber
3. In some of the multiunit smooth muscle fibers, a gap is present between varicosities and the membrane of smooth muscle fibers, which resembles the synaptic cleft in skeletal muscle. The width of this gap is 30 to 40 nm. This gap is called contact junction and it functions as neuromuscular junction of skeletal muscle.

CONTROL OF SMOOTH MUSCLE

Smooth muscle fibers are controlled by:

1. Nervous factors
2. Humoral factors.

NERVOUS FACTORS

Smooth muscles are supplied by both sympathetic and parasympathetic nerves, which antagonize (act opposite to) each other and control the activities of smooth muscles. However, these nerves are not responsible for the initiation of any activity in smooth muscle. The tonus of smooth muscles is also independent of nervous control.

HUMORAL FACTORS

Activity of smooth muscle is also controlled by humoral factors, which include hormones, neurotransmitters and other humoral factors.

Hormones and Neurotransmitters

Action of the hormones and neurotransmitters depends upon the type of receptors present in membrane of smooth muscle fibers in particular area. The receptors are of two types, excitatory receptors and inhibitory receptors.

If excitatory receptors are present, the hormones or the neurotransmitters contract the muscle by producing depolarization. If inhibitory receptors are present, the hormones or the neurotransmitters relax the muscles by producing hyperpolarization.

Hormones and neurotransmitters, which act on smooth muscles are:

1. Acetylcholine
2. Antidiuretic hormone (ADH)
3. Adrenaline
4. Angiotensin II, III and IV
5. Endothelin
6. Histamine
7. Noradrenaline
8. Oxytocin
9. Serotonin.

Other Humoral Factors

Humoral factors other than the hormones cause relaxation of smooth muscle fibers.

Humoral factors which relax the smooth muscles:

1. Lack of oxygen
2. Excess of carbon dioxide
3. Increase in hydrogen ion concentration
4. Adenosine
5. Lactic acid
6. Excess of potassium ion
7. Decrease in calcium ion
8. Nitric oxide (NO), the **endothelium-derived relaxing factor** (EDRF).

Chapter 7

Electromyogram and Disorders of Skeletal Muscle

- DEFINITION
- ELECTROMYOGRAPHIC TECHNIQUE
- ELECTROMYOGRAM
- DISORDERS OF SKELETAL MUSCLE – MYOPATHY
  - MUSCULAR DYSTROPHY
  - DISEASES INVOLVING MUSCLE TONE
  - FIBRILLATION AND DENERVATION HYPERSENSITIVITY
  - MYASTHENIA GRAVIS
  - LAMBERT-EATON SYNDROME
  - McARDLE DISEASE
  - MITOCHONDRIAL MYOPATHY
  - NEMALINE MYOPATHY

DEFINITION

Electromyography is the study of electrical activity of the muscle. Electromyogram (EMG) is the graphical registration of the electrical activity of the muscle.

ELECTROMYOGRAPHIC TECHNIQUE

Cathode ray oscilloscope or a polygraph is used to record the electromyogram. Two types of electrodes are used for recording the electrical activities of the muscle:

1. Surface electrode or skin electrode for studying the activity of a muscle.
2. Needle electrodes for studying the electrical activity of a single motor unit.

ELECTROMYOGRAM

Structural basis for electromyogram is the motor unit. Electrical potential developed by the activation of one motor unit is called motor unit potential. It lasts for 5 to 8 milliseconds and has an amplitude of 0.5 mV. Mostly it is monophasic (Fig. 34.1).

Electrical potential recorded from the whole muscle shows smaller potentials if the force of contraction is less. When the force increases, larger potentials are obtained due to the recruitment of more and more number of motor neurons.

Uses of Electromyogram

Electromyogram is useful in the diagnosis of neuro-muscular diseases such as motor neuron lesions, peripheral nerve injury and myopathies.

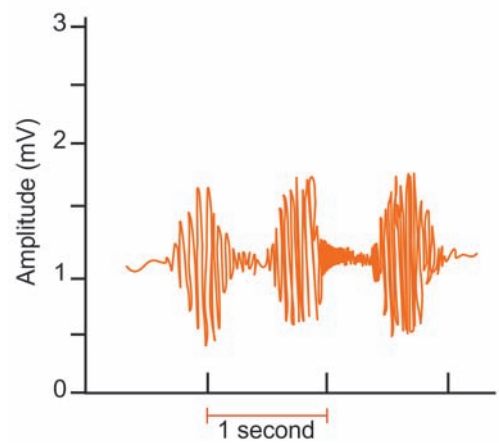


FIGURE 34.1: Electromyogram during alternate contraction and relaxation of biceps muscle

DISORDERS OF SKELETAL MUSCLES – MYOPATHY

Myopathy is a muscular disorder in which the dysfunction of muscle fiber leads to muscular weakness. Myopathies may be acquired or genetically derived. These diseases may or may not involve the nervous system.

Common diseases of skeletal muscles are:

1. Muscular dystrophy
2. Diseases involving muscle tone
3. Fibrillation and denervation hypersensitivity
4. Myasthenia gravis
5. Lambert-Eaton syndrome
6. McArdle disease
7. Mitochondrial myopathy
8. Nemaline myopathy.

1. MUSCULAR DYSTROPHY

Muscular dystrophy is a disease characterized by progressive degeneration of muscle fibers, without the involvement of nervous system. Mostly it has a hereditary origin. The muscles fail to regenerate, resulting in progressive weakness and confinement to a wheelchair. Eventually, death occurs. Common types of muscular dystrophy are Duchenne muscular dystrophy and Becker muscular dystrophy.

Duchenne Muscular Dystrophy

Duchenne muscular dystrophy is a sex-linked recessive disorder. It is due to the absence of a gene product called **dystrophin** in the X chromosome. Dystrophin is necessary for the stability of sarcolemma. This disease is characterized by degeneration and necrosis of muscle fibers. The degenerated muscle fibers are replaced by fat and fibrous tissue. Common symptom is the muscular weakness. Sometimes, there is **enlargement of muscles (pseudohypertrophy).** In severe conditions, the respiratory muscles become weak, resulting in difficulty in breathing and death.

Becker Muscular Dystrophy

Becker muscular dystrophy is also a sex-linked disorder. It occurs due to the reduction in quantity or alteration of dystrophin. Common features of this disorder are slow progressive weakness of legs and pelvis, pseudohypertrophy of calf muscles, difficulty in walking, fatigue and mental retardation.

2. DISEASES INVOLVING MUSCLE TONE

Hypertonia

Hypertonia or hypertonicity is a muscular disease characterized by increased muscle tone and inability of the muscle to stretch.

Causes

Hypertonia occurs in upper motor neuron lesion.During the lesion of upper motor neuron, inhibition of lower motor neurons (gamma-motor-neurons in the spinal cord) is lost. It causes exaggeration of lower motor neuron activity, resulting in hypertonia.

In children, hypertonia is associated with cerebral palsy (permanent disorder caused by brain damage, which occurs at or before birth and is characterized by muscular impairment). Here also, the motor pathway is affected. Such children usually have speech and language delays, with lack of communication skills.

Hypertonia and spasticity

Hypertonia may be related to spasticity, but it is present with or without spasticity. Spasticity is a motor disorder characterized by stiffness of the certain muscles due to continuous contraction. Hypertonicity is one of the major symptoms of spasticity. **Paralysis** (complete loss of function) of the muscle due to hypertonicity is called spastic paralysis.

In hypertonia, there is a resistance to passive movement and it does not depend on velocity (the speed at which the movement occurs), where as in spasticity there is an increase in resistance to sudden passive movement. It is velocity dependent, i.e. faster the passive movement stronger the resistance.

Hypotonia

Hypotonia is the muscular disease characterized by decreased muscle tone. The tone of the muscle is decreased or lost. Muscle offers very little resistance to stretch. Muscle becomes flaccid (lack of firmness) and the condition is called flaccidity.

Causes

Major cause for hypotonia is lower motor neuron lesion. The paralysis of muscle with hypotonicity is called flaccid paralysis and it results in wastage of muscles.

Hypotonia may also occur because of central nervous system dysfunction, genetic disorders or muscular disorders.

Clinical conditions associated with hypotonia are:

i. **Down syndrome** (chromosomal disorder, characterized by physical and learning disabilities)
ii. **Myasthenia gravis** (see below)
iii. **Kernicterus** (brain damage caused by jaundice in infants; Chapter 163)
iv. Congenital **cerebellar ataxia** (incoordination)
v. Muscular dystrophy

vi. Congenital hypothyroidism
vii. Hypervitaminosis D
viii. Rickets (Chapter 68)
ix. Infant botulism (paralysis due to *botulinum* toxin).

Myotonia

Myotonia is a congenital disease characterized by continuous contraction of muscle and slow relaxation even after the cessation of voluntary act. The main feature of this disease is the muscle stiffness, which is sometimes referred as cramps. Muscle relaxation is delayed.

This type of muscular stiffness with delayed relaxation causes discomfort during simple actions like walking, grasping and chewing. The muscles are enlarged (hypertrophy) because of the continuous contraction. Myotonia sets in during early to late childhood and it is not progressive.

Cause

Myotonia is caused by mutation in the genes of channel proteins in sarcolemma. Such disorders are called channelopathies.

Types

Myotonia is of two types:

i. **Becker-type myotonia** or **generalized myotonia,** which is more common than Thomsen-type myotonia. It is an autosomal recessive disorder produced by defective genes contributed by both the parents
ii. **Thomsen-type myotonia** is relatively rare and it is an autosomal recessive disorder produced by defective gene contributed by one parent.

■ 3. FIBRILLATION AND DENERVATION HYPERSENSITIVITY

Denervation of a skeletal muscle (lower motor neuron lesion) causes fibrillation with flaccid paralysis and denervation hypersensitivity.

Fibrillation

Fibrillation means fine irregular contractions of individual muscle fibers.

Denervation Hypersensitivity

After denervation, the muscle becomes highly sensitive to acetylcholine, which is released from neuromuscular junction. It is called denervation hypersensitivity.

■ 4. MYASTHENIA GRAVIS

Myasthenia gravis is an autoimmune disease of neuromuscular junction caused by antibodies to cholinergic receptors. It is characterized by grave weakness of the muscle due to the inability of neuromuscular junction to transmit impulses from nerve to the muscle. It is a serious and sometimes a fatal disease.

Causes

Myasthenia gravis is caused due to the development of **autoantibodies** (IgG autoantibodies) against the receptors of acetylcholine. That is, the body develops antibodies against its own acetylcholine receptors. These antibodies prevent binging of acetylcholine with it receptors or destroy the receptors. So, though the acetylcholine release is normal, it cannot execute its action.

Symptoms

Muscles which are more susceptible for myasthenia gravis are muscles of neck, limbs, eyeballs and the muscle responsible for eyelid movements, chewing, swallowing, speech and respiration.

Common symptoms are:

i. Slow and weak muscular contraction because of the defective neuromuscular activity
ii. Inability to maintain the prolonged contraction of skeletal muscle
iii. Quick fatigability when the patient attempts repeated muscular contractions
iv. Weakness and fatigability of arms and legs
v. Double vision and droopy eyelids due to the weakness of ocular muscles
vi. Difficulty in swallowing due to weakness of throat muscles
vii. Difficulty in speech due to weakness of muscles of speech.

In severe conditions, there is paralysis of muscles. Patient dies mostly due to the paralysis of respiratory muscles.

Treatment

Myasthenia gravis is treated by administration of cholinesterase inhibitors such as **neostigmine** and **pyridostigmine.** These drugs inhibit cholinesterase, which degrades acetylcholine. So acetylcholine remaining in the synaptic cleft for long period can bind with its receptors.

5. LAMBERT-EATON SYNDROME

Lambert-eaton syndrome is a disorder of neuromuscular junction caused by development of antibodies against **calcium channel** in the nerve terminal, resulting in reduction in the release of quanta of acetylcholine. This disease is commonly associated with carcinoma. So, it is also called **carcinomatous myopathy.** This disease is characterized by several features of myasthenia gravis. In addition, the patients have blurred vision and dry mouth.

6. McARDLE DISEASE

McArdle disease is a glycogen storage disease (accumulation of glycogen in muscles) due to the mutation of genes involving the **muscle glycogen phosphorylase,** necessary for the breakdown of glycogen in muscles. Muscular pain and stiffness are the common features of this disease.

7. MITOCHONDRIAL MYOPATHY

Mitochondrial myopathy is an inherited disease due to the defects in the mitochondria (which provide critical source of energy) of muscle fibers.

8. NEMALINE MYOPATHY

Nemaline myopathy is a congenital myopathy characterized by microscopic changes and formation of small rod-like structures in the muscle fibers. It is also called **nemaline-rod myopathy.** The features are delayed development of motor activities and weakness of muscles.

Chapter 8

Endurance of Muscle

- STRENGTH OF THE MUSCLE
  - TYPES OF MUSCLE STRENGTH
- POWER OF THE MUSCLE
- ENDURANCE OF THE MUSCLE

Three factors are essential for the contraction of skeletal muscle:

1. Strength of the muscle
2. Power of the muscle
3. Endurance of the muscle.

Strength and power of the muscle are the two factors which determine the endurance of the muscle. Power of the muscle is developed by strength of the muscle

STRENGTH OF THE MUSCLE

Maximum force that can be developed during contraction is known as strength of the muscle. It is defined as the maximal contractile force produced per square centimeter of the cross-sectional area of a skeletal muscle. The normal force produced by a muscle is about 3 to 4 kg/cm^2 area of muscle. If the size of the muscle is more, the strength developed also will be more.

The size of the muscle can be increased either by exercise or by some hormones like androgens. For example, weight lifters will have the quadriceps muscle with cross-sectional area of about 150 cm^2. So, the total strength of the quadriceps muscles is between 500 and 550 kg/cm^2.

TYPES OF MUSCLE STRENGTH

Strength of the muscle is of two types:

1. Contractile strength
2. Holding strength.

1. *Contractile Strength*

Contractile strength is the strength of the muscle during the actual contraction or shortening of muscle fibers. For example, while jumping, when a person takes his body off the ground, there is contraction of the leg muscles. This is called the contractile strength.

2. *Holding Strength*

Holding strength is the force produced while stretching the contracted muscles. For example, while landing after jumping, the leg muscles are stretched. The force developed by the muscles at that time is called the holding strength. The holding strength is greater than the contractile strength.

POWER OF THE MUSCLE

Amount of work done by the muscle in a given unit of time is called the power. Power of the muscle depends upon three factors. Muscle power is directly proportional to these factors:

1. Strength of the muscle.
2. Force of contraction.
3. Frequency of contraction.

Muscle power is generally expressed in kilogram-meter per min (kg-m/min), i.e. the weight lifted by a muscle to a height of 1 meter for one minute. The maximum power achieved by all the muscles in the body of a highly trained athlete, with all the muscles working together is approximately,

First 8 to 10 seconds : 7,000 kg-m/min
Next 1 minute : 4,000 kg-m/min
Next 30 minute : 1,700 kg-m/min

This shows that the maximum power is developed only for a short period of time.

■ ENDURANCE OF THE MUSCLE

Capacity of the muscle to withstand the power produced during activity is called endurance. It depends mostly on the supply of nutrition to the muscle.

Most important nutritive substance for the muscle is glycogen. This is actually stored in the muscle before the beginning of the activity. More amount of glycogen can be stored in the muscles if a person takes diet containing more carbohydrates than the diet containing fat or a mixed diet. Following is the amount of glycogen stored in the muscle in persons taking different diets.

High carbohydrate diet	:	40 gm/kg muscle
Mixed diet	:	20 gm/kg muscle
High fat diet	:	6 gm/kg muscle.

QUESTIONS IN MUSCLE PHYSIOLOGY

LONG QUESTIONS

1. Enumerate the properties of muscles and give an account on contractile property of the skeletal muscle.
2. List the various changes taking place during muscular contraction and explain the molecular basis of contraction.
3. Write about the electrical changes during muscular contraction.
4. Explain the ionic basis of electrical events during contraction of skeletal muscle.
5. Describe the neuromuscular junction with a suitable diagram. Add a note on neuromuscular transmission

SHORT QUESTIONS

1. Compare skeletal muscle and cardiac muscle.
2. Compare skeletal muscle and smooth muscle.
3. Sarcomere.
4. Contractile elements of the muscle.
5. Muscle proteins.
6. Sarcotubular system.
7. Sarcoplasmic reticulum.
8. Composition of muscle.
9. Excitability or strength-duration curve.
10. Factors affecting force of muscular contraction.
11. Simple muscle curve.
12. Latent period.
13. Differences between pale and red muscles.
14. Effects of two successive stimuli on muscle.
15. Effects of temperature variation on muscle.
16. Rigor.
17. Effects of repeated stimuli on skeletal muscle.
18. Fatigue.
19. Tetanus.
20. Starling's law of muscle.
21. Refractory period.
22. Muscle tone.
23. Resting membrane potential.
24. Action potential.
25. Graded potential.
26. Patch clamp.
27. Actomyosin complex.
28. Excitation-contraction coupling.
29. Sliding theory of muscular contraction.
30. Chemical changes during muscular contraction.
31. Liberation of energy for muscular contraction.
32. Thermal changes during muscular contraction.
33. Electrical activity in smooth muscle.
34. Molecular basis of smooth muscular contraction.
35. Neuromuscular junction.
36. Neuromuscular transmission.
37. Endplate potential.
38. Neuromuscular blockers.
39. Motor unit.
40. Electromyogram.
41. Myopathy.
42. Muscular dystrophy.
43. Myasthenia gravis.
44. Hypertonia.
45. Hypotonia.

Chapter 9

Venous Pressure

DEFINITION AND NORMAL VALUES

Venous pressure is the pressure exerted by the contained blood in the veins. The pressure in vena cava and right atrium is called **central venous pressure.** The pressure in peripheral veins is called **peripheral venous pressure.**

Pressure is not same in all the veins. It varies in different veins in the extremities of the body and also varies from central veins to peripheral veins.

VENOUS PRESSURE IN EXTREMITIES OF THE BODY

Venous pressure is less in the parts of the body above the level of the heart and it is more in parts below the level of the heart. Pressure in:

Jugular vein: 5.1 mm Hg (6.9 cm H_2O)
Dorsal venous arch of foot: 13.2 mm Hg (17.9 cm H_2O).
(1 mm Hg pressure = 1.359 cm H_2O pressure)

VENOUS PRESSURE IN CENTRAL AND PERIPHERAL VEINS

Pressure is greater in peripheral veins than in central veins. Pressure in:

Antecubital vein: 7.1 mm Hg (9.6 cm H_2O)
Superior vena cava: 4.6 mm Hg (6.2 cm H_2O).

VARIATIONS OF VENOUS PRESSURE

Venous pressure is altered both in physiological and pathological conditions.

■ PHYSIOLOGICAL VARIATIONS

Venous pressure increases in:

1. Changing from standing to supine position
2. Tilting the body
3. Forced expiration (Valsalva maneuver)
4. Contraction of abdominal and limb muscles
5. Effect of gravity during prolonged travelling or standing
6. Excitement.

■ PATHOLOGICAL VARIATIONS

Venous pressure increases in:

1. Low cardiac output
2. Congestive heart failure
3. Venous obstruction
4. Failure of valves in veins
5. Paralysis of muscles
6. Immobilization of parts of body
7. Renal failure.

Venous pressure decreases in:

1. Severe hemorrhage
2. Surgical shock.

■ MEASUREMENT OF VENOUS PRESSURE

■ DIRECT METHOD

Central venous pressure is measured by a catheter introduced through median cubital vein of forearm. Position of tip of the catheter is checked by fluoroscopy. Other end of catheter is connected to a manometer, which measures the pressure. Peripheral venous pressure is measured by using a needle connected to a manometer.

■ INDIRECT METHOD

Measurement of venous pressure is done by using an apparatus designed by Ranger. By this apparatus, collapse of the vein is noticed by the reflection of light through a transparent device. Pressure required to cause the collapse of peripheral vein denotes the pressure in the particular vein.

■ FACTORS REGULATING VENOUS PRESSURE

■ 1. LEFT VENTRICULAR CONTRACTION OR *VIS A TERGO*

Left ventricular contraction is also called *vis a tergo* or force from behind. It forces the blood through the arteries, arterioles, capillaries and veins to the right atrium. Venous pressure is **directly proportional** to left ventricular pressure. By the time blood passes through capillaries and reaches the venules, the pressure becomes less than 8 mm Hg and when it reaches right atrium, the pressure may be less than 1 mm Hg.

■ 2. RIGHT ATRIAL PRESSURE OR *VIS A FRONTE*

Right atrial pressure is also called *vis a fronte* or force from front. It determines the venous return. It is also called central venous pressure, which in turn regulates the peripheral venous pressure. Normal right atrial pressure is 0 mm Hg.

■ 3. RESISTANCE OR *VIS A LATRE*

Resistance offered to blood flow through the veins is also called *vis a latre* or force from side. Venous pressure is **directly proportional** to the resistance, which is due to venous tone and extravascular factors. Because of the thin-walled nature, veins and venules are compressed by the extravascular factors such as:

i. Compression of arm vein while passing over first rib
ii. Compression of neck veins in erect posture due to fall in pressure and by atmospheric pressure
iii. Compression of abdominal veins by increased intra-abdominal pressure
iv. Compression of veins while passing in between the muscles.

■ 4. VOLUME OF VENOUS BLOOD

Venous pressure is **directly proportional** to the volume of blood in the venous system.

■ 5. PERIPHERAL RESISTANCE

Venous pressure is **inversely proportional** to peripheral resistance. When peripheral resistance is more, arterioles constrict and the veins are filled with less blood. Hence, the pressure decreases. When peripheral resistance is less, the veins are filled with more blood and venous pressure increases.

■ 6. GRAVITY AND POSTURE

Pressure is more in the veins below the level of heart and the pressure is less in veins above the level of heart.

Weight of the column of blood in veins influences the venous pressure. During prolonged standing, the pressure in lower extremities is more (90 cm H_2O). It is

TABLE 104.1: Valsalva maneuver Vs Müeller maneuver

Features	Valsalva maneuver	Müeller maneuver
1. Intrathoracic pressure	Increases up to +50 mm Hg	Decreases up to –70 mm Hg
2. Central vein in thorax	Compressed	Dilated and blood rushes
3. Venous return to right atrium	Decreases	Increases
4. Peripheral venous pressure	Increases to 30 cm H_2O	Decreases to 3 cm H_2O
5. Central venous pressure	Decreases	Increases

because of pooling of blood in the legs due to gravity. It increases the weight of the column of blood, leading to increase in pressure. During the movement, the venous pressure in foot decreases.

In head region, the venous pressure is –10 cm H_2O because of the hydrostatic suction below the skull. So, there is always a negative venous pressure in the head.

■ EFFECT OF RESPIRATION ON VENOUS PRESSURE

During normal quiet breathing, the central venous pressure is altered in accordance with intrathoracic pressure. Thus, during inspiration, the central venous pressure decreases because of decreased intrathoracic pressure. During expiration, it increases because of increased intrathoracic pressure.

The effect of respiration on venous pressure is demonstrated by some procedures which exaggerate these effects on venous pressure. Such procedures are Valsalva maneuver and Mueller maneuver.

■ VALSALVA MANEUVER OR VALSALVA EXPERIMENT

Valsalva maneuver is the forced expiratory effort with closed glottis. It is performed by attempting to exhale forcibly, while keeping the mouth and nose closed.

Effects of Valsalva Maneuver

During this maneuver, the intrathoracic pressure becomes positive and increases greatly. It may reach +50 mm Hg. High intrathoracic pressure produces the following effects (Table 104.1):

1. Compression of central vein in thorax
2. Decrease in venous return to right atrium
3. Increase in peripheral venous pressure to about 30 cm H_2O, due to accumulation of blood in peripheral veins such as veins of neck, face and limbs
4. Decrease in central venous pressure.

Uses of Valsalva Maneuver

1. Valsalva maneuver is used as a diagnostic tool to evaluate the cardiovascular disorders. Best example is the 30 minutes endurance test.
2. Valsalva maneuver is practiced to relieve chest pain
3. It is used to correct the abnormal heart rhythms.

30 seconds endurance test

The subject is asked to blow against sphygmomanometer, in which the pressure is maintained at 40 mm Hg for 30 seconds. Then the changes in heart rate, blood pressure or murmurs are observed to evaluate the cardiovascular disorders.

■ MÜELLER MANEUVER OR MÜELLER EXPERIMENT

Müeller maneuver or experiment is the forced inspiratory effort with closed glottis. It is performed by attempting to inhale forcibly, while keeping the mouth and nose closed. It is also called reverse Valsalva maneuver.

Effects of Müeller Maneuver

During this maneuver, the intrathoracic pressure decreases greatly (becomes more negative). It is about –70 mm Hg. This pressure produces the following effects (Table 104.1):

1. Dilatation of right atrium and central vein because of increase in negative intrathoracic pressure
2. Rapid emptying of blood from peripheral veins into the central veins and increase in venous return to right atrium
3. Decrease in peripheral venous pressure to less than 3 to 4 cm H_2O
4. Increase in central venous pressure.

Uses of Müeller Maneuver

Müeller maneuver is used to evaluate:

1. Upper respiratory tract problems
2. Sleep apnea syndrome.

Capillary Pressure

Chapter 10

- INTRODUCTION
- REGIONAL VARIATIONS
- MEASUREMENT
- REGULATION
- CAPILLARY ONCOTIC PRESSURE

INTRODUCTION

Definition

Capillary pressure is the pressure exerted by the blood contained in capillary. It is also called **capillary hydrostatic pressure.**

Significance

Capillary pressure is responsible for the exchange of various substances between blood and interstitial fluid through capillary wall.

Normal Values

Generally, the pressure in the arterial end of the capillary is about 30 to 32 mm Hg and in venous end it is 15 mm Hg. However, capillary pressure varies depending upon the function of the organ or region of the body.

REGIONAL VARIATIONS

Regional variation in capillary pressure is in relation to the physiological activities of the particular region. So, it has some functional significance. Capillary pressure remarkably varies in kidneys and lungs.

Capillary Pressure in Kidneys

In kidneys, the glomerular capillary pressure is high. It is about 60 mm Hg. This high capillary pressure is responsible for glomerular filtration.

Capillary Pressure in Lungs

In lungs, the pulmonary capillary pressure is low and it is about 7 mm Hg. It favors exchange of gases between blood and alveoli.

MEASUREMENT

Direct Method

Capillary pressure was first measured by **EM Landis,** when he was a medical student. Minute vessels in the web of foot in a frog were cannulated by using micropipette, with a diameter of 5 µ at the tip with the aid of microscope. The cannula was connected to a manometer.

This method was later followed to measure capillary pressure in other organs.

Indirect Method

Indirect method is based upon the principle of exerting an external pressure necessary to obstruct the flow of blood in capillaries. The capillaries are observed under microscope.

REGULATION

Arterioles play an important role in regulating the capillary pressure and the pressure in capillaries is considered as a function of arteriolar resistance.

When the arterioles constrict, resistance increases in arterioles, which raises the arterial blood pressure. At

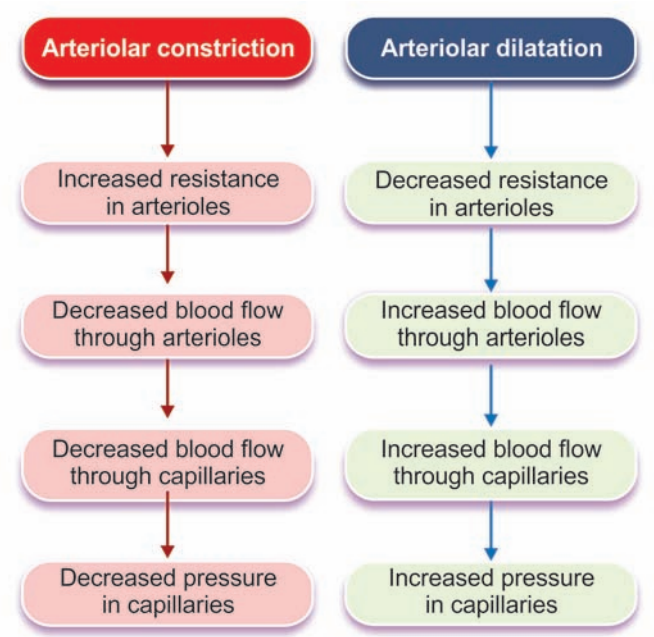


FIGURE 105.1: Regulation of capillary pressure

the same time, the volume of blood flowing into capillaries decreases, leading to fall in capillary pressure.

On the other hand, during dilatation of arterioles, the resistance decreases and arterial blood pressure decreases. But the capillary pressure increases because of increase in volume of blood flowing into capillaries (Fig. 105.1).

■ CAPILLARY ONCOTIC PRESSURE

Capillary membrane is permeable to all substances except plasma proteins. So, the plasma proteins stay within the capillaries and exert some pressure which is called oncotic pressure or colloidal osmotic pressure. Normal oncotic pressure is about 25 mm Hg. Among the plasma proteins, albumin exerts 70% of oncotic pressure.

Oncotic pressure plays an important role in filtration across capillary membrane, particularly in renal glomerular capillaries.

Venous Pulse

Chapter 11

INTRODUCTION

Venous pulse is defined as the pressure changes transmitted in the form of waves from right atrium to veins near heart. Venous pulse is observed only in larger veins near the heart such as jugular vein.

Observation of venous pulse is an integral part of the physical examination because it reflects right atrial pressure and the hemodynamic events in right atrium.

SIGNIFICANCE

1. Venous pulse recording is used to determine the rate of atrial contraction, just as the record of arterial pulse is used to determine the rate of ventricular contraction
2. Many phases of cardiac cycle can be recognized by means of venous pulse tracing
3. Venous pulse tracing is the simple and accurate method to measure the duration of different phases in diastole
4. Venous pulse also represents the atrial pressure changes taking place during cardiac cycle.

EXAMINATION OF VENOUS PULSE

Inspection of jugular vein pulsations is routinely done by bedside examination of neck veins. It provides valuable information about the cardiac function.

To observe the pulsation of internal jugular vein, head of the subject is tilted upwards at 45°. However, in patients with increased venous pressure, the head should be tilted as much as 90°. Pulsations of jugular vein can be noticed when light is passed across the skin overlying internal jugular vein with relaxed neck muscles. Simultaneous palpation of the left carotid artery helps the examiner confirm the venous pulsations.

METHODS TO RECORD VENOUS PULSE

A small **funnel** covered by thin **rubber membrane** is placed over the skin at the level of external jugular vein, in the **supraclavicular fossa.** Slight pressure is exerted to provide perfect contact between edge of the funnel and skin.

Pressure changes in the vein cause some oscillations in rubber membrane through the skin. The oscillations are transmitted through rubber tube to a recording device like **Marey tambour.** Nowadays, **electronic transducer** is used for this purpose.

The subject should be in such a position so as to avoid the effect of gravity, which tends to empty veins and reduce the amplitude of the venous pulse.

RECORDING OF VENOUS PULSE – JUGULAR VENOUS PULSE TRACING

Recording of jugular venous pulse is called **phlebogram.** It is similar to intra-atrial pressure curve (Fig. 107.1).

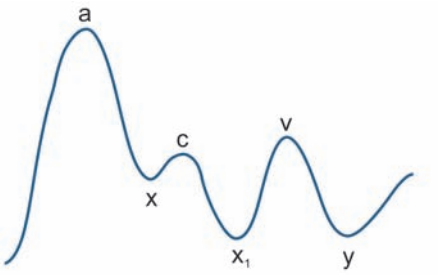


FIGURE 107.1: Phlebogram

Like intra-atrial pressure curve, phlebogram also has three positive waves, namely a, c, v and three negative waves namely x, x_1, y.

'a' Wave

'a' wave is the first positive wave. It is due to rise in atrial pressure during **atrial systole.** It precedes ventricular systole.

'x' Wave

'x' wave is a negative wave due to fall in atrial pressure. It coincides with **atrial diastole** and beginning of **ventricular systole.**

'c' Wave

'c' wave is a positive wave due to rise in atrial pressure during **isometric contraction period.** During this period, the atrioventricular valves bulge into the atria and increase the pressure in the atria slightly.

Earlier, it was thought that this wave was due to transmission of pulse from neighboring carotid artery. Hence, it was called 'c' wave.

'x_1' Wave

'x_1' wave is a negative wave due to fall in atrial pressure during **ejection period.** During ejection period, the atrioventricular ring is pulled towards ventricles causing distention of atria. So, the atrial pressure falls.

'v' Wave

'v' wave is a positive wave due to rise in atrial pressure. The pressure increases because of filling of atria (venous return). It is obtained during **isometric relaxation period** or during atrial diastole.

'y' Wave

'y' wave is a negative wave which denotes fall in atrial pressure. Pressure falls due to the opening of atrioventricular valve and emptying of blood into the ventricle. This wave appears during **rapid and slow filling periods.** 'y' wave is followed by 'a' wave and the cycle is repeated.

■ APPLIED PHYSIOLOGY – ABNORMAL VENOUS PULSE

■ ELEVATED JUGULAR VENOUS PULSE

Elevated jugular venous pulse indicates the rise in right ventricular pressure.

It occurs in:

1. Bradycardia
2. Pericardial effusion
3. Constrictive pericarditis
4. Tricuspid stenosis
5. Pulmonary hypertension.

■ KUSSMAUL SIGN

Kussmaul sign is the increase in venous distention and venous pressure. Normally, it occurs during inspiration.

Pathological Conditions when Kussmaul Sign occurs

1. Cardiac tamponade
2. Constrictive pericarditis
3. Restrictive cardiomyopathy
4. Right ventricular infarction.

■ ABNORMALITIES OF WAVES IN JUGULAR PULSE TRACING

1. *Elevation of 'a' Wave*

Elevation of 'a' wave occurs in:

i. Tricuspid stenosis
ii. Pulmonary hypertension.

2. *Cannon 'a' Wave*

Giant 'a' wave with abrupt fall (downward deflection) is called Cannon 'a' wave. It appears in:

i. Complete heart block
ii. Paroxysmal atrioventricular nodal tachycardia
iii. Ventricular tachycardia.

3. *Abnormal 'v' Wave*

'v' wave becomes abnormal in tricuspid incompetence.

4. *Abnormal 'x' Wave*

Abnormal 'x' wave appears in:

i. Atrial fibrillation
ii. Cardiac temponade
iii. Constrictive pericarditis.

5. *Abnormal 'y' Wave*

'y' wave becomes abnormal in:

i. Tricuspid regurgitation
ii. Constrictive pericarditis.

Chapter 12

Coronary Circulation

DISTRIBUTION OF CORONARY BLOOD VESSELS

CORONARY ARTERIES

Heart muscle is supplied by two coronary arteries, namely right and left coronary arteries, which are the first branches of aorta. Arteries encircle the heart in the manner of a **crown,** hence the name coronary arteries (Latin word corona = crown).

Right and Left Coronary Arteries

Right coronary artery supplies whole of the right ventricle and posterior portion of left ventricle. Left coronary artery supplies mainly the anterior and lateral parts of left ventricle. There are many variations in diameter of coronary arteries.

Variations in Coronary Arteries

1. In 50% to 60% of human beings, the right coronary artery is larger (right dominant) and supplies more blood to heart than left coronary artery
2. In 15% to 20% of human beings, the left coronary artery is larger (left dominant)
3. In 20% to 30% of human beings, both arteries supply almost equal amount of blood.

Branches of Coronary Arteries

Coronary arteries divide and subdivide into smaller branches, which run all along the surface of the heart. Smaller branches are called **epicardiac arteries** and give rise to further smaller branches known as **final arteries** or **intramural vessels.** Final arteries run at right

angles through the heart muscle, near the inner aspect of wall of the heart.

■ VENOUS DRAINAGE

Venous drainage from heart muscle is by three types of vessels.

1. *Coronary Sinus*

Coronary sinus is the larger vein draining 75% of total coronary flow. It drains blood from left side of the heart and opens into right atrium near tricuspid valve.

2. *Anterior Coronary Veins*

Anterior coronary veins drain blood from right side of the heart and open directly into right atrium.

3. *Thebesian Veins*

Thebesian veins drain deoxygenated blood from myocardium, directly into the concerned chamber of the heart.

■ PHYSIOLOGICAL SHUNT

Physiological shunt is the diverted route (diversion), through which the venous (deoxygenated) blood is mixed with arterial blood. Deoxygenated blood flowing from thebesian veins into cardiac chambers makes up the part of normal physiological shunt.

Other component of physiological shunt is the drainage of deoxygenated blood from bronchial circulation into pulmonary vein, without being oxygenated. Refer Chapter 119 for more details about physiological shunt.

■ CORONARY BLOOD FLOW AND ITS MEASUREMENT

■ NORMAL CORONARY BLOOD FLOW

Normal blood flow through coronary circulation is about 200 mL/minute. It forms 4% of cardiac output. It is about 65 to 70 mL/minute/100 g of cardiac muscle.

■ MEASUREMENT OF CORONARY BLOOD FLOW

Direct Method

Coronary blood flow is measured by using an **electromagnetic flowmeter.** It is directly placed around any coronary artery (refer Chapter 98 for details of electromagnetic flowmeter).

Indirect Method

1. *By Fick principle*

Coronary blood flow is measured by applying Fick principle (Chapter 98) using **nitrous oxide** (N_2O). The subject is asked to inhale a known quantity of the gas with atmospheric air. Then, blood samples are collected from an artery and from coronary sinus, by using a catheter. The blood flow is determined by using the formula:

$$\text{Blood flow} = \frac{\text{Amount of } N_2O \text{ taken up/minute}}{\text{Arteriovenous difference of } N_2O \text{ content}}$$

2. *By using Doppler flowmeter*

Piezoelectric crystals are used in the Doppler flowmeter probe, to transmit and receive the pulses of high frequency sound waves. The Doppler flowmeter probe is mounted to a catheter and positioned at the ostium of right or left coronary artery to measure the velocity of phasic flow of blood. The cross-sectional area of the artery is determined by angiography. From velocity of blood flow and cross-sectional area, the volume of blood flow is calculated.

3. *By videodensitometry*

Videodensitometry is the technique used to measure both velocity of blood flow and the cross-sectional area of coronary arteries, simultaneously. From these two values, the coronary blood flow can be calculated.

■ PHASIC CHANGES IN CORONARY BLOOD FLOW

Blood flow through coronary arteries is not constant. It decreases during systole and increases during diastole (Fig. 108.1).

Intramural vessels or final arteries supplying myocardium are perpendicular to the cardiac muscles. So, during systole, the intramural vessels are compressed and blood flow is reduced. During diastole, the compression is released and the blood vessels are distended. So, the blood flow increases.

■ PHASIC CHANGES IN LEFT VENTRICLE

In left ventricle, during the onset of isometric contraction, blood flow declines sharply due to two reasons, namely increase in myocardial tissue pressure and decrease in aortic pressure.

During ejection period, rise in aortic pressure causes a sharp rise in flow into left coronary artery. However,

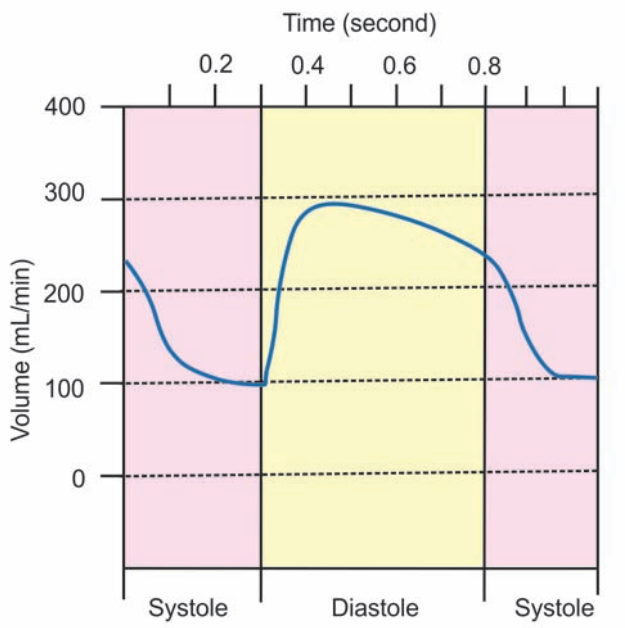


FIGURE 108.1: Phasic changes in coronary blood flow

the flow of blood through coronary capillaries is less. It is due to the high intramural myocardial pressure in the contracting ventricle. Decreased blood flow is maintained until the closure of aortic valve, i.e. till the end of systole.

During the onset of diastole, blood flow rises and it reaches the peak sharply. During the later part of diastole, the flow is reduced slightly along with decreasing aortic pressure. Once again, there is a sharp fall in flow during the onset of systole.

■ PHASIC CHANGES IN RIGHT VENTRICLE

A small amount of blood flows into right ventricle during systole. It is because the force of contraction is not as severe as in the case of left ventricle. Still, the amount of blood flowing is very much less than that during diastole.

■ FACTORS REGULATING CORONARY BLOOD FLOW

Autoregulation

Like any other organ, heart also has the capacity to regulate its own blood flow by autoregulation (Chapter 102). Coronary blood flow is not affected when mean arterial pressure varies between 60 and 150 mm Hg. Several factors are involved in the autoregulation mechanism.

Coronary blood flow is regulated mainly by local vascular response to the needs of cardiac muscle.

Factors regulating coronary blood flow:

1. Need for oxygen
2. Metabolic factors
3. Coronary perfusion pressure
4. Nervous factors.

■ 1. NEED FOR OXYGEN

Oxygen is the most important factor maintaining blood flow through the coronary blood vessels. Amount of blood passing through coronary circulation is directly proportional to the consumption of oxygen by cardiac muscle.

Even in resting condition, a large amount of oxygen, i.e. 70% to 80% is consumed from the blood by heart muscle than by any other tissues. In conditions associated with increased cardiac activity, the need for oxygen increases enormously.

Thus, the need for oxygen, i.e. hypoxia immediately causes coronary vasodilatation and increases the blood flow to heart.

■ 2. METABOLIC FACTORS

Coronary vasodilatation during hypoxic conditions occurs because of some metabolic products, which increase the coronary blood flow by vasodilatation.

Reactive Hyperemia

Reactive hyperemia is the increase in blood flow due to the vasodilator effects of metabolites.

Metabolic Products which Increase the Coronary Blood Flow

Adenosine

Adenosine is a potent vasodilator and it increases the blood flow to cardiac muscle. During hypoxia, ATP in the muscle is degraded in large amount, forming ADP. Some ADP molecules are further degraded into adenosine, which is released into tissue fluids of heart muscle.

Other substances

Other substances which increase the coronary blood flow by vasodilatation are:

i. Potassium
ii. Hydrogen
iii. Carbon dioxide
iv. Adenosine phosphate compounds.

3. CORONARY PERFUSION PRESSURE

Perfusion pressure is the balance between mean arterial pressure and venous pressure (Chapter 102). Thus, coronary perfusion pressure is the balance between mean arterial pressure in aorta and the right atrial pressure. Since right aterial pressure is low, the mean arterial pressure becomes the major factor that maintains the coronary blood flow. Range of mean arterial pressure at which the coronary blood flow can be maintained is given above.

4. NERVOUS FACTORS

Coronary blood vessels are innervated both by para-sympathetic and sympathetic divisions of autonomic nervous system. It is not known whether the autonomic nerves have direct effect on blood flow in various conditions. However, these nerves influence the coronary blood flow indirectly by acting on the musculature of heart.

For example, stimulation of sympathetic nerves increases the rate and force of contraction of heart. This in turn, causes liberation of more metabolites which dilate the blood vessels and increase the coronary blood flow. Similarly, when parasympathetic nerves are stimulated, the cardiac functions are inhibited and the production of metabolites is less. Coronary blood flow decreases.

APPLIED PHYSIOLOGY – CORONARY ARTERY DISEASE

Coronary artery disease (CAD) is the heart disease that is caused by inadequate blood supply to cardiac muscle due to occlusion of coronary artery. It is also called coronary heart disease.

CORONARY OCCLUSION

Definition

Coronary occlusion is the partial or complete obstruction of the coronary artery.

Cause

Coronary occlusion is caused by atherosclerosis, a condition associated with deposition of cholesterol on the walls of the artery. In due course, this part of the arterial wall becomes fibrotic and it is called **atherosclerotic plaque.** The plaque is made up of cholesterol, calcium and other substances from blood. Because of the atherosclerotic plaque, the lumen of the coronary artery becomes narrow. In severe conditions, the artery is completely occluded.

Development of atherosclerotic plaque is common in coronary arteries near the origin from aorta. This plaque activates platelets, resulting in **thrombosis** and the blood clot is called **thrombus.** When three fourth of the lumen of the coronary artery is obstructed either by atherosclerotic plaque or thrombus, the blood flow to myocardium is reduced. It results in **ischemia** of myocardium. Coronary thrombosis is associated with **spasm** of coronary artery.

Smaller blood vessels are occluded by the thrombus or part of atherosclerotic plaque, detached from coronary artery. This thrombus or part of the plaque is called **embolus.**

MYOCARDIAL ISCHEMIA AND NECROSIS

Myocardial Ischemia

Myocardial ischemia is the reaction of a part of myocardium in response to hypoxia. Hypoxia develops when blood flow to a part of myocardium decreases severely due to occlusion of a coronary artery.

Blood flow is usually restored if a small quantum of myocardium is affected by ischemia due to obstruction of smaller blood vessels. It is due to rapid development of **coronary collateral arteries.**

Necrosis

Necrosis refers to death of cells or tissues by injury or disease in a localized area. Ischemia leads to necrosis of myocardium if a large part of myocardium is involved or the occlusion is severe involving larger blood vessels. Necrosis is irreversible.

MYOCARDIAL INFARCTION – HEART ATTACK

Myocardial infarction is the necrosis of myocardium caused by insufficient blood flow due to embolus, thrombus or vascular spasm. It is also called heart attack. In myocardial infarction, death occurs rapidly due to ventricular fibrillation.

Myocardial Stunning

Myocardial stunning is a type of transient mechanical dysfunction of heart, caused by a mild reduction in blood flow. A substantial reduction in coronary blood flow causes ischemia followed by necrosis. A mild reduction in blood flow causes only ischemia and it may not be sufficient to cause necrosis of myocardium. However,

it produces some transient (short lived) mechanical disturbances or dysfunction of the heart. Since it is short lived, heart recovers completely from this.

Symptoms of Myocardial Infarction

Common symptoms of myocardial infarction:

1. Cardiac pain
2. Nausea
3. Vomiting
4. Palpitations
5. Difficulty in breathing
6. Extreme weakness
7. Sweating
8. Anxiety.

■ CARDIAC PAIN – ANGINA PECTORIS

Cardiac pain is the **chest pain** that is caused by myocardial ischemia. It is also called angina pectoris. It is the common manifestation of coronary artery disease. Pain starts beneath the sternum and radiates to the surface of left arm and left shoulder. Cardiac pain is a referred pain and it is felt over the body, away from heart. It is because, heart and left arm develop from the same dermatomal segment in embryo.

Cause for Cardiac Pain

Ischemia is mainly due to hypoxia. During myocardial ischemia, there is accumulation of anaerobic metabolic end products such as uric acid. Metabolites and other pain producing substances like substance P, histamine and kinin stimulate the sensory nerve endings, leading to pain.

Sensory Pathway

Sensory pathway from the heart is as follows:

1. Inferior cervical sympathetic nerve fibers (Chapter 101) carrying the sensations of pain (or stretch) from the heart reach the posterior gray horn of first 4 thoracic segments of spinal cord
2. Here, these fibers synapse with second order neurons (substantial gelatinosa of Rolando) of lateral spinothalamic tract
3. Fibers from substantial gelatinosa of Rolando form lateral spinothalamic tract and reach the sensory cortex via thalamus.

If hypoxia in myocardium is relieved by coronary collateral circulation or by treatment, the pain producing substances are washed away by blood flow.

Chronic Angina Pectoris

In chronic angina pectoris, the patient does not feel the pain normally. The pain is felt only when the workload of heart increases. The workload of the heart increases in conditions like exercise and emotional outburst.

When the frequency of angina attack increases, the patient is prone to develop acute myocardial infarction.

Treatment for Angina Pectoris

1. *By using drugs*

   i. *Vasodilator drugs:* Vasodilator drugs like glycerol trinitrate or sodium nitrite relieve the pain by dilating coronary arteries. However, the main therapeutic effect of such drugs is to dilate splanchnic blood vessels, which cause reduction in venous return, cardiac output, workload of the heart and oxygen consumption in myocardium so that, release of pain promoting substances is inhibited.

   ii. *Calcium **channel blockers:*** These drugs block the influx of calcium into the cells. When calcium influx is blocked, the myocardial contractility and workload of the heart are decreased.

   iii. *Sympathetic blocking agents:* Sympathetic blocking agents like propranolol **(beta blockers)** block the beta-adrenergic receptors and inhibit the cardiac activity. This decreases heart rate, stroke volume, workload on heart and oxygen consumption. It also stops the production of nociceptive substances in myocardium.

2. *By thrombolysis*

3. *By surgical methods*

   i. *Aortic-coronary artery bypass graft:* Part of myocardium affected by coronary occlusion is detected by **angiography.** Then, the anastomosis is made between aorta and the coronary artery beyond occlusion, by a technique called aortic-coronary artery bypass graft. Mostly, a small vein from lower limb is used for anastomosis. Though this method can relieve the pain, it is not useful if the myocardium is damaged extensively.

   ii. *Percutaneous transluminal coronary angioplasty (PTCA):*

   iii. *Laser coronary angioplasty:*

Chapter 13

Ventilation

- VENTILATION
- PULMONARY VENTILATION
  - DEFINITION
  - NORMAL VALUE AND CALCULATION
- ALVEOLAR VENTILATION
  - DEFINITION
  - NORMAL VALUE AND CALCULATION
- DEAD SPACE
  - DEFINITION
  - TYPES
  - NORMAL VALUE
  - MEASUREMENT
- VENTILATION-PERFUSION RATIO
  - DEFINITION
  - NORMAL VALUE AND CALCULATION
  - SIGNIFICANCE
  - WASTED AIR AND WASTED BLOOD
  - VARIATIONS

VENTILATION

In general, the word 'ventilation' refers to circulation of replacement of air or gas in a space. In respiratory physiology, ventilation is the rate at which air enters or leaves the lungs. Ventilation in **respiratory physiology** is of two types:

1. Pulmonary ventilation
2. Alveolar ventilation.

PULMONARY VENTILATION

DEFINITION

Pulmonary ventilation is defined as the volume of air moving in and out of respiratory tract in a given unit of time during quiet breathing. It is also called **minute ventilation** or **respiratory minute volume** (RMV).

Pulmonary ventilation is a cyclic process, by which fresh air enters the lungs and an equal volume of air leaves the lungs.

NORMAL VALUE AND CALCULATION

Normal value of pulmonary ventilation is 6,000 mL (6 L)/minute. It is the product of tidal volume (TV) and the rate of respiration (RR).

It is calculated by the formula:

Pulmonary ventilation
= Tidal volume × Respiratory rate
= 500 mL × 12/minute
= 6,000 mL/minute.

ALVEOLAR VENTILATION

DEFINITION

Alveolar ventilation is the amount of air utilized for gaseous exchange every minute.

Alveolar ventilation is different from pulmonary ventilation. In pulmonary ventilation, 6 L of air moves in and out of respiratory tract every minute. But the

whole volume of air is not utilized for exchange of gases. Volume of air subjected for exchange of gases is the alveolar ventilation. Air trapped in the respiratory passage (dead space) does not take part in gaseous exchange.

■ NORMAL VALUE AND CALCULATION

Normal value of alveolar ventilation is 4,200 mL (4.2 L)/minute.

It is calculated by the formula:

Alveolar ventilation
= (Tidal volume – Dead space) x Respiratory rate
= (500 – 150) mL × 12/minute
= 4,200 mL (4.2 L)/minute.

■ DEAD SPACE

■ DEFINITION

Dead space is defined as the part of the respiratory tract, where gaseous exchange does not take place. Air present in the dead space is called dead space air.

■ TYPES OF DEAD SPACE

Dead space is of two types:

1. Anatomical dead space
2. Physiological dead space.

Anatomical Dead Space

Anatomical dead space extends from nose up to terminal bronchiole. It includes nose, pharynx, trachea, bronchi and branches of bronchi up to terminal bronchioles. These structures serve only as the passage for air movement. Gaseous exchange does not take place in these structures.

Physiological Dead Space

Physiological dead space includes anatomical dead space plus two additional volumes.

Additional volumes included in physiological dead space are:

1. Air in the alveoli, which are **non-functioning**. In some respiratory diseases, alveoli do not function because of dysfunction or destruction of alveolar membrane.
2. Air in the alveoli, which do not receive adequate blood flow. Gaseous exchange does not take place during inadequate blood supply.

These two additional volumes are generally considered as wasted ventilation.

Wasted ventilation and wasted air

Wasted ventilation is the volume of air that ventilates physiological dead space. Wasted air refers to air that is not utilized for gaseous exchange. Dead space air is generally considered as wasted air.

■ NORMAL VALUE OF DEAD SPACE

Volume of normal dead space is 150 mL. Under normal conditions, physiological dead space is equal to anatomical dead space. It is because, all the alveoli are functioning and all the alveoli receive adequate blood flow in normal conditions.

Physiological dead space increases during respiratory diseases, which affect the pulmonary blood flow or the alveoli.

■ MEASUREMENT OF DEAD SPACE – NITROGEN WASHOUT METHOD

Dead space is measured by single breath nitrogen washout method. The subject respires normally for few minutes. Then, he takes a sudden inhalation of pure oxygen.

Oxygen replaces the air in dead space (air passage), i.e. the dead space air contains only oxygen and it pushes the other gases into alveoli.

Now, the subject exhales through a nitrogen meter. Nitrogen meter shows the concentration of nitrogen in expired air continuously.

First portion of expired air comes from upper part of respiratory tract or air passage, which contains only oxygen. Next portion of expired air comes from the alveoli, which contains nitrogen. Now, the nitrogen meter shows the nitrogen concentration, which rises sharply and reaches the plateau soon. By using data obtained from nitrogen meter, a graph is plotted. From this graph, the dead space is calculated (Fig. 122.1).

The graph has two areas, area without nitrogen and area with nitrogen. Area of the graph is measured by a planimeter or by computer. Area without nitrogen indicates dead space air.

It is calculated by the formula:

$$\text{Dead space} = \frac{\text{Area without } N_2}{\text{Area with } N_2 + \text{Area without } N_2} \times \text{Volume of expired air}$$

For example, in a subject:
Area with nitrogen = 70 sq cm
Area without nitrogen = 30 sq cm
Volume of air expired = 500 mL

$$\text{Dead space} = \frac{30}{70 + 30} \times 500$$

$$= \frac{30}{100} \times 500$$

$$= 150 \text{ mL.}$$

VENTILATION-PERFUSION RATIO

DEFINITION

Ventilation-perfusion ratio is the ratio of alveolar ventilation and the amount of blood that perfuse the alveoli.

It is expressed as V_A/Q. V_A is alveolar ventilation and Q is the blood flow (perfusion).

NORMAL VALUE AND CALCULATION

Normal Value

Normal value of ventilation-perfusion ratio is about 0.84.

Calculation

Alveolar ventilation is calculated by the formula:

$$\text{Ventilation-perfusion ratio} = \frac{\text{Alveolar ventilation}}{\text{Pulmonary blood flow}}$$

$$\text{Alveolar ventilation} = (\text{Tidal volume} - \text{Dead space}) \times \text{Respiratory rate}$$

$$= (500 - 150) \text{ mL} \times 12/\text{minute}$$

$$= 4{,}200 \text{ mL/minute}$$

$$\text{Blood flow through alveoli (Pulmonary blood flow)} = 5{,}000 \text{ mL/minute}$$

Therefore,

$$\text{Ventilation-perfusion ratio} = \frac{4{,}200}{5{,}000}$$

$$= 0.84$$

SIGNIFICANCE OF VENTILATION-PERFUSION RATIO

Ventilation-perfusion ratio signifies the gaseous exchange. It is affected if there is any change in alveolar ventilation or in blood flow.

Ventilation without perfusion = dead space

Perfusion without ventilation = shunt

WASTED AIR AND WASTED BLOOD

Ventilation-perfusion ratio is not perfect because of existence of two factors on either side of alveolar membrane.

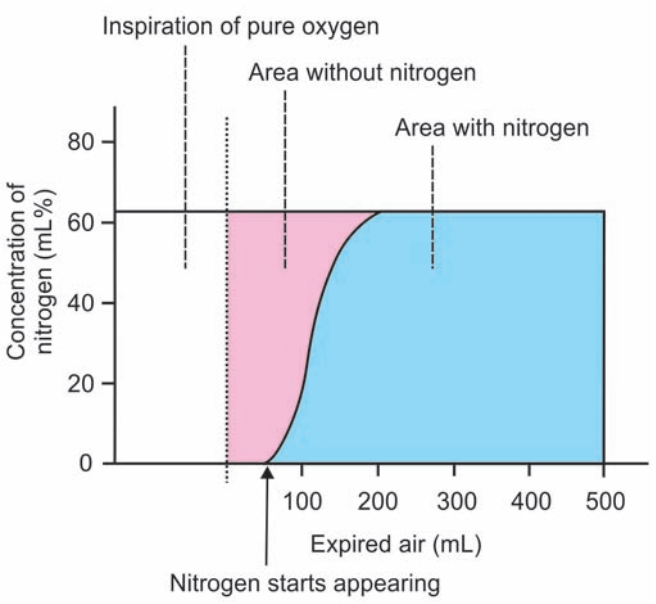


FIGURE 122.1: Measurement of dead space

These factors are:

1. Physiological dead space, which includes wasted air (see above)
2. Physiological shunt, which includes wasted blood (Chapter 119).

VARIATIONS IN VENTILATION-PERFUSION RATIO

Physiological Variation

1. Ratio increases, if ventilation increases without any change in blood flow
2. Ratio decreases, if blood flow increases without any change in ventilation
3. In sitting position, there is reduction in blood flow in the upper part of the lungs (zone 1) than in the lower part (zone 3). Therefore, in zone 1 of lungs ventilation-perfusion ratio increases three times. At the same time, in zone 3 of the lungs, because of increased blood flow ventilation-perfusion ratio decreases.

Pathological Variation

In chronic obstructive pulmonary diseases (COPD), ventilation is affected because of obstruction and destruction of alveolar membrane. So, ventilation-perfusion ratio reduces greatly.

Inspired Air, Alveolar Air and Expired Air

Chapter 14

- INSPIRED AIR
  - DEFINITION
  - COMPOSITION
- ALVEOLAR AIR
  - DEFINITION
  - COMPOSITION
  - RENEWAL
  - METHOD OF COLLECTION
- EXPIRED AIR
  - DEFINITION
  - COMPOSITION
  - METHOD OF COLLECTION

INSPIRED AIR

DEFINITION

Inspired air is the atmospheric air, which is inhaled during inspiration.

COMPOSITION

Composition of inspired air is given in Table 123.1.

ALVEOLAR AIR

DEFINITION

Alveolar air is the air present in alveoli of lungs. Its composition is given in Table 123.1.

Alveolar Air Vs Inspired Air

Alveolar air is different from inspired air in four ways:

TABLE 123.1: Composition of inspired air, alveolar air and expired air

Air	Inspired (atmospheric) air		Alveolar air		Expired air	
Gas	Content (mL%)	Partial pressure (mm Hg)	Content (mL%)	Partial pressure (mm Hg)	Content (mL%)	Partial pressure (mm Hg)
Oxygen	20.84	159.00	13.60	104.00	15.70	120.00
Carbon dioxide	0.04	0.30	5.30	40.00	3.60	27.00
Nitrogen	78.62	596.90	74.90	569.00	74.50	566.00
Water vapor, etc.	0.50	3.80	6.20	47.00	6.20	47.00
Total	100.00	760.00	100.00	760.00	100.00	760.00

1. Alveolar air is partially replaced by the atmospheric air during each breath
2. Oxygen diffuses from the alveolar air into pulmonary capillaries constantly
3. Carbon dioxide diffuses from pulmonary blood into alveolar air constantly
4. Dry atmospheric air is humidified, while passing through respiratory passage before entering the alveoli (Table 123.1).

■ COMPOSITION

Composition of alveolar air is given in Table 123.1.

■ RENEWAL

Alveolar air is constantly renewed. Rate of renewal is slow during normal breathing. During each breath, out of 500 mL of tidal volume only 350 mL of air enters the alveoli and the remaining quantity of 150 mL (30%) becomes dead space air. Hence, the amount of alveolar air replaced by new atmospheric air with each breath is only about 70% of the total alveolar air.

Thus,

$$\text{Alveolar air} = \frac{350}{500} \times 100 = 70\%$$

Slow renewal of alveolar air is responsible for prevention of sudden changes in concentration of gases in the blood.

■ METHOD OF COLLECTION

Alveolar air is collected by using **Haldane-Priestely tube.** This tube consists of a canvas rubber tube, which is 1 m long and having a diameter of 2.5 cm. It is opened on both ends.

A mouthpiece is fitted at one end of the tube. Near the mouthpiece, there is a side tube, which is fixed with a sampling tube. Mouthpiece and the side tube are interconnected by means of a three-way cock. By keeping the mouthpiece in the mouth, the subject makes a forceful expiration through the mouthpiece. Alveolar air is expired at the end of forced expiration. So, by using the three-way cock, the last portion of expired air (alveolar air) is collected in the sampling tube.

■ EXPIRED AIR

■ DEFINITION

Expired air is the amount of air that is exhaled during expiration. It is a combination of dead space air and alveolar air.

■ COMPOSITION

Concentration of gases in expired air is somewhere between inspired air and alveolar air. Composition of expired air is given in Table 123.1 along with composition of inspired air and alveolar air.

■ METHOD OF COLLECTION

Expired air is collected by using **Douglas bag.**

Exchange of Respiratory Gases

Chapter 15

INTRODUCTION

Oxygen is essential for the cells. Carbon dioxide, which is produced as waste product in the cells must be expelled from the cells and body. Lungs serve to exchange these two gases with blood.

EXCHANGE OF RESPIRATORY GASES IN LUNGS

In the lungs, exchange of respiratory gases takes place between the alveoli of lungs and the blood. Oxygen enters the blood from alveoli and carbon dioxide is expelled out of blood into alveoli. Exchange occurs through **bulk flow diffusion**.

Exchange of gases between blood and alveoli takes place through respiratory membrane. Refer Chapter 118 for details.

RESPIRATORY MEMBRANE

Respiratory membrance is a membranous structure through which exchange of respiratory gases takes place. It is formed by **epithelium** of respiratory unit and **endothelium** of pulmonary capillary. Epithelium of respiratory unit is a very thin layer. Since, the capillaries are in close contact with this membrane, alveolar air is in close proximity to capillary blood. This facilitates gaseous exchange between air and blood (Fig. 124.1).

Respiratory membrane is formed by different layers of structures belonging to the alveoli and capillaries.

Layers of Respiratory Membrane

Different layers of respiratory membrane from within outside are given in Table 124.1.

In spite of having many layers, respiratory membrane is very thin with an average thickness of 0.5 µ. Total

surface area of the respiratory membrane in both the lungs is about 70 square meter.

Average diameter of pulmonary capillary is only 8 µ, which means that the RBCs with a diameter of 7.4 µ actually squeeze through the capillaries. Therefore, the membrane of RBCs is in close contact with capillary wall. This facilitates quick exchange of oxygen and carbon dioxide between the blood and alveoli.

■ DIFFUSING CAPACITY

Diffusing capacity is defined as the volume of gas that diffuses through the respiratory membrane each minute for a pressure gradient of 1 mm Hg.

TABLE 124.1: Layers of respiratory membrane

Portion	Layers
Alveolar portion	1. Monomolecular layer of surfactant, which spreads over the surface of alveoli 2. Thin fluid layer that lines the alveoli 3. Alveolar epithelial layer, which is composed of thin epithelial cells resting on a basement membrane
Between alveolar and capillary portions	4. An interstitial space
Capillary portion	5. Basement membrane of capillary 6. Capillary endothelial cells

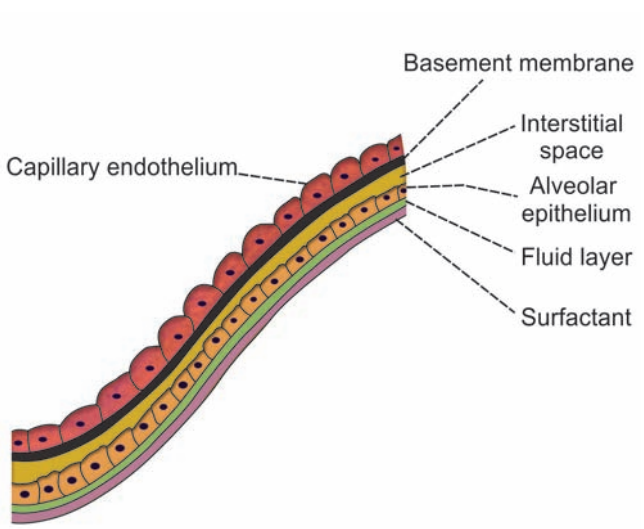


FIGURE 124.1: Structure of respiratory membrane

Diffusing Capacity for Oxygen and Carbon Dioxide

Diffusing capacity for oxygen is 21 mL/minute/1 mm Hg. Diffusing capacity for carbon dioxide is 400 mL/minute/1 mm Hg. Thus, the diffusing capacity for carbon dioxide is about 20 times more than that of oxygen.

Factors Affecting Diffusing Capacity

1. *Pressure gradient*

Diffusing capacity is **directly proportional** to pressure gradient. Pressure gradient is the difference between the partial pressure of a gas in alveoli and pulmonary capillary blood (see below). It is the major factor, which affects the diffusing capacity.

2. *Solubility of gas in fluid medium*

Diffusing capacity is **directly proportional** to solubility of the gas. If the solubility of a gas is more in the fluid medium, a large number of molecules dissolve in it and diffuse easily.

3. *Total surface area of respiratory membrane*

Diffusing capacity is **directly proportional** to surface area of respiratory membrane. Surface area of respiratory membrane in each lung is about 70 sq m. If the total surface area of respiratory membrane decreases, the diffusing capacity for the gases is decreased. Diffusing capacity is decreased in emphysema in which many of the alveoli are collapsed because of heavy smoking or oxidant gases.

4. *Molecular weight of the gas*

Diffusing capacity is **inversely proportional** to molecular weight of the gas. If the molecular weight is more, the density is more and the rate of diffusion is less.

5. *Thickness of respiratory membrane*

Diffusion is **inversely proportional** to the thickness of respiratory membrane. More the thickness of respiratory membrane less is the diffusion. It is because the distance through which the diffusion takes place is long. In conditions like fibrosis and edema, the diffusion rate is reduced, because the thickness of respiratory membrane is increased.

Relation between Diffusing Capacity and Factors Affecting it

Relation between diffusing capacity and the factors affecting it is expressed by the following formula:

$$DC \propto \frac{Pg \times S \times A}{Mw \times D}$$

DC = Diffusing capacity
Pg = Pressure gradient
S = Solubility of gas
A = Surface area of respiratory membrane
Mw = Molecular weight
D = Thickness of respiratory membrane.

■ DIFFUSION COEFFICIENT AND FICK LAW OF DIFFUSION

Diffusion Coefficient

Diffusion coefficient is defined as a constant (a factor of proportionality), which is the measure of a substance diffusing through the concentration gradient. It is also known as **diffusion constant.** It is related to size and shape of the molecules of the substance.

Fick Law of Diffusion

Diffusion is well described by Fick law of diffusion. According to this law, amount of a substance crossing a given area is directly proportional to the area available for diffusion, concentration gradient and a constant known as diffusion coefficient.

Thus,
Amount diffused = Area × Concentration gradient × Diffusion coefficient

Formula of Fick law:

$$J = -D \times A \times \frac{dc}{dx}$$

Where,
J = Amount of substance diffused
D = Diffusion coefficient
A = Area through which diffusion occurs
dc/dx = Concentration gradient.

Negative sign in the formula indicates that diffusion occurs from region of higher concentration to region of lower concentration. Diffusion coefficient reduces when the molecular size of diffusing substance is increased. It increases when the size is decreased, i.e. the smaller molecules diffuse rapidly than the larger ones.

■ DIFFUSION OF OXYGEN

Diffusion of Oxygen from Atmospheric Air into Alveoli

Partial pressure of oxygen in the atmospheric air is 159 mm Hg and in the alveoli, it is 104 mm Hg. Because of

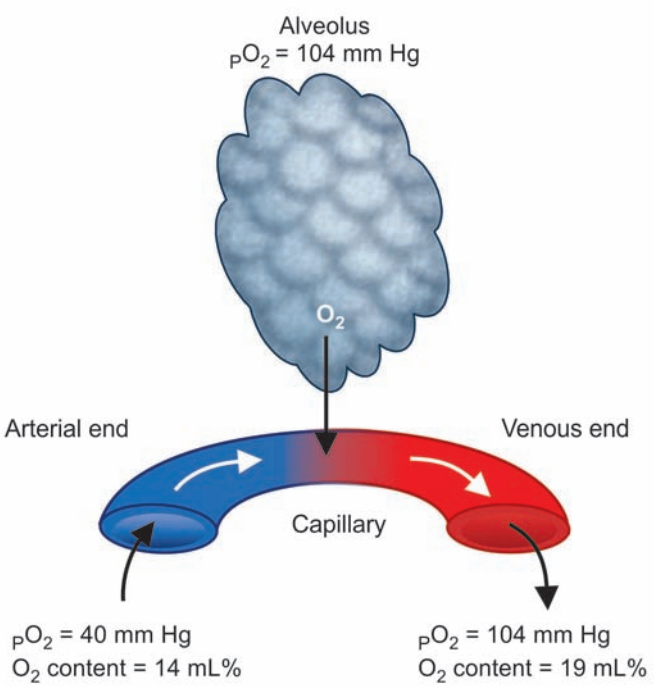


FIGURE 124.2: Diffusion of oxygen from alveolus to pulmonary capillary

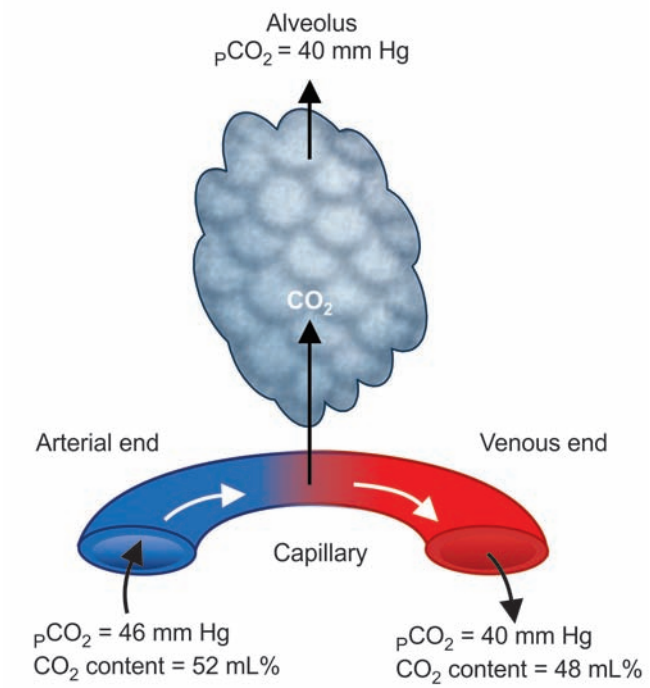


FIGURE 124.3: Diffusion of carbon dioxide from pulmonary capillary to alveolus

TABLE 124.2: Partial pressure and content of oxygen and carbon dioxide in alveoli, capillaries and tissue

Gas	Arterial end of pulmonary capillary	Alveoli	Venous end of pulmonary capillary	Arterial end of systemic capillary	Tissue	Venous end of systemic capillary
pO_2 (mm Hg)	40	104	104	95	40	40
Oxygen content (mL%)	14	–	19	19	–	14
pCO_2 (mm Hg)	46	40	40	40	46	46
Carbon dioxide content (mL%)	52	–	48	48	–	52

the pressure gradient of 55 mm Hg, oxygen easily enters from atmospheric air into the alveoli (Table 124.2).

Diffusion of Oxygen from Alveoli into Blood

When blood passes through pulmonary capillary, RBC is exposed to oxygen only for 0.75 second at rest and only for 0.25 second during severe exercise. So, diffusion of oxygen must be quicker and effective. Fortunately, this is possible because of pressure gradient.

Partial pressure of oxygen in the pulmonary capillary is 40 mm Hg and in the alveoli, it is 104 mm Hg. Pressure gradient is 64 mm Hg. It facilitates the diffusion of oxygen from alveoli into the blood (Fig. 124.2).

■ DIFFUSION OF CARBON DIOXIDE

Diffusion of Carbon Dioxide from Blood into Alveoli

Partial pressure of carbon dioxide in alveoli is 40 mm Hg whereas in the blood it is 46 mm Hg. Pressure gradient of 6 mm Hg is responsible for the diffusion of carbon dioxide from blood into the alveoli (Fig. 124.3).

Diffusion of Carbon Dioxide from Alveoli into Atmospheric Air

In atmospheric air, partial pressure of carbon dioxide is very insignificant and is only about 0.3 mm Hg whereas, in the alveoli, it is 40 mm Hg. So, carbon dioxide enters passes to atmosphere from alveoli easily.

■ EXCHANGE OF RESPIRATORY GASES AT TISSUE LEVEL

Oxygen enters the cells of tissues from blood and carbon dioxide is expelled from cells into the blood.

■ DIFFUSION OF OXYGEN FROM BLOOD INTO THE TISSUES

Partial pressure of oxygen in venous end of pulmonary capillary is 104 mm Hg. However, partial pressure of

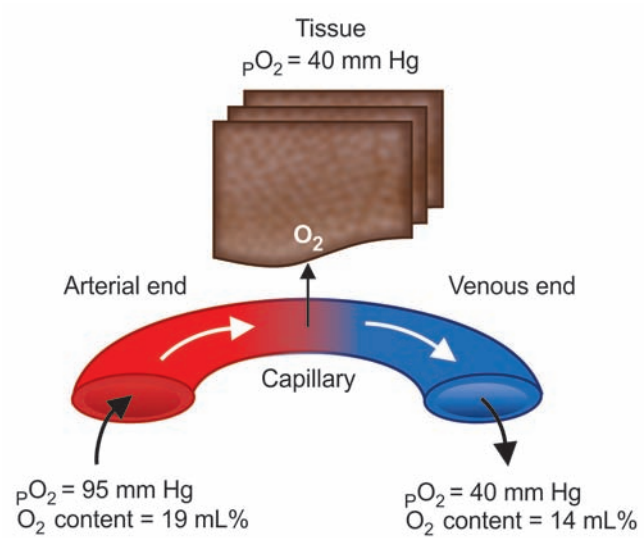


FIGURE 124.4: Diffusion of oxygen from capillary to tissue

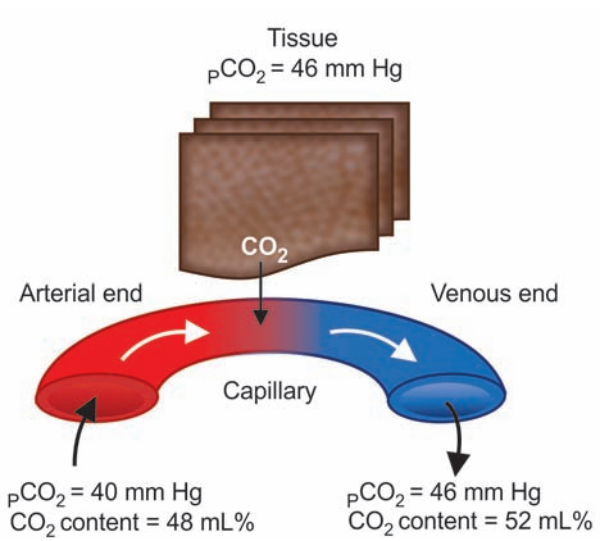


FIGURE 124.5: Diffusion of carbon dioxide from tissue to capillary

oxygen in the arterial end of systemic capillary is only 95 mm Hg. It may be because of physiological shunt in lungs. Due to **venous admixture** in the **shunt** (Chapter 119), 2% of blood reaches the heart without being oxygenated.

Average oxygen tension in the tissues is 40 mm Hg. It is because of continuous metabolic activity and constant utilization of oxygen. Thus, a pressure gradient of about 55 mm Hg exists between capillary blood and the tissues so that oxygen can easily diffuse into the tissues (Fig. 124.4).

Oxygen content in arterial blood is 19 mL% and in the venous blood, it is 14 mL%. Thus, the diffusion of oxygen from blood to tissues is 5 mL/100 mL of blood.

■ DIFFUSION OF CARBON DIOXIDE FROM TISSUES INTO THE BLOOD

Due to continuous metabolic activity, carbon dioxide is produced constantly in the cells of tissues. So, the partial pressure of carbon dioxide is high in the cells and is about 46 mm Hg. Partial pressure of carbon dioxide in arterial blood is 40 mm Hg. Pressure gradient of 6 mm Hg is responsible for the diffusion of carbon dioxide from tissues to the blood (Figs. 124.5 and 124.6).

Carbon dioxide content in arterial blood is 48 mL%. And in the venous blood, it is 52 mL%. So, the diffusion of carbon dioxide from tissues to blood is 4 mL/100 mL of blood (Fig. 124.5).

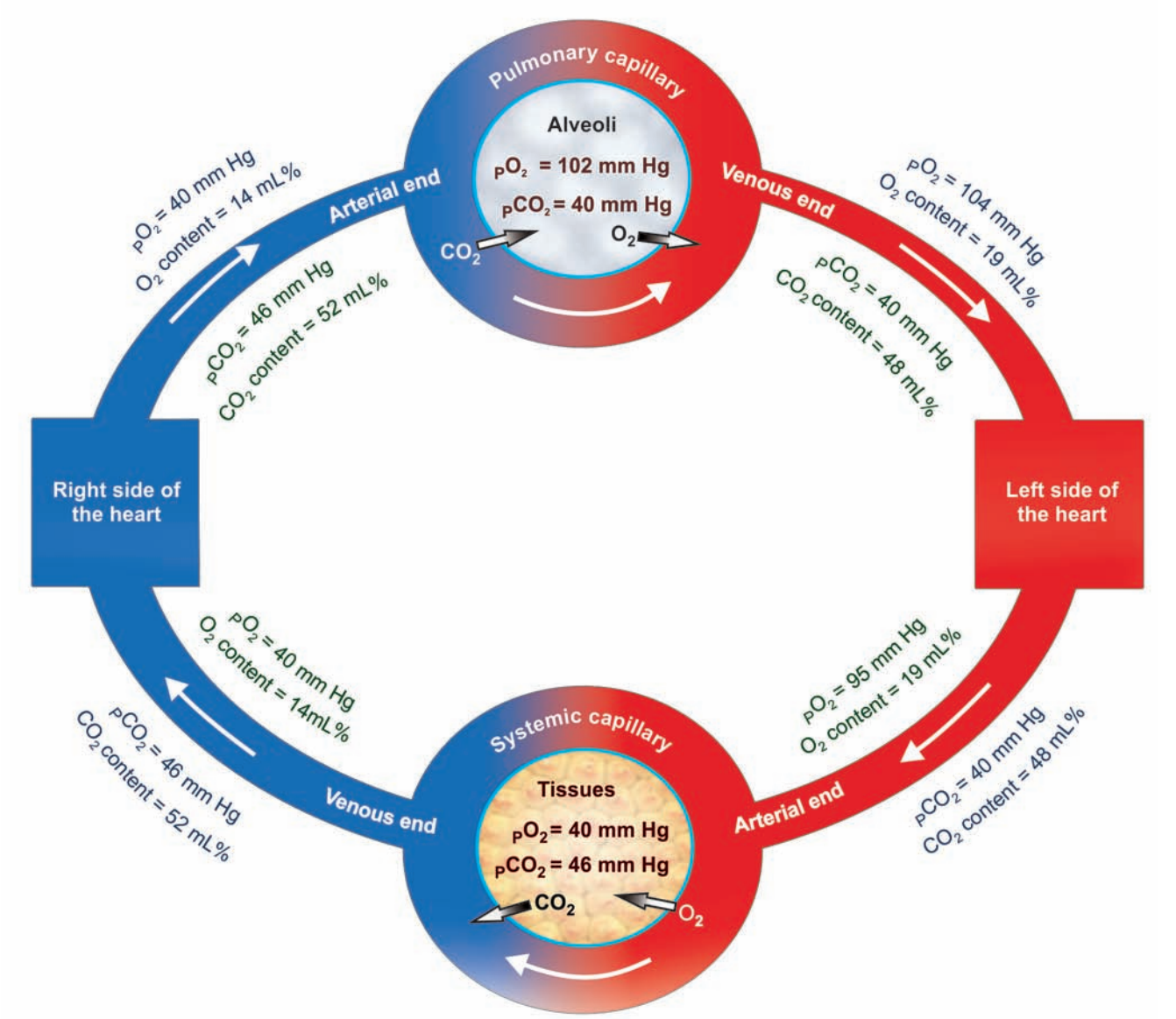


FIGURE 124.6: Partial pressure and content of oxygen and carbon dioxide in blood, alveoli and tissues

RESPIRATORY EXCHANGE RATIO

DEFINITION

Respiratory exchange ratio (R) is the ratio between the net output of carbon dioxide from tissues to simultaneous net uptake of oxygen by the tissues.

$$R = \frac{CO_2 \text{ output}}{O_2 \text{ uptake}}$$

NORMAL VALUES

Value of R depends upon the type of food substance that is metabolized.

When a person utilizes only carbohydrates for metabolism, R is 1.0. That means during carbohydrate metabolism, the amount of carbon dioxide produced in the tissue is equal to the amount of oxygen consumed.

If only fat is used for metabolism, the R is 0.7. When fat is utilized, oxygen reacts with fats and a large portion of oxygen combines with hydrogen ions to form water instead of carbon dioxide. So, the carbon dioxide output is less than the oxygen consumed. And the R is less.

If only protein is utilized, R is 0.803.

However, when a balanced diet containing average quantity of proteins, carbohydrates and lipids is utilized, the R is about 0.825. In steady conditions, respiratory exchange ratio is equal to respiratory quotient.

RESPIRATORY QUOTIENT

DEFINITION

Respiratory quotient is the molar ratio of carbon dioxide production to oxygen consumption. It is used to determine the utilization of different foodstuffs.

NORMAL VALUE

For about 1 hour after meals the respiratory quotient is 1.0. It is because usually, immediately after taking meals, only the carbohydrates are utilized by the tissues. During the metabolism of carbohydrates, one molecule of carbon dioxide is produced for every molecule of oxygen consumed by the tissues. Respiratory quotient is 1.0, which is equal to respiratory exchange ratio.

After utilization of all the carbohydrates available, body starts utilizing fats. Now the respiratory quotient becomes 0.7. When the proteins are metabolized, it becomes 0.8.

During exercise, the respiratory quotient increases.

Transport of Respiratory Gases

Chapter 16

INTRODUCTION

Blood serves to transport the respiratory gases. Oxygen, which is essential for the cells is transported from alveoli of lungs to the cells. Carbon dioxide, which is the waste product in cells is transported from cells to lungs.

TRANSPORT OF OXYGEN

Oxygen is transported from alveoli to the tissue by blood in two forms:

1. As simple physical solution
2. In combination with hemoglobin.

Partial pressure and content of oxygen in arterial blood and venous blood are given in Table 125.1.

TABLE 125.1: Gases in arterial and venous blood

Gas		Arterial blood	Venous blood
Oxygen	Partial pressure (mm Hg)	95	40
	Content (mL%)	19	14
Carbon dioxide	Partial pressure (mm Hg)	40	46
	Content (mL%)	48	52

AS SIMPLE SOLUTION

Oxygen dissolves in water of plasma and is transported in this **physical form.** Amount of oxygen transported in this way is very negligible. It is only 0.3 mL/100 mL of plasma. It forms only about 3% of total oxygen in blood. It is because of poor solubility of oxygen in water content of plasma. Still, transport of oxygen in this form becomes important during the conditions like muscular exercise to meet the excess demand of oxygen by the tissues.

IN COMBINATION WITH HEMOGLOBIN

Oxygen combines with hemoglobin in blood and is transported as **oxyhemoglobin.** Transport of oxygen in this form is important because, maximum amount (97%) of oxygen is transported by this method.

Oxygenation of Hemoglobin

Oxygen combines with hemoglobin only as a physical combination. It is only **oxygenation** and not **oxidation.** This type of combination of oxygen with hemoglobin has got some advantages. Oxygen can be readily released from hemoglobin when it is needed.

Hemoglobin accepts oxygen readily whenever the partial pressure of oxygen in the blood is more. Hemoglobin gives out oxygen whenever the partial pressure of oxygen in the blood is less.

Oxygen combines with the iron in heme part of hemoglobin. Each molecule of hemoglobin contains 4 atoms of iron. Iron of the hemoglobin is present in ferrous form. Each iron atom combines with one molecule of oxygen. After combination, iron remains in ferrous form only. That is why the combination of oxygen with hemoglobin is called oxygenation and not oxidation.

Oxygen Carrying Capacity of Hemoglobin

Oxygen carrying capacity of hemoglobin is the amount of oxygen transported by 1 gram of hemoglobin. It is 1.34 mL/g.

Oxygen Carrying Capacity of Blood

Oxygen carrying capacity of blood refers to the amount of oxygen transported by blood. Normal hemoglobin content in blood is 15 g%.

Since oxygen carrying capacity of hemoglobin is 1.34 mL/g, blood with 15 g% of hemoglobin should carry 20.1 mL% of oxygen, i.e. 20.1 mL of oxygen in 100 mL of blood.

But, blood with 15 g% of hemoglobin carries only 19 mL% of oxygen, i.e. 19 mL of oxygen is carried by 100 mL of blood (Table 125.1). Oxygen carrying capacity of blood is only 19 mL% because the hemoglobin is not fully saturated with oxygen. It is saturated only for about 95%.

Saturation of Hemoglobin with Oxygen

Saturation is the state or condition when hemoglobin is unable to hold or carry any more oxygen. Saturation of hemoglobin with oxygen depends upon partial pressure of oxygen. And it is explained by oxygen-hemoglobin dissociation curve.

■ OXYGEN-HEMOGLOBIN DISSOCIATION CURVE

Oxygen-hemoglobin dissociation curve is the curve that demonstrates the relationship between partial pressure of oxygen and the percentage saturation of hemoglobin with oxygen. It explains hemoglobin's affinity for oxygen.

Normally in the blood, hemoglobin is saturated with oxygen only up to 95%. Saturation of hemoglobin with oxygen depends upon the partial pressure of oxygen. When the partial pressure of oxygen is more, hemoglobin accepts oxygen and when the partial pressure of oxygen is less, hemoglobin releases oxygen.

Method to Plot Oxygen-hemoglobin Dissociation Curve

Ten flasks or tonometers are taken. Each one is filled with a known quantity of blood with known concentration of hemoglobin. Blood in each tonometer is exposed to oxygen at different partial pressures. Tonometer is rotated at a constant temperature till the blood takes as much of oxygen as it can. Then, blood is analyzed to measure the percentage saturation of hemoglobin with oxygen. Partial pressure of oxygen and saturation of hemoglobin are plotted to obtain the oxygen-hemoglobin dissociation curve.

Normal Oxygen-hemoglobin Dissociation Curve

Under normal conditions, oxygen-hemoglobin dissociation curve is 'S' shaped or **sigmoid shaped** (Fig.125.1). Lower part of the curve indicates dissociation of oxygen from hemoglobin. Upper part of the curve indicates the uptake of oxygen by hemoglobin depending upon partial pressure of oxygen.

P_{50}

P_{50} is the partial pressure of oxygen at which hemoglobin saturation with oxygen is 50%. When the partial pressure of oxygen is 25 to 27 mm Hg, the hemoglobin is

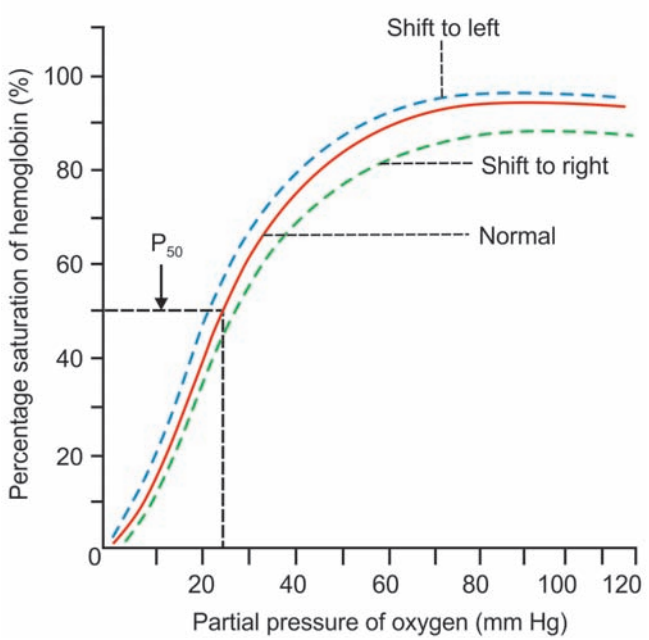


FIGURE 125.1: Oxygen-hemoglobin dissociation curve

saturated to about 50%. That is, the blood contains 50% of oxygen. At 40 mm Hg of partial pressure of oxygen, the saturation is 75%. It becomes 95% when the partial pressure of oxygen is 100 mm Hg.

Factors Affecting Oxygen-hemoglobin Dissociation Curve

Oxygen-hemoglobin dissociation curve is shifted to left or right by various factors:

1. Shift to left indicates acceptance **(association)** of oxygen by hemoglobin
2. Shift to right indicates **dissociation** of oxygen from hemoglobin.

1. *Shift to right*

Oxygen-hemoglobin dissociation curve is shifted to right in the following conditions:

i. Decrease in partial pressure of oxygen
ii. Increase in partial pressure of carbon dioxide (Bohr effect)
iii. Increase in hydrogen ion concentration and decrease in pH (acidity)
iv. Increased body temperature
v. Excess of 2,3-diphosphoglycerate (DPG) in RBC. It is also called 2,3-biphosphoglycerate (BPG). DPG is a byproduct in Embden-Meyerhof pathway of carbohydrate metabolism. It combines with β-chains of hemoglobin. In conditions like muscular exercise and in high attitude, the DPG increases in RBC. So, the oxygen-hemoglobin dissociation curve shifts to right to a great extent.

2. *Shift to left*

Oxygen-hemoglobin dissociation curve is shifted to left in the following conditions:

i. In fetal blood because, fetal hemoglobin has got more affinity for oxygen than the adult hemoglobin
ii. Decrease in hydrogen ion concentration and increase in pH (alkalinity).

Bohr Effect

Bohr effect is the effect by which presence of carbon dioxide decreases the affinity of hemoglobin for oxygen. Bohr effect was postulated by **Christian Bohr** in 1904. In the tissues, due to continuous metabolic activities, the partial pressure of carbon dioxide is very high and the partial pressure of oxygen is low.

Due to this pressure gradient, carbon dioxide enters the blood and oxygen is released from the blood to the tissues. Presence of carbon dioxide decreases the affinity of hemoglobin for oxygen. It enhances further release of oxygen to the tissues and oxygen-dissociation curve is shifted to right.

Factors influencing Bohr effect

All the factors, which shift the oxygen-dissociation curve to right (mentioned above) enhance the Bohr effect.

■ TRANSPORT OF CARBON DIOXIDE

Carbon dioxide is transported by the blood from cells to the alveoli.

Carbon dioxide is transported in the blood in four ways:

1. As dissolved form (7%)
2. As carbonic acid (negligible)
3. As bicarbonate (63%)
4. As carbamino compounds (30%).

■ AS DISSOLVED FORM

Carbon dioxide diffuses into blood and dissolves in the fluid of plasma forming a simple solution. Only about 3 mL/100 mL of plasma of carbon dioxide is transported as dissolved state. It is about 7% of total carbon dioxide in the blood.

■ AS CARBONIC ACID

Part of dissolved carbon dioxide in plasma combines with the water to form carbonic acid. Transport of carbon dioxide in this form is negligible.

■ AS BICARBONATE

About 63% of carbon dioxide is transported as bicarbonate. From plasma, carbon dioxide enters the RBCs. In the RBCs, carbon dioxide combines with water to form carbonic acid. The reaction inside RBCs is very rapid because of the presence of carbonic anhydrase. This enzyme accelerates the reaction. Carbonic anhydrase is present only inside the RBCs and not in plasma. That is why carbonic acid formation is at least 200 to 300 times more in RBCs than in plasma.

Carbonic acid is very unstable. Almost all carbonic acid (99.9%) formed in red blood corpuscles, dissociates into bicarbonate and hydrogen ions. Concentration of bicarbonate ions in the cell increases more and more. Due to high concentration, bicarbonate ions diffuse through the cell membrane into plasma.

Chloride Shift or Hamburger Phenomenon

Chloride shift or Hamburger phenomenon is the exchange of a chloride ion for a bicarbonate ion across RBC membrane. It was discovered by **Hartog Jakob Hamburger** in 1892.

Chloride shift occurs when carbon dioxide enters the blood from tissues. In plasma, plenty of sodium chloride is present. It dissociates into sodium and chloride ions (Fig. 125.2). When the negatively charged bicarbonate ions move out of RBC into the plasma, the negatively charged chloride ions move into the RBC in order to maintain the **electrolyte equilibrium (ionic balance).**

Anion exchanger 1 (band 3 protein), which acts like antiport pump in RBC membrane is responsible for the exchange of bicarbonate ions and chloride ions. Bicarbonate ions combine with sodium ions in the plasma and form sodium bicarbonate. In this form, it is transported in the blood.

Hydrogen ions dissociated from carbonic acid are buffered by hemoglobin inside the cell.

Reverse Chloride Shift

Reverse chloride shift is the process by which chloride ions are moved back into plasma from RBC shift. It occurs in lungs. It helps in elimination of carbon dioxide from the blood. Bicarbonate is converted back into carbon dioxide, which has to be expelled out. It takes place by the following mechanism:

When blood reaches the alveoli, sodium bicarbonate in plasma dissociates into sodium and bicarbonate ions. Bicarbonate ion moves into the RBC. It makes chloride ion to move out of the RBC into the plasma, where it combines with sodium and forms sodium chloride.

Bicarbonate ion inside the RBC combines with hydrogen ion forms carbonic acid, which dissociates into water and carbon dioxide. Carbon dioxide is then expelled out.

■ AS CARBAMINO COMPOUNDS

About 30% of carbon dioxide is transported as carbamino compounds. Carbon dioxide is transported in blood in combination with hemoglobin and plasma proteins. Carbon dioxide combines with hemoglobin to form carbamino hemoglobin or carbhemoglobin. And it combines with plasma proteins to form carbamino proteins. Carbamino hemoglobin and carbamino proteins are together called carbamino compounds.

Carbon dioxide combines with proteins or hemoglobin with a loose bond so that, carbon dioxide is easily released into alveoli, where the partial pressure of carbon dioxide is low. Thus, the combination of carbon dioxide with proteins and hemoglobin is a reversible one. Amount of carbon dioxide transported in combination with plasma proteins is very less compared to the amount transported in combination with hemoglobin. It is because the quantity of proteins in plasma is only half of the quantity of hemoglobin.

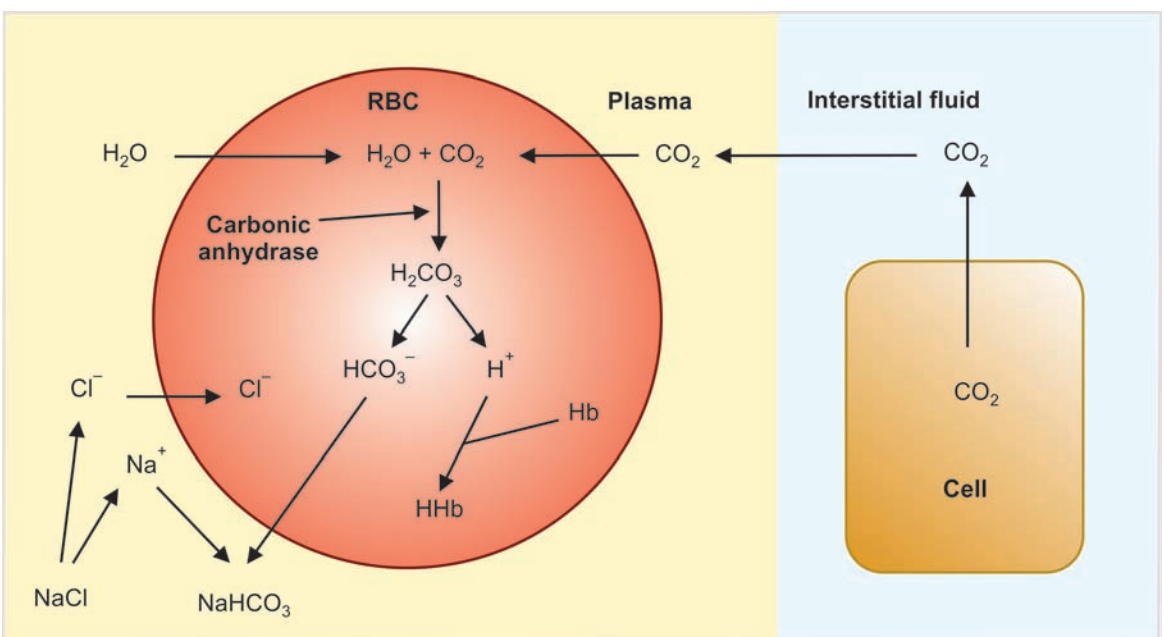


FIGURE 125.2: Transport of carbon dioxide in blood in the form of bicarbonate and chloride shift

■ CARBON DIOXIDE DISSOCIATION CURVE

Carbon dioxide is transported in blood as physical solution and in combination with water, plasma proteins and hemoglobin. The amount of carbon dioxide combining with blood depends upon the partial pressure of carbon dioxide.

Carbon dioxide dissociation curve is the curve that demonstrates the relationship between the partial pressure of carbon dioxide and the quantity of carbon dioxide that combines with blood.

Normal Carbon Dioxide Dissociation Curve

Normal carbon dioxide dissociation curve shows that the carbon dioxide content in the blood is 48 mL% when the partial pressure of carbon dioxide is 40 mm Hg and it is 52 mL% when the partial pressure of carbon dioxide is 48 mm Hg. Carbon dioxide content becomes 70 mL% when the partial pressure is about 100 mm Hg (Fig. 125.3).

Haldane Effect

Haldane effect is the effect by which combination of oxygen with hemoglobin displaces carbon dioxide from hemoglobin. It was first described by **John Scott Haldane** in 1860. Excess of oxygen content in blood causes shift of the carbon dioxide dissociation curve to right.

Causes for Haldane effect

Due to the combination with oxygen, hemoglobin becomes strongly acidic. It causes displacement of carbon dioxide from hemoglobin in two ways:

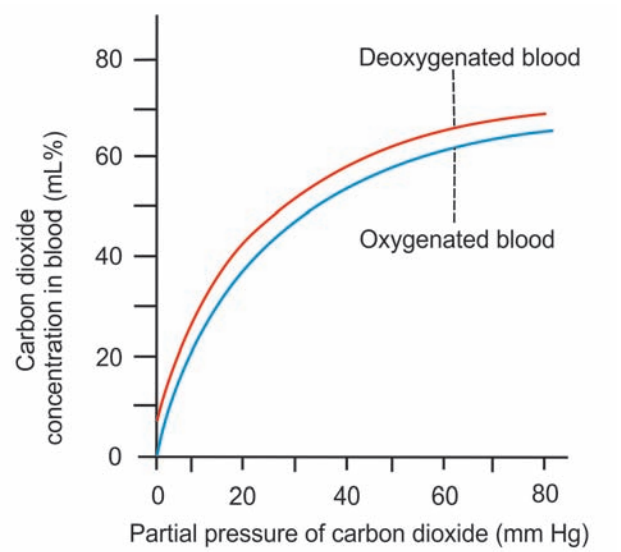


FIGURE 125.3: Carbon dioxide dissociation curve

1. Highly acidic hemoglobin has low tendency to combine with carbon dioxide. So, carbon dioxide is displaced from blood.
2. Because of the acidity, hydrogen ions are released in excess. Hydrogen ions bind with bicarbonate ions to form carbonic acid. Carbonic acid in turn dissociates into water and carbon dioxide. Carbon dioxide is released from blood into alveoli.

Significance of Haldane effect

Haldane effect is essential for:

1. Release of carbon dioxide from blood into the alveoli of lungs
2. Uptake of oxygen by the blood.

Chapter 17

Regulation of Respiration

INTRODUCTION

Respiration is a reflex process. But it can be controlled voluntarily for a short period of about 40 seconds. However, by practice, breathing can be withheld for a long period. At the end of that period, the person is forced to breathe.

Respiration is subjected to variation, even under normal physiological conditions. For example, emotion and exercise increase the rate and force of respiration. But the altered pattern of respiration is brought back to normal, within a short time by some regulatory mechanisms in the body.

Normally, quiet regular breathing occurs because of two regulatory mechanisms:

1. Nervous or neural mechanism
2. Chemical mechanism.

NERVOUS MECHANISM

Nervous mechanism that regulates the respiration includes:

1. Respiratory centers
2. Afferent nerves
3. Efferent nerves.

RESPIRATORY CENTERS

Respiratory centers are group of neurons, which control the rate, rhythm and force of respiration. These centers are bilaterally situated in reticular formation of the brainstem (Fig. 126.1). Depending upon the situation in brainstem, the respiratory centers are classified into two groups:

A. Medullary centers consisting of
   1. Dorsal respiratory group of neurons
   2. Ventral respiratory group of neurons

B. Pontine centers
   3. Apneustic center
   4. Pneumotaxic center.

MEDULLARY CENTERS

1. *Dorsal Respiratory Group of Neurons*

Situation

Dorsal respiratory group of neurons are diffusely situated in the nucleus of **tractus solitarius** which is present in the upper part of the medulla oblongata (Fig. 126.1). Usually, these neurons are collectively called **inspiratory center.**

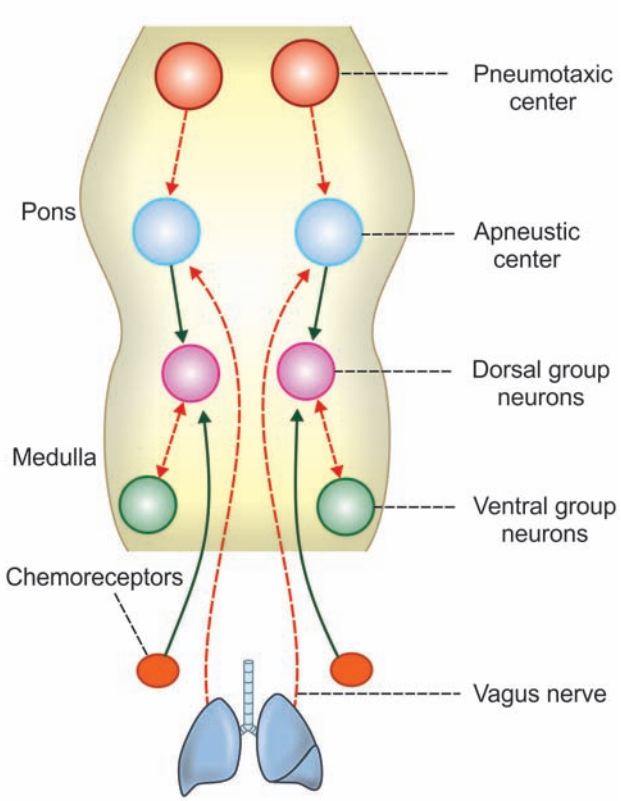


FIGURE 126.1: Nervous regulation of respiration.
Solid green line = Stimulation, Dotted red line = Inhibition.

All the neurons of dorsal respiratory group are **inspiratory neurons** and generate **inspiratory ramp** by the virtue of their **autorhythmic property** (Table 126.1).

Function

Dorsal group of neurons are responsible for basic rhythm of respiration (see below for details).

Experimental evidence

Electrical stimulation of these neurons in animals by using needle electrode causes contraction of inspiratory muscles and **prolonged inspiration.**

2. *Ventral Respiratory Group of Neurons*

Situation

Ventral respiratory group of neurons are present in **nucleus ambiguous** and **nucleus retroambiguous.** These two nuclei are situated in the medulla oblongata, anterior and lateral to the nucleus of tractus solitarius. Earlier, the ventral group neurons were collectively called **expiratory center.**

Ventral respiratory group has both **inspiratory** and **expiratory neurons.** Inspiratory neurons are found in the central area of the group. Expiratory neurons are in the caudal and rostral areas of the group.

Function

Normally, ventral group neurons are inactive during quiet breathing and become active during forced breathing. During forced breathing, these neurons stimulate both inspiratory muscles and expiratory muscles.

Experimental evidence

Electrical stimulation of the inspiratory neurons in ventral group causes contraction of inspiratory muscles and prolonged inspiration. Stimulation of expiratory neurons causes contraction of expiratory muscles and **prolonged expiration.**

■ PONTINE CENTERS

3. *Apneustic Center*

Situation

Apneustic center is situated in the reticular formation of lower pons.

Function

Apneustic center increases depth of inspiration by acting directly on dorsal group neurons.

Experimental evidence

Stimulation of apneustic center causes **apneusis.** Apneusis is an abnormal pattern of respiration, charac-

TABLE 126.1: Medullary centers

Features	Dorsal group	Ventral group
Situation	Diffusely situated in nucleus of tractus solitarius	In nucleus ambiguous and nucleus retroambiguous
Type of neurons	Inspiratory neurons	Inspiratory and expiratory neurons
Function	Always active Generate inspiratory ramp Has autorhythmic property	Inactive during quiet breathing Active during forced breathing

terized by prolonged inspiration followed by short, inefficient expiration.

4. Pneumotaxic Center

Situation

Pneumotaxic center is situated in the dorsolateral part of **reticular formation** in **upper pons.** It is formed by neurons of medial **parabrachial** and **subparabrachial nuclei.** Subparabrachial nucleus is also called **ventral parabrachial** or **Kölliker-Fuse nucleus.**

Function

Primary function of pneumotaxic center is to control the medullary respiratory centers, particularly the dorsal group neurons. It acts through apneustic center. Pneumotaxic center inhibits the apneustic center so that the dorsal group neurons are inhibited. Because of this, inspiration stops and expiration starts. Thus, pneumotaxic center influences the switching between inspiration and expiration.

Pneumotaxic center increases respiratory rate by reducing the duration of inspiration.

Experimental evidence

Stimulation of pneumotaxic center does not produce any typical effect, except slight **prolongation of expiration,** by inhibiting the dorsal respiratory group of neurons through apneustic center. Destruction or inactivation of pneumotaxic center results in apneusis.

■ CONNECTIONS OF RESPIRATORY CENTERS

Efferent Pathway

Nerve fibers from respiratory centers leave the brainstem and descend in anterior part of lateral columns of spinal cord.

These nerve fibers terminate on motor neurons in the anterior horn cells of cervical and thoracic segments of spinal cord. From motor neurons of spinal cord, two sets of nerve fibers arise:

1. Phrenic nerve fibers (C3 to C5), which supply the diaphragm
2. Intercostal nerve fibers (T1 to T11), which supply the external intercostal muscles.

Vagus nerve also contains some efferent fibers from the respiratory centers.

Afferent Pathway

Respiratory centers receive afferent impulses from:

1. Peripheral chemoreceptors and baroreceptors via branches of glossopharyngeal and vagus nerves
2. Stretch receptors of lungs via vagus nerve.

By receiving afferent impulses from these receptors, respiratory centers modulate the movements of thoracic cage and lungs through efferent nerve fibers.

■ INTEGRATION OF RESPIRATORY CENTERS

Role of Medullary Centers

Rhythmic discharge of inspiratory impulses

Dorsal respiratory group of neurons are responsible for the normal rhythm of respiration. These neurons maintain the normal rhythm of respiration by discharging impulses (action potentials) **rhythmically.** These impulses are transmitted to respiratory muscles by phrenic and intercostal nerves.

Inspiratory ramp

Inspiratory ramp is the pattern of impulse discharge from dorsal respiratory group of neurons. These impulses are characterized by steady increase in amplitude of the action potential. Impulse discharge from these neurons is not sudden and it is also not uniform.

Inspiratory ramp signals

To start with, the amplitude of action potential is low. It is due to the activation of only few neurons. Later, more and more neurons are activated, leading to gradual increase in the amplitude of action potential in a ramp fashion. Impulses of this type discharged from dorsal group of neurons are called inspiratory ramp signals.

Ramp signals are not produced continuously but only for a period of 2 seconds, during which inspiration occurs. After 2 seconds, ramp signals stop abruptly and do not appear for another 3 seconds. Switching off the ramp signals causes expiration. At the end of 3 seconds, inspriatory ramp signals reappear in the same pattern and the cycle is repeated.

Normally, during inspiration, dorsal respiratory group neurons inhibit expiratory neurons of ventral group. During expiration, the expiratory neurons inhibit the dorsal group neurons. Thus, the medullary respiratory centers control each other.

Significance of inspiratory ramp signals

Significance of inspiratory ramp signals is that there is a slow and steady inspiration, so that the filling of lungs with air is also steady.

Role of Pontine Centers

Pontine respiratory centers regulate the medullary centers. Apneustic center accelerates the activity of

dorsal group of neurons and the stimulation of this center causes prolonged inspiration.

Pneumotaxic center inhibits the apneustic center and restricts the duration of inspiration.

Pre-Bötzinger Complex

Pre-Bötzinger complex (**pre-BötC)** is an **additional respiratory center** found in animals. It is formed by a group of neurons called **pacemaker neurons,** located in the ventrolateral part of medulla. Pacemaker neurons generate the rhythmic respiratory impulses. Medullary centers send nerve fibers into this complex. Exact functioning mechanism of this complex is not known.

■ FACTORS AFFECTING RESPIRATORY CENTERS

Respiratory centers regulate the respiratory movements by receiving impulses from various sources in the body.

1. *Impulses from Higher Centers*

Higher centers alter the respiration by sending impulses directly to dorsal group of neurons. Impulses from anterior cingulate gyrus, genu of corpus callosum, olfactory tubercle and posterior orbital gyrus of cerebral cortex inhibit respiration. Impulses from motor area and Sylvian area of cerebral cortex cause **forced breathing.**

2. *Impulses from Stretch Receptors of Lungs: Hering-Breuer Reflex*

Hering-Breuer reflex is a **protective reflex** that restricts inspiration and prevents overstretching of lung tissues. It is initiated by the stimulation of stretch receptors of air passage.

Stretch receptors are the receptors which give response to stretch of the tissues. These receptors are situated on the wall of the bronchi and bronchioles.

Expansion of lungs during inspiration stimulates the stretch receptors. Impulses from stretch receptors reach the dorsal group neurons via vagal afferent fibers and inhibit them. So, inspiration stops and expiration starts (Fig. 126.2). Thus, the overstretching of lung tissues is prevented.

However, Hering-Breuer reflex does not operate during quiet breathing. It operates, only when the tidal volume increases beyond 1,000 mL.

Hering-Breuer inflation reflex and deflation reflex

The above mentioned reflex is called **Hering-Breuer inflation reflex** since it restricts the inspiration and limits the overstretching of lung tissues. Reverse of this reflex is called **Hering-Breuer deflation reflex** and it takes place during expiration. During expiration, as the stretching of lungs is absent, deflation occurs.

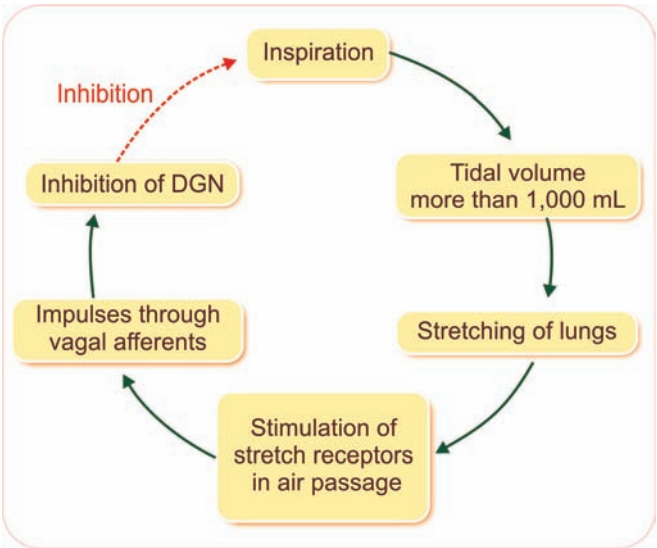


FIGURE 126.2: Hering-Breuer inflation reflex. DGN = Dorsal respiratory group of neurons. Dashed red arrow indicates inhibition.

3. *Impulses from 'J' Receptors of Lungs*

'J' receptors are **juxtacapillary receptors** which are present on the wall of the alveoli and have close contact with the pulmonary capillaries. **AS Paintal** discovered that these receptors are the sensory nerve endings of vagus. Nerve fibers from these receptors are non-myelinated and belong to C type. Few receptors are found on the wall of the bronchi.

Conditions when 'J' receptors are stimulated

i. Pulmonary congestion
ii. Pulmonary edema
iii. Pneumonia
iv. Over inflation of lungs
v. Microembolism in pulmonary capillaries
vi. Stimulation by exogenous and endogenous chemical substances such as histamine, halothane, bradykinin, serotonin and phenyldiguanide.

Effect of stimulation of 'J' receptors

Stimulation of the 'J' receptors produces a reflex response, which is characterized by **apnea.** Apnea is

followed by hyperventilation, bradycardia, hypotension and weakness of skeletal muscles.

Role of 'J' receptors in physiological conditions is not clear. However, these receptors are responsible for hyperventilation in patients affected by pulmonary congestion and left heart failure.

4. *Impulses from Irritant Receptors of Lungs*

Besides stretch receptors, there is another type of receptors in the bronchi and bronchioles of lungs, called irritant receptors. Irritant receptors are stimulated by irritant chemical agents such as ammonia and sulfur dioxide. These receptors send afferent impulses to respiratory centers via vagal nerve fibers.

Stimulation of irritant receptors produces **reflex hyperventilation** along with **bronchospasm.** Hyperventilation along with bronchospasm prevents further entry of harmful agents into the alveoli.

5. *Impulses from Baroreceptors*

Baroreceptors or **pressoreceptors** are the receptors which give response to change in blood pressure. Refer Chapter 101 for details of baroreceptors.

Function

Baroreceptors in carotid sinus and arch of aorta give response to increase in blood pressure. Whenever arterial blood pressure increases, baroreceptors are activated and send inhibitory impulses to vasomotor center in medulla oblongata. This causes decrease in blood pressure and inhibition of respiration. However, in physiological conditions, the role of baroreceptors in regulation of respiration is insignificant.

6. *Impulses from Chemoreceptors*

Chemoreceptors play an important role in the chemical regulation of respiration. Details of chemoreceptors and chemical regulation of respiration are explained later in this Chapter.

7. *Impulses from Proprioceptors*

Proprioceptors are the receptors which give response to change in the position of body. These receptors are situated in joints, tendons and muscles. Proprioceptors are stimulated during the muscular exercise and send impulses to brain, particularly cerebral cortex, through somatic afferent nerves. Cerebral cortex in turn causes hyperventilation by sending impulses to medullary respiratory centers.

8. *Impulses from Thermoreceptors*

Thermoreceptors are cutaneous receptors, which give response to change in the environmental temperature. Thermoreceptors are of two types, namely receptors for cold and receptors for warmth. When body is exposed to cold or when cold water is applied over the body, cold receptors are stimulated and send impulses to cerebral cortex via somatic afferent nerves. Cerebral cortex in turn, stimulates the respiratory centers and causes hyperventilation.

9. *Impulses from Pain Receptors*

Pain receptors are those which give response to pain stimulus. Whenever pain receptors are stimulated, the impulses are sent to cerebral cortex via somatic afferent nerves. Cerebral cortex in turn, stimulates the respiratory centers and causes hyperventilation (Fig. 126.3).

■ CHEMICAL MECHANISM

Chemical mechanism of regulation of respiration is operated through the chemoreceptors. Chemoreceptors are the sensory nerve endings, which give response to changes in chemical constituents of blood.

Changes in Chemical Constituents of Blood which Stimulate Chemoreceptors

1. Hypoxia (decreased pO_2)
2. Hypercapnea (increased pCO_2)
3. Increased hydrogen ion concentration.

Types of Chemoreceptors

Chemoreceptors are classified into two groups:

1. Central chemoreceptors
2. Peripheral chemoreceptors.

■ CENTRAL CHEMORECEPTORS

Central chemoreceptors are the chemoreceptors present in the brain.

Situation

Central chemoreceptors are situated in deeper part of medulla oblongata, close to the dorsal respiratory group of neurons. This area is known as **chemosensitive area** and the neurons are called chemoreceptors. Chemoreceptors are in close contact with blood and cerebrospinal fluid.

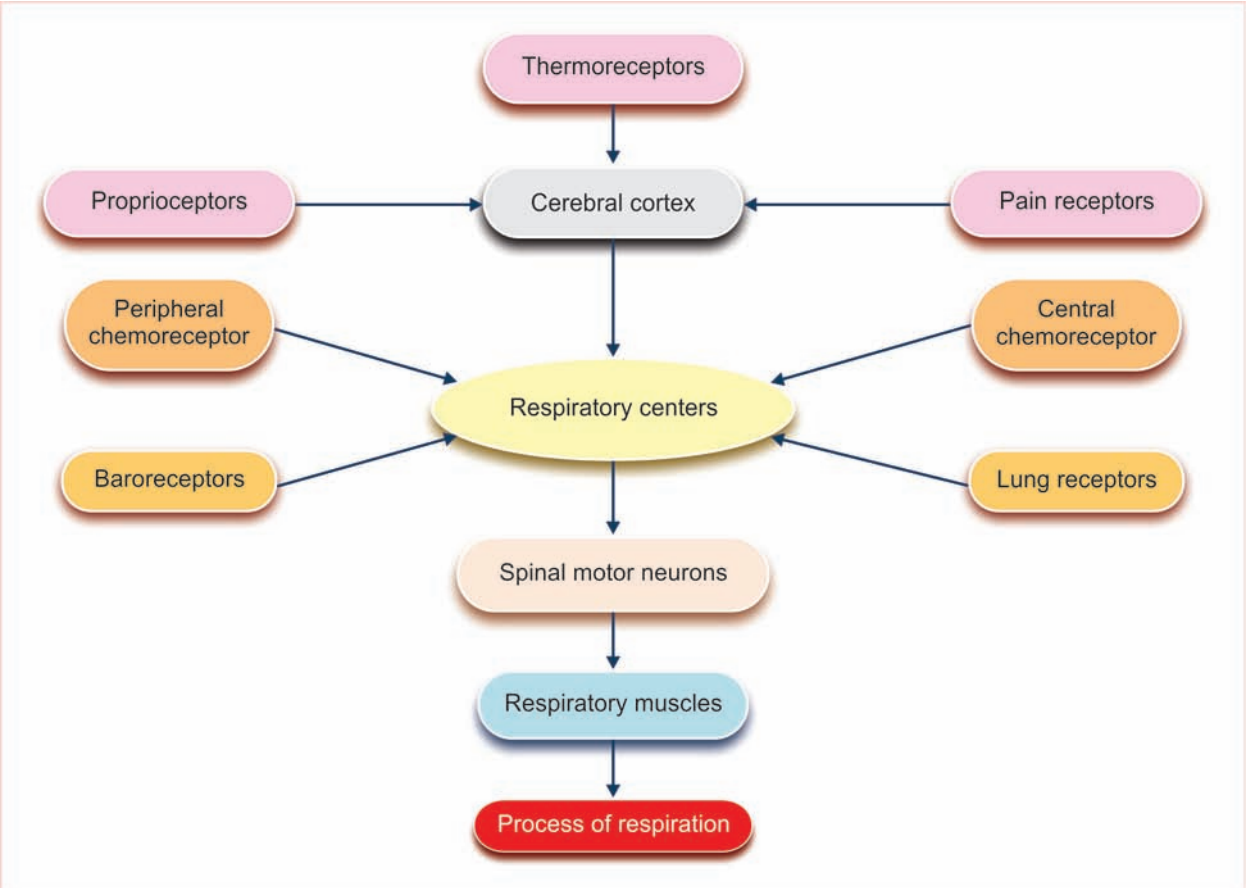


FIGURE 126.3: Factors affecting respiratory centers

Mechanism of Action

Central chemoreceptors are connected with respiratory centers, particularly the dorsal respiratory group of neurons through synapses. These chemoreceptors act slowly but effectively. Central chemoreceptors are responsible for 70% to 80% of increased ventilation through chemical regulatory mechanism.

Main stimulant for central chemoreceptors is the increased hydrogen ion concentration. However, if hydrogen ion concentration increases in the blood, it cannot stimulate the central chemoreceptors because, the hydrogen ions from blood cannot cross the **blood-brain barrier** and **blood-cerebrospinal fluid barrier.**

On the other hand, if carbon dioxide increases in the blood, it can easily cross the blood-brain barrier and blood-cerebrospinal fluid barrier and enter the interstitial fluid of brain or the cerebrospinal fluid. There, the carbon dioxide combines with water to form carbonic acid. Since carbonic acid is unstable, it immediately dissociates into hydrogen ion and bicarbonate ion (Fig. 126.4).

$$CO_2 + H_2O \longrightarrow H_2CO_3 \longrightarrow H^+ + HCO_3^-$$

Hydrogen ions stimulate the central chemoreceptors. From chemoreceptors, the excitatory impulses are sent to dorsal respiratory group of neurons, resulting in increased ventilation (increased rate and force of breathing). Because of this, excess carbon dioxide is washed out and respiration is brought back to normal. Lack of oxygen does not have significant effect on the central chemoreceptors, except that it generally depresses the overall function of brain.

■ PERIPHERAL CHEMORECEPTORS

Peripheral chemoreceptors are the chemoreceptors present in carotid and aortic region. Refer Chapter 101 for details.

Mechanism of Action

Hypoxia is the most potent stimulant for peripheral chemoreceptors. It is because of the presence of

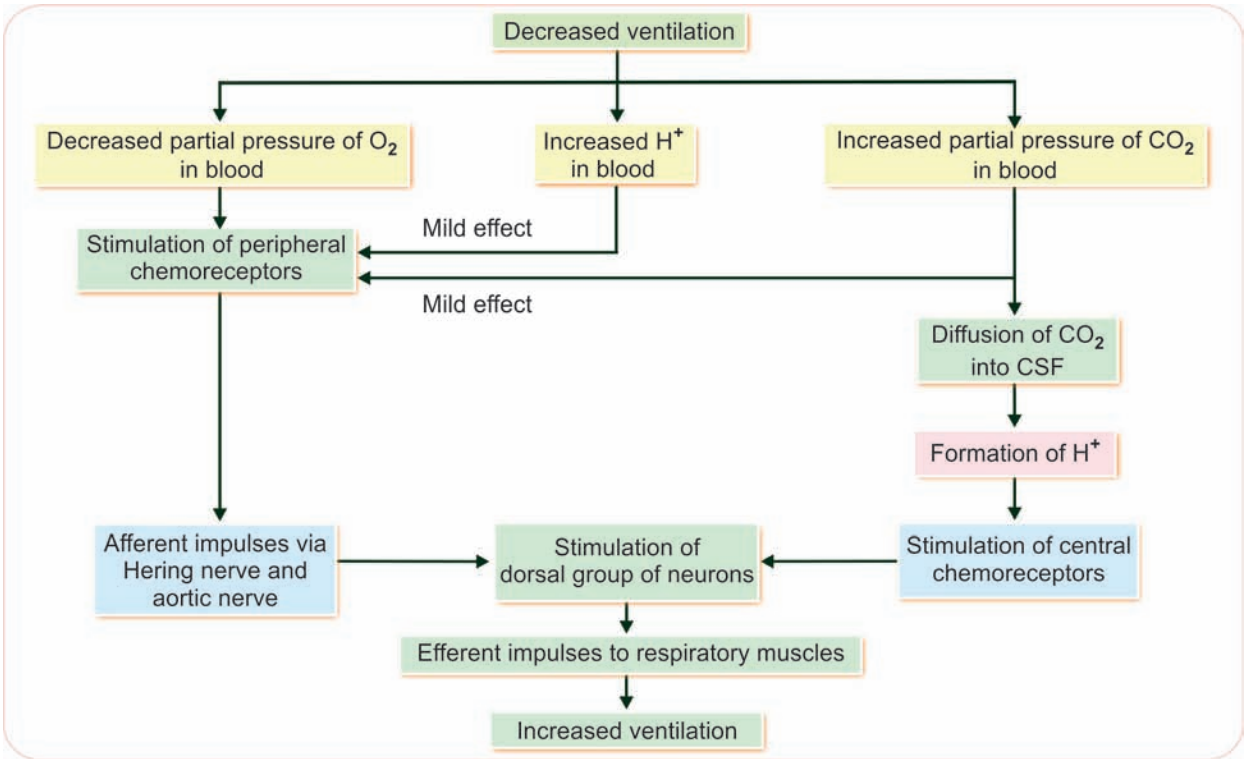


FIGURE 126.4: Chemical regulation of respiration. CSF = Cerebrospinal fluid.

oxygen sensitive potassium channels in the glomus cells of peripheral chemoreceptors.

Hypoxia causes closure of oxygen sensitive potassium channels and prevents potassium efflux. This leads to depolarization of **glomus cells** (receptor potential) and generation of action potentials in nerve ending.

These impulses pass through aortic and Hering nerves and excite the dorsal group of neurons. Dorsal group of neurons in turn, send excitatory impulses to respiratory muscles, resulting in increased ventilation. This provides enough oxygen and rectifies the lack of oxygen.

In addition to hypoxia, peripheral chemoreceptors are also stimulated by hypercapnea and increased hydrogen ion concentration. However, the sensitivity of peripheral chemoreceptors to hypercapnea and increased hydrogen ion concentration is mild.

Effects of Exercise on Respiration

Chapter 18

INTRODUCTION

Muscular exercise brings about a lot of changes on various systems of the body. Degree of changes depends upon the severity of exercise.

EFFECTS OF EXERCISE ON RESPIRATION

EFFECT ON PULMONARY VENTILATION

Pulmonary ventilation is the amount of air that enters and leaves the lungs in 1 minute. It is the product of tidal volume and respiratory rate. It is about 6 liter/minute, with a normal tidal volume of 500 mL and respiratory rate of 12/minute.

During exercise, hyperventilation, which includes increase in rate and force of respiration occurs. In moderate exercise, respiratory rate increases to about 30/minute and tidal volume increases to about 2,000 mL. Thus, the pulmonary ventilation increases to about 60 L/minute during moderate exercise. In severe muscular exercise, it rises still further up to 100 L/minute.

Factors increasing pulmonary ventilation during exercise

1. Higher centers
2. Chemoreceptors
3. Proprioceptors
4. Body temperature
5. Acidosis.

1. *Higher Centers*

Rate and depth of respiration increase during the onset of exercise. Sometimes, before starting the exercise, thought or anticipation of exercise itself increases the rate and force of respiration. It is a **psychic phenomenon** due to the activation of higher centers like Sylvian cortex and motor cortex of brain. Higher centers, in turn accelerate the respiratory processes by stimulating respiratory centers.

2. *Chemoreceptors*

Chemoreceptors which are stimulated by exercise-induced hypoxia and hypercapnea, send impulses to the respiratory centers. Respiratory centers, in turn increase the rate and force of respiration.

3. *Proprioceptors*

Proprioceptors, which are activated during exercise, send impulses to cerebral cortex through the somatic afferent nerves. Cerebral cortex, in turn causes hyperventilation by sending impulses to the medullary respiratory centers. Refer Chapter for proprioceptors.

4. *Body Temperature*

Body temperature which increases by muscular activity, increases the ventilation by stimulating the respiratory centers.

5. *Acidosis*

Acidosis developed during exercise also stimulates the respiratory centers, resulting in hyperventilation.

■ EFFECT ON DIFFUSING CAPACITY FOR OXYGEN

Diffusing capacity for oxygen is about 21 mL/minute at resting condition. It rises to 45 to 50 mL/minute during moderate exercise because of increased blood flow through pulmonary capillaries.

■ EFFECT ON CONSUMPTION OF OXYGEN

Oxygen consumed by the tissues, particularly the skeletal muscles is greatly enhanced during exercise. Because of vasodilatation in muscles during exercise, more amount of blood flows through the muscles and more amount of oxygen diffuses into the muscles from blood. The amount of oxygen utilized by the muscles is directly proportional to the amount of oxygen available.

■ EFFECT ON OXYGEN DEBT

Oxygen debt is the extra amount of oxygen required by the muscles during recovery from severe muscular exercise. After a period of severe muscular exercise, amount of oxygen consumed is greatly increased. Oxygen required is more than the quantity available to the muscle. This much of oxygen is required not only for the activity of the muscle but also for reversal of some metabolic processes such as:

1. Reformation of glucose from lactic acid, accumulated during exercise
2. Resynthesis of ATP and creatine phosphate
3. Restoration of amount of oxygen dissociated from hemoglobin and myoglobin.

Thus, for the above reversal phenomena, an extra amount of oxygen must be made available in the body after severe muscular exercise. Oxygen debt is about six times more than the amount of oxygen consumed under resting conditions.

■ EFFECT ON VO_2 MAX

VO_2 max is the amount of oxygen consumed under maximal aerobic metabolism. It is the product of maximal cardiac output and maximal amount of oxygen consumed by the muscle.

In a normal active and healthy male, the VO_2 max is 35 to 40 mL/kg body weight/minute. In females, it is 30 to 35 mL/kg body weight/minute. During exercise, VO_2 max increases by 50%.

■ EFFECT ON RESPIRATORY QUOTIENT

Respiratory quotient is the molar ratio of carbon dioxide production to oxygen consumption.

Respiratory quotient in resting condition is 1.0 and during exercise it increases to 1.5 to 2. However, at the end of exercise, the respiratory quotient reduces to 0.5.

QUESTIONS IN RESPIRATORY SYSTEM AND ENVIRONMENTAL PHYSIOLOGY

LONG QUESTIONS

1. Describe the various movements of thoracic cage and lungs during respiration.
2. Describe in detail the pulmonary circulation.
3. Give the definition and normal values of lung volumes and lung capacities and explain the measurement of the same.
4. Explain the transport of oxygen in blood.
5. Explain the transport of carbon dioxide in blood.
6. Describe the nervous regulation of respiration.
7. Describe the chemical regulation of respiration.
8. What is hypoxia? Describe the types, causes and effects of hypoxia. Add a note on oxygen therapy.
9. Describe the changes in the body at high altitude and explain the acclimatization.
10. Describe in detail the respiratory and cardio-vascular changes during exercise.

SHORT QUESTIONS

1. Respiratory unit.
2. Respiratory membrane.
3. Non-respiratory functions of respiratory tract.
4. Physiological shunt.
5. Characteristic features of pulmonary circulation.
6. Collapsing tendency of lungs.
7. Surfactant.
8. Respiratory pressures.
9. Compliance.
10. Work of breathing.
11. Spirometry.
12. Measurement of functional residual capacity.
13. Measurement of residual volume.
14. Vital capacity.
15. MBC or MVV.
16. Forced expiratory volume.
17. Plethysmography.
18. Peak expiratory flow rate.
19. Alveolar ventilation.
20. Dead space.
21. Ventilation perfusion ratio.
22. Respiratory quotient or respiratory exchange ratio.
23. Alveolar air.
24. Oxygen hemoglobin dissociation curve.
25. Carbon dioxide dissociation curve.
26. Bohr effect.
27. Haldane effect.
28. Chloride shift.
29. Diffusing capacity.
30. Exchange of gases between alveoli and blood.
31. Exchange of gases between blood and tissues.
32. Respiratory centers.
33. Inspiratory ramp.
34. Hering-Breuer reflex.
35. Receptors of lungs taking part in control of breathing.
36. Chemoreceptors.
37. Apnea.
38. Hypoxia.
39. Hyperventilation and hypoventilation.
40. Hypercapnea and hypocapnea.
41. Asphyxia.
42. Dyspnea.
43. Periodic breathing.
44. Cyanosis.
45. Oxygen toxicity (poisoning).
46. Carbon monoxide poisoning.
47. Pneumothorax.
48. Pneumonia.
49. Pulmonary edema.
50. Mountain sickness.
51. Acclimatization.
52. Effect of G force.
53. Decompression sickness.
54. Nitrogen narcosis.
55. Effects of sudden exposure to cold.
56. Effects of sudden exposure to heat.
57. Heatstroke or sunstroke.
58. Artificial respiration.
59. Respiratory changes during exercise.
60. Oxygen debt.
61. VO_2 max.
62. Fetal respiration and first breath.

Chapter 19

Pancreas

FUNCTIONAL ANATOMY AND NERVE SUPPLY OF PANCREAS

Pancreas is a dual organ having two functions, namely **endocrine function** and **exocrine function.** Endocrine function is concerned with the production of hormones (Chapter 69). The exocrine function is concerned with the secretion of digestive juice called pancreatic juice.

FUNCTIONAL ANATOMY OF EXOCRINE PART OF PANCREAS

Exocrine part of pancreas resembles salivary gland in structure. It is made up of **acini** or **alveoli.** Each acinus has a single layer of acinar cells with a lumen in the center. Acinar cells contain zymogen granules, which possess digestive enzymes.

A small duct arises from lumen of each alveolus. Some of these ducts from neighboring alveoli unite to form **intralobular duct.** All the intralobular ducts unite to form the main duct of pancreas called **Wirsung duct.** Wirsung duct joins common bile duct to form **ampulla of Vater,** which opens into duodenum (see Fig. 40.3).

In some persons, an accessory duct called **duct of Santorini** exists. It also opens into duodenum, proximal to the opening of ampulla of Vater.

NERVE SUPPLY TO PANCREAS

Pancreas is supplied by both sympathetic and parasympathetic fibers. Sympathetic fibers are supplied through splanchnic nerve and parasympathetic fibers are supplied through vagus nerve.

PROPERTIES AND COMPOSITION OF PANCREATIC JUICE

PROPERTIES OF PANCREATIC JUICE

Volume : 500 to 800 mL/day
Reaction : Highly alkaline with a pH of 8 to 8.3
Specific gravity : 1.010 to 1.018

COMPOSITION OF PANCREATIC JUICE

Pancreatic juice contains 99.5% of water and 0.5% of solids. The solids are the organic and inorganic substances. Composition of pancreatic juice is given in Fig. 39.1.

Bicarbonate content is very high in pancreatic juice. It is about 110 to 150 mEq/ L, against the plasma level of 24 mEq/L. High bicarbonate content of pancreatic juice is important because of two reasons:

i. High bicarbonate content makes the pancreatic juice **highly alkaline,** so that it protects the intestinal mucosa from acid chyme by neutralizing it
ii. Bicarbonate ions provide the required pH (7 to 9) for the activation of pancreatic enzymes.

FUNCTIONS OF PANCREATIC JUICE

Pancreatic juice has digestive functions and neutralizing action.

DIGESTIVE FUNCTIONS OF PANCREATIC JUICE

Pancreatic juice plays an important role in the digestion of proteins and lipids. It also has mild digestive action on carbohydrates.

DIGESTION OF PROTEINS

Major proteolytic enzymes of pancreatic juice are trypsin and chymotrypsin. Other proteolytic enzymes are carboxypeptidases, nuclease, elastase and collagenase.

1. *Trypsin*

Trypsin is a single polypeptide with a molecular weight of 25,000. It contains 229 amino acids.

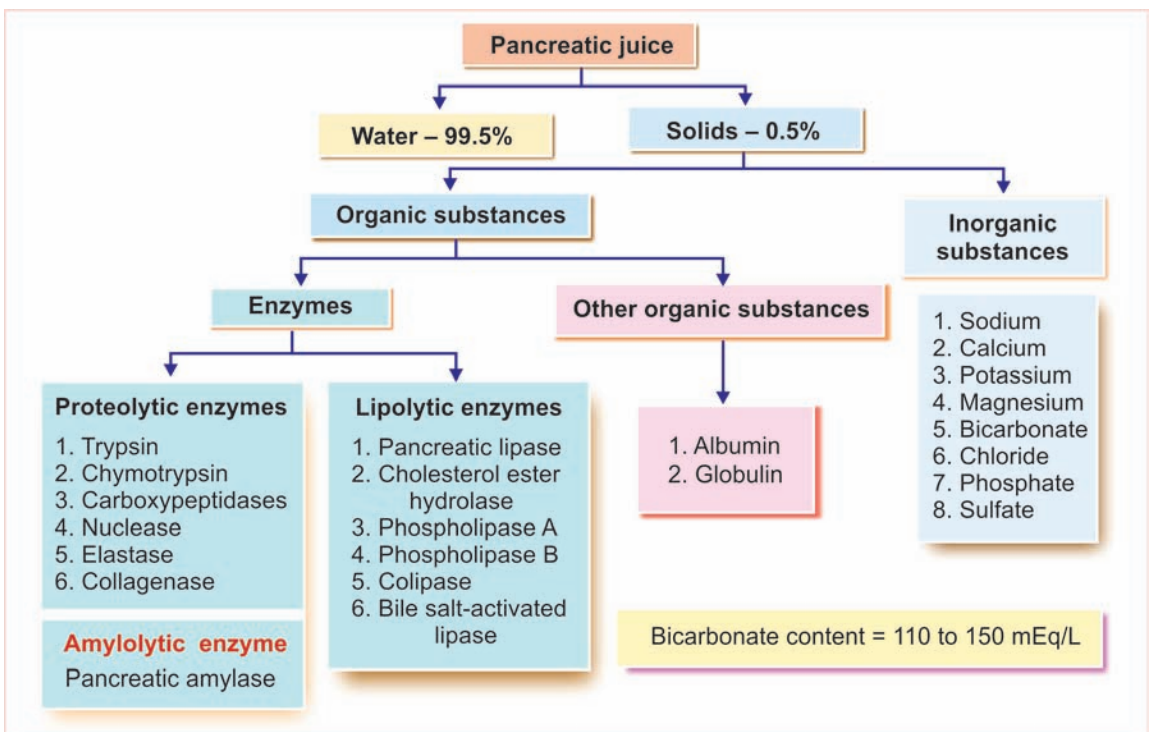


FIGURE 39.1: Composition of pancreatic juice

It is secreted as inactive trypsinogen, which is converted into active trypsin by **enterokinase.** Enterokinase is also called **enteropeptidase** and it is secreted by the brush-bordered cells of duodenal mucus membrane. Once formed, trypsin itself activates trypsinogen by means of **autocatalytic** or **autoactive action.**

Trypsin inhibitor

Trypsinogen is activated only when it reaches the small intestine. If trypsin is activated when it is in pancreas, it may hydrolyze the pancreatic tissue proteins, resulting in pancreatic damage. But its activation in the secretory cells, acini and ducts of pancreas is prevented by an inhibitor protein called trypsin inhibitor. Any abnormality or deficiency of the trypsin inhibitor will result in unopposed trypsin activity, which damages the pancreas.

Actions of trypsin

i. Digestion of proteins: Trypsin is the most powerful proteolytic enzyme. It is an **endopeptidase** and breaks the interior bonds of the protein molecules and converts proteins into proteoses and polypeptides
ii. Curdling of milk: It converts **caseinogen** in the milk into **casein**
iii. Blood clotting: It accelerates blood clotting
iv. It activates the other enzymes of pancreatic juice, viz.
    a. Chymotrypsinogen into chymotrypsin
    b. Procarboxypeptidases into carboxypeptidases
    c. Proelastase into elastase
    d. Procolipase into colipase
v. Trypsin also activates collagenase, phospholipase A and phospholipase B
vi. Autocatalytic action: Once formed, trypsin itself converts trypsinogen into trypsin.

2. *Chymotrypsin*

Chymotrypsin is a polypeptide with a molecular weight of 25,700 and 246 amino acids. It is secreted as inactive chymotrypsinogen, which is activated into chymotrypsin by trypsin.

Actions of chymotrypsin

i. *Digestion of proteins:* Chymotrypsin is also an endopeptidase and it converts proteins into polypeptides
ii. *Digestion of milk:* Chymotrypsin digests caseinogen faster than trypsin. Combination of both enzymes causes rapid digestion of milk
iii. *On blood clotting:* No action.

3. *Carboxypeptidases*

Carboxypeptidases are carboxypeptidase A and carboxypeptidase B. Carboxypeptidase A is derived from the precursor procarboxypeptidase A. Carboxypeptidase B is derived from procarboxypeptidase B. Procarboxypeptidases are activated into carboxypeptidases by trypsin.

Actions of carboxypeptidases

Carboxypeptidases are **exopeptidases** and break the terminal bond of protein molecules. Exopeptidases split the polypeptides and other proteins into amino acids.

Carboxypeptidase A splits the proteins into amino acids having aromatic or aliphatic side chains. Carboxypeptidase B converts the proteins into amino acids having basic side chains.

4. *Nucleases*

Nucleases of pancreatic juice are ribonuclease and deoxyribonuclease, which are responsible for the digestion of nucleic acids. These enzymes convert the ribonucleic acid (RNA) and deoxyribonucleic acid (DNA) into mononucleotides.

5. *Elastase*

Elastase is secreted as inactive proelastase, which is activated into elastase by trypsin. Elastase digests the elastic fibers.

6. *Collagenase*

Collagenase is secreted as inactive procollagenase, which is activated into collagenase by trypsin. It digests collagen.

■ DIGESTION OF LIPIDS

Lipolytic enzymes present in pancreatic juice are pancreatic lipase, cholesterol ester hydrolase, phospholipase A, phospholipase B, colipase and bile-salt-activated lipase.

1. *Pancreatic lipase*

Pancreatic lipase is a powerful lipolytic enzyme. It digests triglycerides into monoglycerides and fatty

acids. Activity of pancreatic lipase is accelerated in the presence of bile. Optimum pH required for activity of this enzyme is 7 to 9.

Digestion of fat by pancreatic lipase requires two more factors:

i. Bile salts, which are responsible for the emulsification of fat, prior to their digestion
ii. Colipase, which is a coenzyme necessary for the pancreatic lipase to digest the dietary lipids.

About 80% of the fat is digested by pancreatic lipase. Deficiency or absence of this enzyme leads to excretion of undigested fat in feces (steatorrhea; see below).

2. *Cholesterol ester hydrolase*

Cholesterol ester hydrolase or cholesterol esterase converts cholesterol ester into free cholesterol and fatty acid by hydrolysis.

3. *Phospholipase A*

Phospholipase A is activated by trypsin. Phospholipase A digests phospholipids, namely **lecithin** and **cephalin** and converts them into **lysophospholipids.** It converts lecithin into lysolecithin and **cephalin** into **lysocephalin.**

4. *Phospholipase B*

Phospholipase B is also activated by trypsin. It converts lysophospholipids (lysolecithin and lysocephalin) to **phosphoryl choline** and free fatty acids.

5. *Colipase*

Colipase is a small coenzyme, secreted as inactive procolipase. Procolipase is activated into colipase by trypsin. Colipase facilitates digestive action of pancreatic lipase on fats.

6. *Bile-salt-activated lipase*

Bile-salt-activated lipase is the lipolytic enzyme activated by bile salt. It is also called **carboxyl ester lipase** or **cholesterol esterase.** This enzyme has a weak lipolytic action than pancreatic lipase. But it hydrolyses a variety of lipids such as phospholipids, cholesterol esters and triglycerides. **Human milk** contains an enzyme similar to bile-salt-activated lipase (Table 39.1).

■ DIGESTION OF CARBOHYDRATES

Pancreatic amylase is the amylolytic enzyme present in pancreatic juice. Like salivary amylase, the pancreatic amylase also converts starch into dextrin and maltose.

■ NEUTRALIZING ACTION OF PANCREATIC JUICE

When acid chyme enters intestine from stomach, pancreatic juice with large quantity of bicarbonate is released into intestine. Presence of large quantity of bicarbonate ions makes the pancreatic juice highly alkaline. This alkaline pancreatic juice neutralizes acidity of chyme in the intestine.

Neutralizing action is an important function of pancreatic juice because it protects the intestine from the destructive action of acid in the chyme.

■ MECHANISM OF PANCREATIC SECRETION

■ SECRETION OF PANCREATIC ENZYMES

Pancreatic enzymes are synthesized in ribosomes, which are attached to the endoplasmic reticulum of acinar cells in pancreas. The raw materials for the synthesis of pancreatic enzymes are the amino acids, which are derived from the blood. After synthesis, the enzymes are packed into different zymogen granules by Golgi apparatus and stored in cytoplasm. When stimulated, the acinar cells release zymogen granules into the pancreatic duct. From the granules, the enzymes are liberated into intestine.

■ SECRETION OF BICARBONATE IONS

Bicarbonate ions of pancreatic juice are secreted from the cells of pancreatic ductules and released into the pancreatic duct.

Mechanism of bicarbonate secretion

1. Carbon dioxide derived from blood or metabolic process combines with water inside the cell to form carbonic acid in the presence of carbonic anhydrase
2. Carbonic acid dissociates into hydrogen and bicarbonate ions
3. Bicarbonate ions are actively transported out of the cell into the lumen
4. Hydrogen ion is actively transported into blood in exchange for sodium ion
5. Sodium ion from the cell is transported into the lumen, where it combines with bicarbonate to form sodium bicarbonate
6. Because of the loss of sodium and bicarbonate ions from the blood, there is some disturbance in the **osmotic equilibrium** of the blood. To maintain

TABLE 39.1: Digestive enzymes of pancreatic juice

Enzyme	Activator	Acts on (substrate)	End products
Trypsin	Enterokinase Trypsin	Proteins	Proteoses and polypeptides
Chymotrypsin	Trypsin	Proteins	Polypeptides
Carboxypeptidases	Trypsin	Polypeptides	Amino acids
Nucleases	Trypsin	RNA and DNA	Mononucleotides
Elastase	Trypsin	Elastin	Amino acids
Collagenase	Trypsin	Collagen	Amino acids
Pancreatic lipase	Alkaline medium	Triglycerides	Monoglycerides and fatty acids
Cholesterol ester hydrolase	Alkaline medium	Cholesterol ester	Cholesterol and fatty acids
Phospholipase A	Trypsin	Phospholipids	Lysophospholipids
Phospholipase B	Trypsin	Lysophospholipids	Phosphoryl choline and free fatty acids
Colipase	Trypsin	Facilitates action of pancreatic lipase	–
Bile-salt-activated lipase	Trypsin	Phospholipids	Lysophospholipids
		Cholesterol esters	Cholesterol and fatty acids
		Triglycerides	Monoglycerides and fatty acids
Pancreatic amylase	–	Starch	Dextrin and maltose

the osmotic equilibrium, water leaves the blood and enters the lumen of pancreatic duct by osmosis

7. In the lumen, bicarbonate combines with water forming the solution of bicarbonate.

REGULATION OF PANCREATIC SECRETION

Secretion of pancreatic juice is regulated by both nervous and hormonal factors.

STAGES OF PANCREATIC SECRETION

Pancreatic juice is secreted in three stages (Fig. 39.2) like the gastric juice:

1. Cephalic phase
2. Gastric phase
3. Intestinal phase.

These three phases of pancreatic secretion correspond with the three phases of gastric secretion.

1. CEPHALIC PHASE

As in case of gastric secretion, cephalic phase is regulated by nervous mechanism through reflex action.

Two types of reflexes occur:

1. Unconditioned reflex
2. Conditioned reflex.

Unconditioned Reflex

Unconditioned reflex is the inborn reflex. When food is placed in the mouth, salivary secretion and gastric secretion are induced. Simultaneously, pancreatic secretion also occurs.

Stages of reflex action:

i. Presence of food in the mouth stimulates the **taste buds** and other receptors in the mouth
ii. Sensory (afferent) impulses from mouth reach dorsal nucleus of vagus and efferent impulses reach pancreatic acini via vagal efferent nerve fibers
iii. Vagal efferent nerve endings secrete acetyl-choline, which stimulates pancreatic secretion.

Conditioned Reflex

Conditioned reflex is the reflex response acquired by previous experience. Presence of food in the mouth is not necessary to elicit this reflex. The sight, smell, hearing or thought of food, which induce salivary secretion and gastric secretion induce pancreatic secretion also.

Stages of reflex action:

i. Impulses from the special sensory organs (eye, ear and nose) pass through afferent fibers of

neural circuits to the cerebral cortex. Thinking of food stimulates the cerebral cortex directly

ii. From cerebral cortex, the impulses pass through dorsal nucleus of vagus and vagal efferents and reach pancreatic acini

iii. Vagal nerve endings secrete acetylcholine, which stimulates pancreatic secretion.

■ 2. GASTRIC PHASE

Secretion of pancreatic juice when food enters the stomach is known as gastric phase. This phase of pancreatic secretion is under hormonal control. The hormone involved is gastrin.

When food enters the stomach, gastrin is secreted from stomach. When gastrin is transported to pancreas through blood, it stimulates the pancreatic secretion. The pancreatic juice secreted during gastric phase is rich in enzymes.

■ 3. INTESTINAL PHASE

Intestinal phase is the secretion of pancreatic juice when the chyme enters the intestine. This phase is also under hormonal control.

When chyme enters the intestine, many hormones are released. Some hormones stimulate the pancreatic secretion and some hormones inhibit the pancreatic secretion.

Hormones Stimulating Pancreatic Secretion

i. Secretin

ii. Cholecystokinin.

Secretin

Secretin is produced by S cells of mucous membrane in duodenum and jejunum. It is secreted as inactive prosecretin, which is activated into secretin by acid chyme.

The stimulant for the release and activation of prosecretin is the acid chyme entering intestine. Products of protein digestion also stimulate the hormonal secretion.

Action of secretin

Secretin stimulates the secretion of watery juice which is rich in of bicarbonate ion and high in volume. It increases the pancreactic secretion by acting on pancreatic ductules via cyclic AMP (messenger).

Cholecystokinin

Cholecystokinin (CCK) is also called cholecystokinin-pancreozymin (CCK-PZ). It is secreted by I cells in duodenal and jejunal mucosa. The stimulant for the

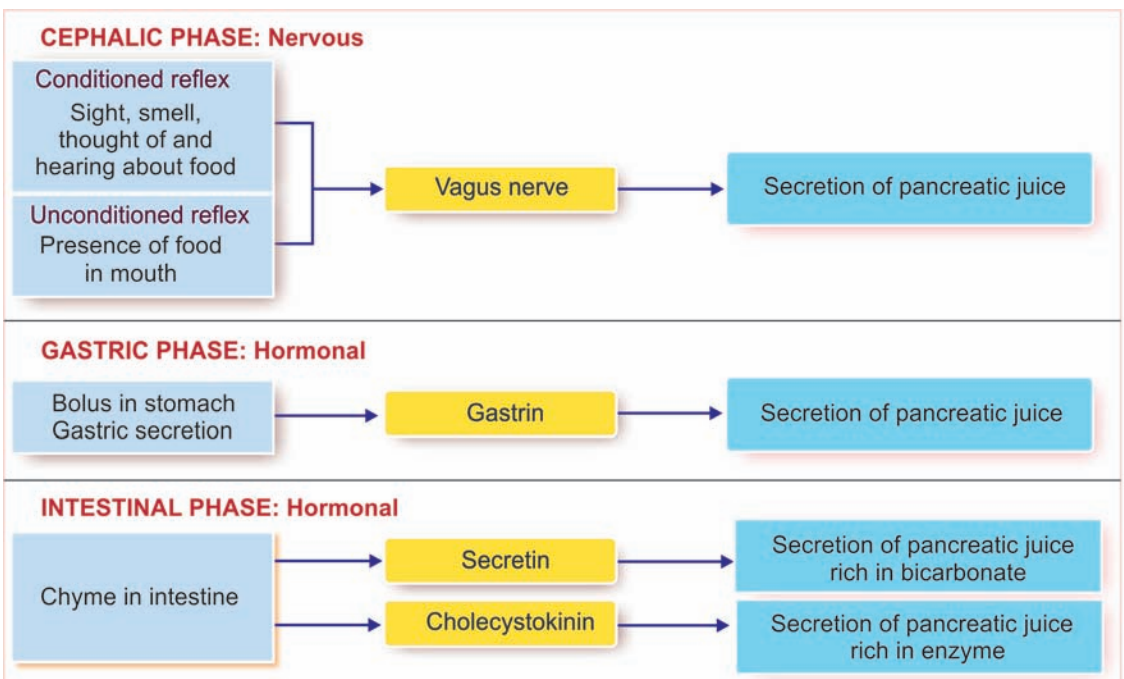


FIGURE 39.2: Schematic diagram showing the regulation of pancreatic secretion

release of this hormone is the chyme containing digestive products such as fatty acids, peptides and amino acids.

Action of cholecystokinin

Cholecystokinin stimulates the secretion of pancreatic juice which is rich in enzyme and low in volume, by acting on pancreatic acinar cells via inosine triphosphate (second messenger).

Hormones Inhibiting Pancreatic Secretion

i. Pancreatic polypeptide (PP) secreted by PP cells in islets of Langerhans of pancreas
ii. Somatostatin secreted by D cells in islets of Langerhans of pancreas
iii. Peptide YY secreted by intestinal mucosa
iv. Peptides like ghrelin and leptin

Refer Chapter 44 for details of these hormones.

■ COLLECTION OF PANCREATIC JUICE

■ IN ANIMALS

In animals, the pancreatic juice is collected by connecting a fistula between the pancreatic duct and the opening in the abdominal wall.

■ IN HUMAN

In human beings, a multilumen tube is inserted through nose or mouth, till the tip of this tube reaches the intestine near the ampulla of Vater. The tube has a marking. The entrance of the tip of the tube into the intestine near the ampulla is indicated when this line comes near the mouth. The tube has three lumens. Small balloons are attached to the two outer lumens. When balloons are inflated by air, the intestine near the ampulla is enlarged. Now, the pancreatic juice is collected through the middle lumen by means of aspiration.

■ APPLIED PHYSIOLOGY

■ PANCREATITIS

Pancreatitis is the inflammation of pancreatic acini. It is a rare but dangerous disease.

Pancreatitis is of two types:

1. Acute pancreatitis
2. Chronic pancreatitis.

1. *Acute Pancreatitis*

Acute pancreatitis is more severe and it occurs because of heavy alcohol intake or gallstones.

Features of acute pancreatitis:

i. Severe upper abdominal pain
ii. Nausea and vomiting
iii. Loss of appetite and weight
iv. Fever
v. Shock.

2. *Chronic Pancreatitis*

Chronic pancreatitis develops due to repeated acute inflammation or chronic damage to pancreas.

Causes of chronic pancreatitis

i. Long-time consumption of alcohol
ii. Chronic obstruction of ampulla of Vater by gallstone
iii. Hereditary cause (passed on genetically from one generation to another)
iv. Congenital abnormalities of pancreatic duct
v. **Cystic fibrosis,** a generalized disorder affecting the functions of many organs such as lungs (due to excessive mucus), exocrine glands like pancreas, biliary system and immune system
vi. Malnutrition (poor nutrition; mal = bad)
vii. Idiopathic pancreatitis (due to unknown cause).

Features of chronic pancreatitis

i. *Complete destruction of pancreas:* During the obstruction of biliary ducts, more amount of trypsinogen and other enzymes are accumulated. In spite of the presence of trypsin inhibitor in acini, some trypsinogen is activated. Trypsin in turn activates other proteolytic enzymes. All these enzymes destroy the pancreatic tissues completely
ii. *Absence of pancreatic enzymes:* Pancreatitis is more dangerous because the destruction of acinar cells in pancreas leads to deficiency or total absence of pancreatic enzymes. So the digestive processes are affected; worst affected

is fat digestion that results in steatorrhea (see below)

iii. Severe pain in upper abdominal region, which radiates to the back
iv. Fever, nausea and vomiting
v. Tender and swollen abdomen
vi. Weight loss.

■ STEATORRHEA

Steatorrhea is the formation of bulky, foul-smelling, frothy and clay-colored stools with large quantity of undigested fat because of impaired digestion and absorption of fat.

Causes of Steatorrhea

Any condition that causes indigestion or malabsorption of fat leads to steatorrhea. Various causes of steatorrhea are:

1. *Lack of pancreatic lipase:* Since most of the fat is digested only by pancreatic lipase, its deficiency leads to steatorrhea
2. *Liver disease affecting secretion of bile:* Bile salts are essential for the digestion of fat by lipase and absorption of fat from intestine. Absence of bile salts results in excretion of fatty stool
3. *Celiac disease:* Atrophy of intestinal villi leads to malabsorption, resulting in steatorrhea
4. Cystic fibrosis (see above).

Chapter 20

Proprioceptors

- PROPRIOCEPTORS
- MUSCLE SPINDLE
  - STRUCTURE
  - NERVE SUPPLY
  - FUNCTIONS
- GOLGI TENDON ORGAN
  - STRUCTURE
  - NERVE SUPPLY
  - FUNCTIONS
- PACINIAN CORPUSCLE
- FREE NERVE ENDING

■ PROPRIOCEPTORS

It is necessary to know about the proprioceptors to understand the maintenance of posture and equilibrium, which is explained in the next chapter.

Definition

Proprioceptors are the receptors, which detect and give response to movement and change in position of different parts of the body. These receptors are also called **kinesthetic receptors.**

Situation

Proprioceptors are situated in labyrinth, muscles, tendon of the muscles, joints, ligaments and fascia (Table 156.1).

Different Proprioceptors

1. Muscle spindle
2. Golgi tendon organ
3. Pacinian corpuscle
4. Free nerve ending
5. Proprioceptors in labyrinth.

Proprioceptors in the labyrinth are described in

TABLE 156.1: Situation of proprioceptors

Proprioceptor	Situation
Muscle spindle	Skeletal muscles
Golgi tendon organ	Tendons
Pacinian corpuscle	Skin Fascia over muscles Tendons Tissues around joint Joint capsule
Free nerve ending	Skin Skeletal muscles Tendons Fascia over muscles Joints
Labyrinthine proprioceptors	Labyrinth

■ MUSCLE SPINDLE

Muscle spindle is a spindle-shaped **proprioceptor** situated in the skeletal muscle. It is formed by modified skeletal muscle fibers called **intrafusal muscle fibers.**

■ STRUCTURE OF MUSCLE SPINDLE

Muscle spindle has a central bulged portion and two tapering ends. Each muscle spindle is formed by 5 to 12

intrafusal muscle fibers. All these fibers are enclosed by a capsule, which is formed by connective tissue. Intrafusal fibers are attached to the capsule on either end. The capsule is attached to either side of extrafusal fibers or the tendon of the muscle. Thus, intrafusal fibers are placed parallel to the extrafusal fibers. Intrafusal fibers are thin and striated (Fig. 156.1).

Central portion of the intrafusal fibers does not contract because it has only few or no actin and myosin filaments. So, this portion acts only as a receptor. Only the end portion of intrafusal fibers can contract. The discharge from gamma motor neurons causes the contraction of intrafusal fibers.

Types of Intrafusal Fibers

Muscle spindle is formed by two types of intrafusal fibers:

1. Nuclear bag fiber
2. Nuclear chain fiber.

1. *Nuclear bag fiber*

Central portion of this fiber is enlarged like a **bag** and contains many nuclei. Hence, it is called the nuclear bag fiber.

2. *Nuclear chain fiber*

In nuclear chain fiber, central portion is not bulged and the nuclei are arranged in the center in the form of a chain. Nuclear chain fiber is attached to the side of end portion of nuclear bag fiber.

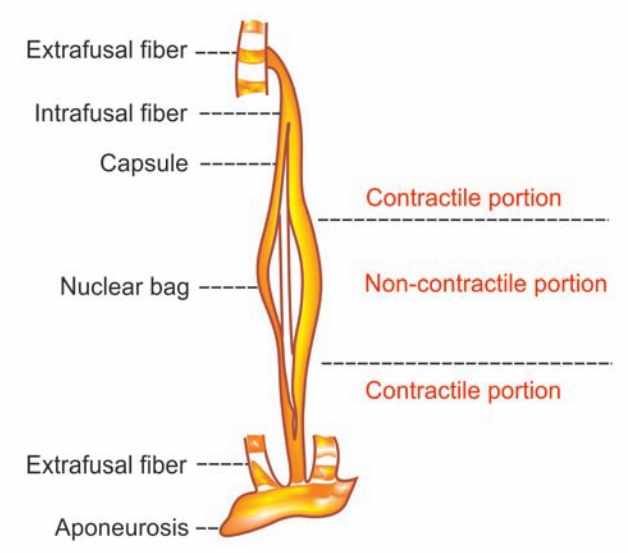


FIGURE 156.1: Muscle spindle

■ NERVE SUPPLY TO MUSCLE SPINDLE

Muscle spindle is innervated by both sensory and motor nerves. It is the **only receptor** in the body, which has both **sensory** and **motor nerve supply.**

Sensory Nerve Supply

Each muscle spindle receives two types of sensory nerve fibers:

1. Primary sensory nerve fiber
2. Secondary sensory nerve fiber.

1. Primary sensory nerve fiber

Primary sensory nerve fiber belongs to **type Iα (Aα)** nerve fiber. Each sensory (afferent) nerve fiber has two branches. One of the branches supplies the central portion of nuclear bag fiber (Fig. 156.2). The other branch ends in central portion of the nuclear chain fiber. These branches end in the form of rings around central portion of nuclear bag and nuclear chain fibers. Therefore, these nerve endings are called **annulospiral endings.**

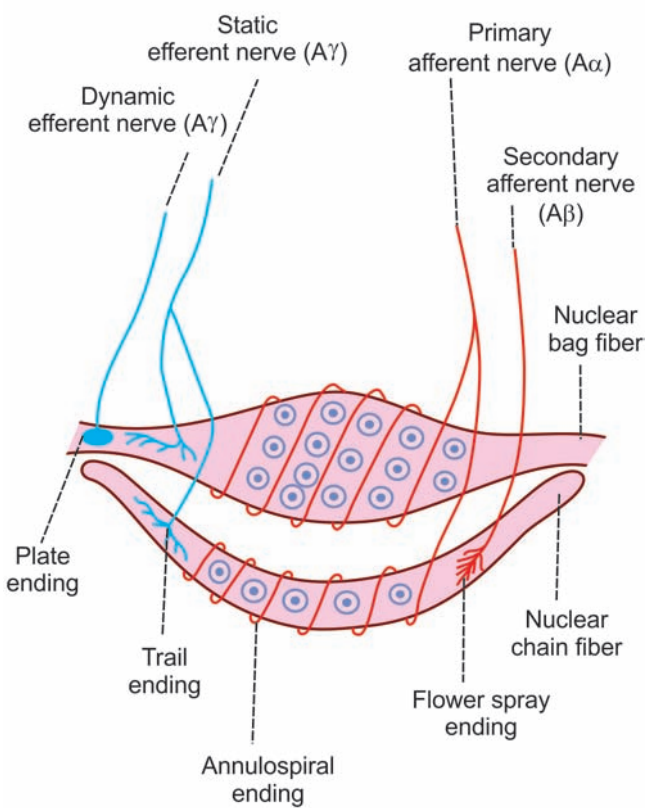


FIGURE 156.2: Nerve supply to muscle spindle. Red = Afferent (sensory) nerve fibers, Blue = Efferent (motor) nerve fibers. Letters in parenthesis indicate the type of nerve fibers.

2. *Secondary sensory nerve fiber*

Secondary sensory nerve fiber is a **type II (Aβ)** nerve fiber. It innervates only the nuclear chain fiber and ends near the end portion of nuclear chain fiber like the petals of the flower. So, this nerve ending is called **flower spray ending.**

Motor Nerve Supply

Motor (efferent) nerve fiber supplying the muscle spindle belongs to gamma motor neuron **(Aγ) type.**

Motor nerve supply to nuclear bag fiber

Gamma motor nerve fiber supplying the nuclear bag fiber ends as motor end plate. This nerve ending is called **plate ending.** Functionally, it is known as **dynamic gamma efferent** (motor) nerve fiber.

Motor nerve supply to nuclear chain fiber

Gamma motor nerve fiber supplying the nuclear chain fiber divides into many branches, which form a network called **trail ending.** Functionally, it is known as **static gamma efferent** (motor) nerve fiber. Sometimes, it gives a branch to nuclear bag fiber also.

■ FUNCTIONS OF MUSCLE SPINDLE

Muscle spindle gives response to change in the length of the muscle. It detects how much the muscle is being stretched and sends this information to central nervous system (CNS) via sensory nerve fibers. The information is processed in CNS to determine the position of different parts of the body. By detecting the change in length of the muscle, the spindle plays an important role in preventing the overstretching of the muscles.

Muscle spindle has two functions:

1. It forms the receptor organ for stretch reflex
2. It plays an important role in maintaining muscle tone.

1. *Role of Muscle Spindle in Stretch Reflex*

Stretch reflex

Stretch reflex is the reflex contraction of muscle when it is stretched. It is also called **myotatic reflex.** It is a **monosynaptic reflex** and the quickest of all the reflexes. Extensor muscles, particularly the antigravity muscles exhibit a severe and prolonged contraction during stretch reflex. Stretch reflex plays an important role in maintaining posture.

Muscle spindle as the receptor organ for stretch reflex

Stimulation of muscle spindle elicits the stretch reflex. Intrafusal muscle fibers are situated parallel to the extrafusal muscle fibers and are attached to the tendon of the muscle by means of capsule. So, stretching of the muscle causes **stretching of the muscle spindle** also. This stimulates the muscle spindle and it discharges the sensory impulses. These impulses are transmitted via the primary and secondary sensory nerve fibers to the alpha motor neurons in spinal cord. Alpha motor neurons in turn send motor impulse to muscles through their fibers and cause contraction of extrafusal fibers (Fig. 156.3).

Response of muscle spindle to stretch

When the muscle is stretched, primary sensory nerve fibers from muscle spindle discharge impulses. This response is of two types:

i. Dynamic response
ii. Static response.

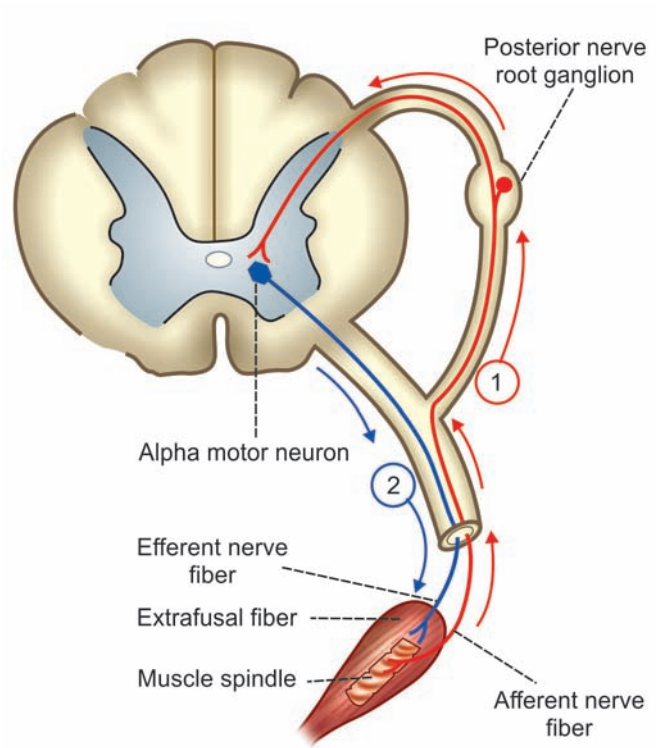


FIGURE 156.3: Stretch reflex. 1. Afferent impulses from muscle spindle of stretched muscle. 2. Efferent impulses from α-motor neurons causing contraction of muscle.

i. *Dynamic response*

Dynamic response is the response in which the primary sensory nerve fibers discharge rapidly. When there is a change in length of the muscle by stretching, primary sensory nerve fibers from nuclear bag fiber start discharging impulses very rapidly. But, the discharge becomes less or nil during continuous stretching of the muscle. Discharge of impulses start only if there is change in degree of stretching of the muscle. Thus, the response depends upon rate of change in length of the muscle.

ii. *Static response*

Static response is the response in which impulses are discharged rapidly and continuously throughout the period of muscle stretch by primary sensory nerve fibers of the nuclear chain fibers.

Thus, the muscle spindle gives response to change in length of the muscle as well as rate of change in length.

Physiologic tremor

Physiologic tremor is the continuous discharge of actions potentials with low voltage and ineffective frequency from primary and secondary sensory nerve fibers of muscle spindle at resting condition. Physiological tremor plays an important role in the feedback regulation of muscle length.

2. *Role of Muscle Spindle in the Maintenance of Muscle Tone*

The state of continuous and partial contraction of the muscle is called muscle tone. It is due to the continuous discharge of impulses from gamma motor neurons.

Gamma motor neurons innervate the intrafusal fibers. Motor impulses from gamma motor neurons stimulate the intrafusal fibers of muscle spindle, which in turn sends sensory impulses back to spinal cord. Now the alpha motor neurons in spinal cord are activated resulting in contraction of extrafusal fibers of muscle.When the frequency of discharge from gamma motor neurons increases, activity of muscle spindle is increased and the muscle tone also increases.

■ GOLGI TENDON ORGAN

■ STRUCTURE OF GOLGI TENDON ORGAN

Golgi tendon organ is situated in the **tendon** of skeletal muscle near the attachment of extrafusal fibers. It is placed in series between the muscle fibers and the tendon. Golgi tendon organ is formed by a group of nerve endings covered by a connective tissue capsule (Fig. 156.4).

■ NERVE SUPPLY TO GOLGI TENDON ORGAN

Sensory nerve fiber supplying the Golgi tendon organ belongs to **Ib type.** The nerve fiber supplying Golgi tendon organ ramifies into many branches. Each branch ends in the form of a knob.

■ FUNCTIONS OF GOLGI TENDON ORGAN

Golgi tendon organ gives response to the change in the force or tension developed in the skeletal muscle during contraction. It is also the receptor for inverse stretch reflex and lengthening reaction and thereby prevents damage of muscle due to overstretching.

1. *Role of Golgi Tendon Organ in Forceful Contraction*

During powerful contraction, tension in the muscles increases and stimulates Golgi tendon organ, which discharges the sensory impulses. Impulses are transmitted by Ib sensory nerve fiber to an inhibitory interneuron in the spinal cord. Interneuron, in turn, causes development of **inhibitory postsynaptic potential** (IPSP) in motor neurons, which supply the muscle. Now, the contraction of the muscle is inhibited.

2. *Role of Golgi Tendon Organ in Inverse Stretch Reflex*

Inverse stretch reflex

Inverse stretch reflex is the sudden decrease in resistance due to relaxation (instead of contraction) when a

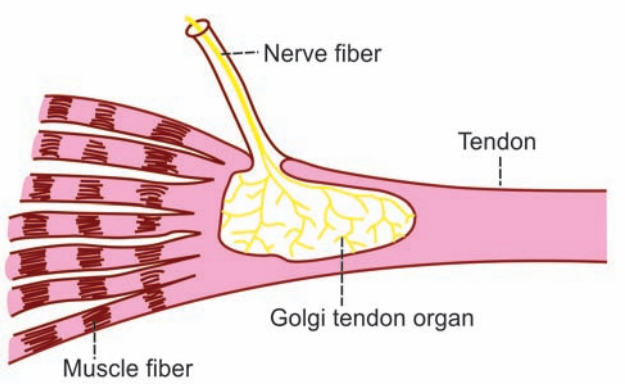


FIGURE 156.4: Golgi tendon apparatus

muscle is stretched excessively. It is also called **inverse myotatic reflex** and it is a **polysynaptic reflex.**

Inverse stretch reflex is actually the inhibition of contraction due to excessive stretching. So, it is also called the **autogenic inhibition.**

Mechanism of inverse stretch reflex

Excessive stretch of the muscle leads to activation of Golgi tendon organ, which send afferent impulses which cause:

i. Stimulation of inhibitory internuncial neuron, which in turn inhibits alpha motor neuron of the stretched muscle resulting in relaxation
ii. Stimulation of excitatory internuncial neuron, which in turn activates alpha motor neuron of the antagonistic muscle. It leads to contraction of antagonistic muscle and relaxation of stretched muscle.

3. Role of Golgi Tendon Organ in Lengthening Reaction

When tension increases during muscular contraction caused by stretch reflex, the Golgi tendon organ is activated. It causes development of a spinal reaction, which is called the lengthening reaction. It can be demonstrated in a decerebrate preparation.

In **decerebrate rigidity,** the extension of limbs is due to **spastic contraction** of extensor muscles. It is because of increased discharge from gamma motor neurons, which facilitates the **stretch reflex.**

In a decerebrate animal, some resistance is offered when the arm is flexed at elbow joint passively. That is, the arm cannot be flexed easily. This type of resistance is offered because of the stretch reflex developed in the triceps muscle. However, if forearm is flexed forcefully, resistance to flexion is abolished suddenly, leading to quick flexion of arm. It is called the lengthening reaction.

Lengthening reaction is due to the activation of Golgi tendon organ. The sudden flexion of arm is called the **Phillipson reflex** or **clasp knife reflex.**

■ PACINIAN CORPUSCLE

Pacinian corpuscle is a **mechanoreceptor** that senses pressure and vibration. It is situated in the deeper layers of skin. It is also situated in the tissues surrounding the joints such as fascia over the muscle, tendons and joint capsule. Pacinian corpuscles situated in these tissues are responsible for determining the position of joints.

Since pacinian corpuscle is a rapidly adapting receptor **(phasic receptor)** it is very sensitive to quick changes in the position of joints. So it is believed to send information about joint movement to CNS.

■ FREE NERVE ENDING

Free nerve ending is the receptor for pain sensation situated in skin, muscles, tendon, fascia and joints. As it is a slow adapting receptor **(tonic receptor)** it is maximally stimulated at specific joint positions. So it is believed to send information about joint position to CNS.

Chapter 21

Posture and Equilibrium

DEFINITION

Subconscious **adjustment of tone** in different muscles in relation to every movement is known as the **posture.** Significance of posture is to make the movement smooth and accurate and to maintain the line of gravity constant or to keep the body in equilibrium with line of gravity. Posture is not an active movement. It is the **passive movement** associated with **redistribution of tone** in different groups of related muscles.

BASIC PHENOMENA OF POSTURE

Basic phenomena for maintenance of posture are muscle tone and stretch reflex.

MUSCLE TONE

Definition

Muscle tone is defined as the state of continuous and passive partial contraction of muscle with certain vigor and tension. It is also called **tonus.** It is also defined as resistance offered by the muscle to stretch.

Significance of Muscle Tone

Muscle tone plays an important role in maintenance of posture. Change in muscle tone enables movement of different parts of the body. Muscle tone is present in all the skeletal muscles. However, tone is more in antigravity muscles such as extensors of lower limb, trunk muscles and neck muscles.

Development of Muscle Tone

Gamma motor neurons and muscle spindle are responsible for the development and maintenance of muscle tone.

Muscle tone is purely a reflex process. This reflex is a **spinal segmental reflex.** It is developed by continual synchronous discharge of motor impulses from the gamma motor neurons present in the anterior gray horn of the spinal cord (Figs. 157.1 and 157.2).

Sequence of events

1. Impulses from the gamma motor neurons cause contraction of end portions of intrafusal fibers (stimulus)
2. This stretches and activates the central portion of the intrafusal fibers, which initiates the reflex action for development of muscle tone by discharging the impulses
3. Impulses from the central portion of intrafusal fibers pass through primary sensory nerve fibers (afferent fibers) and reach the anterior gray horn of spinal cord
4. These impulses stimulate the alpha motor neurons in anterior gray horn (center)

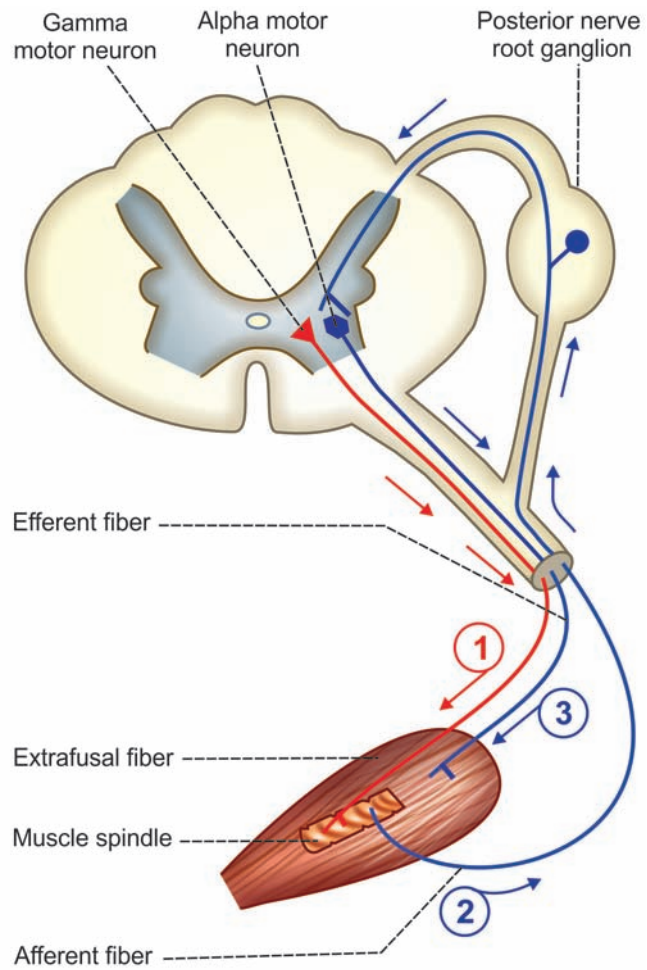


FIGURE 157.1: Development of muscle tone.1. Impulses from γ-motor neuron stimulate muscle spindle. 2. Afferent impulses from muscle spindle to α-motor neuron. 3. Efferent impulses from α-motor neuron produce contraction of extrafusal fibers and develop muscle tone.

5. Alpha motor neurons in turn, send impulses to extrafusal fibers of the muscle through spinal nerve fibers (efferent fibers)
6. These impulses produce partial contraction of the muscle fibers resulting in development of muscle tone (response).

When the frequency of discharge from gamma motor neurons increases, the activity of muscle spindle is increased and muscle tone also increases.

Stimulation of gamma motor neurons increases the muscle tone. Lesion in gamma motor neurons leads to loss of tone in muscles.

Regulation of Muscle Tone

Though the muscle tone is developed by discharges from gamma motor neurons, it is maintained continuously

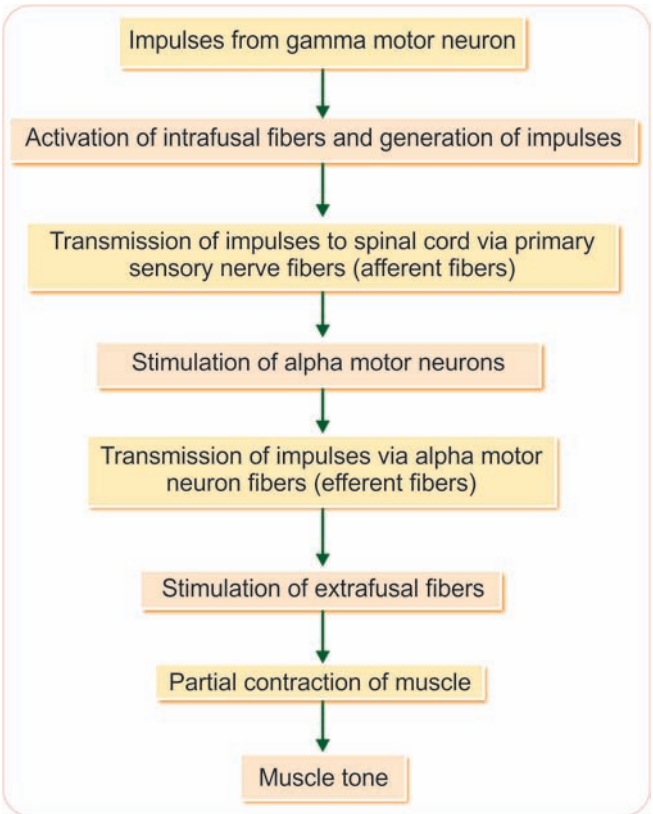


FIGURE 157.2: Schematic diagram showing development of muscle tone

and regulated by some supraspinal centers situated in different parts of brain. Some of these centers increase the muscle tone by sending **facilitatory impulses** while other centers decrease the muscle tone by **inhibitory impulses.**

Supraspinal facilitatory centers

Supraspinal centers, which increase the muscle tone:
1. Motor area 4 in cerebral cortex
2. Cerebellum
3. Descending facilitatory reticular system
4. Red nucleus
5. Vestibular nucleus.

Supraspinal inhibitory centers

Supraspinal centers, which decrease the muscle tone:
1. Suppressor areas of cerebral cortex
2. Basal ganglia
3. Descending inhibitory reticular system.

Role of motor area of cerebral cortex – coactivation

Motor area of cerebral cortex influences the activity of lower motor neurons by sending motor impulses through the pyramidal tract fibers. Motor impulses

from cerebral cortex stimulate both α-motor neurons and γ-motor neurons simultaneously. This type of simultaneous stimulation is called coactivation. It is also called **α-γ coactivation.** Stimulation of **α-motor** neurons causes contraction of **extrafusal fibers.** S timulation of **γ-motor** neurons causes contraction of **intrafusal fibers,** which leads to increase in muscle tone.

Role of cerebellum and basal ganglia

It is interesting to find that cerebellum and basal ganglia influence the muscle tone without sending direct fibers to γ-motor neurons. These parts of brain influence the muscle tone indirectly through brainstem centers.

Role of brainstem centers

Brainstem centers which influence the γ-motor neurons are in reticular formation, red nucleus and vestibular nucleus. These centers modulate the discharge from γ-motor neurons by receiving signals from cerebral cortex, cerebellum and basal ganglia.

■ STRETCH REFLEX

Basic reflex involved in maintenance of posture is the stretch reflex, which is described in detail in the previous chapter.

This reflex is normally present and serves particularly to maintain the body in an upright position. Such reflexes are, therefore more pronounced in extensor muscles.

■ POSTURAL REFLEXES

Postural reflexes are the reflexes which are responsible for maintenance of posture. Afferent impulses for the maintenance of posture arise from proprioceptors, vestibular apparatus and retina of eye and reach the centers in central nervous system (CNS). The centers, which maintain the posture, are located at different levels of CNS particularly cerebral cortex, cerebellum, brainstem and spinal cord. These centers send motor impulses to the different groups of skeletal muscles so that appropriate movements occur to maintain the posture.

■ CLASSIFICATION OF POSTURAL REFLEXES

Postural reflexes are generally classified into two groups:

A. Static reflexes
B. Statokinetic reflexes.

■ STATIC REFLEXES

Static reflexes are the postural reflexes that maintain posture at rest. Static reflexes are of four types:

I. General static reflexes or righting reflexes
II. Local static reflexes or supporting reflexes
III. Segmental static reflexes
IV. Statotonic or attitudinal reflexes.

I. *General Static Reflexes or Righting Reflexes*

General static reflexes are otherwise called righting reflexes because these reflexes help to maintain an upright position of the body. Righting reflexes help to govern the orientation of the head in space, position of the head in relation to the body and appropriate adjustment of the limbs and eyes in relation to the position of the head, so that upright position of the body is maintained.

When a cat, held with its back downwards, is allowed to fall through the air, it lands upon its paws, with the head and body assuming the normal attitude in a flash. A fish resists any attempt to turn it from its normal position and if it is placed in water upon its back, it flips almost instantly into the normal swimming position. All these actions occur because of the righting reflexes.

Righting reflexes consist of a chain of reactions, which occur one after another in an orderly sequence. Each reflex causes the development of the succeeding one.

Righting reflexes are divided into five types:

1. Labyrinthine righting reflexes acting on the neck muscles
2. Neck righting reflexes acting on the body
3. Body righting reflexes acting on the head
4. Body righting reflexes acting on the body
5. Optical righting reflexes.

First four reflexes are easily demonstrated on a thalamic animal or a normal animal, which is blindfolded.

1. *Labyrinthine righting reflexes acting on the neck muscles*

When a **thalamic animal** (rabbit) is suspended by holding at the pelvic region, its head turns up, until it assumes its normal position. It is because of reflexes arising from labyrinth, the sensory organ concerned with equilibrium of head, in regard to the position of the body. Turning the body of animal through air into different positions is followed by compensatory movements of the head. After extirpation of labyrinths, the head shows no compensatory movements when the rabbit is suspended. It hangs simply like that of a dead rabbit.

2. *Neck righting reflexes acting on the body*

It is noticed that during labyrinthine righting reflexes, the head raises up to normal position. It is because of the contraction of neck muscles. Now, the contraction of neck muscles produces proprioceptive impulses, which act on the body and rotate the body in relation to position of head. This reflex is well noticed, if the animal is laid down in resting position upon its side on a table.

3. *Body righting reflexes acting on the head*

Labyrinthine righting reflexes are not the only reflexes acting on neck muscles to cause rotation of head. If the animal is laid down upon its side on a table, the unequal distribution of pressure on that particular side of the body stimulates exteroceptors on the skin. Impulses thus generated by exteroceptors, act on neck muscles and rotate the head.

4. *Body righting reflexes acting on the body*

When the same animal is laid down on the table on its side, with head held down to table, to eliminate labyrinthine and neck righting reflexes, the body attempts to right itself by raising the lower parts. It is because of the impulses from exteroceptors on that side of body acting on the body itself.

5. *Optical righting reflexes*

Optical righting reflexes are initiated through the retinal impulses. Center for optical righting reflexes is in the occipital lobe of cerebral cortex. So, these reflexes are absent in thalamic animal. Optical righting reflexes help to correct the position of the body or head with the help of sight. It is proved in a labyrinthectomized animal. When such an animal is suspended, it rotates its head to normal position with the help of sight. But, the movements of head do not occur if eyes of the animal are closed.

Summary of righting reflexes

Following are the sequential events of righting reflexes:

i. When the animal is placed upon its back, labyrinthine reflexes acting upon neck muscles turn the head into its normal position in space, in relation to body
ii. Proprioceptive reflexes of neck muscles then bring the body into its normal position in relation to position of head
iii. When resting upon a rigid support, these reflexes are reinforced by the body righting reflexes on the head as well as on the body
iv. If the animal happens to be a **labyrinthectomized** one, then it makes an attempt to recover its upright position as a result of operation of the optical righting reaction. If the optical righting reflexes are abolished by covering the eyes, the righting ability is lost.

Optical righting reflexes are also demonstrated in 3 or 4 weeks old baby. When laid down on belly, i.e. prone position, the baby tries to raise the head to a vertical position.

Centers for righting reflexes

Centers for the first four righting reflexes are in **red nucleus** situated in midbrain. Center for optical righting reflexes is in the **occipital lobe** of cerebral cortex (Table 157.1).

II. *Local Static Reflexes or Supporting Reflexes*

Local static reflexes or supporting reactions support the body in different positions against gravity and also protect the limbs against hyperextension or hyperflexion.

Supporting reactions are classified into two types:

1. Positive supporting reflexes
2. Negative supporting reflexes.

1. *Positive supporting reflexes*

Positive supporting reflexes are the reactions, which help to fix the joints and make the limbs rigid like pillars, so that limbs can support the weight of the body against gravity. It is brought about by the simultaneous reflex contractions of both extensor and flexor muscles and other opposing muscles. The impulses for these reflexes arise from proprioceptors present in the muscles, joints and tendons and the exteroceptors, particularly pressure receptors present in deeper layers of the skin of sole. While standing, the positive supporting reflexes are developed in the following manner:

i. When an animal stands on its limbs, the pressure of the animal's paw upon the ground produces proprioceptive impulses from flexor and extensor muscles of the limbs, particularly in terminal segments of the limbs like digits, ankle or wrist. The proprioceptive impulses cause reflex contraction of the muscles of limbs making the limbs rigid.
ii. Excessive extension at the joints is checked or guarded by the **myotatic reflexes** setting up in the flexor muscles. When the flexor muscles are simultaneously contracting, extensor muscles cannot be stretched beyond the physiological limits. Similarly, over activity of the flexor muscles is prevented by the **stretch reflexes** developed in the extensor muscles.

TABLE 157.1: Static postural reflexes

Reflex		Center	Animal preparation to demonstrate
General static reflexes (Righting reflexes)	1. Labyrinthine righting reflexes acting on the neck muscles	Red nucleus situated in midbrain	Thalamic or normal blindfolded animal
	2. Neck righting reflexes acting on the body		
	3. Body righting reflexes acting on the head		
	4. Body righting reflexes acting on the body		
	5. Optical righting reflexes	Occipital lobe	Labyrinthectomized animal
Local static reflexes	1. Positive supporting reflexes	Spinal cord	Decorticate animal
	2. Negative supporting reflexes		
Segmental static reflexes	Crossed extensor reflex	Spinal cord	Spinal animals
Statotonic or attitudinal reflexes	1. Tonic labyrinthine and neck reflexes acting on the limbs	Medulla oblongata	Decerebrate animal
	2. Labyrinthine and neck reflexes acting on the eyes		

iii. Impulses arise even from exteroceptors while standing, when the sole remains in contact with the ground. It causes stimulation of the pressure receptors, which are present in deeper layers of the skin. These impulses from pressure receptors reinforce the rigidity of the limbs caused by the proprioceptive impulses.

2. *Negative supporting reflexes*

Relaxation of the muscles and unfixing of the joints enable the limbs to flex and move to a new position. It is called negative supporting reaction. It is brought about by raising the leg off the ground and plantar flexion of toes and ankle. When the leg is lifted off the ground, the exteroceptive impulses are stopped. When the toes and ankle joints are plantar flexed, the stretch stimulus for the plantar muscles is stopped. So, unlocking of the limbs occurs. Moreover, by the plantar flexion of the toes and ankle, the dorsiflexor muscles are stretched, causing relaxation of the extensors and contraction of the flexors of the knee.

The positive and negative supporting reactions are demonstrated well on a **decorticate animal.** The centers for the supporting reflexes are located in the spinal cord.

III. *Segmental Static Reflexes*

Segmental static reflexes are very essential for **walking.** During walking, in one leg, the flexors are active and the extensors are inhibited. On the opposite leg, the flexors are inhibited and extensors are active. Thus, the flexors and extensors of the same limb are not active simultaneously. It is known as **crossed extensor reflex.** It is due to the **reciprocal inhibition** and the neural mechanism responsible for this reflex is called **Sherrington reciprocal innervation.**

Segmental static reflexes are demonstrated in **spinal animal.** And, the centers for these reflexes are situated in the spinal cord.

IV. *Statotonic or Attitudinal Re lexes*

Statotonic or attitudinal reflexes are developed accord-ing to the attitude of the body and are of two types:

1. Tonic labyrinthine and neck reflexes acting on the limbs
2. Labyrinthine and neck reflexes acting on the eyes.

1. *Tonic labyrinthine and neck reflexes acting on the limbs*

Tonic labyrinthine and neck reflexes decrease or increase the tone of the skeletal muscles of the limbs in accordance to the attitude or position of the head. These reflexes are best studied in decerebrate animal. The proprioceptors concerned with these reflexes are in the labyrinthine apparatus. Whenever the position of the head is altered, the receptors present in the labyrinth are stimulated and generate impulses. The impulses are also generated from the neck muscles when the position of the head is altered. The impulses

from labyrinth produce the same effect on all the four limbs. But the impulses from neck muscles cause opposite effects in the forelimbs and hind limbs.

The labyrinthine reflexes are particularly effective on extensor muscles. When the head is dorsiflexed, all the four limbs are extended maximally and when the head is ventriflexed, all the four limbs are flexed.

In a labyrinthectomized animal where only neck reflexes are operated, during dorsiflexion of the head, there is extension of the forelimbs and flexion of the hind limbs. The ventriflexion of the head causes flexion of the forelimbs and extension of the hind limbs.

The importance of these reflexes is understood well, while observing the movements during change in the attitude of a normal animal. When an animal turns to one side, the limbs of that side become rigid in order to support the weight of the body. A cat looking upwards, keeps the hind limbs flexed but forelimbs remain extended. It gives a suitable inclination to the back of the animal, which improves the positions of the head and eyes. When the cat looks down, forelimbs are flexed and hind limbs are extended, giving the proper supported inclination at the neck region.

2. *Labyrinthine and neck reflexes acting on the eyes*

According to the changes in the position of the head and neck, the eyes are also moved. These reflexes arise from labyrinth and neck muscles. Turning the head downward causes upward movement of the eyes. The eyes remain in this position as long as the position of the head is retained.

When the head is moved down, the tone in the superior recti and inferior oblique are increased and tone of inferior recti and superior oblique are reduced, so that the eyeballs move upwards. When the head is turned to one side, a corresponding compensatory movement of the eyes occurs.

When the head is turned to one side, the eyes deviate outward or inward in relation to the head. The eyes are moved in a direction opposite to that of the head movement. It is because of external and internal recti.

Centers for statotonic reflexes are present in the medulla oblongata.

■ STATOKINETIC REFLEXES

Statokinetic reflexes are the postural reflexes that maintain posture during movement. These reflexes are concerned with both angular **(rotatory)** and linear **(progressive)** movements. The vestibular apparatus is responsible for these reflexes. So, it is essential to study the structure and functions of vestibular apparatus to understand the statokinetic reflexes.

Epilepsy

Chapter 22

- INTRODUCTION
- TYPES OF EPILEPSY
- GENERALIZED EPILEPSY
  - GRAND MAL
  - PETIT MAL
  - PSYCHOMOTOR EPILEPSY
- LOCALIZED EPILEPSY

INTRODUCTION

Epilepsy

Epilepsy is a brain disorder characterized by convulsive seizures or loss of consciousness or both.

Convulsion and Convulsive Seizure

Convulsion refers to uncontrolled involuntary muscular contractions. Convulsive seizure means sudden attack of uncontrolled involuntary muscular contractions. It occurs due to **paroxysmal** (sudden and usually recurring periodically) **uncontrolled discharge** of impulses from neurons of brain, particularly cerebral cortex.

Epileptic

Patient affected by epilepsy is called epileptic. The person with epilepsy remains normal in between seizures. Epileptic attack develops only when excitability of the neuron is increased, causing excessive neuronal discharge.

TYPES OF EPILEPSY

Epilepsy is divided into two categories:

1. Generalized epilepsy
2. Localized epilepsy.

GENERALIZED EPILEPSY

Generalized epilepsy is the type of epilepsy that occurs due to excessive discharge of impulses from all parts of the brain. It is also called general onset seizure or general onset epilepsy.

Generalized epilepsy is subdivided into three types:

1. Grand mal
2. Petit mal
3. Psychomotor epilepsy.

GRAND MAL

Grand mal is characterized by sudden loss of consciousness, followed by convulsion. Just before the onset of convulsions, the person feels the warning sensation in the form of some **hallucination.** It is called **epileptic aura.**

Convulsions occur in two stages:

a. Tonic stage
b. Clonic stage.

Tonic Stage

Initially, seizure is characterized by **tonic contractions** of muscle leading to **spasm.** Spasm causes twisting facial features, flexion of arm and extension of lower limbs.

Clonic Stage

Clonic convulsions develop after the tonic stage. This stage is characterized by violent jerky movements of limbs and face due to alternate severe contraction and relaxation of muscles.

At the end of attack, alternative tonic and clonic convulsions are seen. During the entire period of seizure, tongue may be bitten.

Electroencephalogram (EEG) shows fast waves with a frequency of 15 to 30 per second during tonic stage. Slow and large waves appear during clonic phase. After the attack, slow waves are recorded for some time. In between seizures, EEG shows delta waves in all types of epileptics.

Causes of Grand Mal

Cause of grand mal epilepsy is the excess neural activity in all parts of brain. Cause for stoppage of attack is neuronal fatigue. Factors which accelerate the neural activity resulting in grand mal epilepsy are:

i. Strong emotional stimuli
ii. Hyperventilation and alkalosis
iii. Effects of some drugs
iv. Uncontrolled high fever
v. Loud noises or bright light
vi. Traumatic lesions in any part of brain.

■ PETIT MAL

In this type of epilepsy, the person becomes **unconscious** suddenly without any warning. The unconsciousness lasts for a very short period of 3 to 30 seconds. Convulsions do not occur. However, the muscles of face show twitch-like contractions and there is blinking of eyes. Afterwards, the person recovers automatically and becomes normal. Frequency of attack may be once in many months or many attacks may appear in rapid series. It usually occurs in late childhood and disappears completely at the age of 30 or above.

EEG recording shows slow and large waves during the attack. Each wave is followed by a sharp spike. This type of waves appear from recording over any part of the cerebral cortex indicating the involvement of whole brain. Delta waves appear in between the seizures.

Causes of Petit Mal

Cause of petit mal is not known. It occurs in conditions like head injury, stroke, brain tumor and brain infection.

■ PSYCHOMOTOR EPILEPSY

Psychomotor epilepsy is characterized by **emotional outbursts** such as abnormal rage, sudden anxiety, fear or discomfort. There is **amnesia** or a confused mental state for some period. Some persons have the tendency to attack others bodily or rub their own face vigorously. In most cases, the persons are not aware of their activities. Some persons are very well aware of the actions, but still the abnormal actions cannot be controlled.

EEG recordings show low frequency rectangular waves, ranging between 2 and 4 per second.

Causes of Psychomotor Epilepsy

Causes of psychomotor epilepsy are the abnormalities in temporal lobe and tumor in hypothalamus and other regions of limbic system like amygdala and hippocampus.

■ LOCALIZED EPILEPSY

Epilepsy that occurs because of excessive discharge of impulses from one part of brain is called localized epilepsy. It is otherwise known as **local** or **focal epilepsy** or **local seizure.** It involves only a localized area of cerebral cortex or the deeper parts of cerebellum, which are affected by tumor, abscess or vascular defects. The abnormality starts from a particular area and spreads to adjacent areas, developing slow-spreading muscular contractions. Contractions usually start in the mouth region and spread down towards the legs. This type of seizure is also known as **jacksonian epilepsy.**

Causes of Localized Epilepsy

Localized epilepsy is caused by brain tumor.

Digestion, Absorption and Metabolism of Carbohydrates

Chapter 23

- CARBOHYDRATES IN DIET
- DIGESTION
- ABSORPTION
- METABOLISM
- DIETARY FIBER

CARBOHYDRATES IN DIET

Human diet contains three types of carbohydrates:

1. POLYSACCHARIDES

Large polysaccharides are glycogen, amylose and amylopectin, which are in the form of starch (glucose polymers). Glycogen is available in **non-vegetarian diet.** Amylose and amylopectin are available in **vegetarian diet** because of their plant origin.

2. DISACCHARIDES

Two types of disaccharides are available in the diet.

i. Sucrose (Glucose + Fructose), which is called table sugar or cane sugar
ii. Lactose (Glucose + Galactose), which is the sugar available in milk.

3. MONOSACCHARIDES

Monosaccharides consumed in human diet are mostly glucose and fructose.

Other carbohydrates in the diet include

i. Alcohol
ii. Lactic acid
iii. Pyruvic acid
iv. Pectins
v. Dextrins
vi. Carbohydrates in meat.

Diet also contains large amount of **cellulose,** which cannot be digested in the human GI tract so it is not considered as a food for human beings.

DIGESTION OF CARBOHYDRATES

IN THE MOUTH

Enzymes involved in the digestion of carbohydrates are known as **amylolytic enzymes.** The only amylolytic enzyme present in saliva is the salivary amylase or ptyalin.

IN THE STOMACH

Gastric juice contains a **weak amylase,** which plays a minor role in digestion of carbohydrates.

IN THE INTESTINE

Amylolytic enzymes present in the small intestine are derived from pancreatic juice and succus entericus (Table 45.1).

Amylolytic Enzyme in Pancreatic Juice

Pancreatic juice contains **pancreatic amylase** (Chapter 39).

Amylolytic Enzymes in Succus Entericus

Amylolytic enzymes present in succus entericus are **maltase, sucrase, lactase, dextrinase** and **trehalase** .

FINAL PRODUCTS OF CARBOHYDRATE DIGESTION

Final products of carbohydrate digestion are monosaccharides, which are glucose, fructose and galactose.

TABLE 45.1: Digestion of carbohydrates

Area	Juice	Enzyme	Substrate	End product
Mouth	Saliva	Salivary amylase	Polysaccharides – cooked starch	Disaccharides – dextrin and maltose
Stomach	Gastric juice	Gastric amylase	Weak amylase	The action is negligible
Small intestine	Pancreatic juice	Pancreatic amylase	Polysaccharides	Disaccharides – Dextrin, maltose and maltriose
	Succus entericus	Sucrase	Sucrose	Glucose and fructose
		Maltase	Maltose and maltriose	Glucose
		Lactase	Lactose	Glucose and galactose
		Dextrinase	Dextrin, maltose and maltriose	Glucose
		Trehalase	Trehalose	Glucose

Glucose represents 80% of the final product of carbohydrate digestion. Galactose and fructose represent the remaining 20%.

■ ABSORPTION OF CARBOHYDRATES

Carbohydrates are absorbed from the small intestine mainly as monosaccharides, viz. glucose, galactose and fructose.

■ ABSORPTION OF GLUCOSE

Glucose is transported from the lumen of small intestine into the epithelial cells in the mucus membrane of small intestine, by means of sodium cotransport. Energy for this is obtained by the binding process of sodium ion and glucose molecule to carrier protein.

From the epithelial cell, glucose is absorbed into the portal vein by **facilitated diffusion.** However, sodium ion moves laterally into the intercellular space. From here, it is transported into blood by active transport, utilizing the energy liberated by breakdown of ATP.

■ ABSORPTION OF GALACTOSE

Galactose is also absorbed from the small intestine in the same mechanism as that of glucose.

■ ABSORPTION OF FRUCTOSE

Fructose is absorbed into blood by means of **facilitated diffusion.** Some molecules of fructose are converted into glucose. Glucose is absorbed as described above.

■ METABOLISM OF CARBOHYDRATES

Metabolism is the process in which food substances undergo chemical and energy transformation. After digestion and absorption, food substances must be utilized by the body. The utilization occurs mainly by oxidative process in which the carbohydrates, proteins and lipids are burnt slowly to release energy. This process is known as catabolism.

Part of the released energy is utilized by tissues for physiological actions and rest of the energy is stored as rich energy phosphate bonds and in the form of proteins, carbohydrates and lipids in the tissues. This process is called anabolism.

Metabolism of carbohydrates is given in the form of schematic diagram.

■ DIETARY FIBER

Dietary fiber or roughage is a group of food particles which pass through stomach and small intestine, without being digested and reach the large intestine unchanged. Other nutritive substances of food are digested and absorbed before reaching large intestine.

Characteristic feature of dietary fiber is that it is not digestible by digestive enzymes. So it escapes digestion in small intestine and passes to large intestine. It provides substrate for microflora of large intestine and increases the bacterial mass. The anaerobic bacteria in turn, degrade the fermentable components of the fiber. Thus, in large intestine, some of the components of fiber are broken down and absorbed and remaining components are excreted through feces.

Components of Dietary Fiber

Major components of dietary fiber are cellulose, hemicelluloses, D-glucans, pectin, lignin and gums. Cellulose, hemicelluloses and pectin are partially degradable, while other components are indigestible. Dietary fiber also contains minerals, antioxidants and other chemicals that are useful for health.

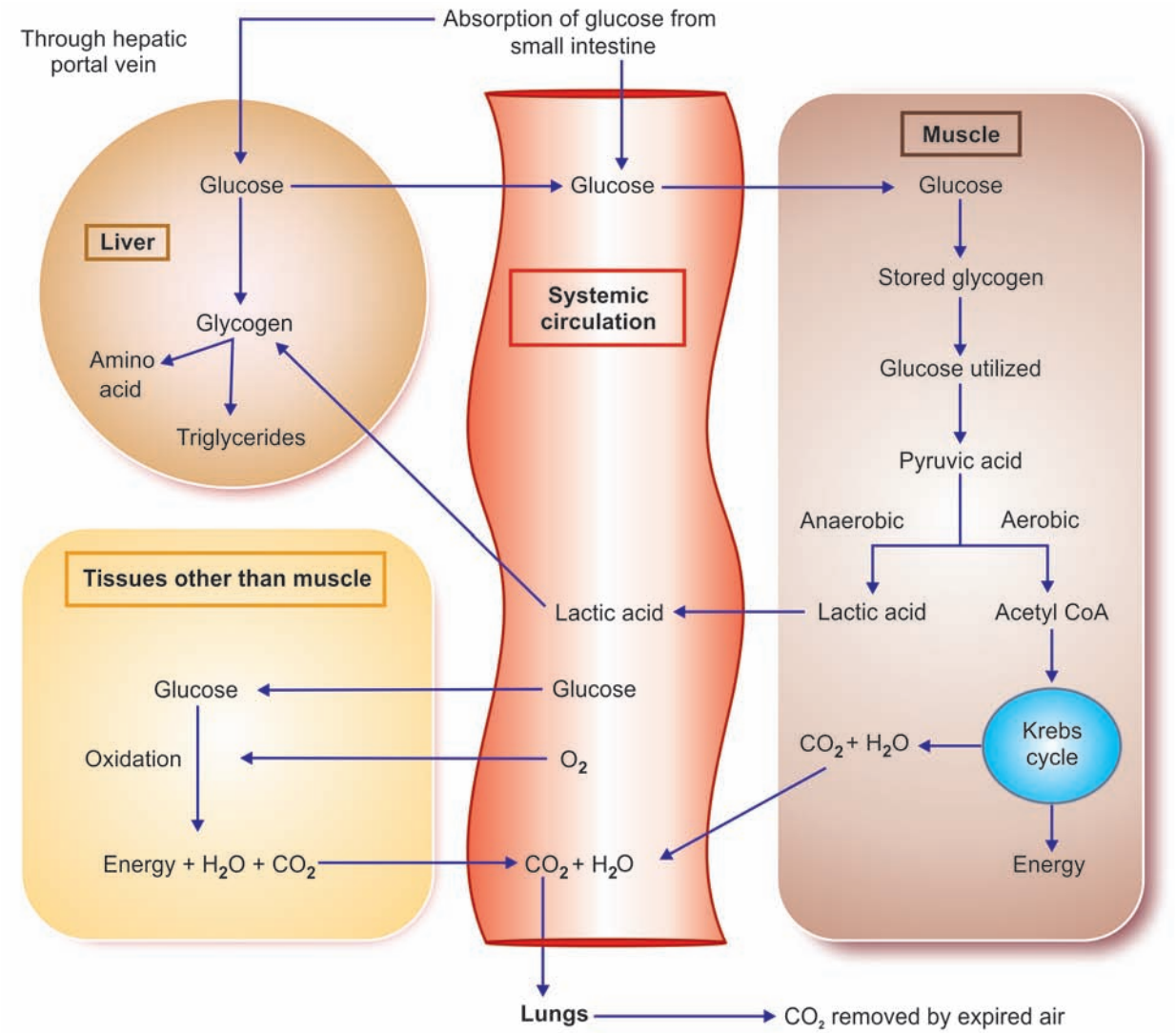


FIGURE 45.1: Schematic diagram of carbohydrate metabolism

Source of Dietary Fiber

Source of dietary fiber are fruits, vegetables, cereals, bread and wheat grain (particularly its outer layer).

Health Benefits of Dietary Fiber

1. By intake of high dietary fiber food, some disease-producing food substances may be decreased in quantity or completely excluded in diet
2. Dietary fiber helps in weight maintenance because it requires more chewing and promotes **hunger satisfaction** by delaying the emptying of stomach and by giving the person a sense of fullness of stomach
3. Diet with high fiber content tends to be low in energy and it is also useful in reducing the body weight
4. Dietary fiber increases the formation of bulk and soft feces and eases defecation
5. It contains some useful substances such as antioxidants
6. Some components of dietary fiber also reduce blood cholesterol level and thereby, decrease the risk of some diseases such as **coronary heart disease** and **gallstones**
7. Dietary fiber is also suggested to prevent or to treat some disorders such as **constipation, bowel syndrome, diabetics, ulcer** and **cancer.**

Digestion, Absorption and Metabolism of Proteins

Chapter 24

- PROTEINS IN DIET
- DIGESTION
- ABSORPTION
- METABOLISM

PROTEINS IN DIET

Foodstuffs containing high protein content are meat, fish, egg and milk. Proteins are also available in wheat, soybeans, oats and various types of pulses.

Proteins present in common foodstuffs are:

1. *Wheat:* Glutenin and gliadin, which constitute gluten
2. *Milk:* Casein, lactalbumin, albumin and myosin
3. *Egg:* Albumin and vitellin
4. *Meat:* Collagen, albumin and myosin.

Dietary proteins are formed by long chains of amino acids, bound together by peptide linkages.

DIGESTION OF PROTEINS

Enzymes responsible for the digestion of proteins are called **proteolytic enzymes.**

IN THE MOUTH

Digestion of proteins does not occur in mouth, since saliva does not contain any proteolytic enzymes. So, the digestion of proteins starts only in stomach (Table 46.1).

TABLE 46.1: Digestion of proteins

Area	Juice	Enzyme	Substrate	End product
Mouth	Saliva	No proteolytic enzyme	Polysaccharides – cooked starch	Disaccharides – dextrin and maltose
Stomach	Gastric juice	Pepsin	Proteins	Proteoses, peptones, large polypeptides
Small intestine	Pancreatic juice	Trypsin	Proteoses Peptones	Dipeptides Tripeptides Polypeptides
		Chymotrypsin		
		Carboxypeptidases A and B	Dipeptides Tripeptides Polypeptides	Amino acids
	Succus entericus	Dipeptidases	Dipeptides	Amino acids
		Tripeptidases	Tripeptides	
		Amino peptidases	Large polypeptides	

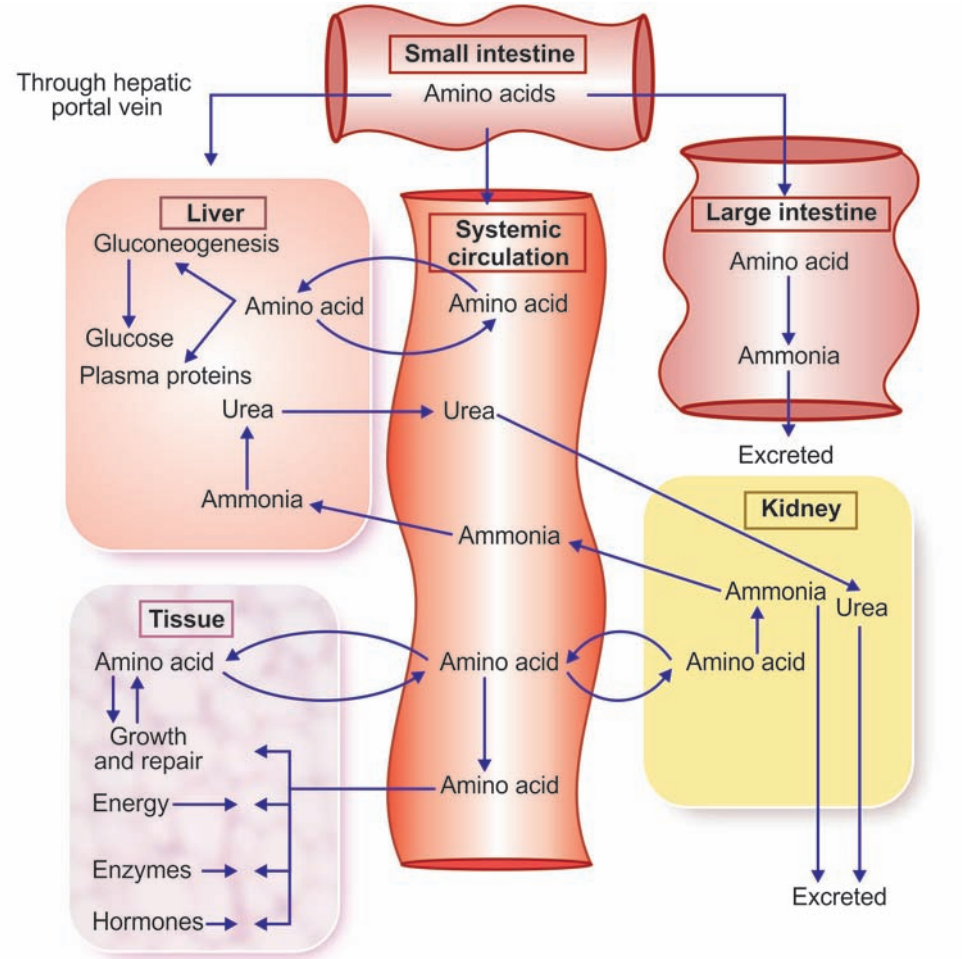


FIGURE 46.1: Schematic diagram of protein metabolism

■ IN THE STOMACH

Pepsin is the only proteolytic enzyme in gastric juice. **Rennin** is also present in gastric juice. But it is absent in human.

■ IN THE SMALL INTESTINE

Most of the proteins are digested in the duodenum and jejunum by the proteolytic enzymes of the pancreatic juice and succus entericus.

Proteolytic Enzymes in Pancreatic Juice

Pancreatic juice contains **trypsin, chymotrypsin** and **carboxypeptidases.** Trypsin and chymotrypsin are called **endopeptidases,** as these two enzymes break the interior bonds of the protein molecules.

Proteolytic Enzymes in Succus Entericus

Final digestion of proteins is by the proteolytic enzymes present in the succus entericus. It contains dipeptidases, tripeptidases and aminopeptidases.

■ FINAL PRODUCTS OF PROTEIN DIGESTION

Final products of protein digestion are the amino acids, which are absorbed into blood from intestine.

■ ABSORPTION OF PROTEINS

Proteins are absorbed in the form of amino acids from small intestine. The levo amino acids are actively absorbed by means of **sodium cotransport,** whereas, the dextro amino acids are absorbed by means of **facilitated diffusion.**

Absorption of amino acids is faster in duodenum and jejunum and slower in ileum.

■ METABOLISM OF PROTEINS

Metabolism of proteins is given in the form of a schematic diagram (Fig. 46.1).

Digestion, Absorption and Metabolism of Lipids

Chapter 25

- LIPIDS IN DIET
- DIGESTION
- ABSORPTION
- STORAGE
- TRANSPORT IN BLOOD – LIPOPROTEINS
- ADIPOSE TISSUE
- METABOLISM
- LIPID PROFILE

LIPIDS IN DIET

Lipids are mostly consumed in the form of **neutral fats,** which are also known as **triglycerides.** Triglycerides are made up of glycerol nucleus and free fatty acids. Triglycerides form the major constituent in foods of animal origin and much less in foods of plant origin. Apart from triglycerides, usual diet also contains small quantities of **cholesterol** and **cholesterol esters.**

Dietary fats are classified into two types:

1. Saturated fats
2. Unsaturated fats.

SATURATED FATS

Saturated fats are the fats which contain triglycerides formed from only saturated fatty acids. The fatty acids having maximum amount of hydrogen ions without any double bonds between carbon atoms are called saturated fatty acids.

UNSATURATED FATS

Fats containing unsaturated fatty acids are known as unsaturated fats. Unsaturated fatty acids are fatty acids formed by dehydrogenation of saturated fatty acids.

Unsaturated fats are classified into three types:

1. Monounsaturated fats
2. Polyunsaturated fats
3. Trans fats.

1. *Monounsaturated Fats*

Unsaturated fats which contain one double bond between the carbon atoms are called monounsaturated fats.

2. *Polyunsaturated Fats*

Unsaturated fats with more than one double bond between the carbon atoms are called polyunsaturated fats. Polyunsaturated fats belong to the family of essential fatty acids (fatty acids required in diet).

Polyunsaturated fats are of two types:

1. **Omega-3** fats or omega-3 fatty acids having double bond in the third space from the end of the carbon chain
2. **Omega-6** fats or omega-6 fatty acids having double bond in the sixth space from the end of the carbon chain.

Both omega-3 and omega-6 fatty acids are beneficial to the body. However, consuming too much of omega-6 fatty acids results in hazards than benefits. So, the diet containing 3 : 1 ratio of omega-6 to omega-3 fatty acids is often recommended by experts.

3. *Trans Fats*

Trans fats or trans fatty acids are unsaturated fatty acids, with molecules containing trans (across or opposite side) double bonds between carbon atoms.

Sources and the functions of the different types of dietary fats are listed in Table 47.1.

■ DIGESTION OF LIPIDS

Lipids are digested by **lipolytic enzymes.**

■ IN THE MOUTH

Saliva contains **lingual lipase.** This enzyme is secreted by lingual glands of mouth and swallowed along with saliva. So, the lipid digestion does not commence in the mouth (Table 47.2).

■ IN THE STOMACH

Gastric lipase or **tributyrase** is the lipolytic enzyme present in gastric juice.

■ IN THE INTESTINE

Almost all the lipids are digested in the small intestine because of the availability of bile salts, **pancreatic lipolytic enzymes** and **intestinal lipase.**

Role of Bile Salts

Bile salts play an important role in the digestion of lipids.

Lipolytic Enzymes in Pancreatic Juice

Pancreatic lipase is the most important enzyme for the digestion of fats. Other lipolytic enzymes of pancreatic juice are cholesterol ester hydrolase, phospholipase A and phospholipase B.

Lipolytic Enzyme in Succus Entericus

Intestinal lipase is the only lipolytic enzyme present in succus entericus.

■ FINAL PRODUCTS OF FAT DIGESTION

Fatty acids, cholesterol and monoglycerides are the final products of lipid digestion.

■ ABSORPTION OF LIPIDS

Monoglycerides, cholesterol and fatty acids from the micelles enter the cells of intestinal mucosa by simple diffusion.

From here, further transport occurs as follows:

1. In the mucosal cells, most of the monoglycerides are converted into triglycerides. Triglycerides are also formed by **re-esterification** of fatty acids with more than 10 to 12 carbon atoms. Some of the cholesterol is also esterified.

TABLE 47.1: Sources and functions of dietary fats

Type of fat	Sources	Functions
Saturated fats	Full fat milk, cheese, cream, butter. Commercially baked biscuits and pastries Deep-fried fast food Coconut oil and palm oil Fatty meat	Increase blood cholesterol and thereby increase the risk of atherosclerosis and coronary heart diseases
Monounsaturated fats	Oils (canola, olive and peanut oils) Nuts (cashews, almonds, hazelnuts and peanuts) Margarine	Decrease blood cholesterol and thereby decrease the risk of coronary heart diseases
Polyunsaturated fats	*Fruits and vegetables* Vegetable oils (sunflower, safflower, corn or soy oils) Nuts (walnuts) Flax seeds Polyunsaturated margarines Lean meat Fish and sea foods Egg	*Decrease* Blood cholesterol and triglycerides and thereby reduces blood pressure Risk of coronary heart diseases Risk of obesity Platelet aggregation and prevents excess blood clotting Inflammation throughout body *Increase* Disease-countering actions in the body
Trans fats	Milk Cheese and table margarines Lamb and beef	Increase low density lipoproteins and thereby increase the risk of atherosclerosis and coronary heart diseases

TABLE 47.2: Digestion of lipids

Area	Juice	Enzyme	Substrate	End product
Mouth	Saliva	Lingual lipase	Triglycerides	Fatty acid 1, 2-diacylglycerol
Stomach	Gastric juice	Gastric lipase (weak lipase)	Triglycerides	Fatty acids Glycerol
Small intestine	Pancreatic juice	Pancreatic lipase	Triglycerides	Monoglycerides Fatty acid
		Cholesterol ester hydrolase	Cholesterol ester	Free cholesterol Fatty acid
		Phospholipase A	Phospholipids	Lysophospholipids
		Phospholipase B	Lysophospholipids	Phosphoryl choline Free fatty acids
		Colipase	Facilitates action of pancreatic lipase	–
		Bile-salt-activated lipase	Phospholipids	Lysophospholipids
			Cholesterol esters	Cholesterol and fatty acids
	Succus entericus	Intestinal lipase	Triglycerides	Fatty acids Glycerol (weak action)

Triglycerides and cholesterol esters are coated with a layer of protein, cholesterol and phospholipids to form the particles called **chylomicrons.**

Chylomicrons cannot pass through the membrane of the blood capillaries because of the larger size. So, these lipid particles enter the lymph vessels and then are transferred into blood from lymph.

2. Fatty acids containing less than 10 to 12 carbon atoms enter the portal blood from mucosal cells and are transported as free fatty acids or unesterified fatty acids. Most of the fats are absorbed in the upper part of small intestine. Presence of bile is essential for fat absorption.

■ STORAGE OF LIPIDS

Lipids are stored in adipose tissue and liver. Fat stored in adipose tissue is called **neutral fat** or **tissue fat.** When chylomicrons are traveling through capillaries of adipose tissue or liver, the enzyme called **lipoprotein lipase** present in the capillary endothelium hydrolyzes triglycerides of chylomicrons into free fatty acids (FFA) and glycerol. FFA and glycerol enter the **fat cells** (adipocytes or lipocytes) of the adipose tissue or liver cells. Then, the FFA and glycerol are again converted into triglycerides and stored in these cells. Other contents of chylomicrons such as cholesterol and phospholipids, which are released into the blood combine with proteins to form lipoproteins.

When other tissues of the body need energy, triglycerides stored in adipose tissue is hydrolyzed into FFA and glycerol. FFA is transported to the body tissues through blood.

■ TRANSPORT OF LIPIDS IN BLOOD – LIPOPROTEINS

Free fatty acids are transported in the blood in combination with albumin. Other lipids are transported in the blood, in the form of lipoproteins.

■ LIPOPROTEINS

Lipoproteins are the small particles in the blood which contain cholesterol, phospholipids, triglycerides and proteins. Proteins are beta-globulins called **apoproteins.**

Classification of Lipoproteins

Lipoproteins are classified into four types on the basis of their density:

1. *Very-low-density lipoproteins (VLDL):* Contain high concentration of triglycerides (formed from FFA and glycerol) and moderate concentration of cholesterol and phospholipids
2. *Intermediate-density lipoproteins (IDL):* Formed by the removal of large portion of triglycerides from VLDL by lipoprotein lipase. Concentration of

cholesterol and phospholipids increases because of removal of triglycerides

3. *Low-density lipoproteins (LDL):* Formed from IDL by the complete removal of triglycerides. These lipoproteins contain only cholesterol and phospholipids
4. *High-density lipoproteins (HDL):* Contain high concentrations of proteins with low concentration of cholesterol and phospholipids.

All the lipoproteins are synthesized in liver. HDL is synthesized in intestine also.

Functions of Lipoproteins

Primary function of lipoproteins is to transport the lipids via blood to and from the tissues. Functions of each type of lipoproteins are given in Table 47.3.

Importance of Lipoproteins

High-density lipoprotein

High-denisty lipoprotein (HDL) is referred as the **'good cholesterol'** because it carries cholesterol and phospholipids from tissues and organs back to the liver for degradation and elimination. It prevents the deposition of cholesterol on the walls of arteries, by carrying cholesterol away from arteries to the liver.

High level of HDL is a good indicator of a healthy heart, because it reduces the blood cholesterol level. HDL also helps in the normal functioning of some hormones and certain tissues of the body. It is also used for the formation of bile in liver.

Low-density lipoprotein

Low-density lipoprotein (LDL) is considered as the **'bad cholesterol'** because it carries cholesterol and phospholipids from the liver to different areas of the body, viz. muscles, other tissues and organs such as heart. It is responsible for deposition of cholesterol on walls of arteries causing **atherosclerosis** (blockage and hardening of the arteries). High level of LDL increases the **risk of heart disease.**

TABLE 47.3: Functions of lipoproteins

Lipoproteins	Functions
VLDL	Transports triglycerides from liver to adipose tissue
IDL	Transports triglycerides, cholesterol and phospholipids from liver to peripheral tissues
LDL	Transports cholesterol and phospholipids from liver to tissues and organs like heart
HDL	Transports cholesterol and phospholipids from tissues and organs like heart back to liver

Very-low-density lipoprotein

Very-low-density lipoprotein (VLDL) carries cholesterol from liver to organs and tissues in the body. It is also associated with **atherosclerosis** and **heart disease.**

■ ADIPOSE TISSUE

Adipose tissue or fat is a loose connective tissue that forms the storage site of fat in the form of triglycerides. It is composed of **adipocytes,** which are also called **fat cells** or **lipocytes.** Obesity does not depend on the body weight, but on the amount of body fat, specifically adipose tissue.

Adipose tissue is of two types, white adipose tissue and brown adipose tissue.

■ WHITE ADIPOSE TISSUE OR WHITE FAT

White adipose tissue is distributed through the body beneath the skin, forming **subcutaneous fat.** It also surrounds the internal organs. This adipose tissue is formed by fat cells which are **unilocular,** i.e. these cells contain one large vacuole filled with fat.

Functions of White Adipose Tissue

White adipose tissue has three functions:

1. Storage of energy: Main function of white adipose tissue is the storage of lipids. Utilization or storage of fat is regulated by hormones, particularly insulin, depending upon the blood glucose level. If the blood glucose level increases, insulin stimulates synthesis and storage of fat in white adipose tissue (Chapter 69). On the other hand, if blood glucose level decreases insulin causes release of fat from adipose tissue. Released fat is utilized for energy
2. Heat insulation: **Insulation function** is due to the presence of adipose tissue beneath the skin (subcutaneous adipose tissue)
3. Protection of internal organs: White adipose tissue protects the body and internal organs by surrounding them and by acting like a **mechanical cushion.**

■ BROWN ADIPOSE TISSUE OR BROWN FAT

Brown adipose tissue is a specialized form of adipose tissue, having the function opposite to that of white adipose tissue. It is present only in certain areas of the body such as back of neck and intrascapular region. It is abundant in infants forming about 5% of total adipose tissue. After infancy, brown adipose tissue disappears gradually and forms only about 1% of total adipose tissue in adults. It is formed by fat cells which are **multilocular,** i.e. these cells contain many small

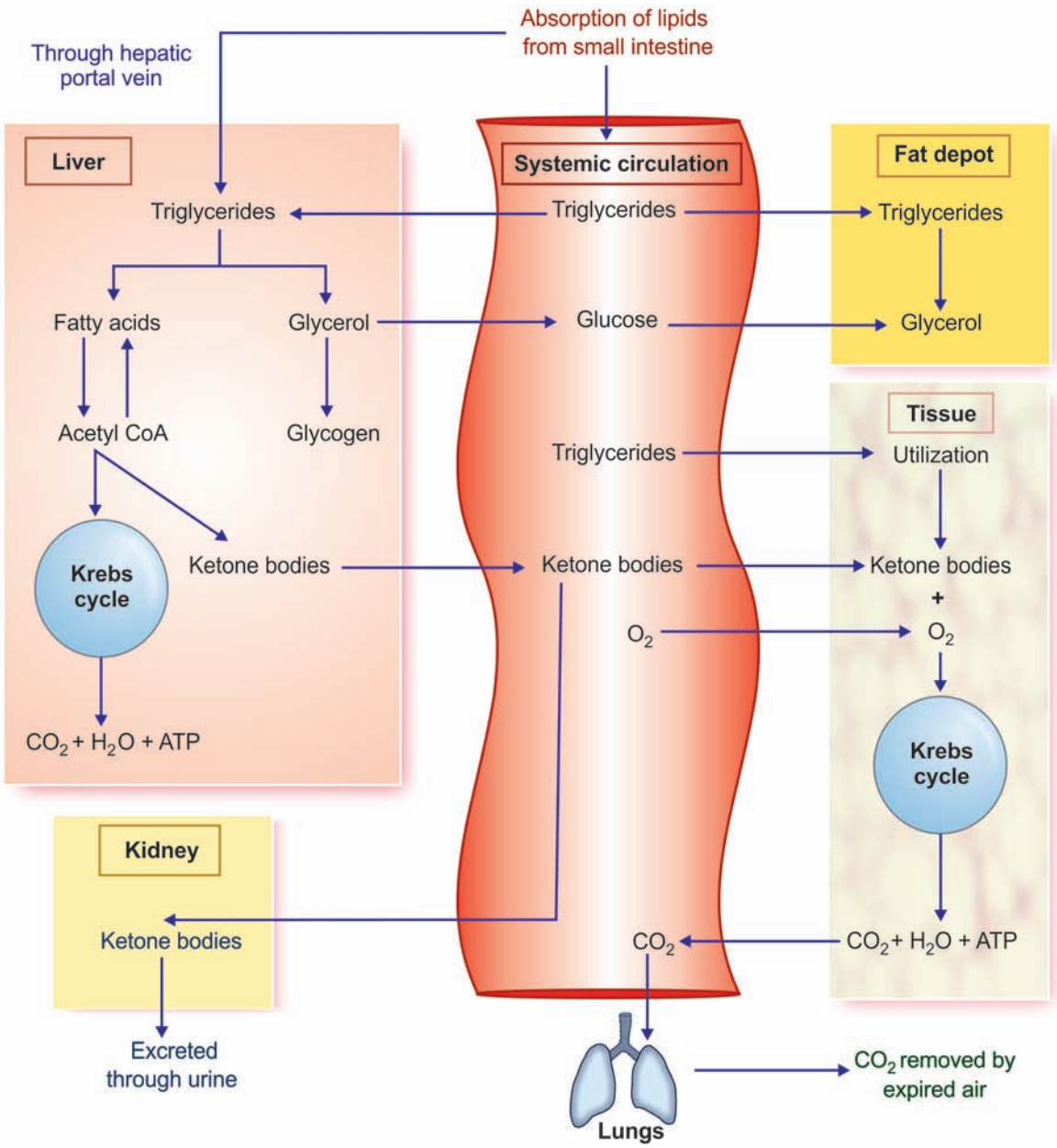


FIGURE 47.1: Schematic diagram of lipid metabolism

vacuoles filled with fat. The coloration of this adipose tissue is due to high vascularization and large number of **iron-rich mitochondria.**

Functions of Brown Adipose Tissue

Brown adipose tissue does not store lipids but generates heat by burning lipids. In infants and hibernating animals, brown adipose tissue plays an important role in regulating body temperature via **non-shivering thermogenesis.** Heat production in brown fat is very essential for survival of infants and small animals in cold environment. It is because, the lipid in this tissue releases energy directly as heat.

The mitochondria found in brown adipose tissue contain a unique uncoupling protein called **mitochondrial uncoupling protein 1** (UCP1). Also called **thermogenin,** this protein allows the controlled entry of protons without adenosine triphosphate (ATP) synthesis, in order to generate heat.

TABLE 47.4: Values of lipid profile

Lipids	Desirable optimal level	Borderline range	High-risk level
Total cholesterol	< 200 mg/dL	200 to 240 mg/dL	> 240 mg/dL
Triglycerides	< 150 mg/dL	150 to 200 mg/dL	> 200 mg/dL
HDL	> 60 mg/dL	40 to 60 mg/dL	< 40 mg/dL
LDL	< 60 mg/dL	60 to 100 mg/dL	> 100 mg/dL
Total cholesterol – HDL ratio	< 2	2 to 6	> 6

■ METABOLISM OF LIPIDS

Metabolism of lipids is given in the form of schematic diagram (Fig. 47.1).

■ LIPID PROFILE

Lipid profile is a group of **blood tests** which are carried out to determine the risk of **coronary artery diseases** (CAD). Results of lipid profile are considered as good indicators of whether someone is prone to develop **stroke** or **heart attack,** caused by **atherosclerosis.** In order to plan the course of treatment, the results of the lipid profile are correlated with age, sex and other risk factors of heart disease.

Tests included in lipid profile are total cholesterol, triglyceride, HDL, LDL, VLDL and total cholesterol – HDL ratio.

Total cholesterol to HDL ratio is helpful in predicting atherosclerosis and CAD. It is obtained by dividing total cholesterol by HDL. High total cholesterol and low HDL increases the ratio. The increase in the ratio is undesirable. Conversely, high HDL and low total cholesterol lowers the ratio and the decrease in the ratio is desirable. The values of lipid profile are given in Table 47.4.

QUESTIONS IN DIGESTIVE SYSTEM

LONG QUESTIONS

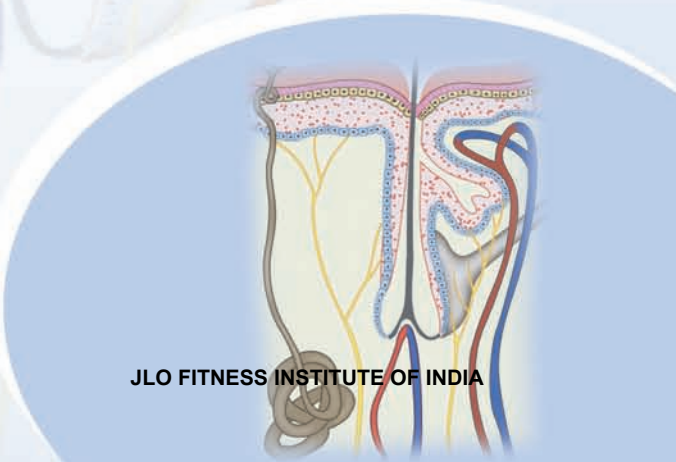
1. What are the different types of salivary glands? Describe the composition, functions and regulation of secretion of saliva.
2. Explain the composition and functions of gastric juice and give an account of hormonal regulation of gastric secretion.
3. Describe the different phases of gastric secretion with experimental evidences.
4. Explain the composition, functions and regulation of secretion of pancreatic juice.
5. Describe the composition, functions and regulation of secretion of bile. Enumerate the differences between the liver bile and gallbladder bile. Add a note on enterohepatic circulation.
6. Give an account of succus entericus.
7. Write an essay on gastric motility. What are the factors influencing gastric emptying?
8. Describe in detail, the gastrointestinal movements.

SHORT QUESTIONS

1. Properties and composition of saliva.
2. Functions of saliva.
3. Nerve supply to salivary glands.
4. Glands of stomach.
5. Functions of stomach.
6. Properties and composition of gastric juice.
7. Functions of gastric juice
8. Mechanism of secretion of hydrochloric acid in stomach.
9. Pavlov's pouch.
10. Sham feeding.
11. Cephalic phase of gastric secretion.
12. Gastrin.
13. Hormones acting on stomach.
14. FTM.
15. Peptic ulcer.
16. Exocrine function of pancreas.
17. Properties and composition of pancreatic juice.
18. Functions of pancreatic juice.
19. Regulation of exocrine function of pancreas.
20. Steatorrhea.
21. Secretin.
22. Cholecystokinin.
23. Composition of bile.
24. Functions of bile.
25. Bile salts.
26. Bile pigments.
27. Enterohepatic circulation.
28. Functions of liver.
29. Differences between liver bile and gallbladder bile.
30. Functions of gallbladder.
31. Jaundice.
32. Hepatitis.
33. Gallstones.
34. Succus entericus.
35. Functions of small intestine.
36. Functions of large intestine.
37. Mastication.
38. Swallowing.
39. Dysphagia.
40. Movements of stomach.
41. Filling and emptying of stomach.
42. Hunger contractions.
43. Vomiting.
44. Movements of small intestine.
45. Peristalsis.
46. Movements of large intestine.
47. Defecation.
48. Constipation.
49. Diarrhea.
50. Gastrointestinal hormones.
51. Digestion and absorption of carbohydrates.
52. Dietary fiber.
53. Digestion and absorption of proteins.
54. Digestion and absorption of lipids.
55. Lipoproteins.
56. Brown fat.

LEVEL 5

Renal Physiology



Kidney

Chapter 26

INTRODUCTION

Excretion is the process by which the unwanted substances and metabolic wastes are eliminated from the body.

A large amount of waste materials and carbon di-oxide are produced in the tissues during metabolic process. In addition, residue of undigested food, heavy metals, drugs, toxic substances and pathogenic organisms like bacteria are also present in the body.

All these substances must be removed to keep the body in healthy condition. Various systems/organs in the body are involved in performing the excretory function, viz.

1. **Digestive system** excretes food residues in the form of feces. Some bacteria and toxic substances also are excreted through feces
2. **Lungs** remove carbon dioxide and water vapor
3. **Skin** excretes water, salts and some wastes. It also removes heat from the body
4. **Liver** excretes many substances like bile pigments, heavy metals, drugs, toxins, bacteria, etc. through bile.

Although various organs are involved in removal of wastes from the body, their excretory capacity is limited. But renal system or urinary system has maximum excretory capacity and so it plays a major role in homeostasis.

Renal system includes:

1. A pair of kidneys
2. Ureters
3. Urinary bladder
4. Urethra.

Kidneys produce the urine. Ureters transport the urine to urinary bladder. Urinary bladder stores the urine until it is voided (emptied). Urine is voided from bladder through urethra (Fig. 48.1).

FUNCTIONS OF KIDNEY

Kidneys perform several vital functions besides formation of urine. By excreting urine, kidneys play the principal role in homeostasis. Thus, the functions of kidney are:

1. ROLE IN HOMEOSTASIS

Primary function of kidneys is **homeostasis.** It is accomplished by the formation of urine. During the formation of urine, kidneys regulate various activities in the body, which are concerned with homeostasis such as:

i. *Excretion of Waste Products*

Kidneys excrete the unwanted waste products, which are formed during metabolic activities:

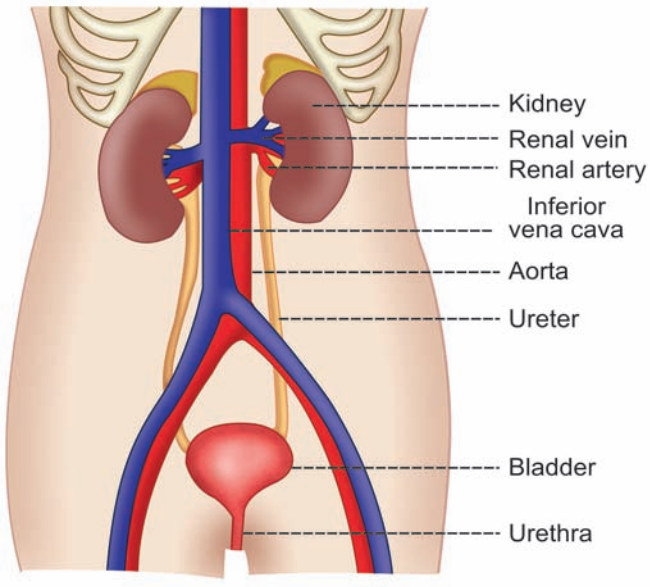


FIGURE 48.1: Urinary system

a. Urea (end product of amino acid metabolism)
b. Uric acid (end product of nucleic acid metabolism)
c. Creatinine (end product of metabolism in muscles)
d. Bilirubin (end product of hemoglobin degradation)
e. Products of metabolism of other substances.

Kidneys also excrete harmful foreign chemical substances such as toxins, drugs, heavy metals pesticides, etc.

ii. *Maintenance of Water Balance*

Kidneys maintain the water balance in the body by conserving water when it is decreased and excreting water when it is excess in the body. This is an important process for homeostasis.

iii. *Maintenance of Electrolyte Balance*

Maintenance of electrolyte balance, especially sodium is in relation to water balance. Kidneys retain sodium if the **osmolarity** of body water decreases and eliminate sodium when osmolarity increases.

iv. *Maintenance of Acid–Base Balance*

The pH of the blood and body fluids s hould be maintained within narrow range for healthy living. It is achieved by the function of kidneys (Chapter 54). Body is under constant threat to develop **acidosis,** because of production of lot of acids during metabolic activities. However, it is prevented by kidneys, lungs and blood buffers, which eliminate these acids. Among these organs, kidneys play major role in preventing acidosis. In fact, kidneys are the only organs, which are capable of eliminating certain metabolic acids like sulfuric and phosphoric acids.

■ 2. HEMOPOIETIC FUNCTION

Kidneys stimulate the production of erythrocytes by secreting **erythropoietin.** Erythropoietin is the important stimulating factor for erythropoiesis (Chapter 10). Kidney also secretes another factor called **thrombopoietin,** which stimulates the production of thrombocytes (Chapter 18).

■ 3. ENDOCRINE FUNCTION

Kidneys secrete many hormonal substances in addition to erythropoietin and thrombopoietin .

Hormones secreted by kidneys

i. Erythropoietin
ii. Thrombopoietin
iii. Renin
iv. 1,25-dihydroxycholecalciferol (calcitriol)
v. Prostaglandins.

■ 4. REGULATION OF BLOOD PRESSURE

Kidneys play an important role in the long-term regulation of arterial blood pressure (Chapter 103) by two ways:

i. By regulating the volume of extracellular fluid
ii. Through **renin-angiotensin** mechanism.

■ 5. REGULATION OF BLOOD CALCIUM LEVEL

Kidneys play a role in the regulation of blood calcium level by activating 1,25-dihydroxycholecalciferol into **vitamin D.** Vitamin D is necessary for the absorption of calcium from intestine.

■ FUNCTIONAL ANATOMY OF KIDNEY

Kidney is a compound tubular gland covered by a connective tissue capsule. There is a depression on the medial border of kidney called hilum, through which renal artery, renal veins, nerves and ureter pass.

■ DIFFERENT LAYERS OF KIDNEY

Components of kidney are arranged in three layers (Fig. 48.2):

1. Outer cortex
2. Inner medulla
3. Renal sinus.

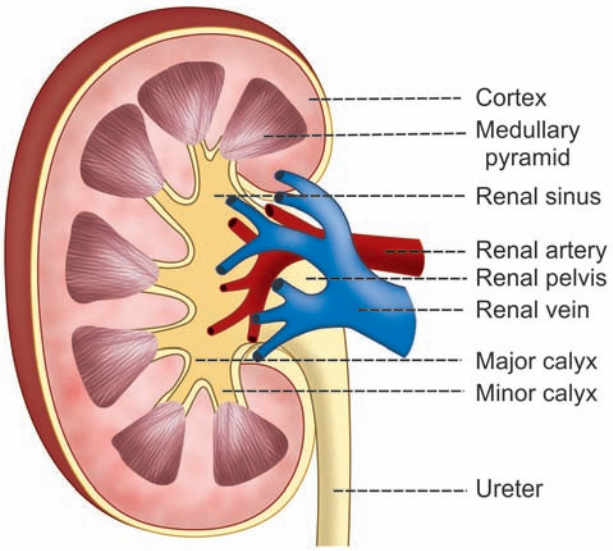


FIGURE 48.2: Longitudinal section of kidney

1. *Outer Cortex*

Cortex is dark and granular in appearance. It contains renal corpuscles and convoluted tubules. At intervals, cortical tissue penetrates medulla in the form of columns, which are called renal columns or **columns of Bertini.**

2. *Inner Medulla*

Medulla contains tubular and vascular structures arranged in parallel radial lines. Medullary mass is divided into 8 to 18 **medullary** or **Malpighian pyramids.** Broad base of each pyramid is in contact with cortex and the apex projects into **minor calyx.**

3. *Renal Sinus*

Renal sinus consists of the following structures:

i. Upper expanded part of ureter called **renal pelvis**
ii. Subdivisions of pelvis: 2 or 3 **major calyces** and about 8 minor calyces
iii. Branches of nerves, arteries and tributaries of veins
iv. Loose connective tissues and fat.

■ TUBULAR STRUCTURES OF KIDNEY

Kidney is made up of closely arranged tubular structures called **uriniferous tubules.** Blood vessels and interstitial connective tissues are interposed between these tubules.

Uriniferous tubules include:

1. Terminal or secretary tubules called **nephrons,** which are concerned with formation of urine
2. **Collecting ducts** or tubules, which are concerned with transport of urine from nephrons to pelvis of ureter.

Collecting ducts unite to form **ducts of Bellini,** which open into minor calyces through **papilla.**

Chapter 27

Nephron

INTRODUCTION

Nephron is defined as the structural and functional unit of kidney. Each kidney consists of 1 to 1.3 millions of nephrons. The number of nephrons starts decreasing after about 45 to 50 years of age at the rate of 0.8% to 1% every year.

Each nephron is formed by two parts (Fig. 49.1):

1. A blind end called renal corpuscle or **Malpighian corpuscle**
2. A tubular portion called **renal tubule.**

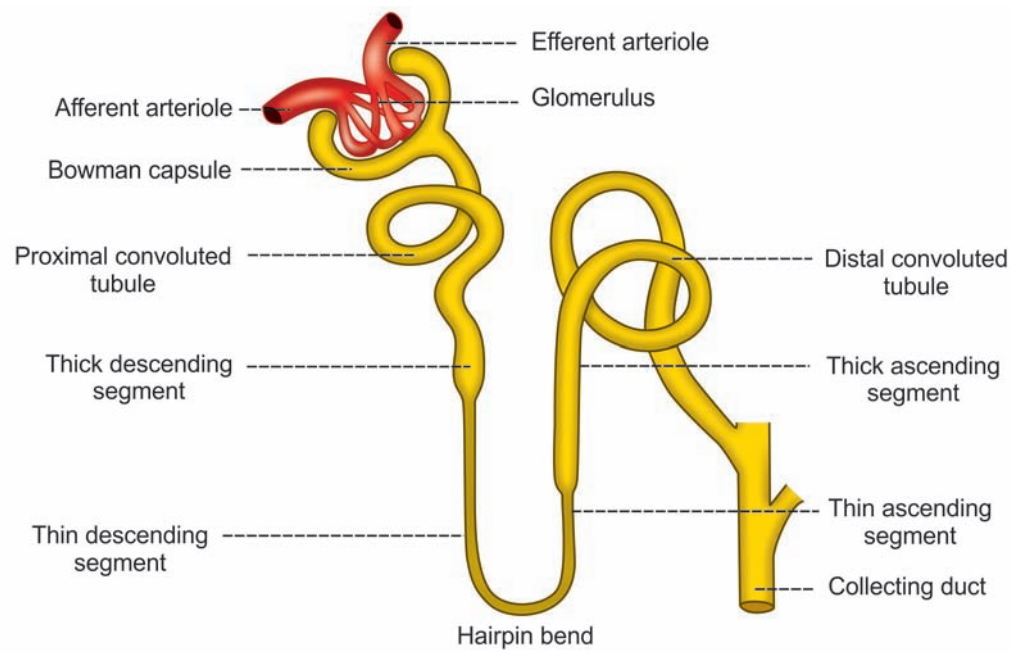


FIGURE 49.1: Structure of nephron

■ RENAL CORPUSCLE

Renal corpuscle or Malpighian corpuscle is a spheroidal and slightly flattened structure with a diameter of about 200 µ.

Function of the renal corpuscle is the filtration of blood which forms the first phase of urine formation.

■ SITUATION OF RENAL CORPUSCLE AND TYPES OF NEPHRON

Renal corpuscle is situated in the cortex of the kidney either near the periphery or near the medulla.

Classification of Nephrons

Based on the situation of renal corpuscle, the nephrons are classified into two types:

1. **Cortical nephrons** or superficial nephrons: Nephrons having the corpuscles in outer cortex of the kidney near the periphery (Fig. 49.2). In human kidneys, 85% nephrons are cortical nephrons.
2. **Juxtamedullary nephrons:** Nephrons having the corpuscles in inner cortex near medulla or corticomedullary junction.

Features of the two types of nephrons are given in Table 49.1.

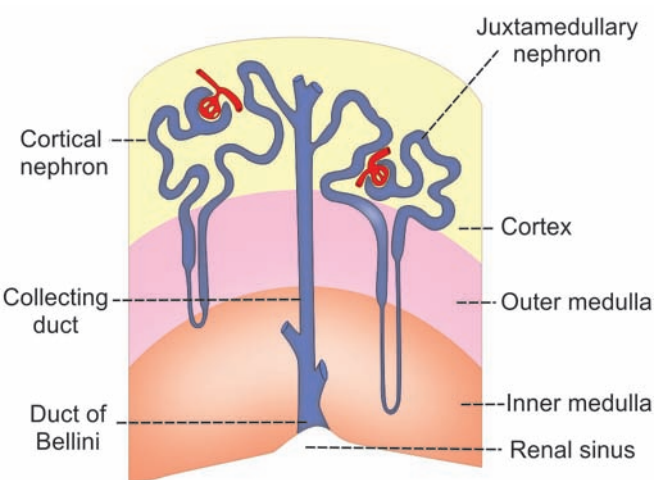


FIGURE 49.2: Types of nephron

■ STRUCTURE OF RENAL CORPUSCLE

Renal corpuscle is formed by two portions:

1. Glomerulus
2. Bowman capsule.

Glomerulus

Glomerulus is a tuft of capillaries enclosed by Bowman capsule. It consists of glomerular capillaries interposed between afferent arteriole on one end and efferent arteriole on the other end. Thus, the vascular system in the glomerulus is purely arterial (Fig. 49.3).

Glomerular capillaries arise from the afferent arteriole. After entering the Bowman capsule, the afferent

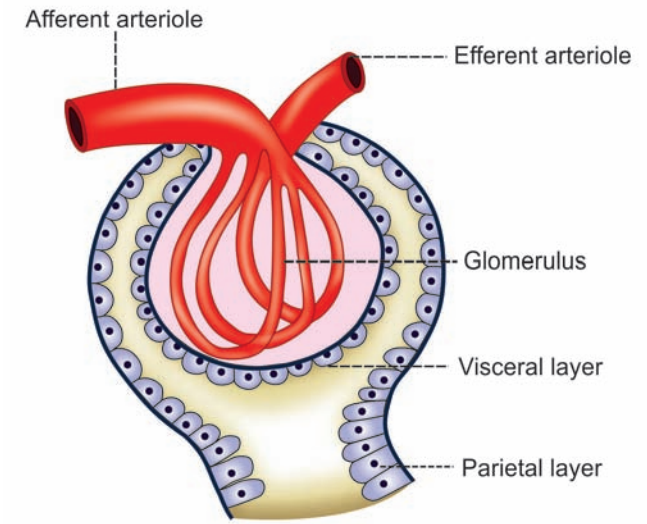


FIGURE 49.3: Renal corpuscle

TABLE 49.1: Features of two types of nephron

Features	Cortical nephron	Juxtamedullary nephron
Percentage	85%	15%
Situation of renal corpuscle	Outer cortex near the periphery	Inner cortex near medulla
Loop of Henle	Short	Long
	Hairpin bend penetrates only up to outer zone of medulla	Hairpin bend penetrates up to the tip of papilla
Blood supply to tubule	Peritubular capillaries	Vasa recta
Function	Formation of urine	Mainly the concentration of urine and also formation of urine

arteriole divides into 4 or 5 large capillaries. Each large capillary subdivides into many small capillaries. These small capillaries are arranged in irregular loops and form anastomosis. All the smaller capillaries finally reunite to form the efferent arteriole, which leaves the Bowman capsule.

Diameter of the efferent arteriole is less than that of afferent arteriole. This difference in diameter has got functional significance.

Functional histology

Glomerular capillaries are made up of single layer of endothelial cells, which are attached to a basement membrane. Endothelium has many pores called **fenestrae** or **filtration pores.** Diameter of each pore is 0.1 µ. Presence of the fenestra is the evidence of the filtration function of the glomerulus.

Bowman Capsule

Bowman capsule is a capsular structure, which encloses the glomerulus.

It is formed by two layers:

i. Inner visceral layer
ii. Outer parietal layer.

Visceral layer covers the glomerular capillaries. It is continued as the parietal layer at the visceral pole. Parietal layer is continued with the wall of the tubular portion of nephron. The cleft-like space between the visceral and parietal layers is continued as the lumen of the tubular portion.

Functional anatomy of Bowman capsule resembles a funnel with filter paper. Diameter of Bowman capsule is 200 µ.

Functional histology

Both the layers of Bowman capsule are composed of a single layer of flattened epithelial cells resting on a basement membrane. Basement membrane of the visceral layer fuses with the basement membrane of glomerular capillaries on which the capillary endothelial cells are arranged. Thus, the basement membranes, which are fused together, form the separation between the glomerular capillary endothelium and the epithelium of visceral layer of Bowman capsule.

Epithelial cells of the visceral layer fuse with the basement membrane but the fusion is not complete. Each cell is connected with basement membrane by cytoplasmic extensions of epithelial cells called **pedicles** or feet. These pedicles are arranged in an interdigitating manner leaving small cleft-like spaces in between. The cleft-like space is called **slit pore.** Epithelial cells with pedicles are called **podocytes** (Fig. 49.4).

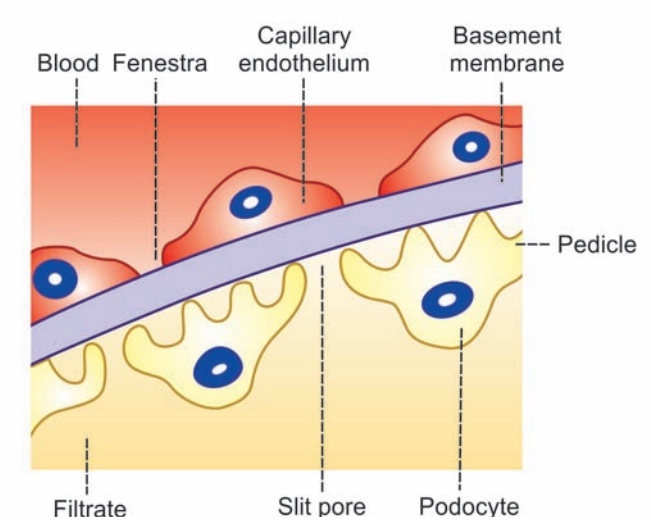


FIGURE 49.4: Filtering membrane in renal corpuscle. It is formed by capillary endothelium on one side (red) and visceral layer of Bowman capsule (yellow) on the other side.

■ TUBULAR PORTION OF NEPHRON

Tubular portion of nephron is the continuation of Bowman capsule.

It is made up of three parts:

1. Proximal convoluted tubule
2. Loop of Henle
3. Distal convoluted tubule.

■ PROXIMAL CONVOLUTED TUBULE

Proximal convoluted tubule is the coiled portion arising from Bowman capsule. It is situated in the cortex. It is continued as descending limb of loop of Henle. Length of proximal convoluted tubule is 14 mm and the diameter is 55 µ. Proximal convoluted tubule is continued as loop of Henle.

Functional histology

Proximal convoluted tubule is formed by single layer of cuboidal epithelial cells. Characteristic feature of these cells is the presence of hair-like projections directed towards the lumen of the tubule. Because of the presence of these projections, the epithelial cells are called **brush-bordered cells.**

■ LOOP OF HENLE

Loop of Henle consists of:

i. Descending limb
ii. Hairpin bend
iii. Ascending limb.

i. *Descending Limb*

Descending limb of loop of Henle is made up of two segments:

a. Thick descending segment
b. Thin descending segment.

Thick descending segment

Thick descending segment is the direct continuation of the proximal convoluted tubule. It descends down into medulla. It has a length of 6 mm and a diameter of 55 µ. It is formed by brush-bordered cuboidal epithelial cells.

Thin descending segment

Thick descending segment is continued as thin descending segment (Fig. 49.5). It is formed by flattened epithelial cells without brush border and it is continued as hairpin bend of the loop.

ii. *Hairpin Bend*

Hairpin bend formed by flattened epithelial cells without brush border and it is continued as the ascending limb of loop of Henle.

iii. *Ascending Limb*

Ascending limb or segment of Henle loop has two parts:

a. Thin ascending segment
b. Thick ascending segment.

Thin ascending segment

Thin ascending segment is the continuation of hairpin bend. It is also lined by flattened epithelial cells without brush border.

Total length of thin descending segment, hairpin bend and thin ascending segment of Henle loop is 10 mm to 15 mm and the diameter is 15 µ.

Thin ascending segment is continued as thick ascending segment.

Thick ascending segment

Thick ascending segment is about 9 mm long with a diameter of 30 µ. Thick ascending segment is lined by cuboidal epithelial cells without brush border.

The terminal portion of thick ascending segment, which runs between the afferent and efferent arterioles of the same nephrons forms the **macula densa.** Macula densa is the part of juxtaglomerular apparatus (Chapter 50).

Thick ascending segment ascends to the cortex and continues as distal convoluted tubule.

Length and Extent of Loop of Henle

Length and the extent of the loop of Henle vary in different nephrons:

i. In cortical nephrons, it is short and the hairpin bend penetrates only up to outer medulla

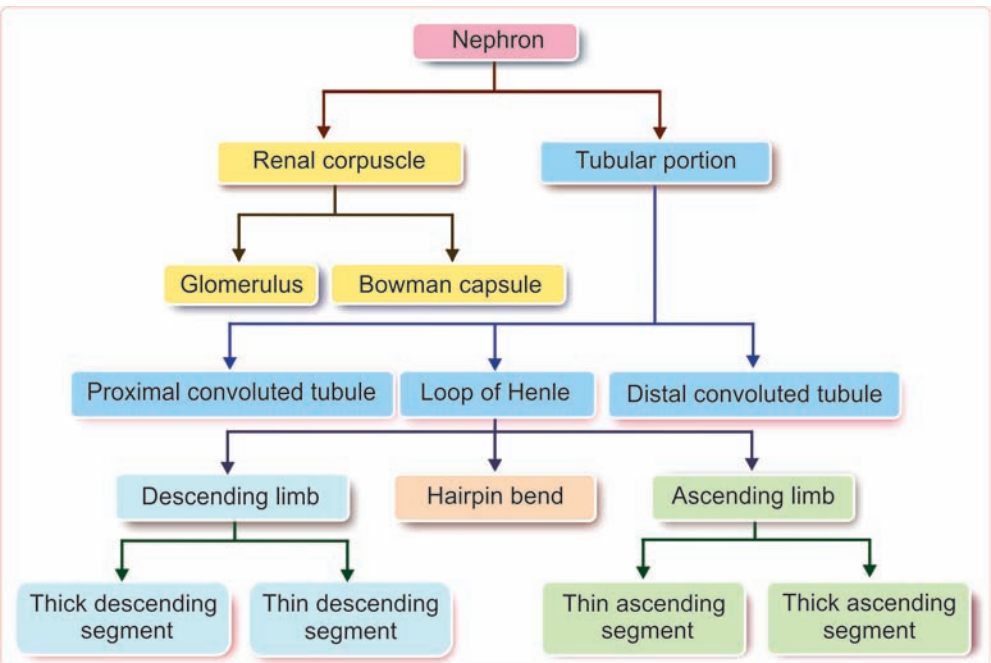


FIGURE 49.5: Parts of nephron

TABLE 49.2: Size and cells of different parts of nephron and collecting duct

Segment	Epithelium	Length (mm)	Diameter (μ)
Bowman Capsule	Flattened epithelium	-	200
Proximal convoluted tubule	Cuboidal cells with brush border	14	55
Thick descending segment	Cuboidal cells with brush border	6	55
Thin descending segment, hairpin bend and thin ascending segment	Flattened epithelium	10 to 15	15
Thick ascending segment	Cuboidal epithelium without brush border	9	30
Distal convoluted tubule	Cuboidal epithelium without brush border	14.5 to 15	22 to 50
Collecting duct	Cuboidal epithelium without brush border	20 to 22	40 to 200

ii. In juxtamedullary nephrons, this is long and the hairpin bend extends deep into the inner medulla. In some nephrons it even runs up to the papilla.

■ DISTAL CONVOLUTED TUBULE

Distal convoluted tubule is the continuation of thick ascending segment and occupies the cortex of kidney. It is continued as collecting duct. The length of the distal convoluted tubule is 14.5 to 15 mm. It has a diameter of 22 to 50 μ (Table 49.2).

Functional histology

Distal convoluted tubule is lined by single layer of cuboidal epithelial cells without brush border. Epithelial cells in distal convoluted tubule are called intercalated cells (I cells).

■ COLLECTING DUCT

Distal convoluted tubule continues as the initial or arched collecting duct, which is in cortex. The lower part of the collecting duct lies in medulla. Seven to ten initial collecting ducts unite to form the straight collecting duct, which passes through medulla.

Length of the collecting duct is 20 to 22 mm and its diameter varies between 40 and 200 μ. Collecting duct is formed by cuboidal or columnar epithelial cells.

Functional histology

Collecting duct is formed by two types of epithelial cells:

1. Principal or **P cells**
2. Intercalated or **I cells.**

These two types of cells have some functional significance (Chapters 53 and 54).

■ PASSAGE OF URINE

At the inner zone of medulla, the straight collecting ducts from each medullary pyramid unite to form **papillary ducts** or **ducts of Bellini,** which open into a 'V' shaped area called **papilla.** Urine from each medullary pyramid is collected in the papilla. From here it is drained into a **minor calyx.** Three or four minor calyces unite to form one **major calyx.** Each kidney has got about 8 minor calyces and 2 to 3 major calyces.

From minor calyces urine passes through major calyces, which open into the **pelvis** of the **ureter.** Pelvis is the expanded portion of ureter present in the renal sinus.

From renal pelvis, urine passes through remaining portion of ureter and reaches urinary bladder.

Chapter 28

Juxtaglomerular Apparatus

- DEFINITION
- STRUCTURE
  - MACULA DENSA
  - EXTRAGLOMERULAR MESANGIAL CELLS
  - JUXTAGLOMERULAR CELLS
- FUNCTIONS
  - SECRETION OF HORMONES
  - SECRETION OF OTHER SUBSTANCES
  - REGULATION OF GLOMERULAR BLOOD FLOW AND GLOMERULAR FILTRATION RATE

DEFINITION

Juxtaglomerular apparatus is a specialized organ situated near the glomerulus of each nephron (juxta = near).

STRUCTURE OF JUXTAGLOMERULAR APPARATUS

Juxtaglomerular apparatus is formed by three different structures (Fig. 50.1):

1. Macula densa
2. Extraglomerular mesangial cells
3. Juxtaglomerular cells.

MACULA DENSA

Macula densa is the end portion of thick ascending segment before it opens into distal convoluted tubule. It is situated between afferent and efferent arterioles of the same nephron. It is very close to afferent arteriole.

Macula densa is formed by tightly packed cuboidal epithelial cells.

EXTRAGLOMERULAR MESANGIAL CELLS

Extraglomerular mesangial cells are situated in the triangular region bound by afferent arteriole, efferent arteriole and macula densa. These cells are also called **agranular cells, lacis cells** or **Goormaghtigh cells.**

Glomerular Mesangial Cells

Besides extraglomerular mesangial cells there is another type of mesangial cells situated in between glomerular capillaries called **glomerular mesangial** or **intraglomerular mesangial cells.**

Glomerular mesangial cells support the glomerular capillary loops by surrounding the capillaries in the form of a cellular network.

These cells play an important role in regulating the glomerular filtration by their contractile property.

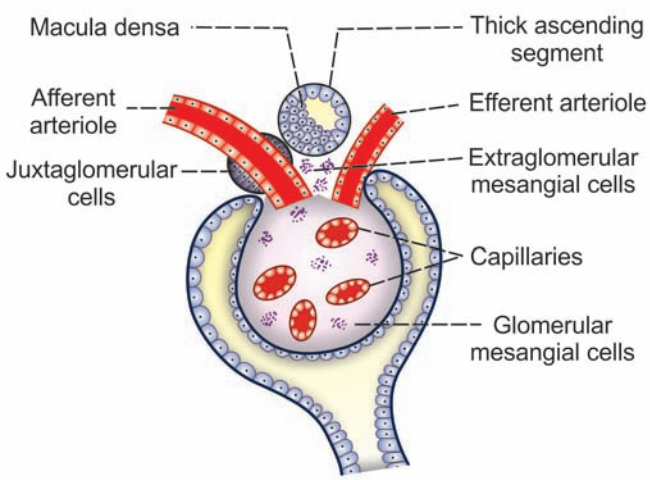


FIGURE 50.1: Juxtaglomerular apparatus

Glomerular mesangial cells are phagocytic in nature. These cells also secrete glomerular **interstitial matrix,** prostaglandins and cytokines.

■ JUXTAGLOMERULAR CELLS

Juxtaglomerular cells are specialized smooth muscle cells situated in the wall of afferent arteriole just before it enters the Bowman capsule. These smooth muscle cells are mostly present in tunica media and tunica adventitia of the wall of the afferent arteriole.

Juxtaglomerular cells are also called **granular cells** because of the presence of secretary granules in their cytoplasm.

Polar Cushion or Polkissen

Juxtaglomerular cells form a thick cuff called **polar cushion** or **polkissen** around the afferent arteriole before it enters the Bowman capsule.

■ FUNCTIONS OF JUXTAGLOMERULAR APPARATUS

Primary function of juxtaglomerular apparatus is the secretion of hormones. It also regulates the glomerular blood flow and glomerular filtration rate.

■ SECRETION OF HORMONES

Juxtaglomerular apparatus secretes two hormones:

1. Renin
2. Prostaglandin.

1. *Renin*

Juxtaglomerular cells secrete renin. Renin is a peptide with 340 amino acids. Along with angiotensins, renin forms the renin-angiotensin system, which is a hormone system that plays an important role in the maintenance of blood pressure.

Stimulants for renin secretion

Secretion of renin is stimulated by four factors:

i. Fall in arterial blood pressure
ii. Reduction in the ECF volume
iii. Increased sympathetic activity
iv. Decreased load of sodium and chloride in macula densa.

Renin-angiotensin system

When renin is released into the blood, it acts on a specific plasma protein called **angiotensinogen** or **renin substrate.** It is the α_2-globulin. By the activity of renin, the angiotensinogen is converted into a **decapeptide** called angiotensin I. Angiotensin I is converted into angiotensin II, which is an **octapeptide** by the activity of **angiotensin-converting enzyme** (ACE) secreted from lungs. Most of the conversion of angiotensin I into angiotensin II takes place in lungs.

Angiotensin II has a short half-life of about 1 to 2 minutes. Then it is rapidly degraded into a **heptapeptide** called angiotensin III by **angiotensinases,** which are present in RBCs and vascular beds in many tissues. Angiotensin III is converted into angiotensin IV, which is a **hexapeptide** (Fig. 50.2).

Actions of Angiotensins

Angiotensin I

Angiotensin I is physiologically inactive and serves only as the precursor of angiotensin II.

Angiotensin II

Angiotensin II is the most active form. Its actions are:

On blood vessels:

i. Angiotensin II increases arterial blood pressure by directly acting on the blood vessels and causing vasoconstriction. It is a potent constrictor of arterioles. Earlier, when its other actions were not found it was called **hypertensin.**
ii. It increases blood pressure indirectly by increasing the release of noradrenaline from postganglionic sympathetic fibers. Noradrenaline is a general vasoconstrictor.

On adrenal cortex:

It stimulates zona glomerulosa of adrenal cortex to secrete aldosterone. Aldosterone acts on renal tubules and increases retention of sodium, which is also responsible for elevation of blood pressure.

On kidney:

i. Angiotensin II regulates glomerular filtration rate by two ways:
   a. It constricts the efferent arteriole, which causes decrease in filtration after an initial increase.
   b. It contracts the glomerular mesangial cells leading to decrease in surface area of glomerular capillaries and filtration (see above)
ii. It increases sodium reabsorption from renal tubules. This action is more predominant on proximal tubules.

On brain:

i. Angiotensin II inhibits the **baroreceptor reflex** and thereby indirectly increases the blood pressure. Baroreceptor reflex is responsible for decreasing the blood pressure.

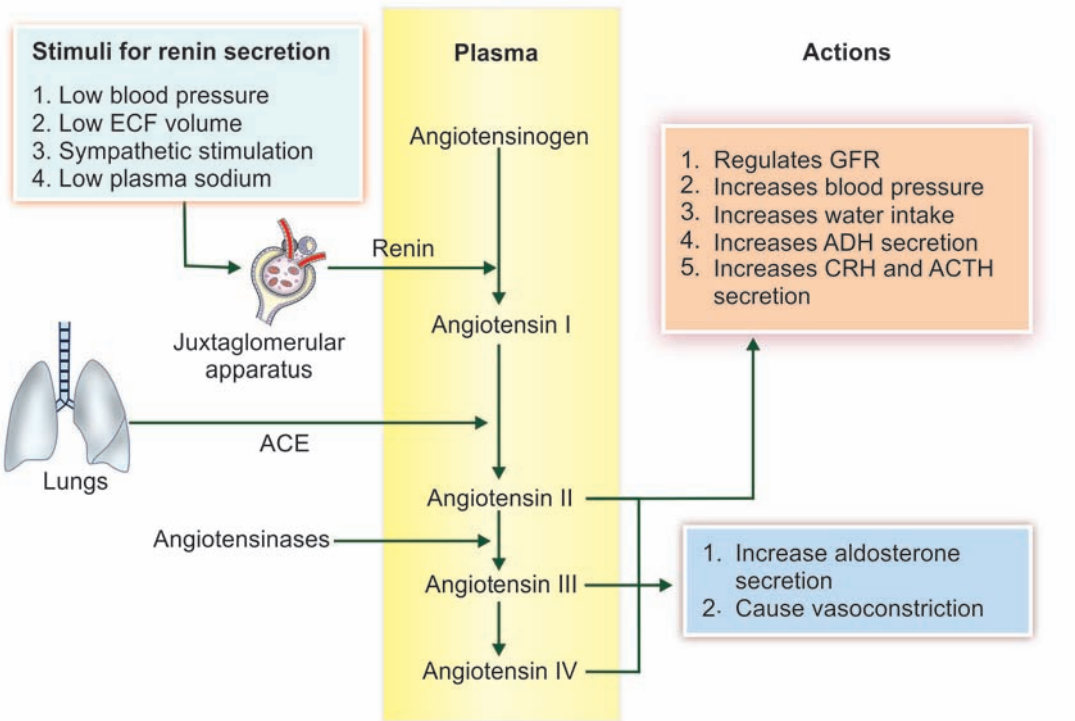


FIGURE 50.2: Renin-angiotensin system. ECF = Extracellular fluid, ACE = Angiotensin-converting enzyme, GFR = Glomerular filtration rate, ADH = Antidiuretic hormone, CRH = Corticotropin-releasing hormone, ACTH = Adrenocorticotropic hormone.

ii. It increases water intake by stimulating the thirst center
iii. It increases the secretion of orticotropin-releasing hormone (CRH) from hypothalamus. CRH in turn increases secretion of adrenocorticotropic hormone (ACTH) from pituitary
iv. It increases secretion of antidiuretic hormone (ADH) from hypothalamus.

Other actions:

Angiotensin II acts as a growth factor in heart and it is thought to cause muscular hypertrophy and cardiac enlargement.

Angiotensin III

Angiotensin III increases the blood pressure and stimulates aldosterone secretion from adrenal cortex. It has 100% adrenocortical stimulating activity and 40% vasopressor activity of angiotensin II.

Angiotensin IV

It also has adrenocortical stimulating and vasopressor activities.

2. Prostaglandin

Extraglomerular mesangial cells of juxtaglomerular apparatus secrete prostaglandin. Prostaglandin is also secreted by interstitial cells of medulla called type I medullary interstitial cells.

■ SECRETION OF OTHER SUBSTANCES

1. Extraglomerular mesangial cells of juxtaglomerular apparatus secrete cytokines like interleukin-2 and tumor necrosis factor.
2. Macula densa secretes thromboxane A_2.

■ REGULATION OF GLOMERULAR BLOOD FLOW AND GLOMERULAR FILTRATION RATE

Macula densa of juxtaglomerular apparatus plays an important role in the feedback mechanism called **tubuloglomerular feedback** mechanism, which regulates the renal blood flow and glomerular filtration rate.

Chapter 29

Renal Circulation

- INTRODUCTION
- RENAL BLOOD VESSELS
- MEASUREMENT OF RENAL BLOOD FLOW
- REGULATION OF RENAL BLOOD FLOW
  - AUTOREGULATION
- SPECIAL FEATURES OF RENAL CIRCULATION

INTRODUCTION

Blood vessels of kidneys are highly specialized to facilitate the functions of nephrons in the formation of urine. In the adults, during resting conditions both the kidneys receive 1,300 mL of blood per minute or about 26% of the cardiac output.

Maximum blood supply to kidneys has got the functional significance. Renal arteries supply blood to the kidneys.

RENAL BLOOD VESSELS

Renal Artery

Renal artery arises directly from abdominal aorta and enters the kidney through the hilus. While passing through renal sinus, the renal artery divides into many segmental arteries.

Segmental Artery

Segmental artery subdivides into interlobar arteries (Fig. 51.1).

Interlobar Artery

Interlobar artery passes in between the medullary pyramids. At the base of the pyramid, it turns and runs parallel to the base of pyramid forming arcuate artery.

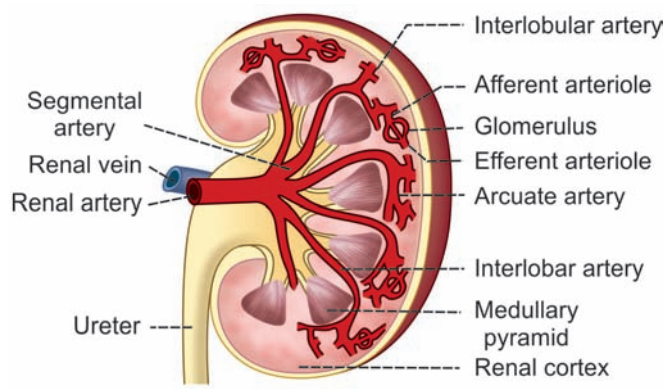


FIGURE 51.1: Renal blood vessels

Arcuate Artery

Each arcuate artery gives rise to interlobular arteries.

Interlobular Artery

Interlobular arteries run through the renal cortex perpendicular to arcuate artery. From each interlobular artery, numerous afferent arterioles arise.

Afferent Arteriole

Afferent arteriole enters the Bowman capsule and forms glomerular capillary tuft. After entering the Bowman capsule, the afferent arteriole divides into 4 or 5 large capillaries.

Glomerular Capillaries

Each large capillary divides into small glomerular capillaries, which form the loops. And, the **capillary loops** unite to form the efferent arteriole, which leaves the Bowman capsule.

Efferent Arteriole

Efferent arterioles form a second capillary network called peritubular capillaries, which surround the tubular portions of the nephrons. Thus, the renal circulation forms a portal system by the presence of two sets of capillaries namely glomerular capillaries and peritubular capillaries.

Peritubular Capillaries and Vasa Recta

Peritubular capillaries are found around the tubular portion of cortical nephrons only. The tubular portion of juxtamedullary nephrons is supplied by some specialized capillaries called vasa recta. These capillaries are straight blood vessels hence the name vasa recta. Vasa recta arise directly from the efferent arteriole of the juxtamedullary nephrons and run parallel to the renal tubule into the medulla and ascend up towards the cortex (Fig. 51.2).

Venous System

Peritubular capillaries and vasa recta drain into the venous system. Venous system starts with peritubular venules and continues as interlobular veins, arcuate veins, interlobar veins, segmental veins and finally the renal vein (Fig. 51.3).

Renal vein leaves the kidney through the hilus and joins inferior vena cava.

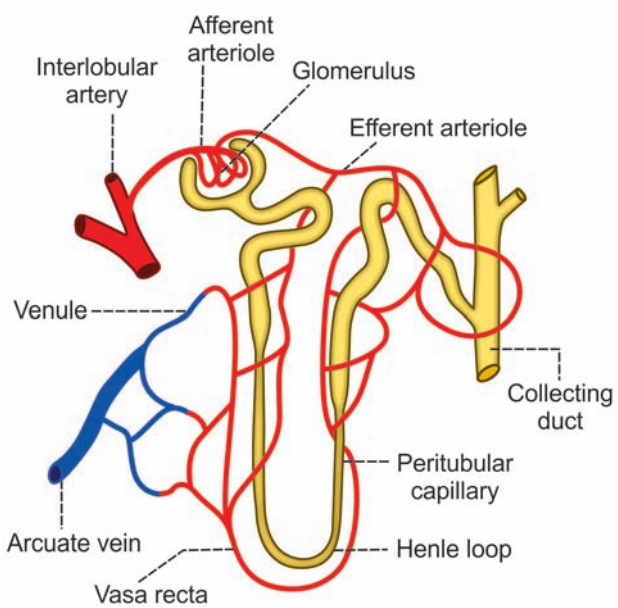


FIGURE 51.2: Renal capillaries

■ MEASUREMENT OF RENAL BLOOD FLOW

Blood flow to kidneys is measured by using plasma clearance of para-aminohippuric acid.

■ REGULATION OF RENAL BLOOD FLOW

Renal blood flow is regulated mainly by autoregulation. The nerves innervating renal blood vessels do not have any significant role in this.

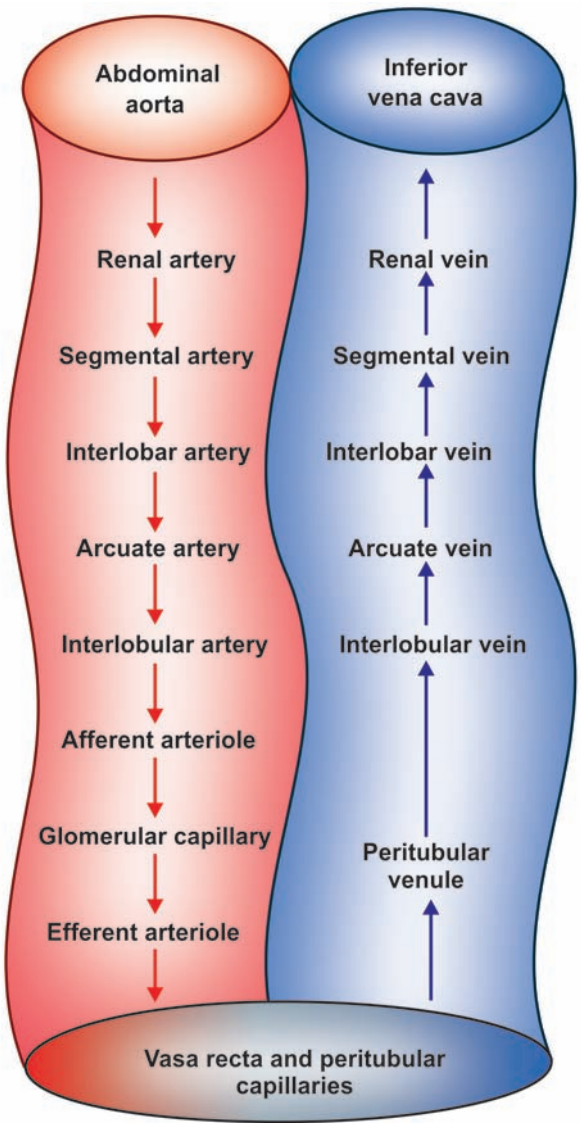


FIGURE 51.3: Schematic diagram showing renal blood flow

AUTOREGULATION

Autoregulation is the intrinsic ability of an organ to regulate its own blood flow. Autoregulation is present in some vital organs in the body such as brain, heart and kidneys. It is highly significant and more efficient in kidneys.

Renal Autoregulation

Renal autoregulation is important to maintain the glomerular filtration rate (GFR). Blood flow to kidneys remains normal even when the mean arterial blood pressure vary widely between 60 mm Hg and 180 mm Hg. This helps to maintain normal GFR.

Two mechanisms are involved in renal autoregulation:

1. Myogenic response
2. Tubuloglomerular feedback.

1. *Myogenic Response*

Whenever the blood flow to kidneys increases, it stretches the elastic wall of the afferent arteriole.

Stretching of the vessel wall increases the flow of calcium ions from extracellular fluid into the cells. The influx of calcium ions leads to the contraction of smooth muscles in afferent arteriole, which causes constriction of afferent arteriole. So, the blood flow is decreased.

2. *Tubuloglomerular Feedback*

Macula densa plays an important role in tubuloglomerular feedback, which controls the renal blood flow and GFR.

SPECIAL FEATURES OF RENAL CIRCULATION

Renal circulation has some special features to cope up with the functions of the kidneys. Such special features are:

1. Renal arteries arise directly from the aorta. So, the high pressure in aorta facilitates the high blood flow to the kidneys.
2. Both the kidneys receive about 1,300 mL of blood per minute, i.e. about 26% of cardiac output. Kidneys are the second organs to receive maximum blood flow, the first organ being the liver, which receives 1,500 mL per minute, i.e. about 30% of cardiac output.
3. Whole amount of blood, which flows to kidney has to pass through the glomerular capillaries before entering the venous system. Because of this, the blood is completely filtered at the renal glomeruli.
4. Renal circulation has a **portal system,** i.e. a double network of capillaries, the glomerular capillaries and peritubular capillaries.
5. Renal glomerular capillaries form **high pressure bed** with a pressure of 60 mm Hg to 70 mm Hg. It is much greater than the capillary pressure elsewhere in the body, which is only about 25 mm Hg to 30 mm Hg. High pressure is maintained in the glomerular capillaries because the diameter of afferent arteriole is more than that of efferent arteriole. The high capillary pressure augments glomerular filtration.
6. Peritubular capillaries form a **low pressure bed** with a pressure of 8 mm Hg to 10 mm Hg. This low pressure helps tubular reabsorption.
7. Autoregulation of renal blood flow is well established.

Chapter 30

Urine Formation

INTRODUCTION

Urine formation is a blood cleansing function. Normally, about 1,300 mL of blood (26% of cardiac output) enters the kidneys. Kidneys excrete the unwanted substances along with water from the blood as urine. Normal **urinary output** is 1 L/day to 1.5 L/day.

Processes of Urine Formation

When blood passes through glomerular capillaries, the plasma is filtered into the Bowman capsule. This process is called glomerular filtration.

Filtrate from Bowman capsule passes through the tubular portion of the nephron. While passing through the tubule, the filtrate undergoes various changes both in quality and in quantity. Many wanted substances like glucose, amino acids, water and electrolytes are reabsorbed from the tubules. This process is called tubular reabsorption.

And, some unwanted substances are secreted into the tubule from peritubular blood vessels. This process is called tubular secretion or excretion (Fig. 52.1).

Thus, the urine formation includes three processes:

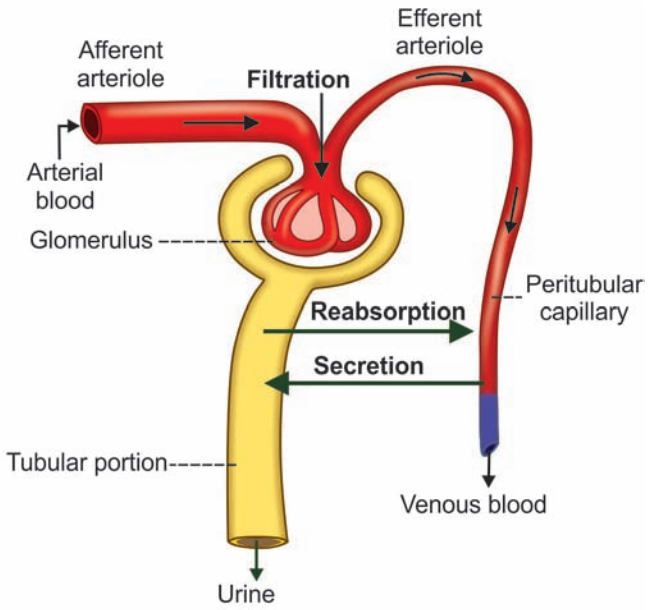


FIGURE 52.1: Events of urine formation

A. Glomerular filtration
B. Tubular reabsorption
C. Tubular secretion.

Among these three processes filtration is the function of the glomerulus. Reabsorption and secretion are the functions of tubular portion of the nephron.

GLOMERULAR FILTRATION

INTRODUCTION

Glomerular filtration is the process by which the blood is filtered while passing through the glomerular capillaries by filtration membrane. It is the first process of urine formation. The structure of filtration membrane is well suited for filtration.

Filtration Membrane

Filtration membrane is formed by three layers:

1. Glomerular capillary membrane
2. Basement membrane
3. Visceral layer of Bowman capsule.

1. *Glomerular capillary membrane*

Glomerular capillary membrane is formed by single layer of endothelial cells, which are attached to the basement membrane. The capillary membrane has many pores called **fenestrae** or **filtration pores** with a diameter of 0.1 µ.

2. *Basement membrane*

Basement membrane of glomerular capillaries and the basement membrane of visceral layer of Bowman capsule fuse together. The fused basement membrane separates the endothelium of glomerular capillary and the epithelium of visceral layer of Bowman capsule.

3. *Visceral layer of Bowman capsule*

This layer is formed by a single layer of flattened epithelial cells resting on a basement membrane. Each cell is connected with the basement membrane by cytoplasmic extensions called **pedicles** or **feet.** Epithelial cells with pedicles are called **podocytes** (Refer to Fig. 49.4). Pedicles interdigitate leaving small cleft-like spaces in between. The cleft-like space is called **slit pore** or **filtration slit.** Filtration takes place through these slit pores.

Process of Glomerular Filtration

When blood passes through glomerular capillaries, the plasma is filtered into the Bowman capsule. All the substances of plasma are filtered except the plasma proteins. The filtered fluid is called **glomerular filtrate.**

Ultrafiltration

Glomerular filtration is called ultrafiltration because even the minute particles are filtered. But, the plasma proteins are not filtered due to their large molecular size. The protein molecules are larger than the slit pores present in the endothelium of capillaries. Thus, the glomerular filtrate contains all the substances present in plasma except the plasma proteins.

METHOD OF COLLECTION OF GLOMERULAR FILTRATE

Glomerular filtrate is collected in experimental animals by micropuncture technique. This technique involves insertion of a **micropipette** into the Bowman capsule and aspiration of filtrate.

GLOMERULAR FILTRATION RATE

Glomerular filtration rate (GFR) is defined as the total quantity of filtrate formed in all the nephrons of both the kidneys in the given unit of time.

Normal GFR is 125 mL/minute or about 180 L/day.

FILTRATION FRACTION

Filtration fraction is the fraction (portion) of the renal plasma, which becomes the filtrate. It is the ratio

between renal plasma flow and glomerular filtration rate. It is expressed in percentage.

$$\text{Filtration fraction} = \frac{\text{GFR}}{\text{Renal plasma flow}} \times 100$$

$$= \frac{125 \text{ mL/min}}{650 \text{ mL/min}} \times 100$$

$$= 19.2\%.$$

Normal filtration fraction varies from 15% to 20%.

■ PRESSURES DETERMINING FILTRATION

Pressures, which determine the GFR are:

1. Glomerular capillary pressure
2. Colloidal osmotic pressure in the glomeruli
3. Hydrostatic pressure in the Bowman capsule.

These pressures determine the GFR by either favoring or opposing the filtration.

1. *Glomerular Capillary Pressure*

Glomerular capillary pressure is the pressure exerted by the blood in glomerular capillaries. It is about 60 mm Hg and, varies between 45 and 70 mm Hg. Glomerular capillary pressure is the highest capillary pressure in the body. This pressure favors glomerular filtration.

2. *Colloidal Osmotic Pressure*

It is the pressure exerted by plasma proteins in the glomeruli. The plasma proteins are not filtered through the glomerular capillaries and remain in the glomerular capillaries. These proteins develop the colloidal osmotic pressure, which is about 25 mm Hg. It opposes glomerular filtration.

3. *Hydrostatic Pressure in Bowman Capsule*

It is the pressure exerted by the filtrate in Bowman capsule. It is also called **capsular pressure.** It is about 15 mm Hg. It also opposes glomerular filtration.

Net Filtration Pressure

Net filtration pressure is the balance between pressure favoring filtration and pressures opposing filtration. It is otherwise known as **effective filtration pressure** or **essential filtration pressure.**

$$\text{Net filtration pressure} = \left\{ \begin{array}{c} \text{Glomerular} \\ \text{capillary} \\ \text{pressure} \end{array} - \begin{array}{c} \text{Colloidal} \\ \text{osmotic} \\ \text{pressure} \end{array} + \begin{array}{c} \text{Hydrostatic} \\ \text{pressure in} \\ \text{Bowman capsule} \end{array} \right\}$$

$$= 60 - (25 + 15) = 20 \text{ mm Hg.}$$

Net filtration pressure is about 20 mm Hg and, it varies between 15 and 20 mm Hg.

Starling Hypothesis and Starling Forces

Determination of net filtration pressure is based on Starling hypothesis. Starling hypothesis states that the net filtration through capillary membrane is proportional to hydrostatic pressure difference across the membrane minus oncotic pressure difference. Hydrostatic pressure within the glomerular capillaries is the glomerular capillary pressure.

All the pressures involved in determination of filtration are called **Starling forces.**

■ FILTRATION COEFFICIENT

Filtration coefficient is the GFR in terms of net filtration pressure. It is the GFR per mm Hg of net filtration pressure. For example, when GFR is 125 mL/min and net filtration pressure is 20 mm Hg.

$$\text{Filtration coefficient} = \frac{125 \text{ mL}}{20 \text{ mm Hg}}$$

$$= 6.25 \text{ mL/mm Hg}$$

■ FACTORS REGULATING (AFFECTING) GFR

1. *Renal Blood Flow*

It is the most important factor that is necessary for glomerular filtration. GFR is directly proportional to renal blood flow. Normal blood flow to both the kidneys is 1,300 mL/minute. The renal blood flow itself is controlled by **autoregulation.** Refer previous chapter for details.

2. *Tubuloglomerular Feedback*

Tubuloglomerular feedback is the mechanism that regulates GFR through renal tubule and macula densa (Fig. 52.2). **Macula densa** of juxtaglomerular apparatus in the terminal portion of thick ascending limb is sensitive to the sodium chloride in the tubular fluid.

When the glomerular filtrate passes through the terminal portion of thick ascending segment, macula densa acts like a sensor. It detects the concentration of sodium chloride in the tubular fluid and accordingly alters the glomerular blood flow and GFR. Macula densa detects the sodium chloride concentration via Na^+-K^+-$2Cl^-$ cotransporter (NKCC2).

When the concentration of sodium chloride increases in the filtrate

When GFR increases, concentration of sodium chloride increases in the filtrate. Macula densa releases **adenosine**

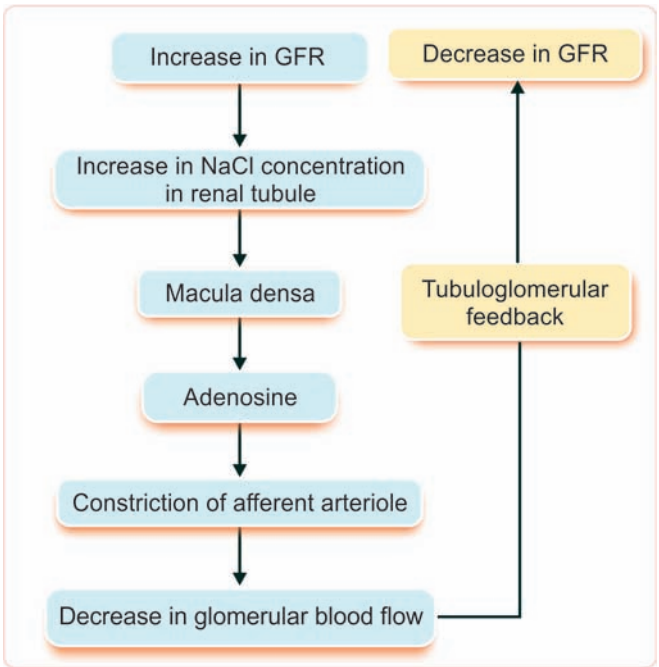


FIGURE 52.2: Tubuloglomerular feedback.
NaCl = Sodium chloride, GFR = Glomerular filtration rate.

from ATP. Adenosine causes constriction of afferent arteriole. So the blood flow through glomerulus decreases leading to decrease in GFR. Adenosine acts on afferent arteriole via adenosine A_1 receptors.

There are several other factors, which increase or decrease the sensitivity of tubuloglomerular feedback.

Factors increasing the sensitivity of tubuloglomerular feedback:

i. Adenosine
ii. Thromboxane
iii. Prostaglandin E_2
iv. Hydroxyeicosatetranoic acid.

Factors decreasing the sensitivity of tubuloglomerular feedback:

i. Atrial natriuretic peptide
ii. Prostaglandin I_2
iii. Cyclic AMP (cAMP)
iv. Nitrous oxide.

When the concentration of sodium chloride decreases in the filtrate

When GFR decreases, concentration of sodium chloride decreases in the filtrate. Macula densa secretes prostaglandin (PGE_2), bradykinin and renin.

PGE_2 and bradykinin cause dilatation of afferent arteriole. Renin induces the formation of angiotensin II, which causes constriction of efferent arteriole. The dilatation of afferent arteriole and constriction of efferent arteriole leads to increase in glomerular blood flow and GFR.

3. *Glomerular Capillary Pressure*

Glomerular filtration rate is directly proportional to glomerular capillary pressure. Normal glomerular capillary pressure is 60 mm Hg. When glomerular capillary pressure increases, the GFR also increases. Capillary pressure, in turn depends upon the renal blood flow and arterial blood pressure.

4. *Colloidal Osmotic Pressure*

Glomerular filtration rate is inversely proportional to colloidal osmotic pressure, which is exerted by plasma proteins in the glomerular capillary blood. Normal colloidal osmotic pressure is 25 mm Hg. When colloidal osmotic pressure increases as in the case of **dehydration** or increased plasma protein level GFR decreases. When colloidal osmotic pressure is low as in **hypoproteinemia,** GFR increases.

5. *Hydrostatic Pressure in Bowman Capsule*

GFR is inversely proportional to this. Normally, it is 15 mm Hg. When the hydrostatic pressure increases in the Bowman capsule, it decreases GFR. Hydrostatic pressure in Bowman capsule increases in conditions like obstruction of urethra and edema of kidney beneath renal capsule.

6. *Constriction of Afferent Arteriole*

Constriction of afferent arteriole reduces the blood flow to the glomerular capillaries, which in turn reduces GFR.

7. *Constriction of Efferent Arteriole*

If efferent arteriole is constricted, initially the GFR increases because of stagnation of blood in the capillaries. Later when all the substances are filtered from this blood, further filtration does not occur. It is because, the efferent arteriolar constriction prevents outflow of blood from glomerulus and no fresh blood enters the glomerulus for filtration.

8. *Systemic Arterial Pressure*

Renal blood flow and GFR are not affected as long as the mean arterial blood pressure is in between 60 and 180 mm Hg due to the autoregulatory mechanism (Chapter 51). Variation in pressure above 180 mm Hg or below 60 mm Hg affects the renal blood flow and GFR

accordingly, because the autoregulatory mechanism fails beyond this range.

9. *Sympathetic Stimulation*

Afferent and efferent arterioles are supplied by sympathetic nerves. The mild or moderate stimulation of sympathetic nerves does not cause any significant change either in renal blood flow or GFR.

Strong sympathetic stimulation causes severe constriction of the blood vessels by releasing the neurotransmitter substance, noradrenaline. The effect is more severe on the efferent arterioles than on the afferent arterioles. So, initially there is increase in filtration but later it decreases. However, if the stimulation is continued for more than 30 minutes, there is recovery of both renal blood flow and GFR. It is because of reduction in sympathetic neurotransmitter.

10. *Surface Area of Capillary Membrane*

GFR is directly proportional to the surface area of the capillary membrane.

If the glomerular capillary membrane is affected as in the cases of some renal diseases, the surface area for filtration decreases. So there is reduction in GFR.

11. *Permeability of Capillary Membrane*

GFR is directly proportional to the permeability of glomerular capillary membrane. In many abnormal conditions like hypoxia, lack of blood supply, presence of toxic agents, etc. the permeability of the capillary membrane increases. In such conditions, even plasma proteins are filtered and excreted in urine.

12. *Contraction of Glomerular Mesangial Cells*

Glomerular mesangial cells are situated in between the glomerular capillaries. Contraction of these cells decreases surface area of capillaries resulting in reduction in GFR.

13. *Hormonal and Other Factors*

Many hormones and other secretory factors alter GFR by affecting the blood flow through glomerulus.

Factors increasing GFR by vasodilatation

i. Atrial natriuretic peptide
ii. Brain natriuretic peptide
iii. cAMP
iv. Dopamine
v. Endothelial-derived nitric oxide
vi. Prostaglandin (PGE_2).

Factors decreasing GFR by vasoconstriction

i. Angiotensin II
ii. Endothelins
iii. Noradrenaline
iv. Platelet-activating factor
v. Platelet-derived growth factor
vi. Prostaglandin (PGF_2).

TUBULAR REABSORPTION

INTRODUCTION

Tubular reabsorption is the process by which water and other substances are transported from renal tubules back to the blood. When the glomerular filtrate flows through the tubular portion of nephron, both quantitative and qualitative changes occur. Large quantity of water (more than 99%), electrolytes and other substances are reabsorbed by the tubular epithelial cells. The reabsorbed substances move into the interstitial fluid of renal medulla. And, from here, the substances move into the blood in peritubular capillaries.

Since the substances are taken back into the blood from the glomerular filtrate, the entire process is called tubular reabsorption.

METHOD OF COLLECTION OF TUBULAR FLUID

There are two methods to collect the tubular fluid for analysis.

1. *Micropuncture Technique*

A micropipette is inserted into the Bowman capsule and different parts of tubular portion in the nephrons of experimental animals, to collect the fluid. The fluid samples are analyzed and compared with each other to assess the changes in different parts of nephron.

2. *Stop-flow Method*

Ureter is obstructed so that the back pressure rises and stops the glomerular filtration. The obstruction is continued for 8 minutes. It causes some changes in the fluid present in different parts of the tubular portion.

Later, the obstruction is released and about 30 samples of 0.5 mL of urine are collected separately at regular intervals of 30 seconds. The first sample contains the fluid from collecting duct. Successive samples contain the fluid from distal convoluted tubule, loops of Henle and proximal convoluted tubule respectively. All the samples are analyzed.

■ SELECTIVE REABSORPTION

Tubular reabsorption is known as selective reabsorption because the tubular cells reabsorb only the substances necessary for the body. Essential substances such as glucose, amino acids and vitamins are completely reabsorbed from renal tubule. Whereas the unwanted substances like metabolic waste products are not reabsorbed and excreted through urine.

■ MECHANISM OF REABSORPTION

Basic transport mechanisms involved in tubular reabsorption are of two types:

1. Active reabsorption
2. Passive reabsorption.

1. *Active Reabsorption*

Active reabsorption is the movement of molecules against the **electrochemical (uphill) gradient.** It needs liberation of energy, which is derived from ATP.

Substances reabsorbed actively

Substances reabsorbed actively from the renal tubule are sodium, calcium, potassium, phosphates, sulfates, bicarbonates, glucose, amino acids, ascorbic acid, uric acid and ketone bodies.

2. *Passive Reabsorption*

Passive reabsorption is the movement of molecules along the **electrochemical (downhill) gradient.** This process does not need energy.

Substances reabsorbed passively

Substances reabsorbed passively are chloride, urea and water.

■ ROUTES OF REABSORPTION

Reabsorption of substances from tubular lumen into the peritubular capillary occurs by two routes:

1. Trancelluar route
2. Paracellular route.

1. *Transcellular Route*

In this route the substances move through the cell.

It includes transport of substances from:

a. Tubular lumen into tubular cell through apical (luminal) surface of the cell membrane
b. Tubular cell into interstitial fluid
c. Interstitial fluid into capillary.

2. *Paracelluar Route*

In this route, the substances move through the intercellular space.

It includes transport of substances from:

i. Tubular lumen into interstitial fluid present in lateral intercellular space through the tight junction between the cells
ii. Interstitial fluid into capillary (Fig. 52.3).

■ SITE OF REABSORPTION

Reabsorption of the substances occurs in almost all the segments of tubular portion of nephron.

1. *Substances Reabsorbed from Proximal Convoluted Tubule*

About 7/8 of the filtrate (about 88%) is reabsorbed in proximal convoluted tubule. The brush border of epithelial cells in proximal convoluted tubule increases the surface area and facilitates the reabsorption.

Substances reabsorbed from proximal convoluted tubule are glucose, amino acids, sodium, potassium, calcium, bicarbonates, chlorides, phosphates, urea, uric acid and water.

2. *Substances Reabsorbed from Loop of Henle*

Substances reabsorbed from loop of Henle are sodium and chloride.

3. *Substances Reabsorbed from Distal Convoluted Tubule*

Sodium, calcium, bicarbonate and water are reabsorbed from distal convoluted tubule.

■ REGULATION OF TUBULAR REABSORPTION

Tubular reabsorption is regulated by three factors:

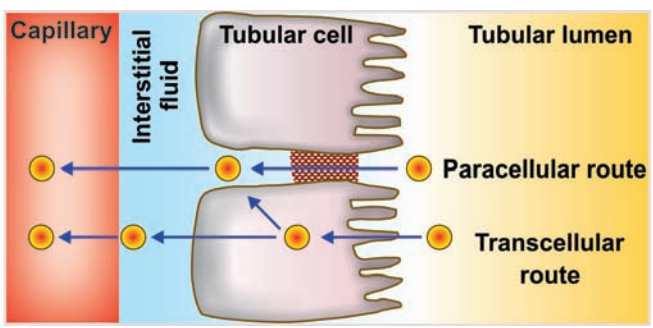


FIGURE 52.3: Routes of reabsorption

1. Glomerulotubular balance
2. Hormonal factors
3. Nervous factors.

1. *Glomerulotubular Balance*

Glomerulotubular balance is the balance between the filtration and reabsorption of solutes and water in kidney. When GFR increases, the tubular load of solutes and water in the proximal convoluted tubule is increased. It is followed by increase in the reabsorption of solutes and water. This process helps in the constant reabsorption of solute particularly sodium and water from renal tubule.

Mechanism of glomerulotubular balance

Glomerulotubular balance occurs because of osmotic pressure in the peritubular capillaries. When GFR increases, more amount of plasma proteins accumulate in the glomerulus. Consequently, the osmotic pressure increases in the blood by the time it reaches efferent arteriole and peritubular capillaries. The elevated osmotic pressure in the peritubular capillaries increases reabsorption of sodium and water from the tubule into the capillary blood.

2. *Hormonal Factors*

Hormones, which regulate GFR are listed in Table 52.1.

3. *Nervous Factor*

Activation of sympathetic nervous system increases the tubular reabsorption (particularly of sodium) from renal tubules. It also increases the tubular reabsorption indirectly by stimulating secretion of renin from juxtaglomerular cells. Renin causes formation of angiotensin II, which increases the sodium reabsorption.

■ THRESHOLD SUBSTANCES

Depending upon the degree of reabsorption, various substances are classified into three categories:

1. High-threshold substances
2. Low-threshold substances
3. Non-threshold substances.

1. *High-threshold Substances*

High-threshold substances are those substances, which do not appear in urine under normal conditions. The food substances like glucose, amino acids, acetoacetate ions and vitamins are completely reabsorbed from renal tubules and do not appear in urine under normal conditions. These substances can appear in urine, only if their concentration in plasma is abnormally high or in renal diseases when reabsorption is affected. So, these substances are called high-threshold substances.

2. *Low-threshold Substances*

Low-threshold substances are the substances, which appear in urine even under normal conditions. The substances such as urea, uric acid and phosphate are reabsorbed to a little extend. So, these substances appear in urine even under normal conditions.

3. *Non-threshold Substances*

Non-threshold substances are those substances, which are not at all reabsorbed and are excreted in urine irrespective of their plasma level. The metabolic end products such as creatinine are the non-threshold substances.

■ TRANSPORT MAXIMUM – Tm VALUE

Tubular transport maximum or Tm is the rate at which the maximum amount of a substance is reabsorbed from the renal tubule.

So, for every actively reabsorbed substance, there is a maximum rate at which it could be reabsorbed. For example, the transport maximum for glucose (TmG) is 375 mg/minute in adult males and about 300 mg/minute in adult females.

TABLE 52.1: Hormones regulating tubular reabsorption

Hormone	Action
Aldosterone	Increases sodium reabsorption in ascending limb, distal convoluted tubule and collecting duct
Angiotensin II	Increases sodium reabsorption in proximal tubule, thick ascending limb, distal tubule and collecting duct (mainly in proximal convoluted tubule)
Antidiuretic hormone	Increases water reabsorption in distal convoluted tubule and collecting duct
Atrial natriuretic factor	Decreases sodium reabsorption
Brain natriuretic factor	Decreases sodium reabsorption
Parathormone	Increases reabsorption of calcium, magnesium and hydrogen Decreases phosphate reabsorption
Calcitonin	Decreases calcium reabsorption

Threshold Level in Plasma for Substances having Tm Value

Renal threshold is the plasma concentration at which a substance appears in urine. Every substance having Tm value has also a threshold level in plasma or blood. Below that threshold level, the substance is completely reabsorbed and does not appear in urine. When the concentration of that substance reaches the threshold, the excess amount is not reabsorbed and, so it appears in urine. This level is called the renal threshold of that substance.

For example, the renal threshold for glucose is 180 mg/dL. That is, glucose is completely reabsorbed from tubular fluid if its concentration in blood is below 180 mg/dL. So, the glucose does not appear in urine. When the blood level of glucose reaches 180 mg/dL it is not reabsorbed completely; hence it appears in urine.

■ REABSORPTION OF IMPORTANT SUBSTANCES

Reabsorption of Sodium

From the glomerular filtrate, 99% of sodium is reabsorbed. Two thirds of sodium is reabsorbed in proximal convoluted tubule and remaining one third in other segments (except descending limb) and collecting duct.

Sodium reabsorption occurs in three steps:

1. Transport from lumen of renal tubules into the tubular epithelial cells
2. Transport from tubular cells into the interstitial fluid
3. Transport from interstitial fluid to the blood.

1. *Transport from Lumen of Renal Tubules into the Tubular Epithelial Cells*

Active reabsorption of sodium ions from lumen into the tubular cells occurs by two ways:

i. In exchange for hydrogen ion by **antiport** (sodium counterport protein) – in proximal convoluted tubules

ii. Along with other substances like glucose and amino acids by **symport** (sodium co-transport protein) – in other segments and collecting duct.

It is believed that some amount of sodium diffuses along the electrochemical gradient from lumen into tubular cell across the luminar membrane. The electrochemical gradient is developed by sodium-potassium pump (see below).

2. *Transport from Tubular Cells into the Interstitial Fluid*

Sodium is pumped outside the cells by sodium-potassium pump. This pump moves three sodium ions from the cell into interstitium and two potassium ions from interstitium into the cell.

Tubular epithelial cells are connected with their neighboring cells by tight junctions at their apical luminal edges. But, beyond the tight junction, a small space is left between the adjoining cells along their lateral borders. This space is called **lateral intercellular space.** The interstitium extends into this space.

Most of the sodium ions are pumped into the lateral intercellular space by sodium-potassium pump. The rest of the sodium ions are pumped into the interstitium by the sodium-potassium pump situated at the basal part of the cell membrane.

(Transport of sodium out of the tubular cell by sodium-potassium pump, decreases the sodium concentration within the cell. This develops an electrochemical gradient between the lumen and tubular cell resulting in diffusion of sodium into the cell).

3. *Transport from Interstitial Fluid to the Blood*

From the interstitial fluid, sodium ions enter the peritubular capillaries by concentration gradient.

In the distal convoluted tubule, the sodium reabsorption is stimulated by the hormone aldosterone secreted by adrenal cortex.

Reabsorption of Water

Reabsorption of water occurs from proximal and distal convoluted tubules and in collecting duct.

Reabsorption of water from proximal convoluted tubule – obligatory water reabsorption

Obligatory reabsorption is the type of water reabsorption in proximal convoluted tubule, which is secondary (obligatory) to sodium reabsorption. When sodium is reabsorbed from the tubule, the osmotic pressure decreases. It causes osmosis of water from renal tubule.

Reabsorption of water from distal convoluted tubule and collecting duct – facultative water reabsorption

Facultative reabsorption is the type of water reabsorption in distal convoluted tubule and collecting duct that occurs by the activity of antidiuretic hormone (ADH). Normally, the distal convoluted tubule and the collecting duct are not permeable to water. But in the presence of ADH, these segments become permeable to water, so it is reabsorbed.

Mechanism of action of ADH – Aquaporins

Antidiuretic hormone increases water reabsorption in distal convoluted tubules and collecting ducts by

stimulating the water channels called aquaporins. ADH combines with vasopressin (V2) receptors in the tubular epithelial membrane and activates adenyl cyclase, to form cyclic AMP. This cyclic AMP activates the aquaporins, which increase the water reabsorption.

Aquaporins (AQP) are the membrane proteins, which function as water channels. Though about 10 aquaporins are identified in mammals only 5 are found in humans. Aquaporin-1, 2 and 3 are present in renal tubules. Aquaporin-4 is present in brain and aquaporin-5 is found in salivary glands. Aquaporin-2 forms the water channels in renal tubules.

Reabsorption of Glucose

Glucose is completely reabsorbed in the proximal convoluted tubule. It is transported by secondary active transport (sodium cotransport) mechanism. Glucose and sodium bind to a common carrier protein in the luminal membrane of tubular epithelium and enter the cell. The carrier protein is called **sodium-dependant glucose cotransporter 2** (SGLT2). From tubular cell glucose is transported into medullary interstitium by another carrier protein called **glucose transporter 2** (GLUT2).

Tubular maximum for glucose (TmG)

In adult male, TmG is 375 mg/minute and in adult females it about 300 mg/minute.

Renal threshold for glucose

Renal threshold for glucose is 180 mg/dL in venous blood. When the blood level reaches 180 mg/dL glucose is not reabsorbed completely and appears in urine.

Splay

Splay means deviation. With normal GFR of 125 mL/minute and TmG of 375 mg/minute in an adult male the predicted (expected) renal threshold for glucose should be 300 mg/dL. But actually it is only 180 mg/dL.

When the renal threshold curves are drawn by using these values, the actual curve deviates from the 'should be' or predicted or ideal curve (Fig. 52.4). This type of deviation is called splay. Splay is because of the fact that all the nephrons do not have the same filtering and reabsorbing capacities.

Reabsorption of Amino Acids

Amino acids are also reabsorbed completely in proximal convoluted tubule. Amino acids are reabsorbed actively by the secondary active transport mechanism along with sodium.

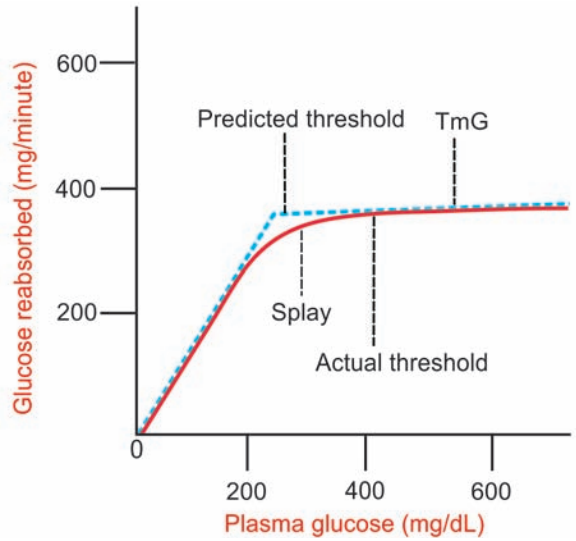


FIGURE 52.4: Splay in renal threshold curve for glucose

Reabsorption of Bicarbonates

Bicarbonate is reabsorbed actively, mostly in proximal tubule (Chapter 54). It is reabsorbed in the form of carbon dioxide.

Bicarbonate is mostly present as sodium bicarbonate in the filtrate. Sodium bicarbonate dissociates into sodium and bicarbonate ions in the tubular lumen. Sodium diffuses into tubular cell in exchange of hydrogen. Bicarbonate combines with hydrogen to form carbonic acid. Carbonic acid dissociates into carbon dioxide and water in the presence of carbonic anhydrase. Carbon dioxide and water enter the tubular cell.

In the tubular cells, carbon dioxide combines with water to form carbonic acid. It immediately dissociates into hydrogen and bicarbonate. Bicarbonate from the tubular cell enters the interstitium. There it combines with sodium to form sodium bicarbonate (Fig. 54.1).

■ TUBULAR SECRETION

■ INTRODUCTION

Tubular secretion is the process by which the substances are transported from blood into renal tubules. It is also called tubular excretion. In addition to reabsorption from renal tubules, some substances are also secreted into the lumen from the peritubular capillaries through the tubular epithelial cells.

Dye phenol red was the first substance found to be secreted in renal tubules in experimental conditions. Later many other substances were found to be secreted.

Such substances are:

1. Para-aminohippuric acid (PAH)
2. Diodrast
3. 5-hydroxyindoleacetic acid (5-HIAA)
4. Amino derivatives
5. Penicillin.

■ SUBSTANCES SECRETED IN DIFFERENT SEGMENTS OF RENAL TUBULES

1. Potassium is secreted actively by sodium-potassium pump in proximal and distal convoluted tubules and collecting ducts
2. Ammonia is secreted in the proximal convoluted tubule
3. Hydrogen ions are secreted in the proximal and distal convoluted tubules. Maximum hydrogen ion secretion occurs in proximal tubule
4. Urea is secreted in loop of Henle.

Thus, urine is formed in nephron by the processes of glomerular filtration, selective reabsorption and tubular secretion.

■ SUMMARY OF URINE FORMATION

Urine formation takes place in three processes (Refer to Fig. 52.1):

1. *Glomerular filtration*

Plasma is filtered in glomeruli and the substances reach the renal tubules along with water as filtrate.

2. *Tubular Reabsorption*

The 99% of filtrate is reabsorbed in different segments of renal tubules.

3. *Tubular Secretion*

Some substances are transported from blood into the renal tubule.

With all these changes, the filtrate becomes urine.

Chapter 31

Concentration of Urine

- INTRODUCTION
- MEDULLARY GRADIENT
- COUNTERCURRENT MECHANISM
- ROLE OF ADH
- SUMMARY OF URINE CONCENTRATION
- APPLIED PHYSIOLOGY

INTRODUCTION

Every day 180 L of glomerular filtrate is formed with large quantity of water. If this much of water is excreted in urine, body will face serious threats. So the concentration of urine is very essential.

Osmolarity of glomerular filtrate is same as that of plasma and it is 300 mOsm/L. But, normally urine is concentrated and its osmolarity is four times more than that of plasma, i.e. 1,200 mOsm/L.

Osmolarity of urine depends upon two factors:

1. Water content in the body
2. Antidiuretic hormone (ADH).

Mechanism of urine formation is the same for dilute urine and concentrated urine till the fluid reaches the distal convoluted tubule. However, dilution or concentration of urine depends upon water content of the body.

FORMATION OF DILUTE URINE

When, water content in the body increases, kidney excretes dilute urine. This is achieved by inhibition of ADH secretion from posterior pituitary. So water reabsorption from renal tubules does not take place (see Fig. 53.4) leading to excretion of large amount of water. This makes the urine dilute.

FORMATION OF CONCENTRATED URINE

When the water content in body decreases, kidney retains water and excretes concentrated urine. Formation of concentrated urine is not as simple as that of dilute urine.

It involves two processes:

1. Development and maintenance of medullary gradient by countercurrent system
2. Secretion of ADH.

MEDULLARY GRADIENT

MEDULLARY HYPEROSMOLARITY

Cortical interstitial fluid is isotonic to plasma with the osmolarity of 300 mOsm/L. Osmolarity of medullary interstitial fluid near the cortex is also 300 mOsm/L.

However, while proceeding from outer part towards the inner part of medulla, the osmolarity increases gradually and reaches the maximum at the inner most part of medulla near renal sinus. Here, the interstitial fluid is hypertonic with osmolarity of 1,200 mOsm/L (Fig. 53.1).

This type of gradual increase in the osmolarity of the medullary interstitial fluid is called the medullary gradient. It plays an important role in the concentration of urine.

DEVELOPMENT AND MAINTENANCE OF MEDULLARY GRADIENT

Kidney has some unique mechanism called countercurrent mechanism, which is responsible for the development and maintenance of medullary gradient and hyperosmolarity of interstitial fluid in the inner medulla.

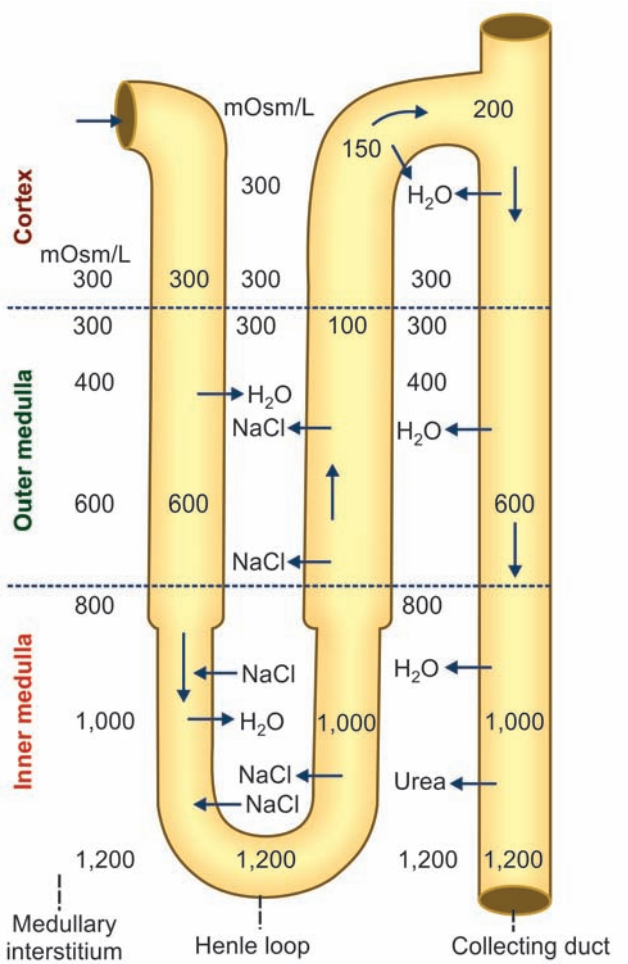


FIGURE 53.1: Countercurrent multiplier. Numerical indicate osmolarity (mOsm/L)

■ COUNTERCURRENT MECHANISM

■ COUNTERCURRENT FLOW

A countercurrent system is a system of 'U'-shaped tubules (tubes) in which, the flow of fluid is in opposite direction in two limbs of the 'U'-shaped tubules.

Divisions of Countercurrent System

Countercurrent system has two divisions:

1. Countercurrent multiplier formed by loop of Henle
2. Countercurrent exchanger formed by vasa recta.

■ COUNTERCURRENT MULTIPLIER

Loop of Henle

Loop of Henle functions as countercurrent multiplier. It is responsible for development of hyperosmolarity of medullary interstitial fluid and medullary gradient.

Role of Loop of Henle in Development of Medullary Gradient

Loop of Henle of juxtamedullary nephrons plays a major role as countercurrent multiplier because loop of these nephrons is long and extends upto the deeper parts of medulla.

Main reason for the hyperosmolarity of medullary interstitial fluid is the active reabsorption of sodium chloride and other solutes from ascending limb of Henle loop into the medullary interstitium. These solutes accumulate in the medullary interstitium and increase the osmolarity.

Now, due to the concentration gradient, the sodium and chlorine ions diffuse from medullary interstitium into the descending limb of Henle loop and reach the ascending limb again via hairpin bend.

Thus, the sodium and chlorine ions are repeatedly re-circulated between the descending limb and ascending limb of Henle loop through medullary interstitial fluid leaving a small portion to be excreted in the urine.

Apart from this there is regular addition of more and more new sodium and chlorine ions into descending limb by constant filtration. Thus, the reabsorption of sodium chloride from ascending limb and addition of new sodium chlorine ions into the filtrate increase or multiply the osmolarity of medullary interstitial fluid and medullary gradient. Hence, it is called countercurrent multiplier.

Other Factors Responsible for Hyperosmolarity of Medullary Interstitial Fluid

In addition to countercurrent multiplier action provided by the loop of Henle, two more factors are involved in hyperosmolarity of medullary interstitial fluid.

i. *Reabsorption of sodium from collecting duct*

Reabsorption of sodium from medullary part of collecting duct into the medullary interstitium, adds to the osmolarity of inner medulla.

ii. *Recirculation of urea*

Fifty percent of urea filtered in glomeruli is reabsorbed in proximal convoluted tubule. Almost an equal amount of urea is secreted in the loop of Henle. So the fluid in distal convoluted tubule has as much urea as amount filtered.

Collecting duct is impermeable to urea. However, due to the water reabsorption from distal convoluted tubule and collecting duct in the presence of ADH, urea concentration increases in collecting duct. Now due to concentration gradient, urea diffuses from inner medullary part of collecting duct into medullary interstitium.

Due to continuous diffusion, the concentration of urea increases in the inner medulla resulting in hyperosmolarity of interstitium in inner medulla.

Again, by concentration gradient, urea enters the ascending limb. From here, it passes through distal convoluted tubule and reaches the collecting duct. Urea enters the medullary interstitium from collecting duct. By this way urea **recirculates** repeatedly and helps to maintain the hyperosmolarity of inner medullary interstitium. Only a small amount of urea is excreted in urine.

Urea recirculation accounts for 50% of hyperosmolarity in inner medulla. Diffusion of urea from collecting duct into medullary interstitium is carried out by **urea transporters,** UT-A1 and UT-A3, which are activated by ADH.

■ COUNTERCURRENT EXCHANGER

Vasa Recta

Vasa recta functions as countercurrent exchanger. It is responsible for the maintenance of medullary gradient, which is developed by countercurrent multiplier (Fig. 53.2).

Role of Vasa Recta in the Maintenance of Medullary Gradient

Vasa recta acts like countercurrent exchanger because of its position. It is also 'U'-shaped tubule with a descending limb, hairpin bend and an ascending limb. Vasa recta runs parallel to loop of Henle. Its descending limb runs along the ascending limb of Henle loop and its ascending limb runs along with descending limb of Henle loop.

The sodium chloride reabsorbed from ascending limb of Henle loop enters the medullary interstitium. From here it enters the descending limb of vasa recta. Simultaneously water diffuses from descending limb of vasa recta into medullary interstitium.

The blood flows very slowly through vasa recta. So, a large quantity of sodium chloride accumulates in descending limb of vasa recta and flows slowly towards ascending limb. By the time the blood reaches the ascending limb of vasa recta, the concentration of sodium chloride increases very much. This causes diffusion of sodium chloride into the medullary interstitium. Simultaneously, water from medullary interstitium enters the ascending limb of vasa recta. And the cycle is repeated.

If the vasa recta would be a straight vessel without hairpin arrangement, blood would leave the kidney quickly at renal papillary level. In that case, the blood would remove all the sodium chloride from medullary

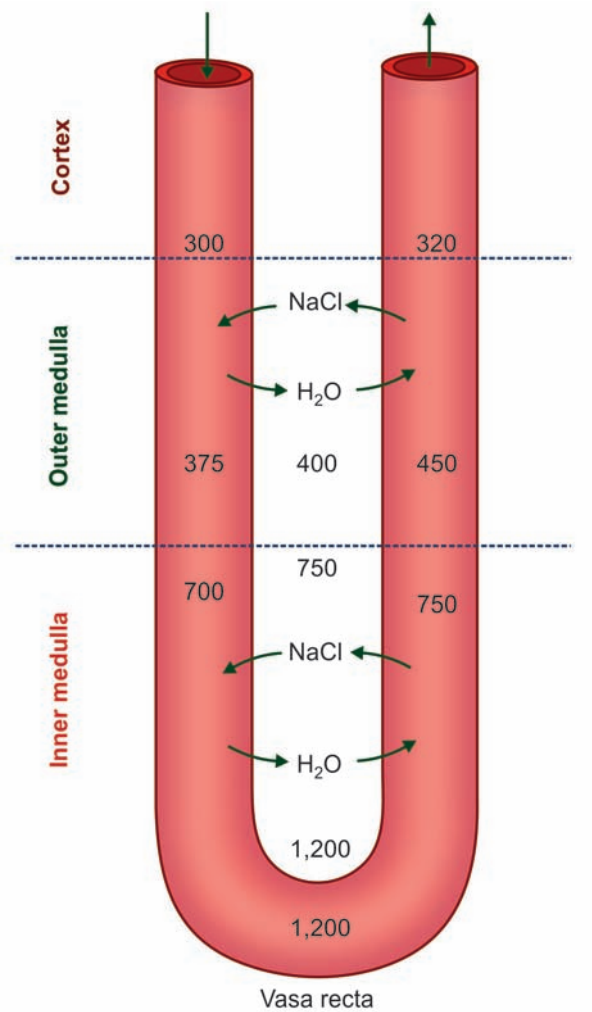


FIGURE 53.2: Countercurrent exchanger. Numerical indicate osmolarity (mOsm/L)

interstitium and thereby the hyperosmolarity will be decreased. However, this does not happen, since the vasa recta has a hairpin bend.

Therefore, when blood passes through the ascending limb of vasa recta, sodium chloride diffuses out of blood and enters the interstitial fluid of medulla and, water diffuses into the blood.

Thus, vasa recta retains sodium chloride in the medullary interstitium and removes water from it. So, the hyperosmolarity of medullary interstitium is maintained. The blood passing through the ascending limb of vasa recta may carry very little amount of sodium chloride from the medulla.

Recycling of urea also occurs through vasa recta. From medullary interstitium, along with sodium chloride, urea also enters the descending limb of vasa recta. When blood passes through ascending limb of vasa

recta, urea diffuses back into the medullary interstitium along with sodium chloride.

Thus, sodium chloride and urea are exchanged for water between the ascending and descending limbs of vasa recta, hence this system is called countercurrent exchanger.

ROLE OF ADH

Final concentration of urine is achieved by the action of ADH. Normally, the distal convoluted tubule and collecting duct are not permeable to water. But the presence of ADH makes them permeable, resulting in water reabsorption. Water reabsorption induced by ADH is called **facultative reabsorption of water**.

A large quantity of water is removed from the fluid while passing through distal convoluted tubule and collecting duct. So, the urine becomes hypertonic with an osmolarity of 1,200 mOsm/L (Fig. 53.3).

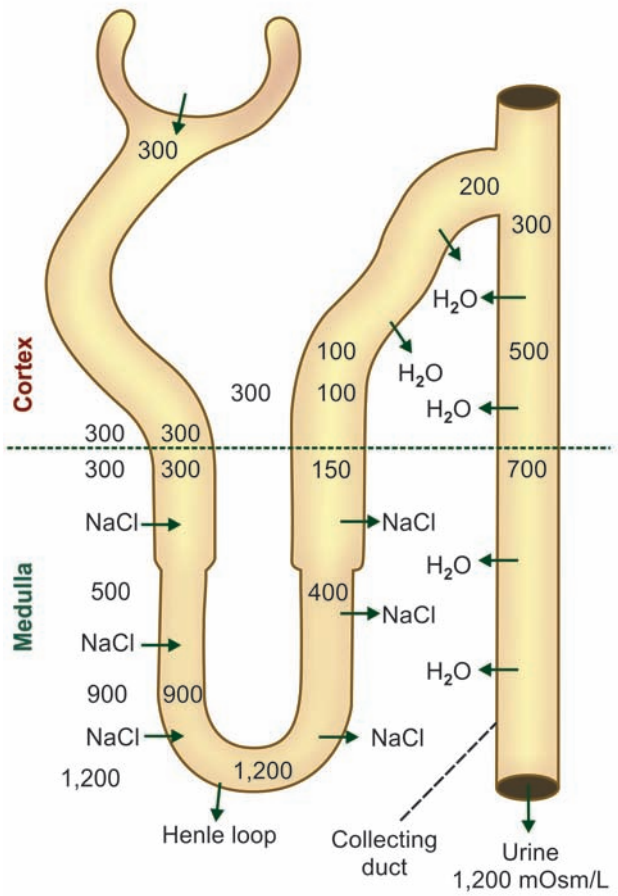


FIGURE 53.3: Role of ADH in the formation of concentrated urine. ADH increases the permeability for water in distal convoluted tubule and collecting duct. Numerical indicate osmolarity (mOsm/L)

SUMMARY OF URINE CONCENTRATION

When the glomerular filtrate passes through renal tubule, its osmolarity is altered in different segments as described below (Fig. 53.4).

1. BOWMAN CAPSULE

Glomerular filtrate collected at the Bowman capsule is **isotonic to plasma**. This is because it contains all the substances of plasma except proteins. Osmolarity of the filtrate at Bowman capsule is 300 mOsm/L.

2. PROXIMAL CONVOLUTED TUBULE

When the filtrate flows through proximal convoluted tubule, there is active reabsorption of sodium and chloride followed by **obligatory reabsorption of water.**

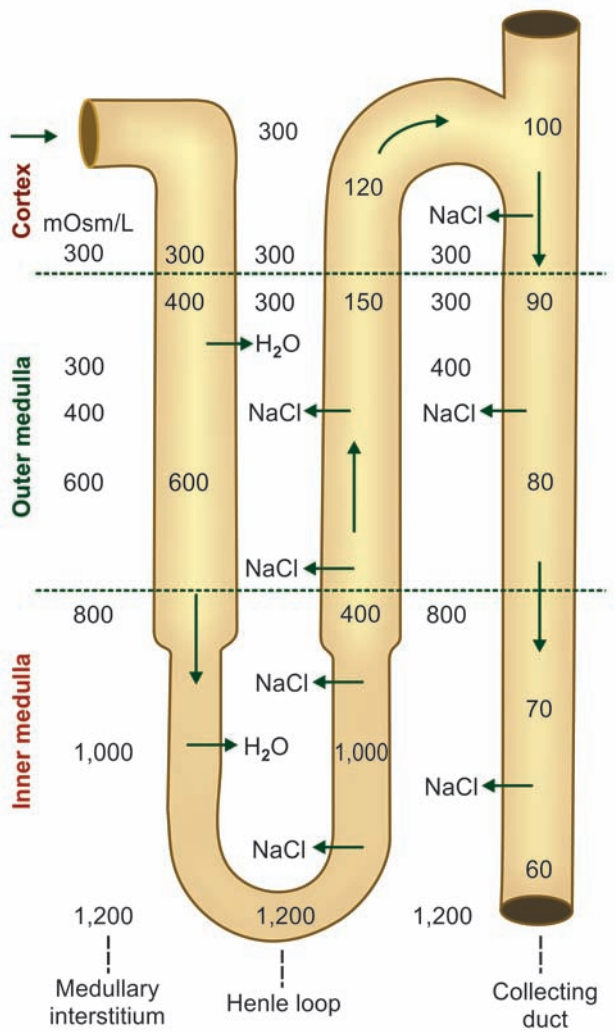


FIGURE 53.4: Mechanism for the formation of dilute urine. Numerical indicate osmolarity (mOsm/L)

So, the osmolarity of fluid remains the same as in the case of Bowman capsule, i.e. 300 mOsm/L. Thus, in proximal convoluted tubules, the fluid is **isotonic to plasma.**

■ 3. THICK DESCENDING SEGMENT

When the fluid passes from proximal convoluted tubule into the thick descending segment, water is reabsorbed from tubule into outer medullary interstitium by means of osmosis. It is due to the increased osmolarity in the medullary interstitium, i.e. outside the thick descending tubule. The osmolarity of the fluid inside this segment is between 450 and 600 mOsm/L. That means the fluid is slightly **hypertonic to plasma.**

■ 4. THIN DESCENDING SEGMENT OF HENLE LOOP

As the thin descending segment of Henle loop passes through the inner medullary interstitium (which is increasingly hypertonic) more water is reabsorbed. This segment is highly permeable to water and so the osmolarity of tubular fluid becomes equal to that of the surrounding medullary interstitium.

In the short loops of cortical nephrons, the osmolarity of fluid at the hairpin bend of loop becomes 600 mOsm/L. And, in the long loops of juxtamedullary nephrons, at the hairpin bend, the osmolarity is 1,200 mOsm/L. Thus in this segment the fluid is **hypertonic to plasma.**

■ 5. THIN ASCENDING SEGMENT OF HENLE LOOP

When the thin ascending segment of the loop ascends upwards through the medullary region, osmolarity decreases gradually.

Due to concentration gradient, sodium chloride diffuses out of tubular fluid and osmolarity decreases to 400 mOsm/L. The fluid in this segment is slightly **hypertonic to plasma.**

■ 6. THICK ASCENDING SEGMENT

This segment is impermeable to water. But there is active reabsorption of sodium and chloride from this. Reabsorption of sodium decreases the osmolarity of tubular fluid to a greater extent. The osmolarity is between 150 and 200 mOsm/L. The fluid inside becomes **hypotonic to plasma.**

■ 7. DISTAL CONVOLUTED TUBULE AND COLLECTING DUCT

In the presence of ADH, distal convoluted tubule and collecting duct become permeable to water resulting in water reabsorption and final concentration of urine. It is found that in the collecting duct, Principal (P) cells are responsible for ADH induced water reabsorption.

Reabsorption of large quantity of water increases the osmolarity to 1,200 mOsm/L (Fig. 53.3). The urine becomes **hypertonic to plasma.**

■ APPLIED PHYSIOLOGY

1. *Osmotic Diuresis*

Diuresis is the excretion of large quantity of water through urine. Osmotic diuresis is the diuresis induced by the osmotic effects of solutes like glucose. It is common in **diabetes mellitus**.

2. *Polyuria*

Polyuria is the increased urinary output with frequent voiding. It is common in **diabetes insipidus.** In this disorder, the renal tubules fail to reabsorb water because of ADH deficiency.

3. *Syndrome of Inappropriate Hypersecretion of ADH (SIADH)*

It is a pituitary disorder characterized by hypersecretion of ADH is the SIADH. Excess ADH causes water retention, which decreases osmolarity of ECF.

4. *Nephrogenic Diabetes Insipidus*

Sometimes, ADH secretion is normal but the renal tubules fail to give response to ADH resulting in polyuria. This condition is called nephrogenic diabetes insipidus.

5. *Bartter Syndrome*

Bartter syndrome is a genetic disorder characterized by defect in the thick ascending segment. This causes decreased sodium and water reabsorption resulting in loss of sodium and water through urine.

Acidification of Urine and Role of Kidney in Acid-base Balance

Chapter 32

INTRODUCTION

Kidney plays an important role in maintenance of acid-base balance by excreting hydrogen ions and retaining bicarbonate ions.

Normally, urine is acidic in nature with a pH of 4.5 to 6. Metabolic activities in the body produce large quantity of acids (with lot of hydrogen ions), which threaten to push the body towards acidosis.

However, kidneys prevent this by two ways:

1. Reabsorption of bicarbonate ions (HCO_3^-)
2. Secretion of hydrogen ions (H^+).

REABSORPTION OF BICARBONATE IONS

About 4,320 mEq of HCO_3^- is filtered by the glomeruli everyday. It is called **filtered load** of HCO_3^-. Excretion of this much HCO_3^- in urine will affect the acid-base balance of body fluids. So, HCO_3^- must be taken back from the renal tubule by reabsorption.

SECRETION OF HYDROGEN IONS

Reabsorption of filtered HCO_3^- occurs by the secretion of H^+ in the renal tubules. About 4,380 mEq of H^+ appear every day in the renal tubule by means of filtration and secretion. Not all the H^+ are excreted in urine. Out of 4,380 mEq, about 4,280 to 4,330 mEq of H^+ is utilized for the reabsorption of filtered HCO_3^-. Only the remaining 50 to 100 mEq is excreted. It results in the acidification of urine.

Secretion of H^+ into the renal tubules occurs by the formation of carbonic acid. Carbon dioxide formed in the tubular cells or derived from tubular fluid combines with water to form carbonic acid in the presence of **carbonic anhydrase.** This enzyme is available in large quantities in the epithelial cells of the renal tubules. The carbonic acid immediately dissociates into H^+ and HCO_3^- (Fig. 54.1).

H^+ is secreted into the lumen of proximal convoluted tubule, distal convoluted tubule and collecting duct. Distal convoluted tubule and collecting duct have a special type of cells called **intercalated cells (I cells)** that are involved in handling hydrogen and bicarbonate ions.

Secretion of H^+ occurs by two pumps:

i. Sodium-hydrogen antiport pump
ii. ATP-driven proton pump.

SODIUM-HYDROGEN ANTIPORT PUMP

When sodium ion (Na^+) is reabsorbed from the tubular fluid into the tubular cell, H^+ is secreted from the cell into the tubular fluid in exchange for Na^+. The sodium-hydrogen antiport pump present in the tubular cells

is responsible for the exchange of Na^+ and H^+. This type of sodium-hydrogen counter transport occurs predominantly in distal convoluted tubule (Table 54.1).

■ ATP-DRIVEN PROTON PUMP

This is an additional pump for H^+ secretion in distal convoluted tubule and collecting duct. This pump operates by energy from ATP.

■ REMOVAL OF HYDROGEN IONS AND ACIDIFICATION OF URINE

Role of Kidney in Preventing Metabolic Acidosis

Kidney plays an important role in preventing metabolic acidosis by excreting H^+.

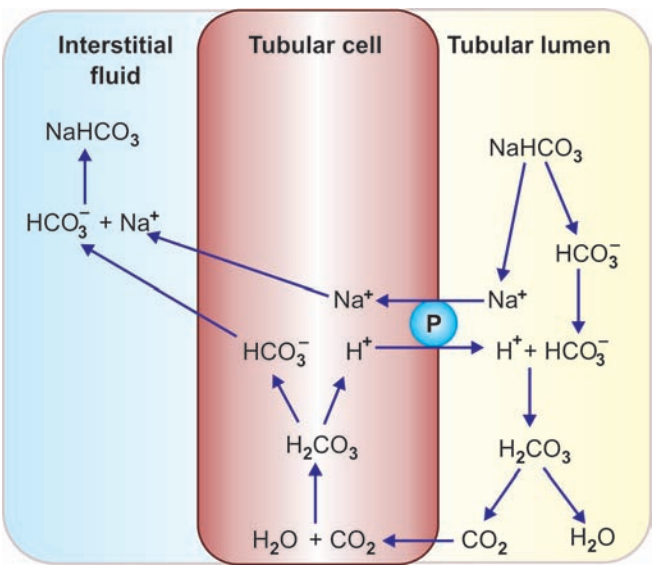


FIGURE 54.1: Reabsorption of bicarbonate ions by secretion of hydrogen ions in renal tubule. P = sodium-hydrogen antiport pump

TABLE 54.1: Mechanisms involved in secretion of hydrogen ions in renal tubule

Mechanism	Segment of renal tubule
Sodium-hydrogen pump	Distal convoluted tubule
ATP-driven proton pump	Distal convoluted tubule Collecting duct
Bicarbonate mechanism	Proximal convoluted tubule Henle loop Distal convoluted tubule
Phosphate mechanism	Distal convoluted tubule Collecting duct
Ammonia mechanism	Proximal convoluted tubule.

Excretion of H^+ occurs by three mechanisms:

1. Bicarbonate mechanism
2. Phosphate mechanism
3. Ammonia mechanism.

■ BICARBONATE MECHANISM

All the filtered HCO_3^- in the renal tubules is reabsorbed. About 80% of it is reabsorbed in proximal convoluted tubule, 15% in Henle loop and 5% in distal convoluted tubule and collecting duct. The reabsorption of HCO_3^- utilizes the H^+ secreted into the renal tubules.

H^+ secreted into the renal tubule, combines with filtered HCO_3^- forming carbonic acid (H_2CO_3). Carbonic acid dissociates into carbon dioxide and water in the presence of carbonic anhydrase. Carbon dioxide and water enter the tubular cell.

In the tubular cells, carbon dioxide combines with water to form carbonic acid. It immediately dissociates into H^+ and HCO_3^-. HCO_3^- from the tubular cell enters the interstitium. Simultaneously Na^+ is reabsorbed from the renal tubule under the influence of aldosterone. HCO_3^- combines with Na^+ to form sodium bicarbonate ($NaHCO_3$). Now, the H^+ is secreted into the tubular lumen from the cell in exchange for Na^+ (Fig. 54.1).

Thus, for every hydrogen ion secreted into lumen of tubule, one bicarbonate ion is reabsorbed from the tubule. In this way, kidneys conserve the HCO_3^-. The reabsorption of filtered HCO_3^- is an important factor in maintaining pH of the body fluids.

■ PHOSPHATE MECHANISM

In the tubular cells, carbon dioxide combines with water to form carbonic acid. It immediately dissociates into H^+ and HCO_3^-. HCO_3^- from the tubular cell enters the interstitium. Simultaneously, Na^+ is reabsorbed from renal tubule under the influence of aldosterone. Na^+ enters the interstitium and combines with HCO_3^-. H^+ is secreted into the tubular lumen from the cell in exchange for Na^+ (Fig. 54.2).

H^+, which is secreted into renal tubules, reacts with phosphate buffer system. It combines with sodium hydrogen phosphate to form sodium dihydrogen phosphate. Sodium dihydrogen phosphate is excreted in urine. The H^+, which is added to urine in the form of sodium dihydrogen, makes the urine acidic. It happens mainly in distal tubule and collecting duct because of the presence of large quantity of sodium hydrogen phosphate in these segments.

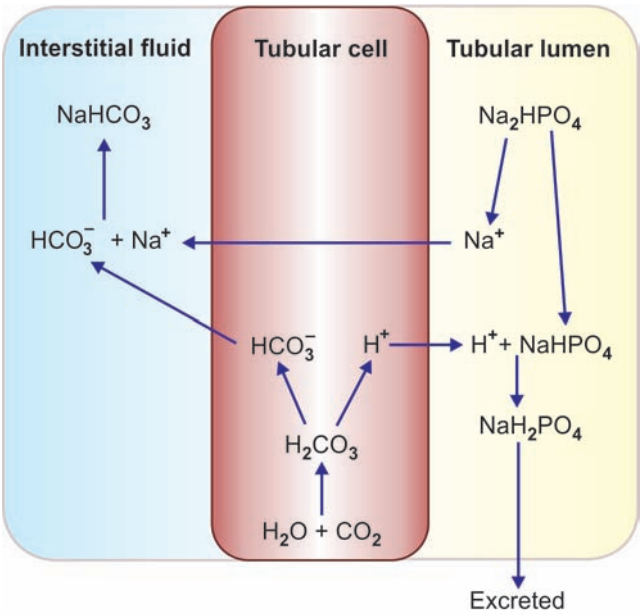


FIGURE 54.2: Excretion of hydrogen ions in combination with phosphate ions

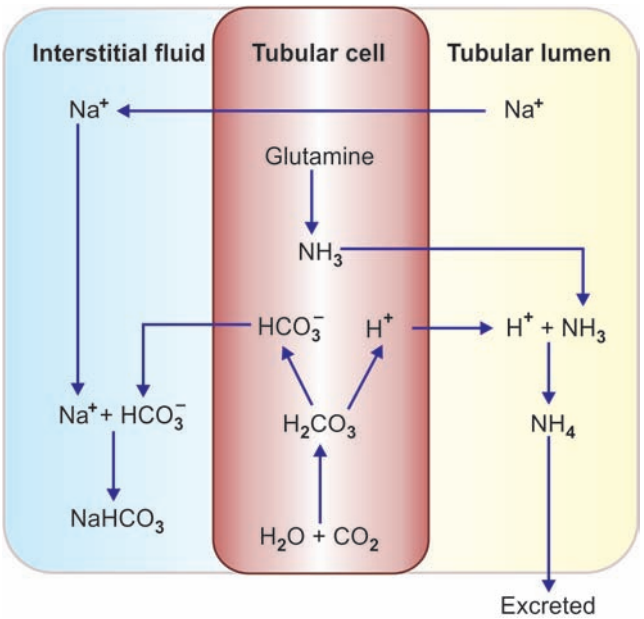


FIGURE 54.3: Excretion of hydrogen ions in combination with ammonia

■ AMMONIA MECHANISM

This is the most important mechanism by which kidneys excrete H^+ and make the urine acidic. In the tubular epithelial cells, ammonia is formed when the amino acid **glutamine** is converted into **glutamic acid** in the presence of the enzyme **glutaminase.** Ammonia is also formed by the deamination of some of the amino acids such as **glycine** and **alanine** (Fig. 54.3).

Ammonia (NH_3) formed in tubular cells is secreted into tubular lumen in exchange for sodium ion. Here, it combines with H^+ to form **ammonium** (NH_4). The tubular cell membrane is not permeable to ammonium. Therefore, it remains in the lumen and then excreted into urine. Thus, H^+ is added to urine in the form of ammonium compounds resulting in acidification of urine. For each NH_4 excreted one HCO_3^- is added to interstitial fluid.

This process takes place mostly in the proximal convoluted tubule because glutamine is converted into ammonia in the cells of this segment.

Thus, by excreting H^+ and conserving HCO_3^-, kidneys produce acidic urine and help to maintain the acid-base balance of body fluids.

■ APPLIED PHYSIOLOGY

Metabolic acidosis occurs when kidneys fail to excrete metabolic acids. **Metabolic alkalosis** occurs when kidneys excrete large quantity of hydrogen.

Chapter 33

Renal Function Tests

PROPERTIES AND COMPOSITION OF NORMAL URINE

PROPERTIES OF URINE

Volume	:	1,000 to 1,500 mL/day
Reaction	:	Slightly acidic with pH of 4.5 to 6
Specific gravity	:	1.010 to 1.025
Osmolarity	:	1,200 mOsm/L
Color	:	Normally, straw colored
Odor	:	Fresh urine has light aromatic odor. If stored for some time, the odor becomes stronger due to bacterial decomposition.

COMPOSITION OF URINE

Urine consists of water and solids. Solids include organic and inorganic substances (Fig. 55.1).

RENAL FUNCTION TESTS

Renal function tests are the group of tests that are performed to assess the functions of kidney.

Renal function tests are of three types:

A. Examination of urine alone

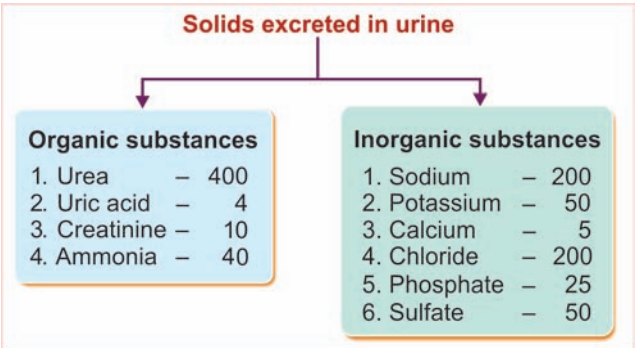


FIGURE 55.1: Quantity of solids excreted in urine (mMols/day)

B. Examination of blood alone

C. Examination of blood and urine.

EXAMINATION OF URINE – URINALYSIS

Routine examination of urine or urinalysis is a group of diagnostic tests performed on the sample of urine.

Urinalysis is done by:

i. Physical examination
ii. Microscopic examination
iii. Chemical analysis.

■ PHYSICAL EXAMINATION

1. *Volume*

Increase in urine volume indicates increase in protein catabolism and renal disorders such as **chronic renal failure, diabetes insipidus** and **glycosuria.**

2. *Color*

Normally urine is straw colored. Abnormal coloration of urine is due to several causes such as **jaundice, hematuria, hemoglobinuria,** medications, excess urobilinogen, ingestion of beetroot or color added to food.

3. *Appearance*

Normally urine is clear. It becomes turbid in both physiological and pathological conditions. Physiological conditions causing turbidity of urine are precipitation of crystals, presence of mucus or vaginal discharge. Pathological conditions causing turbidity are presence of blood cells, bacteria or yeast.

4. *Specific Gravity*

Specific gravity of urine is the measure of dissolved solutes (particles) in urine. It is low in diabetes insipidus and high in **diabetes mellitus, acute renal failure** and excess medications.

5. *Osmolarity*

Osmolarity of urine decreases in diabetes insipidus.

6. *pH and Reaction*

Measurement of pH is useful in determining the metabolic or respiratory acidosis or alkalosis. The pH decreases in renal diseases. In normal conditions, pH of urine depends upon diet. It is slightly alkaline in vegetarians and acidic in non-vegetarians.

■ MICROSCOPIC EXAMINATION

Microscopic examination of centrifuged sediment of urine is useful in determining the renal diseases.

1. *Red Blood Cells*

Presence of red blood cells in urine indicates glomerular disease such as **glomerulonephritis.**

2. *White Blood Cells*

Normally few white blood cells appear in high power field. The number increases in acute **glomerulonephritis,** infection of urinary tract, vagina or cervix.

3. *Epithelial Cells*

Normally few tubular epithelial cells slough into urine. Presence of many epithelial cells suggests **nephrotic syndrome** and **tubular necrosis.**

4. *Casts*

Casts are the cylindrical bodies that are casted (molded) in the shape of renal tubule. Casts may be hyaline, granular or cellular in nature. Hyaline and granular casts, which are formed by precipitation of proteins may appear in urine in small numbers. The number increases in proteinuria due to **glomerulonephritis.**

Cellular casts are formed by sticking together of some cells. Red blood cell casts appear in urine during glomerulonephritis and tubular necrosis. White blood cell casts appear in pyelonephritis. Epithelial casts are formed during acute **tubular necrosis.**

5. *Crystals*

Several types of crystals are present in normal urine. Common crystals are the crystals of calcium oxalate, calcium phosphate, uric acid and triple phosphate (calcium, ammonium and magnesium).

Abnormal crystals such as crystals of cystine and tyrosine appear in liver diseases.

6. *Bacteria*

Bacteria are common in urine specimens because of normal microbial flora of urinary tract, urethra and vagina and because of their ability to multiply rapidly in urine. Culture studies are necessary to determine the presence of bacteria in urine.

■ CHEMICAL ANALYSIS

Chemical analysis of urine helps to determine the presence of abnormal constituents of urine or presence of normal constituents in abnormal quantity. Both the findings reveal the presence of renal abnormality. Following are the common chemical tests of urine:

1. *Glucose*

Glucose appears in urine when the blood glucose level increases above 180 mg/dL. **Glycosuria** (presence of glucose in urine) may be the first indicator of diabetes mellitus.

2. *Protein*

Presence of excess protein **(proteinuria)** particularly albumin **(albuminuria)** in urine indicates renal diseases. Urinary excretion of albumin in a normal healthy adult

is about 30 mg/day. It exceeds this level in glomerulonephritis. It also increases in fever and severe exercise.

3. *Ketone Bodies*

Ketonuria (presence of ketone bodies in urine) occurs in pregnancy, fever, diabetes mellitus, prolonged starvation and glycogen storage diseases.

4. *Bilirubin*

Bilirubin appears in urine **(bilirubinuria)** during hepatic and posthepatic jaundice.

5. *Urobilinogen*

Normally, about 1 to 3.5 mg of urobilinogen is excreted in urine daily. Excess of urobilinogen in urine indicates **hemolytic jaundice.**

6. *Bile Salts*

Presence of bile salts in urine reveals jaundice.

7. *Blood*

Presence of blood in urine **(hematuria)** indicates glomerulonephritis, renal stones, infection or malignancy of urinary tract. Hematuria must be confirmed by microscopic examination since chemical test fails to distinguish the presence of red blood cells or hemoglobin in urine.

8. *Hemoglobin*

Hemoglobin appears in urine **(hemoglobinuria)** during excess hemolysis.

9. *Nitrite*

Presence of nitrite in urine indicates presence of bacteria in urine since some bacteria convert nitrate into nitrite in urine.

■ EXAMINATION OF BLOOD

1. *Estimation of Plasma Proteins*

Normal values of plasma proteins:

Total proteins	:	7.3 g/dL (6.4 to 8.3 g/dL)
Serum albumin	:	4.7 g/dL
Serum globulin	:	2.3 g/dL
Fibrinogen	:	0.3 g/dL

Level of plasma proteins is altered during renal failure.

2. *Estimation of Urea, Uric Acid and Creatinine*

Normal values :

Urea	:	25 to 40 mg/dL
Uric acid	:	2.5 mg/dL
Creatinine	:	0.5 to 1.5 mg/dL

The blood level of these substances increases in renal failure.

■ EXAMINATION OF BLOOD AND URINE

Plasma Clearance

Plasma clearance is defined as the amount of plasma that is cleared off a substance in a given unit of time. It is also known as renal clearance. It is based on Fick principle.

Determination of clearance value for certain substances helps in assessing the following renal functions:

1. Glomerular filtration rate
2. Renal plasma flow
3. Renal blood flow.

Value of following factors is required to determine the plasma clearance of a particular substance:

1. Volume of urine excreted
2. Concentration of the substance in urine
3. Concentration of the substance in blood.

Formula to calculate clearance value

$$C = \frac{U\,V}{P}$$

Where, C = Clearance
U = Concentration of the substance in urine
V = Volume of urine flow
P = Concentration of the substance in plasma.

1. *Measurement of Glomerular Filtration Rate*

A substance that is completely filtered but neither reabsorbed nor secreted should be used to measure glomerular filtration rate (GFR). Inulin is the ideal substance used to measure GFR. It is completely filtered and neither reabsorbed nor secreted. So, inulin clearance indicates GFR.

Inulin clearance

A known amount of inulin is injected into the body. After sometime, the concentration of inulin in plasma and urine and the volume of urine excreted are estimated.

For example,

Concentration of inulin in urine	=	125 mg/dL
Concentration of inulin in plasma	=	1 mg/dL
Volume of urine output	=	1 mL/min

Thus,

$$\text{Glomerular filtration rate} = \frac{U\ V}{P} = \frac{125 \times 1}{1}$$

$$= 125 \text{ mL/min}$$

Creatinine clearance is also used to measure GFR accurately. It is easier than inulin clearance, because, creatinine is already present in body fluids and its plasma concentration is steady throughout the day. It is completely filtered and being a metabolite it is neither reabsorbed nor secreted. The normal value of GFR by this method is approximately the same as determined by inulin clearance.

2. *Measurement of Renal Plasma Flow*

To measure renal plasma flow, a substance, which is filtered and secreted but not reabsorbed, should be used. Such a substance is **para-aminohippuric acid** (PAH). PAH clearance indicates the amount of plasma passed through kidneys.

A known amount of PAH is injected into the body. After sometime, the concentration of PAH in plasma and urine and the volume of urine excreted are estimated.

For example,

Concentration of PAH in urine = 66 mg/dL
Concentration of PAH in plasma = 0.1 mg/dL
Volume of urine output = 1 mL/min

Thus,

$$\text{Renal plasma flow} = \frac{U\ V}{P}$$

$$= \frac{66 \times 1}{0.1}$$

$$= 660 \text{ mL/min}$$

Diodrast clearance also can be used to measure this.

3. *Measurement of Renal Blood Flow*

Values of factors necessary to determine renal blood flow are:

i. Renal plasma flow
ii. Percentage of plasma volume in blood.

i. *Renal plasma flow*

Renal plasma flow is measured by using PAH clearance.

ii. *Percentage of plasma volume in blood*

Percentage of plasma volume is indirectly determined by using packed cell volume (PCV).

For example,

If PCV = 45%

Plasma volume in the blood = 100 – 45 = 55%

That is 55 mL of plasma is present in every 100 mL of blood.

Calculation of renal blood blow

Renal blood flow is calculated with the values of renal plasma volume and percentage of plasma in blood by using a formula given below.

$$\text{Renal blood flow} = \frac{\text{Renal plasma flow}}{\text{\% of plasma in blood}}$$

For example,

Renal plasma flow = 660 mL/min

Amount of plasma in blood = 55%

$$\text{Renal blood flow} = \frac{660}{55/100}$$

$$= 1{,}200 \text{ mL/min}$$

Urea Clearance Test

Urea clearance test is a clinical test to assess renal function by using clearance of urea from plasma by kidney every minute. This test requires a blood sample to determine urea level in blood and two urine sample collected at 1 hour interval to determine the urea cleared by kidneys into urine. Normal value of urea clearance is 70 mL/min.

Urea is a waste product formed during protein metabolism and excreted in urine. So, determination of urea clearance forms a specific test to assess renal function.

Renal Failure

Chapter 34

INTRODUCTION

Renal failure refers to failure of excretory functions of kidney. It is usually, characterized by decrease in glomerular filtration rate (GFR). So GFR is considered as the best index of renal failure. However, decrease in GFR is not affected much during the initial stages of renal failure. If 50% of the nephrons are affected, GFR decreases only by 20% to 30%. It is because of the compensatory mechanism by the unaffected nephrons. The renal failure may be either acute or chronic.

Renal failure is always accompanied by other complications such as:

1. Deficiency of calcitriol (activated vitamin D) resulting in reduction of calcium absorption from intestine and hypocalcemia. Deficiency of cal-citriol and hypocalcemia may cause secondary hyperparathyroidism in some patients
2. Deficiency of erythropoietin resulting in anemia
3. Disturbances in acid-base balance.

ACUTE RENAL FAILURE

Acute renal failure is the abrupt or sudden stoppage of renal functions. It is often reversible within few days to few weeks. Acute renal failure may result in sudden **life-threatening reactions** in the body with the need for emergency treatment.

CAUSES

1. Acute **nephritis** (inflammation of kidneys), which usually develops by immune reaction
2. Damage of renal tissues by poisons like lead, mercury and carbon tetrachloride
3. **Renal ischemia,** which develops during circulatory shock
4. Acute **tubular necrosis** (necrosis of tubular cells in kidney) caused by burns, hemorrhage, snake bite, toxins (like insecticides, heavy metals and carbon tetrachloride) and drugs (like diuretics, aminoglycosides and platinum derivatives)
5. Severe **transfusion reactions**
6. Sudden fall in blood pressure during hemorrhage, diarrhea, severe burns and cholera
7. Blockage of ureter due to the formation of calculi (renal stone) or tumor.

FEATURES

1. **Oliguria** (decreased urinary output)
2. **Anuria** (cessation of urine formation) in severe cases
3. **Proteinuria** (appearance of proteins in urine) including albuminuria (excretion of albumin in urine)
4. **Hematuria** (presence of blood in urine)

5. **Edema** due to increased volume of extracellular fluid (ECF) caused by retention of sodium and water
6. **Hypertension** within few days because of increased ECF volume
7. **Acidosis** due to the retention of metabolic end products
8. **Coma** due to severe acidosis (if the patient is not treated in time) resulting in death within 10 to 14 days.

CHRONIC RENAL FAILURE

Chronic renal failure is the progressive, long standing and irreversible impairment of renal functions.

When some of the nephrons loose the function, the unaffected nephrons can compensate it. However, when more and more nephrons start losing the function over the months or years, the compensatory mechanism fails and chronic renal failure develops.

CAUSES

1. Chronic nephritis
2. Polycystic kidney disease
3. Renal calculi (kidney stones)
4. Urethral constriction
5. Hypertension
6. Atherosclerosis
7. Tuberculosis
8. Slow poisoning by drugs or metals.

FEATURES

1. *Uremia*

Uremia is the condition characterized by excess accumulation of end products of protein metabolism such as urea, nitrogen and creatinine in blood. There is also accumulation of some toxic substances like organic acids and phenols. Uremia occurs because of the failure of kidney to excrete the metabolic end products and toxic substances.

Common features of uremia

i. Anorexia (loss of appetite)
ii. Lethargy
iii. Drowsiness
iv. Nausea and vomiting
v. Pigmentation of skin
vi. Muscular twitching, tetany and convulsion
vii. Confusion and mental deterioration
viii. Coma.

2. *Acidosis*

Uremia results in acidosis, which leads to coma and death.

3. *Edema*

Failure of kidney to excrete sodium and electrolytes causes increase in extracellular fluid volume resulting in development of edema.

4. *Blood Loss*

Gastrointestinal bleeding accompanied by platelet dysfunction leads to heavy loss of blood.

5. *Anemia*

Since, erythropoietin is not secreted in the kidney during renal failure, the production of RBC decreases resulting in normocytic normochromic anemia.

6. *Hyperparathyroidism*

Secondary hyperparathyroidism is developed due to the deficiency of calcitriol (1,25-dihydroxycholecalciferol). It increases the removal of calcium from bones resulting in **osteomalacia.**

Parathyroid Glands and Physiology of Bone

Chapter 35

- INTRODUCTION
- PARATHORMONE
  - ACTIONS OF PARATHORMONE
  - ACTIONS ON BLOOD CALCIUM LEVEL
  - ACTIONS ON BLOOD PHOSPHATE LEVEL
  - MODE OF ACTION
  - REGULATION OF SECRETION
- APPLIED PHYSIOLOGY – DISORDERS OF PARATHYROID GLANDS
  - HYPOPARATHYROIDISM – HYPOCALCEMIA
  - HYPERPARATHYROIDISM – HYPERCALCEMIA
  - PARATHYROID FUNCTION TESTS
- CALCITONIN
  - ACTIONS
  - REGULATION OF SECRETION
- CALCIUM METABOLISM
  - IMPORTANCE OF CALCIUM
  - NORMAL VALUE
  - TYPES OF CALCIUM
  - SOURCE OF CALCIUM
  - DAILY REQUIREMENTS
  - ABSORPTION AND EXCRETION
  - REGULATION OF BLOOD CALCIUM LEVEL
- PHOSPHATE METABOLISM
  - IMPORTANCE OF PHOSPHATE
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  - REGULATION OF PHOSPHATE LEVEL
- PHYSIOLOGY OF BONE
  - FUNCTIONS
  - CLASSIFICATION
  - PARTS
  - COMPOSITION
  - STRUCTURE
  - TYPES OF CELLS IN BONE
  - BONE GROWTH
  - BONE REMODELING
  - REPAIR OF BONE AFTER FRACTURE
  - APPLIED PHYSIOLOGY – DISEASES OF BONE

■ INTRODUCTION

Human beings have four parathyroid glands, which are situated on the posterior surface of upper and lower poles of thyroid gland (Fig. 68.1). Parathyroid glands are very small in size, measuring about 6 mm long, 3 mm wide and 2 mm thick, with dark brown color.

Histology

Each parathyroid gland is made up of **chief cells** and **oxyphil cells.** Chief cells secrete parathormone. Oxyphil cells are the degenerated chief cells and their function is known. However, these cells may secrete parathormone during pathological condition called **parathyroid adenoma.** The number of oxyphil cells increases after puberty.

■ PARATHORMONE

Parathormone secreted by parathyroid gland is essential for the maintenance of blood calcium level within a very narrow critical level. Maintenance of blood calcium level is necessary because calcium is an important inorganic ion for many physiological functions (see below).

Source of Secretion

Parathormone (PTH) is secreted by the chief cells of the parathyroid glands.

Chemistry

Parathormone is protein in nature, having 84 amino acids. Its molecular weight is 9,500.

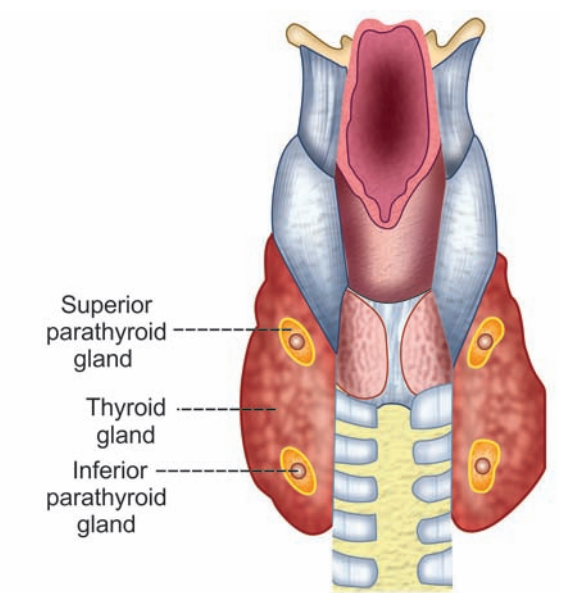

FIGURE 68.1: Parathyroid glands on the posterior surface of thyroid gland

Half-life and Plasma Level

Parathormone has a half-life of 10 minutes. Normal plasma level of PTH is about 1.5 to 5.5 ng/dL.

Synthesis

Parathormone is synthesized from the precursor called **prepro-PTH** containing 115 amino acids. First, the prepro-PTH enters the endoplasmic reticulum of chief cells of parathyroid glands. There it is converted into a prohormone called **pro-PTH,** which contains 96 amino acids. Pro-PTH enters the Golgi apparatus, where it is converted into PTH.

Metabolism

Sixty to seventy percent of PTH is degraded by **Kupffer cells** of liver, by means of proteolysis. Degradation of about 20% to 30% PTH occurs in kidneys and to a lesser extent in other organs.

■ ACTIONS OF PARATHORMONE

PTH plays an important role in maintaining blood calcium level. It also controls blood phosphate level.

■ ACTIONS OF PARATHORMONE ON BLOOD CALCIUM LEVEL

Primary action of PTH is to maintain the blood calcium level within the critical range of 9 to 11 mg/dL. The blood calcium level has to be maintained critically because, it is very important for many of the activities in the body.

PTH maintains blood calcium level by acting on:

1. Bones
2. Kidney
3. Gastrointestinal tract.

1. On Bone

Parathormone enhances the resorption of calcium from the bones **(osteoclastic activity)** by acting on **osteoblasts** and **osteoclasts** of the bone.

Resorption of calcium from bones occurs in two phases:

i. Rapid phase
ii. Slow phase.

Rapid phase

Rapid phase occurs within minutes after the release of PTH from parathyroid glands. Immediately after reaching the bone, PTH gets attached with the receptors on the cell membrane of osteoblasts and osteocytes. The hormone-receptor complex increases the permeability of membranes of these cells for calcium ions. It accelerates

the calcium pump mechanism, so that calcium ions move out of these bone cells and enter the blood at a faster rate.

Slow phase

Slow phase of calcium resorption from bone is due to the activation of osteoclasts by PTH. When osteoclasts are activated, some substances such as proteolytic enzymes, citric acid and lactic acid are released from lysosomes of these cells. All these substances digest or dissolve the organic matrix of the bone, releasing the calcium ions. The calcium ions slowly enter the blood.

PTH increases calcium resorption from bone by stimulating the proliferation of osteoclasts also.

2. *On Kidney*

PTH increases the reabsorption of calcium from the renal tubules along with magnesium ions and hydrogen ions. It increases calcium reabsorption mainly from distal convoluted tubule and proximal part of collecting duct.

PTH also increases the formation of **1,25-dihydroxycholecalciferol** (activated form of vitamin D) from 25-hydroxycholecalciferol in kidneys (see below).

3. *On Gastrointestinal Tract*

PTH increases the absorption of calcium ions from the GI tract indirectly. It increases the formation of 1,25-dihydroxycholecalciferol in the kidneys. This vitamin, in turn increases the absorption of calcium from GI tract.

Thus, the activated vitamin D is very essential for the absorption of calcium from the GI tract. And PTH is essential for the formation of activated vitamin D.

Role of PTH in the activation of vitamin D

Vitamin D is very essential for calcium absorption from the GI tract. But vitamin D itself is not an active substance. Instead, vitamin D has to be converted into 1, 25-dihydroxycholecalciferol in the liver and kidney in the presence of PTH. The 1,25-dihydroxycholecalciferol is the active product.

Activation of vitamin D

There are various forms of vitamin D. But, the most important one is vitamin D3. It is also known as cholecalciferol. Vitamin D3 is synthesized in the skin from 7-dehydrocholesterol, by the action of **ultraviolet rays** from the **sunlight.** It is also obtained from dietary sources.

The activation of vitamin D3 occurs in two steps (Fig. 68.2).

First step

Cholecalciferol (vitamin D3) is converted into 25-hydroxycholecalciferol in the liver. This process is limited and is inhibited by 25-hydroxycholecalciferol itself by feedback mechanism. This inhibition is essential for two reasons:

i. Regulation of the amount of active vitamin D
ii. Storage of vitamin D for months together.

If vitamin D3 is converted into 25-hydroxycholecalciferol, it remains in the body only for 2 to 5 days. But vitamin D3 is stored in liver for several months.

Second step

25-hydroxycholecalciferol is converted into 1,25-dihydroxycholecalciferol **(calcitriol)** in kidney. It is the active form of vitamin D3. This step needs the presence of PTH.

Role of Calcium Ion in Regulating 1, 25-Dihydroxycholecalciferol

When blood calcium level increases, it inhibits the formation of 1,25-dihydroxycholecalciferol. The mechanism involved in the inhibition of the formation of 1,25-dihydroxycholecalciferol is as follows:

i. Increase in calcium ion concentration directly suppresses the conversion of 25-hydroxycholecalciferol into 1,25-dihydroxycholecalciferol. This effect is very mild

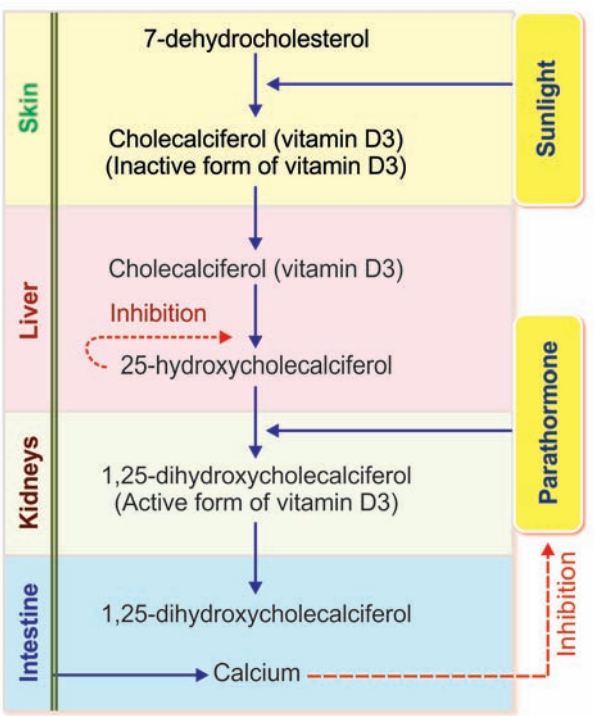

FIGURE 68.2: Schematic diagram showing activation of vitamin D

ii. Increase in calcium ion concentration decreases the PTH secretion, which in turn suppresses the conversion of 25-hydroxycholecalciferol into 1,25-dihydroxycholecalciferol.

This regulates the calcium ion concentration of plasma itself indirectly, i.e. when the PTH synthesis is inhibited, the conversion of 25-hydroxycholecalciferol into 1,25-hydroxycholecalciferol is also inhibited. Lack of 1,25-dihydroxycholecalciferol, decreases the absorption of calcium ions from the intestine, from the bones and from the renal tubules as well. This makes the calcium level in the plasma to fall back to normal.

Actions of 1, 25-Dihydroxycholecalciferol

1. It increases the absorption of calcium from the intestine, by increasing the formation of calcium-binding proteins in the intestinal epithelial cells. These proteins act as carrier proteins for facilitated diffusion, by which the calcium ions are transported. The proteins remain in the cells for several weeks after 1,25-dihydroxycholecalciferol has been removed from the body, thus causing a prolonged effect on calcium absorption
2. It increases the synthesis of calcium-induced ATPase in the intestinal epithelium
3. It increases the synthesis of alkaline phophatase in the intestinal epithelium
4. It increases the absorption of phosphate from intestine along with calcium.

■ ACTIONS OF PARATHORMONE ON BLOOD PHOSPHATE LEVEL

PTH decreases blood level of phosphate by increasing its urinary excretion. It also acts on bone and GI tract.

1. *On Bone*

Along with calcium resorption, PTH also increases phosphate absorption from the bones.

2. *On Kidney*

Phosphaturic action

It is the effect of PTH by which phosphate is excreted through urine. PTH increases phosphate excretion by inhibiting reabsorption of phosphate from renal tubules. It acts mainly on proximal convoluted tubule.

3. *On Gastrointestinal Tract*

Parathormone increases the absorption of phosphate from GI tract through calcitriol.

Sequence of events

i. PTH converts 25-hydroxycholecalciferol into 1,25-dihydroxycholecalciferol (calcitriol: active form of vitamin D3) in kidney
ii. Calcitriol increases the synthesis of calcium induced ATPase in the intestinal epithelium
iii. ATPase increases the synthesis of alkaline phophatase
iv. Alkaline phosphatase increases the absorption of phosphate from intestine along with calcium.

■ MODE OF ACTION OF PARATHORMONE

Parathormone Receptors

Parathormone receptors (PTH receptors) are of three types, PTHR1, PTHR2 and PTHR3, which are G protein-coupled receptors. PTHR1 is physiologically more important than the other two types. PTHR1 mediates the actions of PTH and **PTH-related protein** (see below). Role of PTHR2 and PTHR3 is not known clearly.

On the target cells, PTH binds with PTHR1 which is coupled to G protein and forms hormone-receptor complex. Hormone-receptor complex causes formation of cAMP, which acts as a second messenger for the hormone.

■ REGULATION OF PARATHORMONE SECRETION

Blood level of calcium is the main factor regulating the secretion of PTH. Blood phosphate level also regulates PTH secretion.

Blood Level of Calcium

Parathormone secretion is inversely proportional to blood calcium level. Increase in blood calcium level decreases PTH secretion.

Conditions when PTH secretion decreases are:

1. Excess quantities of calcium in the diet
2. Increased vitamin D in the diet
3. Increased resorption of calcium from the bones, caused by some other factors such as bone diseases.

On the other hand, decrease in calcium ion concentration of blood increases PTH secretion, as in the case of rickets, pregnancy and in lactation.

Blood Level of Phosphate

PTH secretion is directly proportional to blood phosphate level. Whenever the blood level of phosphate increases,

it combines with ionized calcium to form calcium hydrogen phosphate. This decreases ionized calcium level in blood which stimulates PTH secretion.

■ APPLIED PHYSIOLOGY – DISORDERS OF PARATHYROID GLANDS

Disorders of parathyroid glands are of two types:

I. Hypoparathyroidism
II. Hyperparathyroidism.

■ HYPOPARATHYROIDISM – HYPOCALCEMIA

Hyposecretion of PTH is called hypoparathyroidism. It leads to hypocalcemia (decrease in blood calcium level).

Causes for Hypoparathyroidism

1. Surgical removal of parathyroid glands **(parathyroidectomy)**
2. Removal of parathyroid glands during surgical removal of thyroid gland **(thyroidectomy)**
3. Autoimmune disease
4. Deficiency of receptors for PTH in the target cells. In this, the PTH secretion is normal or increased but the hormone cannot act on the target cells. This condition is called **pseudohypoparathyroidism.**

Hypocalcemia and Tetany

Hypoparathyroidism leads to hypocalcemia, by decreasing the resorption of calcium from bones. Hypocalcemia causes neuromuscular hyperexcitability, resulting in hypocalcemic tetany. Normally, tetany occurs when plasma calcium level falls below 6 mg/dL from its normal value of 9.4 mg/dL.

Hypocalcemic Tetany

Tetany is an abnormal condition characterized by violent and painful **muscular spasm** (spasm = involuntary muscular contraction), particularly in feet and hand. It is because of hyperexcitability of nerves and skeletal muscles due to calcium deficiency.

Signs and symptoms of hypocalcemic tetany:

1. *Hyper-reflexia and convulsions*

Increase in neural excitability results in hyper-reflexia (overactive reflex actions) and convulsive muscular contractions.

2. *Carpopedal spasm*

Carpopedal spasm is the spasm in hand and feet that occurs in hypocalcemic tetany. During spasm, the hand shows a peculiar attitude (Fig. 68.3).

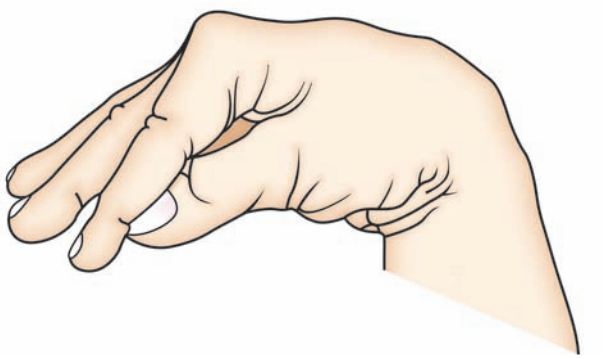

FIGURE 68.3: Carpopedal spasm

Attitude of hand in carpopedal spasm includes:

i. Flexion at wrist joint
ii. Flexion at metacarpophalangeal joints
iii. Extension at interphalangeal joints
iv. Adduction of thumb.

3. *Laryngeal stridor*

Stridor means noisy breathing. Laryngeal stridor means a loud crowing sound during inspiration, which occurs mainly due to **laryngospasm** (involuntary contraction of laryngeal muscles). Laryngeal stridor is a common dangerous feature of hypocalcemic tetany.

4. *Cardiovascular changes*

i. Dilatation of the heart
ii. Prolonged duration of ST segment and QT interval in ECG
iii. Arrhythmias (irregular heartbeat)
iv. Hypotension
v. Heart failure.

5. *Other features*

i. Decreased permeability of the cell membrane
ii. Dry skin with brittle nails
iii. Hair loss
iv. Grand mal, petit mal or other seizures (Chapter 161)
v. Signs of mental retardation in children or dementia in adults.

When the calcium level falls below 4 mg/dL, it becomes fatal. During such severe hypocalcemic conditions, tetany occurs so quickly that a person develops spasm of different groups of muscles in the body. Worst affected are the laryngeal and bronchial muscles which develop respiratory arrest, resulting in death.

Latent Tetany

Latent tetany, also known as **subclinical tetany** is the **neuromuscular hyperexcitability** due to hypocalcemia

that develops before the onset of tetany. It is characterized by general weakness and cramps in feet and hand. Hyperexcitability in these patients is detected by some signs, which do not appear in normal persons.

1. *Trousseau sign*

Trousseau sign is the spasm of the hand that is developed after 3 minutes of arresting the blood flow to lower arm and hand. The blood flow to lower arm and hand is arrested by inflating the blood pressure cuff 20 mm Hg above the patient's systolic pressure.

2. *Chvostek sign*

Chvostek sign is the twitch of the facial muscles, caused by a gentle tap over the facial nerve in front of the ear. It is due to the hyperirritability of facial nerve.

3. *Erb sign*

Hyperexcitability of the skeletal muscles even to a mild electrical stimulus is called Erb sign. It is also called **Erb-Westphal sign.**

■ HYPERPARATHYROIDISM – HYPERCALCEMIA

Hypersecretion of PTH is called hyperparathyroidism. It results in hypercalcemia. Hyperparathyroidism is of three types:

1. Primary hyperparathyroidism

Primary hyperparathyroidism is due to the development of tumor in one or more parathyroid glands. Sometimes, tumor may develop in all the four glands.

2. *Secondary hyperparathyroidism*

Secondary hyperparathyroidism is due to the physiological compensatory hypertrophy of parathyroid glands, in response to hypocalcemia which occurs due to other pathological conditions such as:

i. Chronic renal failure
ii. Vitamin D deficiency
iii. Rickets.

3. *Tertiary hyperparathyroidism*

Tertiary hyperparathyroidism is due to **hyperplasia** (abnormal increase in the number of cells) of all the parathyroid glands that develops due to chronic secondary hyperparathyroidism.

Hypercalcemia

Hypercalcemia is the increase in plasma calcium level. It occurs in hyperparathyroidism because of increased resorption of calcium from bones.

Signs and symptoms of hypercalcemia

i. Depression of the nervous system
ii. Sluggishness of reflex activities
iii. Reduced ST segment and QT interval in ECG
iv. Lack of appetite
v. Constipation.

Depressive effects of hypercalcemia are noticed when the blood calcium level increases to 12 mg/dL. The condition becomes severe with 15 mg/dL and it becomes lethal when blood calcium level reaches 17 mg/dL.

Other effects of hypercalcemia:

i. Development of bone diseases such as osteitis fibrosa cystica
ii. Development of parathyroid poisoning. It is the condition characterized by severe manifestations that occur when blood calcium level rises above 15 mg/dL. In hyperparathyroidism, the concentration of both calcium and phosphate increases leading to formation of calcium-phosphate crystals. Concentration of phosphate also increases because, kidney cannot excrete the excess amount of phosphate resorbed from the bone
iii. Deposition of **calcium-phosphate crystals** in renal tubules, thyroid gland, alveoli of lungs, gastric mucosa and in the wall of the arteries, resulting in dysfunction of these organs. **Renal stones** are formed when it is deposited in kidney.

■ PARATHYROID FUNCTION TESTS

1. Measurement of blood calcium level
2. Chvostek sign and Trousseau sign for hypoparathyroidism.

■ CALCITONIN

Source of Secretion

Calcitonin is secreted by the **parafollicular cells** or **clear cells (C cells),** situated amongst the follicles in thyroid gland. In lower animals, the parafollicular cells are derived from ultimobranchial glands, which develop from fifth pharyngeal pouches. In human being, the ultimobranchial glands and fifth pharyngeal pouches are rudimentary and their cells are incorporated with fourth pharyngeal pouches and distributed amongst the follicles of thyroid gland.

Recently, calcitonin is found in brain, prostate and bronchial cells of lungs. However, the physiological role of calcitonin from non-thyroid tissues is not known.

Chemistry and Synthesis

Calcitonin is a polypeptide chain with 32 amino acids. Its molecular weight is about 3,400. It is synthesized from procalcitonin.

Plasma Level and Half-life

Plasma level of calcitonin is 1 to 2 ng/dL. It has a half-life of 5 to 10 minutes.

Metabolism

Calcitonin is degraded and excreted by liver and kidney.

■ ACTIONS OF CALCITONIN

1. *On Blood Calcium Level*

Calcitonin plays an important role in controlling the blood calcium level. It decreases the blood calcium level and thereby counteracts parathormone.

Calcitonin reduces the blood calcium level by acting on bones, kidneys and intestine.

i. *On bones*

Calcitonin stimulates **osteoblastic activity** and facilitates the deposition of calcium on bones. At the same time, it suppresses the activity of **osteoclasts** and inhibits the resorption of calcium from bones. It inhibits even the development of new osteoclasts in bones.

ii. On kidney

Calcitonin increases excretion of calcium through urine, by inhibiting the reabsorption from the renal tubules.

iii. *On intestine*

Calcitonin prevents the absorption of calcium from intestine into the blood.

2. *On Blood Phosphate Level*

With respect to calcium, calcitonin is an antagonist to PTH. But it has similar actions of PTH, with respect to phosphate. It decreases the blood level of phosphate by acting on bones and kidneys.

i. *On bones*

Calcitonin inhibits the resorption of phosphate from bone and stimulates the deposition of phosphate on bones.

ii. *On kidney*

Calcitonin increases the excretion of phosphate through urine, by inhibiting the reabsorption from renal tubules.

■ REGULATION OF CALCITONIN SECRETION

High calcium content in plasma stimulates the calcitonin secretion through a calcium receptor in parafollicular cells. Gastrin also is known to stimulate the release of calcitonin.

■ CALCIUM METABOLISM

■ IMPORTANCE OF CALCIUM

Calcium is very essential for many activities in the body such as:

1. Bone and teeth formation
2. Neuronal activity
3. Skeletal muscle activity
4. Cardiac activity
5. Smooth muscle activity
6. Secretory activity of the glands
7. Cell division and growth
8. Coagulation of blood.

■ NORMAL VALUE

In a normal young healthy adult, there is about 1,100 g of calcium in the body. It forms about 1.5% of total body weight. 99% of calcium is present in the bones and teeth and the rest is present in the plasma. Normal blood calcium level ranges between 9 and 11 mg/dL.

■ TYPES OF CALCIUM

Calcium in Plasma

Calcium is present in three forms in plasma:

i. Ionized or diffusible calcium: Found freely in plasma and forms about 50% of plasma calcium. It is essential for vital functions such as neuronal activity, muscle contraction, cardiac activity, secretions in the glands, blood coagulation, etc.

ii. Non-ionized or non-diffusible calcium: Present in non-ionic form such as calcium bicarbonate. It is about 8% to 10% of plasma calcium

iii. Calcium bound to albumin: Forms about 40% to 42% of plasma calcium.

Calcium in Bones

Calcium is constantly removed from bone and deposited in bone. Bone calcium is present in two forms:

i. Rapidly exchangeable calcium or exchangeable calcium: Available in small quantity in bone and helps to maintain the plasma calcium level

ii. Slowly exchangeable calcium or stable calcium: Available in large quantity in bones and helps in bone remodeling.

Process of calcium metabolism is explained schematically in Fig. 68.4.

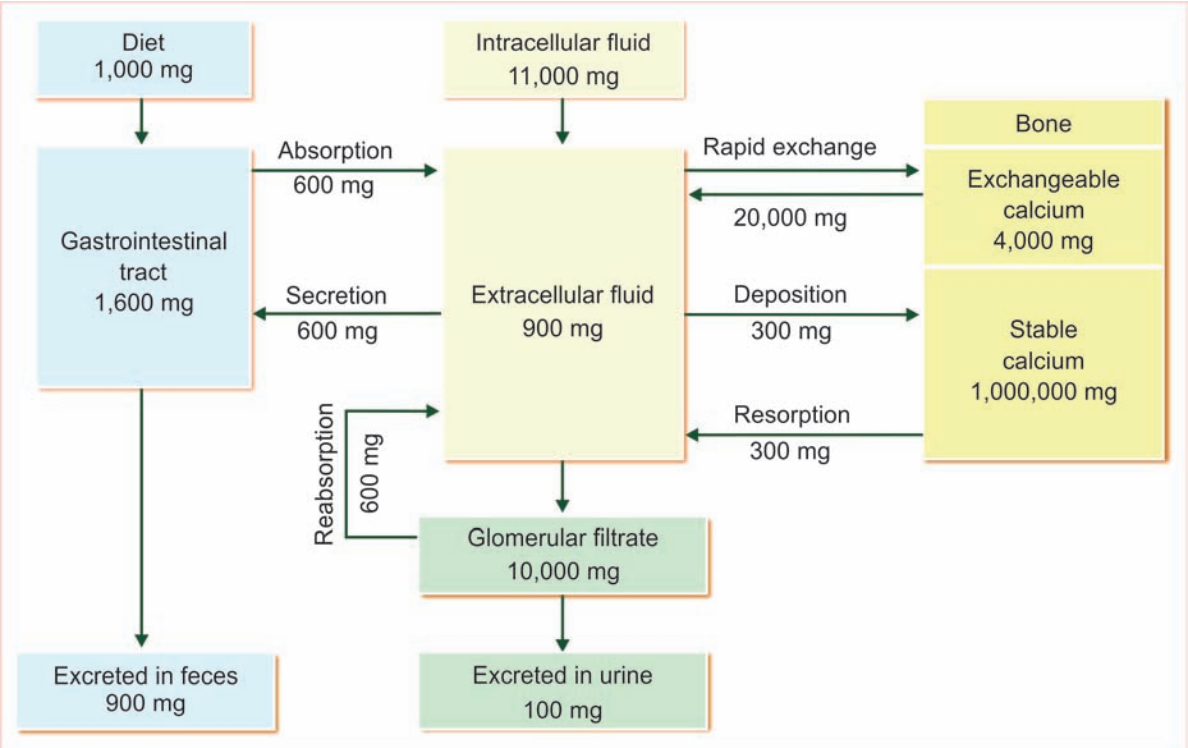

FIGURE 68.4: Schematic diagram showing calcium metabolism. Values belong to adults

■ SOURCE OF CALCIUM

1. *Dietary Source*

Calcium is available in several foodstuffs. Percentage of calcium in different food substance is:

Whole milk	= 10%
Low fat milk	= 18%
Cheese	= 27%
Other dairy products	= 17%
Vegetables	= 7%
Other substances such as meat, egg, grains, sugar, coffee, tea, chocolate, etc.	= 21%

2. *From Bones*

Besides dietary calcium, blood also gets calcium from bone by resorption.

■ DAILY REQUIREMENTS OF CALCIUM

1 to 3 years	= 500 mg
4 to 8 years	= 800 mg
9 to 18 years	= 1,300 mg
19 to 50 years	= 1,000 mg
51 years and above	= 1,200 mg
Pregnant ladies and lactating mothers	= 1,300 mg

■ ABSORPTION AND EXCRETION OF CALCIUM

Calcium taken through dietary sources is absorbed from GI tract into blood and distributed to various parts of the body. Depending upon the blood level, the calcium is either deposited in the bone or removed from the bone (resorption). Calcium is excreted from the body through urine and feces.

Absorption from Gastrointestinal Tract

Calcium is absorbed from duodenum by carrier-mediated active transport and from the rest of the small intestine, by facilitated diffusion. Vitamin D is essential for the absorption of calcium from GI tract.

Excretion

While passing through the kidney, large quantity of calcium is filtered in the glomerulus. From the filtrate, 98% to 99% of calcium is reabsorbed from renal tubules into the blood. Only a small quantity is excreted through urine.

Most of the filtered calcium is reabsorbed in the distal convoluted tubules and proximal part of collecting duct. In distal convoluted tubule, parathormone increases the reabsorption. In collecting duct, vitamin D increases the reabsorption and calcitonin decreases reabsorption.

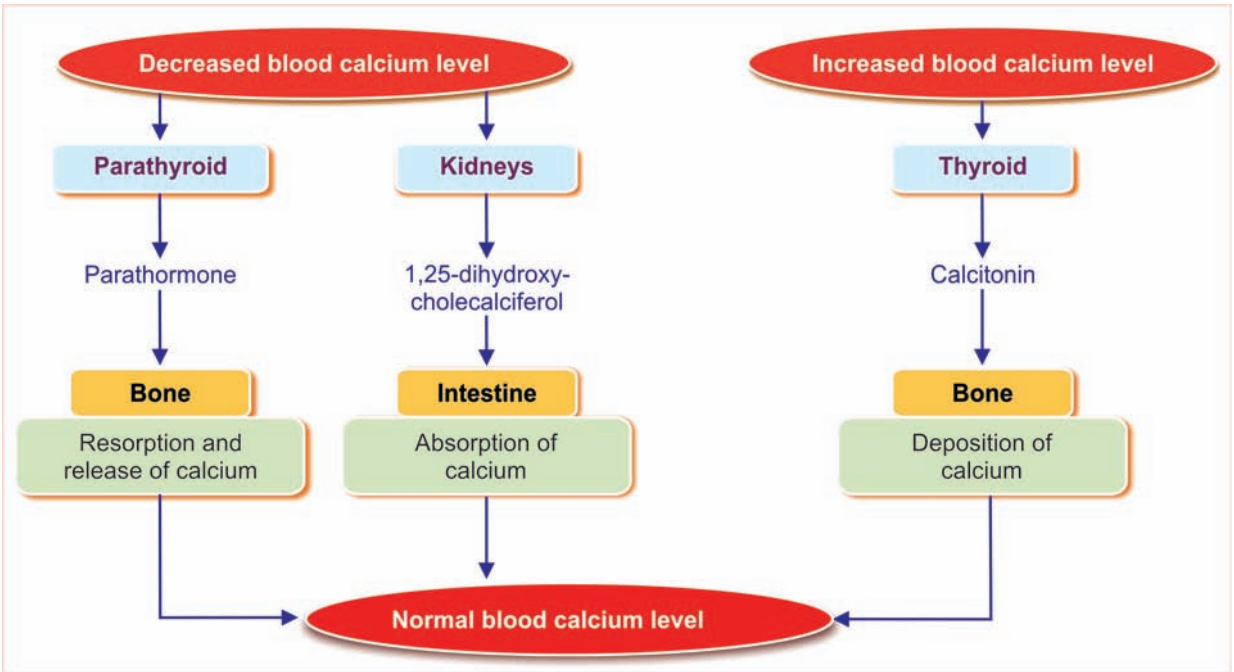

FIGURE 68.5: Schematic diagram showing regulation of blood calcium level

About 1,000 mg of calcium is excreted daily. Out of this, 900 mg is excreted through feces and 100 mg through urine.

■ REGULATION OF BLOOD CALCIUM LEVEL

Blood calcium level is regulated mainly by three hormones (Figs 68.5 and 68.6):

1. Parathormone
2. 1,25-dihydroxycholecalciferol (calcitriol)
3. Calcitonin.

1. *Parathormone*

Parathormone is a protein hormone secreted by parathyroid gland and its main function is to increase the blood calcium level by mobilizing calcium from bone (resorption) (See above for details).

2. *1,25-dihydroxycholecalciferol – Calcitriol*

Calcitriol is a steroid hormone synthesized in kidney. It is the activated form of vitamin D. Its main action is to increase the blood calcium level by increasing the calcium absorption from the small intestine (see above for details).

3. *Calcitonin*

Calcitonin secreted by parafollicular cells of thyroid gland. Thyroid gland is a calcium-lowering hormone. It reduces the blood calcium level mainly by decreasing bone resorption (see above for details).

Effects of Other Hormones

In addition to the above mentioned three hormones, growth hormone and glucocorticoids also influence the calcium level.

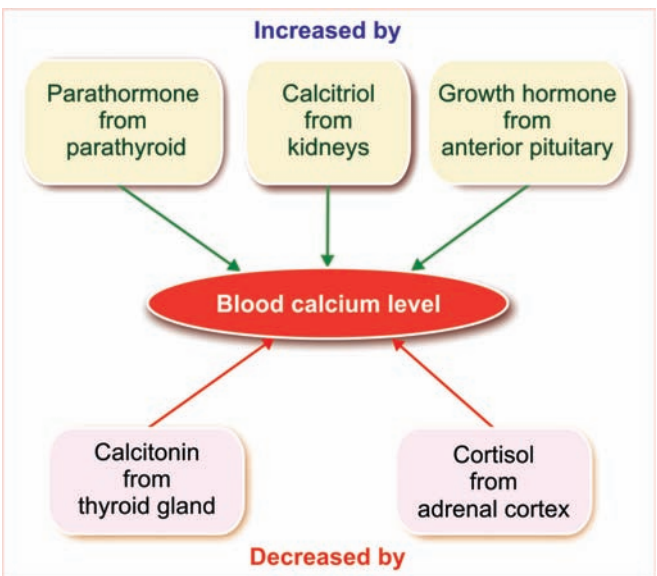

FIGURE 68.6: Effect of hormones on blood calcium level

1. *Growth hormone*

Growth hormone increases the blood calcium level by increasing the intestinal calcium absorption. It is also suggested that it increases the urinary excretion of calcium. However, this action is only transient.

2. *Glucocorticoids*

Glucocorticoids (cortisol) decrease blood calcium by inhibiting intestinal absorption and increasing the renal excretion of calcium.

■ PHOSPHATE METABOLISM

Phosphorus (P) is an essential mineral that is required by every cell in the body for normal function. Phosphorus is present in many food substances, such as peas, dried beans, nuts, milk, cheese and butter. Inorganic phosphorus (Pi) is in the form of the **phosphate** (PO_4). The majority of the phosphorus in the body is found as phosphate. Phosphorus is also the body's source of phosphate. In body, phosphate is the most abundant intracellular anion.

■ IMPORTANCE OF PHOSPHATE

1. Phosphate is an important component of many organic substances such as, ATP, DNA, RNA and many intermediates of metabolic pathways
2. Along with calcium, it forms an important constituent of bone and teeth
3. It forms a buffer in the maintenance of acid-base balance.

■ NORMAL VALUE

Total amount of phosphate in the body is 500 to 800 g. Though it is present in every cell of the body, 85% to 90% of body's phosphate is found in the bones and teeth. Normal plasma level of phosphate is 4 mg/dL.

■ REGULATION OF PHOSPHATE LEVEL

Phosphorus is taken through dietary sources. It is absorbed from GI tract into blood. It is also resorbed from bone. From blood it is distributed to various parts of the body. While passing through the kidney, large quantity of phosphate is excreted through urine.

Blood phosphate level is regulated mainly by three hormones:

1. Parathormone
2. Calcitonin
3. 1,25-dihydroxycholecalciferol (calcitriol).

1. *Parathormone*

Parathormone stimulates resorption of phosphate from bone and increases its urinary excretion. It also increases the absorption of phosphate from gastrointestinal tract through calcitriol. The overall action of parathormone decreases the plasma level of phosphate.

2. *Calcitonin*

Calcitonin also decreases the plasma level of phosphate by inhibiting bone resorption and stimulating the urinary excretion.

3. *1,25-Dihydroxycholecalciferol – Calcitriol*

Calcitriol hormone increases absorption of phosphate from small intestine (Fig. 68.7).

Effects of Other Hormones

In addition to the above mentioned three hormones, growth hormone and glucocorticoids also influence the phosphate level.

1. *Growth hormone*

Growth hormone increases the blood phosphate level by increasing the intestinal phosphate absorption.

2. *Glucocorticoids*

Glucocorticoids (cortisol) decreases blood phosphate by inhibiting intestinal absorption and increasing the renal excretion of phosphate.

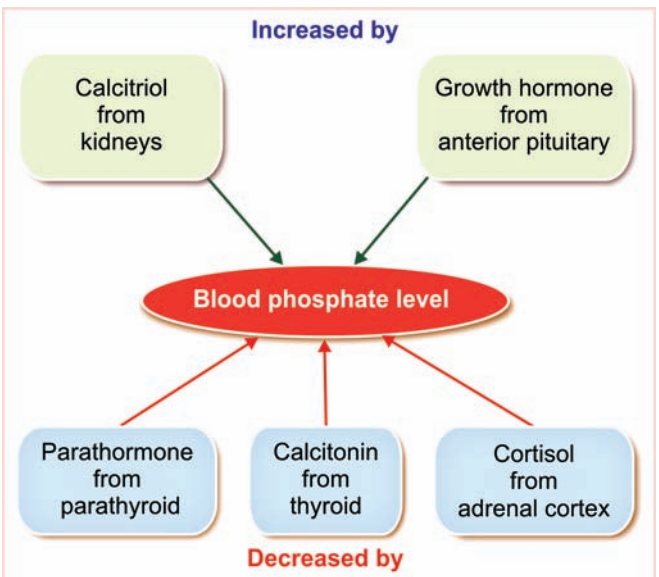

FIGURE 68.7: Effect of hormones on blood phosphate level

PHYSIOLOGY OF BONE

Bone or **osseous tissue** is a specialized rigid connective tissue that forms the skeleton. It consists of special type of cells and tough **intercellular matrix** of ground substance. The matrix is formed by organic substances like **collagen** and it is strengthened by the deposition of mineral salts like calcium phosphate and calcium carbonate. Throughout the life, bone is renewed by the process of bone formation and bone resorption.

FUNCTIONS OF BONE

1. *Protective function:* Protects soft tissues and vital organs of the body
2. *Mechanical function:* Supports the body and brings out various movements of the body by their attachment to the muscles and tendons
3. *Metabolic function:* Plays an important role in the metabolism homeostasis of calcium and phosphate in the body.
4. *Hemopoietic function:* Red bone marrow in the bones is the site of production of blood cells.

CLASSIFICATION OF BONE

Depending upon the size and shape, the bones are classified into five types:

1. Long bones: Bones of the limbs
2. Short bones: Bones in the wrist and ankle
3. Flat bones: Skull bones, mandible, scapula, etc.
4. Irregular bones: Vertebra
5. Sesamoid bones: Patella.

PARTS OF BONE

Long bones are formed by a cylindrical tube of bone tissue, which has three portions:

1. Diaphysis: Midportion or midshaft
2. Epiphysis: Wider extremity or the head on either end
3. Metaphysis: Portion between the diaphysis and the epiphysis (Fig. 68.8).

In growing age, a layer of cartilage called **epiphyseal cartilage** or **epiphyseal plate** or **growth plate** is present in between epiphysis and metaphysis. Epiphyseal plate is responsible for the longitudinal growth of the bones.

COMPOSITION OF BONE

Bone consists of the tough organic matrix to which the bone salts are deposited.

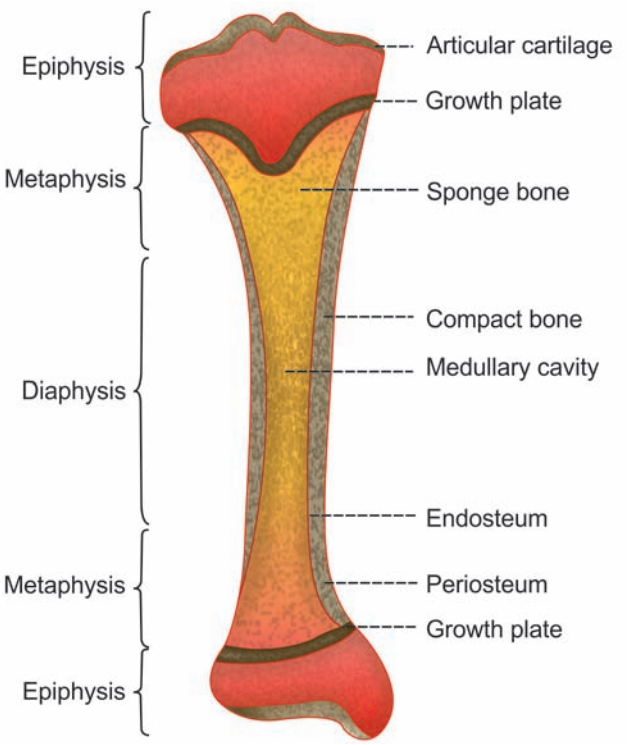

FIGURE 68.8: Parts of long bone

Matrix

Bone matrix is composed of protein fibers called **collagen fibers,** which are embedded in the gelatinous ground substance. These collagen fibers form about 90% of the bone. The ground substance is formed by ECF and **proteoglycans.** Proteoglycans are **chondroitin sulfate** and **hyaluronic acid,** which are concerned with the regulation and deposition of bone salts.

Bone Salts

The crystalline salts present in bones are called **hydroxyapatites,** which contain calcium and phosphate. Apart from these substances, some other salts like sodium, potassium, magnesium and carbonate are also present in the bone. The salts of the bone strengthen the bone matrix.

STRUCTURE OF BONE

Bone is covered by an outer white fibrous connective layer called **periosteum** and an inner dense fibrous membrane called endosteum. The tendons from the muscles are attached to periosteum. The heads (epiphysis) of bone are covered by a **hyaline cartilage.** It forms the synovial joint with adjoining bones.

Bones have two layers of structures:

1. Outer compact bone
2. Inner spongy bone.

In most of the bones, both compact and spongy forms are present. However, the thickness of each type varies in different regions. The epiphysis contains large amount of spongy bone and outer thin compact bone. In diaphysis, the amount of compact bone is more and the spongy bone is very thin.

Compact Bone

Compact or cortical bone is the hard and dense material forming about 80% of bone in the body. Its main functions are mechanical function and the protection of bone marrow.

Compact bone consists of minute cylindrical structures called **osteones** or **Haversian systems** (Fig. 68.9), which are formed by concentric layers of collagen. Collagen lamellae are called **Haversian lamellae.** In the center of each osteon, there is a canal called **Haversian canal** that contains the blood vessels, lymph vessels and nerve fibers. The Haversian systems communicate with each other by transverse canals called **Volkmann canal.**

Within the Haversian systems, there are small cavities called **lacunae,** inside which the **osteocytes** are trapped. Osteocytes send long processes called **canaliculi.** The canaliculi from neighboring osteocytes unite to form tight junctions.

Marrow cavity

Compact bone has a large narrow cavity called **marrow cavity** or medullary cavity, which contains yellow bone marrow.

Spongy Bone

Spongy or **trabecular** or **cancellous bone** forms 20% of bone in the body and it contains red bone marrow. It is made of **bone spicules,** which are separated by spaces.

■ TYPES OF CELLS IN BONE

Bone has three major types of cells:

1. Osteoblasts
2. Osteocytes
3. Osteoclasts.

1. *Osteoblasts*

Osteoblasts are the bone cells concerned with bone formation **(osteoblastic activity).** These cells are situated in the outer surface of bone, the marrow cavity and

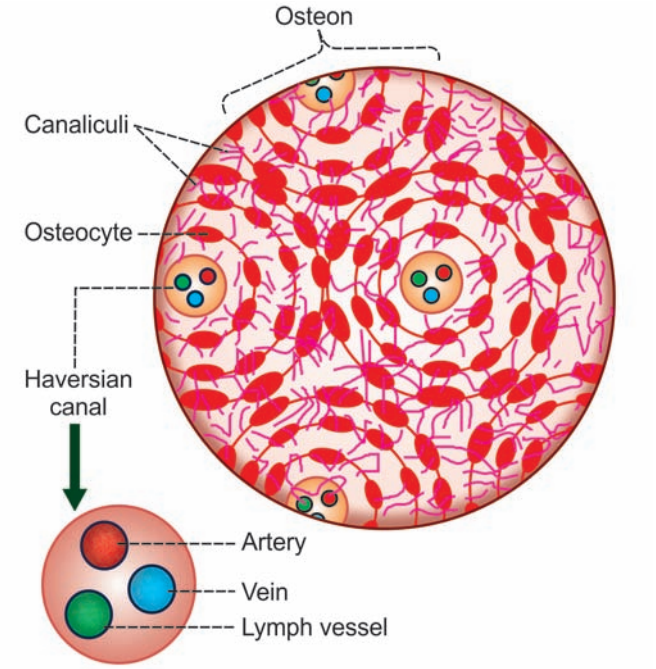

FIGURE 68.9: Structure of compact bone

epiphyseal plate. The osteoblasts arise from the giant multinucleated primitive cells called the **osteoprogenitor** cells. Differentiation of osteoprogenitor cells into osteoblasts (Table 68.1) is accelerated by some hormones and some bone proteins called **skeletal growth factors.** These growth factors stimulate the growth of osteoblasts also.

Functions of osteoblasts

i. *Role in the formation of bone matrix*

Osteoblasts are responsible for the synthesis of bone matrix by secreting type I collagen and a protein called **matrix gla protein** (MGP) or **osteocalcin.** Other proteins involved in the matrix synthesis are also produced by the osteoblasts. Such proteins are transforming growth factor (TGF), insulin-like growth factor (IGF), fibroblast growth factor (FGF) and platelet-derived growth factor (PDGF).

ii. *Role in calcification*

Osteoblasts are rich in enzyme alkaline phosphatase, which is necessary for deposition of calcium in the bone matrix **(calcification).**

iii. *Synthesis of proteins*

Osteoblasts synthesize the proteins called matrix gla protein and osteopontin, which are involved in the calcification.

Fate of osteoblasts

After taking part in bone formation, the osteoblasts differentiate into osteocytes, which are trapped inside the lacunae of calcified bone.

2. Osteocytes

Osteocytes are the bone cells concerned with maintenance of bone. Osteocytes are small flattened and rounded cells, embedded in the bone lacunae. These cells are the major cells in developed bone and are derived from the matured osteoblasts. The cytoplasmic processes from osteocytes run into canaliculi and ramify throughout the bone matrix. The processes from neighboring osteocytes have contact with each other forming tight junctions.

Functions of osteocytes

i. Help to maintain the bone as living tissue because of their metabolic activity
ii. Maintain the exchange of calcium between the bone and ECF.

3. Osteoclasts

Osteoclasts are the bone cells that are concerned with bone resorption **(osteoclastic activity).** Osteoclasts are the **giant phagocytic multinucleated cells** found in the lacunae of bone matrix. These bone cells are derived from hemopoietic stem cells via monocytes colony forming units-M (CFU-M).

Functions of osteoclasts

i. Responsible for bone resorption during bone remodeling
ii. Synthesis and release of lysosomal enzymes necessary for bone resorption into the bone resorbing compartment.

■ BONE GROWTH

Embryo has a cartilaginous skeleton. The **cartilage** is composed of large amount of solid but flexible matrix. The matrix is derived from a protein called **chondrin,** that is secreted by the **cartilage cells** or **chondriocytes.** Some of the cartilage is converted into bones.

Ossification and Calcification

Ossification is the conversion of cartilage into bone. At the time of birth, the skeleton consists of 50% cartilage and 50% bone. At the age of 2 years and thereafter, the skeleton consists 35% cartilage and 65% bone.

Ossification is carried out by the osteoblasts, which enter the cartilage and lay down the matrix around them. Osteoblasts synthesize collagen fibers, which produce the matrix called osteoid. Then, calcium is deposited on the matrix. The deposition of calcium is called calcification.

Growth in Length

During growth, the epiphysis at the end of each long bone is separated from diaphysis by a plate of proliferative cartilage termed as **epiphyseal plate.**

Increase in the length of the bone occurs due to the formation of new bone from epiphyseal plate. The thickness of the epiphyseal plate reduces as the length of bone increases. Increase in length of the bone occurs as long as the epiphyseal plates remain separated from diaphysis (shaft). The growth of the bone stops when the epiphysis fuses with the shaft. The process by which epiphysis fuses with shaft is called the **epiphyseal fusion** or closure. It occurs usually at the time of puberty. Width of the bone increases due to increase in thickness of periosteum or the outer layers of compact bone.

■ BONE REMODELING

Bone remodeling is a dynamic lifelong process in which old bone is resorbed and new bone is formed. Usually, it takes place in groups of bone cells called the **basic multicellular units** (BMU). The entire process of remodeling extends for about 100 days in compact bone and about 200 days in spongy bone.

Processes of bone remodeling

1. Bone resorption: Destruction of bone matrix and removal of calcium (osteoclastic activity).
2. Bone formation: Development and mineralization of new matrix (osteoblastic activity).

Bone Resorption – Osteoclastic Activity

Osteoclastic activity is the process that involves destruction of bone matrix, followed by removal of calcium. Osteoclasts are responsible for bone resorption by their osteoclastic activity.

Part of the bone to be resorbed is known as bone resorbing compartment. The osteoclast present in this compartment attaches itself to the periosteal or endosteal surface of bone through villi-like membranous extensions. This process is mediated by the surface receptors called **integrins.** At the point of attachment, a ruffled border is formed by folding of the cell membrane.

Resorption of that particular compartment occurs by some substances released from membranous extensions of osteoclasts such as:

1. Collagenase
2. Phosphatase

3. Lysosomal enzymes
4. Acids like citric acid and lactic acid.

Sequence of events during bone resorption

1. Citric acid and lactic acid cause acidification of the area and decrease pH to 4
2. Lysosomal enzymes are activated at this pH
3. Activated enzymes digest or dissolve the collagen
4. Enzymes also dissolve the hydroxyapatite and form solution of bone salts
5. All the dissolved materials are now released into ECF
6. Some elements enter the blood
7. Remaining elements are cleaned up by the macrophages
8. A shallow cavity is formed in the bone resorbing compartment.

Bone Formation – Osteoblastic Activity

Osteoblastic activity is the process which involves the synthesis of collagen and formation of bone matrix that is mineralized. Osteoblasts are concerned with bone formation. Osteoblasts synthesize and release collagen into the shallow cavity formed after resorption in the bone resorbing compartment. The collagen fibers arrange themselves in regular units and form the organic matrix called osteoid.

Mineralization

Mineralization is the process by which the minerals are deposited on bone matrix. Mineralization starts about 10 to 12 days after the formation of osteoid. First, a large quantity of calcium phosphate is deposited. Afterwards, the hydroxide and bicarbonate ions are gradually added causing the formation of **hydroxyapatite crystals.** The process of mineralization is accelerated by the enzyme alkaline phosphatase, secreted by osteoblast. The process also requires the availability of adequate amount of calcium and phosphate in the ECF.

The completely mineralized bone surrounds the osteoblast. Now, the synthetic activity of osteoblast is reduced slowly and the cell is converted into osteocytes. Later, the bone is arranged in concentric lamellae on the inner surface of the cavity. At the end of the formation of new bone, the cavity is reduced to form Haversian canal.

Significance of Bone Remodeling

In children

1. Thickness of bone increases
2. Bone obtains strength in proportion to the growth
3. Shape of the bone is realtered in relation to growth of the body.

In adults

1. Toughness of bone is maintained
2. Mechanical integrity of skeleton is ensured throughout life
3. Blood calcium level is maintained.

Regulation of Bone Remodeling

Bone remodeling occurs continuously throughout the life. So a balance is maintained always between the bone resorption and bone formation.

However, in persons like athletes, soldiers and others, in whom the bone stress is more, the bone becomes heavy and strong. It is because of the stimulation of osteoblastic activity and mineralization of bone by repeated physical stress.

Apart from the physical stress, a variety of hormonal substances and growth factors are involved in regulation of bone resorption and bone formation (Table 68.1).

■ REPAIR OF BONE AFTER FRACTURE

The process of healing after bone fracture involves joining of broken ends by the deposition of new bone.

Stages of Bone Repair after Fracture

1. Formation of **hematoma** between the broken ends of bone and surrounding soft tissues. Hematoma means swelling or mass of blood clot confined to a tissue or space due to rupture of blood vessel
2. Development of acute inflammation
3. Phagocytosis of hematoma, debris and fragments of bone by macrophages
4. Formation of granular tissue and development of new blood vessels
5. Development of new osteoblasts and formation of new bone called callus
6. Spreading of new bone to fill the gap between the broken ends of bones
7. Reshaping of new bone by osteoclasts, which remove excess callus and formation of canal in the new bone.

■ APPLIED PHYSIOLOGY – DISEASES OF BONE

1. *Osteoporosis*

Osteoporosis is the bone disease characterized by the loss of bone matrix and minerals. Osteoporosis means **'porous bones'.**

TABLE 68.1: Factors regulating bone remodeling

Event	Stimulating factors	Inhibiting Factors
Bone formation	1. Growth hormone 2. Calcitonin 3. Insulin 4. Testosterone 5. Estrogen 6. Insulin-like growth factor 7. Transforming growth factor-β 8. Skeletal growth factor 9. Bone-derived growth factor 10. Platelet-derived growth factor	Cortisol
Mineralization	1. Calcitonin 2. Insulin 3. Vitamin D	Cortisol
Bone resorption	1. Parathormone 2. Thyroxine 3. Cortisol 4. Prostaglandins 5. Interleukin-1 6. Estrogen 7. Calcitonin	Testosterone

Causes of osteoporosis

Osteoporosis occurs due to excessive bone resorption and decreased bone formation. Osteoporosis is common in women after 60 years. The various risk factors are given in Box 68.1.

Manifestations of osteoporosis

Loss of bone matrix and minerals leads to loss of bone strength, associated with architectural deterioration of bone tissue. Ultimately, the bones become fragile with high risk of fracture. Commonly affected bones are vertebrae and hip.

2. *Rickets*

Rickets is the bone disease in children, characterized by inadequate mineralization of bone matrix. It occurs due to vitamin D deficiency. Vitamin D deficiency develops due to insufficiency in diet or due to inadequate exposure to sunlight.

BOX 68.1: Risk factors for osteoporosis

1. Sedentary life
2. Genetic factor
3. Early menopause or ovariectomy
4. Excessive smoking
5. Excessive alcohol or caffeine intake
6. Prolonged high intake of protein
7. Prolonged medication with drugs like corticosteroids and cyclosporin
8. Endocrine disorders like hypothyroidism, Cushing syndrome, acromegaly and hypogonadism.

Deficiency of vitamin D affects the reabsorption of calcium and phosphorus from renal tubules, resulting in **calcium deficiency.** It causes inadequate mineralization of epiphyseal growth plate in growing bones. This defect produces various manifestations.

Causes of rickets

Causes of rickets are given in Table 68.2.

Features of rickets

i. Collapse of chest wall: Due to the flattening of sides of thorax with prominent sternum. This deformity of the chest with projecting sternum is called **pigeon chest** or **chicken chest** or **pectus carinatum.**
ii. Rachitic rosary: A visible swelling where the ribs join their cartilages. It is because of the development of nodules at sternal end of ribs, which forms the rachitic rosary
iii. Kyphosis: Extreme forward curvature of the upper back bone (thoracic spine) with convexity backward (forward bending). Severe kyphosis

TABLE 68.2: Common causes of rickets and osteomalacia

Deficiency of vitamin D	Low dietary intake Inadequate synthesis in skin Reduced absorption from intestine
Renal diseases	Chronic renal failure Dialysis-induced bone disease Renal tubular acidosis.

causes formation of a hump (protuberance) which is called **humpback, hunchback** or **Pott curvature**

iv. Lordosis: Extreme forward curvature of back bone in lumbar region: also called **hollow back** or **saddle back**
v. Scoliosis: Lateral curvature of spine
vi. Harrison sulcus: A groove in rib cage due to pulling of diaphragm inwards
vii. Bowing of hands and legs
viii. Enlargement of liver and spleen
ix. Tetany: In advanced stages, the patient may die because of tetany, involving the respiratory muscles.

3. *Osteomalacia*

Rickets in adults is called **osteomalacia** or **adult rickets.**

Causes of osteomalacia

Osteomalacia occurs because of deficiency of vitamin D. It also occurs due to prolonged damage of kidney (renal rickets).

Features of osteomalacia

i. Vague pain
ii. Tenderness in bones and muscles
iii. **Myopathy** leading to **waddling gait** (gait means the manner of walking). In waddling gait, the feet are wide apart and walk resembles that of a duck
iv. Occasional hypoglycemic tetany.

Endocrine Functions of Pancreas

Chapter 36

- ISLETS OF LANGERHANS
- INSULIN
- GLUCAGON
- SOMATOSTATIN
- PANCREATIC POLYPEPTIDE
- REGULATION OF BLOOD GLUCOSE LEVEL
- APPLIED PHYSIOLOGY

ISLETS OF LANGERHANS

Endocrine function of pancreas is performed by the islets of Langerhans. Human pancreas contains about 1 to 2 million islets.

Islets of Langerhans consist of four types of cells:

1. A cells or α-cells, which secrete glucagon
2. B cells or β-cells, which secrete insulin
3. D cells or δ-cells, which secrete somatostatin
4. F cells or PP cells, which secrete pancreatic polypeptide.

INSULIN

SOURCE OF SECRETION

Insulin is secreted by B cells or the β-cells in the islets of Langerhans of pancreas.

CHEMISTRY AND HALF-LIFE

Insulin is a polypeptide with 51 amino acids and a molecular weight of 5,808. It has two amino acid chains called α and β chains, which are linked by disulfide bridges. The α-chain of insulin contains 21 amino acids and β-chain contains 30 amino acids. The biological half-life of insulin is 5 minutes.

PLASMA LEVEL

Basal level of insulin in plasma is 10 μU/mL.

SYNTHESIS

Synthesis of insulin occurs in the rough endoplasmic reticulum of β-cells in islets of Langerhans. It is synthesized as **preproinsulin,** that gives rise to **proinsulin.** Proinsulin is converted into insulin and C peptide through a series of peptic cleavages. C peptide is a connecting peptide that connects α and β chains. At the time of secretion, C peptide is detached.

Preproinsulin → Proinsulin
Peptic cleavage ↓
Insulin

METABOLISM

Binding of insulin to insulin receptor is essential for its removal from circulation and degradation. Insulin is degraded in liver and kidney by a cellular enzyme called **insulin protease** or **insulin-degrading enzyme.**

ACTIONS OF INSULIN

Insulin is the important hormone that is concerned with the regulation of carbohydrate metabolism and blood glucose level. It is also concerned with the metabolism of proteins and fats.

1. *On Carbohydrate Metabolism*

Insulin is the only antidiabetic hormone secreted in the body, i.e. it is the only hormone in the body that

reduces blood glucose level. Insulin reduces the blood glucose level by its following actions on carbohydrate metabolism:

i. *Increases transport and uptake of glucose by the cells*

Insulin facilitates the transport of glucose from blood into the cells by increasing the permeability of cell membrane to glucose. Insulin stimulates the rapid uptake of glucose by all the tissues, particularly liver, muscle and adipose tissues. But, it is not required for glucose uptake in some tissues such as brain (except hypothalamus), renal tubules, mucous membrane of intestine and RBCs. Insulin also increases the number of glucose transporters, especially GLUT 4 in the cell membrane.

Glucose transporters: Usually, glucose is transported into the cells by **sodium-glucose symport pump.** In addition to symport pump, most of the cells have another type of transport proteins called **glucose transporters (GLUT).** So far, seven types of GLUT are identified (GLUT 1–7). Among these, **GLUT4** is insulin sensitive and it is located in cytoplasmic vesicles. It is present in large numbers in muscle fibers and adipose cells.

When insulin-receptor complex is formed in the membrane of such cells, the vesicles containing GLUT4 are attracted towards the membrane and GLUT4 is released into the membrane. Now, GLUT4 starts transporting the glucose molecules from extracellular fluid (ECF) into the cell. The advantage of GLUT4 is that it transports glucose at a faster rate.

ii. *Promotes peripheral utilization of glucose*

Insulin promotes the peripheral utilization of glucose. In presence of insulin, glucose which enters the cell is oxidized immediately. The rate of utilization depends upon the intake of glucose.

iii. *Promotes storage of glucose – glycogenesis*

Insulin promotes the rapid conversion of glucose into glycogen (glycogenesis), which is stored in the muscle and liver. Thus, glucose is stored in these two organs in the form of glycogen. Insulin activates the enzymes which are necessary for glycogenesis. In liver, when glycogen content increases beyond its storing capacity, insulin causes conversion of glucose into fatty acids.

iv. *Inhibits glycogenolysis*

Insulin prevents glycogenolysis, i.e. the breakdown of glycogen into glucose in muscle and liver.

v. *Inhibits gluconeogenesis*

Insulin prevents gluconeogenesis, i.e. the formation of glucose from proteins by inhibiting the release of amino acids from muscle and by inhibiting the activities of enzymes involved in gluconeogenesis.

Thus, insulin decreases the blood glucose level by:

i. Facilitating transport and uptake of glucose by the cells
ii. Increasing the peripheral utilization of glucose
iii. Increasing the storage of glucose by converting it into glycogen in liver and muscle
iv. Inhibiting glycogenolysis
v. Inhibiting gluconeogenesis.

2. *On Protein Metabolism*

Insulin facilitates the synthesis and storage of proteins and inhibits the cellular utilization of proteins by the following actions:

i. Facilitating the transport of amino acids into the cell from blood, by increasing the permeability of cell membrane for amino acids
ii. Accelerating protein synthesis by influencing the transcription of DNA and by increasing the translation of mRNA
iii. Preventing protein catabolism by decreasing the activity of cellular enzymes which act on proteins
iv. Preventing conversion of proteins into glucose.

Thus, insulin is responsible for the conservation and storage of proteins in the body.

3. *On Fat Metabolism*

Insulin stimulates the synthesis of fat. It also increases the storage of fat in the adipose tissue.

Actions of insulin on fat metabolism are:

i. *Synthesis of fatty acids and triglycerides*

Insulin promotes the transport of excess glucose into cells, particularly the liver cells. This glucose is utilized for the synthesis of fatty acids and triglycerides. Insulin promotes the synthesis of lipids by activating the enzymes which convert:

a. Glucose into fatty acids
b. Fatty acids into triglycerides.

ii. *Transport of fatty acids into adipose tissue*

Insulin facilitates the transport of fatty acids into the adipose tissue.

iii. *Storage of fat*

Insulin promotes the storage of fat in adipose tissue by inhibiting the enzymes which degrade the triglycerides.

4. *On Growth*

Along with growth hormone, insulin promotes growth of body by its anabolic action on proteins. It enhances the

transport of amino acids into the cell and synthesis of proteins in the cells. It also has the **protein-sparing effect,** i.e. it causes conservation of proteins by increasing the glucose utilization by the tissues.

Houssay Animal

The importance of insulin and growth hormone in the growth of the body is demonstrated by Houssay animal. Houssay animal is one in which both anterior pituitary and pancreas are removed. Administration of either insulin or growth hormone alone does not induce growth in this animal. However, the administration of both the hormones stimulates the growth. This proves the synergistic actions of these two hormones on growth.

■ MODE OF ACTION OF INSULIN

On the target cells, insulin binds with the receptor protein and forms the insulin-receptor complex. This complex executes the action by activating the intracellular enzyme system.

Insulin Receptor

Insulin receptor is a glycoprotein with a molecular weight of 340,000. It is present in almost all the cells of the body.

Subunits of insulin receptor

Insulin receptor is a **tetramer,** formed by four glycoprotein subunits (two α-subunits and two β-subunits). The α-subunits protrude out of the cell and the β-subunits protrude inside the cell (Fig. 69.1). The α and β subunits are linked to each other by disulfide bonds. Intracellular surfaces of α-subunits have the enzyme activity – **protein kinase (tyrosine kinase)** activity.

When insulin binds with α-subunits of the receptor protein, the tyrosine kinase at the β-subunit (that protrudes into the cell) is activated by means of autophosphorylation.

Activated tyrosine kinase acts on many intracellular enzymes by phosphorylating or dephosphorylating them so that some of the enzymes are activated while others are inactivated.

Thus, insulin action is exerted on the target cells by the activation of some intracellular enzymes and by the inactivation of other enzymes.

■ REGULATION OF INSULIN SECRETION

Insulin secretion is mainly regulated by blood glucose level.

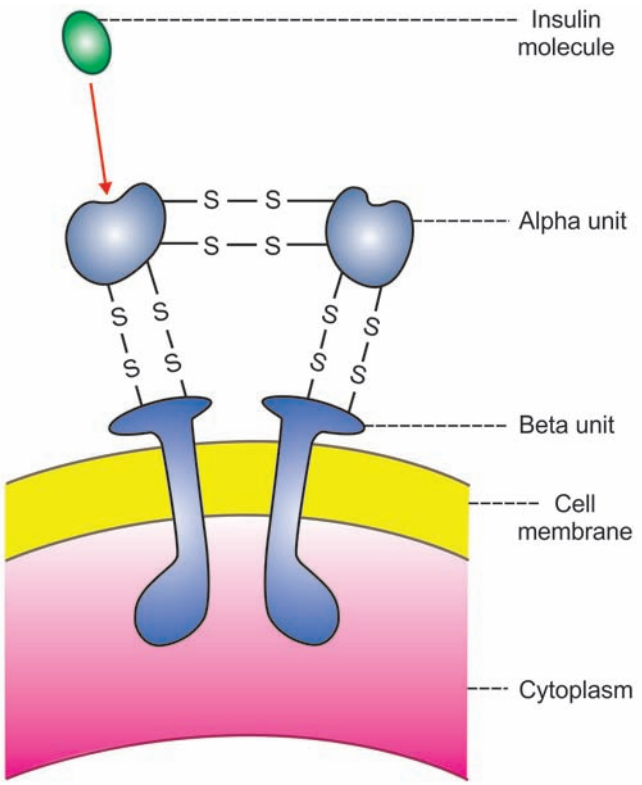

FIGURE 69.1: Diagram showing the structure of insulin receptor. S–S = Disulfide bond.

In addition, other factors like amino acids, lipid derivatives, gastrointestinal and endocrine hormones and autonomic nerve fibers also stimulate insulin secretion.

1. *Role of Blood Glucose Level*

When blood glucose level is normal (80 to 100 mg/dL), the rate of insulin secretion is low (up to 10 μU/minute). When blood glucose level increases between 100 and 120 mg/dL, the rate of insulin secretion rises rapidly to 100 μU/minute. When blood glucose level rises above 200 mg/dL, the rate of insulin secretion also rises very rapidly up to 400 μU/minute.

Biphasic effect of glucose

Action of blood glucose on insulin secretion is biphasic.

i. Initially, when blood glucose level increases after a meal, the release of insulin into blood increases rapidly. Within few minutes, concentration of insulin in plasma increases up to 100 μU/mL from the basal level of 10 μU/mL. It is because of release of insulin that is stored in pancreas. Later, within 10 to 15 minutes, the insulin concentration in the blood reduces to half the value, i.e. up to 40 to 50 μU/mL of plasma.

ii. After 15 to 20 minutes, the insulin secretion rises once again. This time it rises slowly but steadily. It reaches the maximum between 2 and 2½ hours. The prolonged increase in insulin release is due to the formation of new insulin molecules continuously from pancreas (Fig. 69.2).

2. *Role of Proteins*

Excess amino acids in blood also stimulate insulin secretion. Potent amino acids are **arginine** and **lysin.** Without any increase in blood glucose level, the amino acids alone can cause a slight increase in insulin secretion. However, amino acids potentiate the action of glucose on insulin secretion so that, in the presence of amino acids, elevated blood glucose level increases insulin secretion to a great extent.

3. *Role of Lipid Derivatives*

The β-ketoacids such as acetoacetate also increase insulin secretion.

4. *Role of Gastrointestinal Hormones*

Insulin secretion is increased by some of the gastrointestinal hormones such as gastrin, secretin, CCK and GIP.

5. *Role of Endocrine Hormones*

Diabetogenic hormones like glucagon, growth hormone and cortisol also stimulate insulin secretion, indirectly.

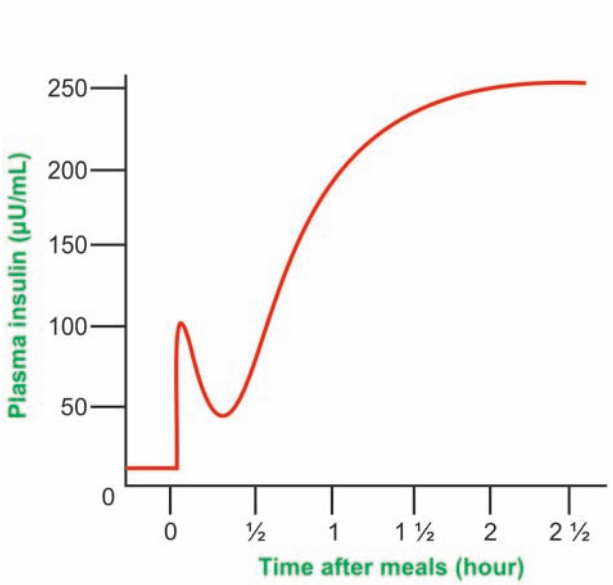

FIGURE 69.2: Changes in plasma level of insulin after meals. Increase in blood glucose level after meals produces biphasic effect on plasma level of insulin.

All these diabetogenic hormones increase the blood glucose level, which stimulates β-cells of islets of Langerhans. So insulin secretion is increased.

Prolonged hypersecretion of these hormones causes exhaustion of β-cells, resulting in diabetes mellitus.

6. *Role of Autonomic Nerves*

Stimulation of parasympathetic nerve to the pancreas (right vagus) increases insulin secretion. Chemical neurotransmitter involved is acetylcholine. Stimulation of sympathetic nerves inhibits the secretion of insulin and the neurotransmitter is noradrenaline.

However, the role of these nerves on the regulation of insulin secretion under physiological conditions is not clear.

■ GLUCAGON

■ SOURCE OF SECRETION

Glucagon is secreted from **A cells** or **α-cells** in the islets of Langerhans of pancreas. It is also secreted from **A cells** of stomach and **L cells** of intestine.

■ CHEMISTRY AND HALF-LIFE

Glucagon is a polypeptide with a molecular weight of 3,485. It contains 29 amino acids. Half-life of glucagon is 3 to 6 minutes.

■ SYNTHESIS

Glucagon is synthesized from the preprohormone precursor called **preproglucagon** in the α-cells of islets. Preproglucagon is converted into **proglucagon,** which gives rise to glucagon.

■ METABOLISM

About 30% of glucagon is degraded in liver and 20% in kidney. The cleaved glucagon fragments are excreted through urine. 50% of the circulating glucagon is degraded in blood itself by enzymes such as **serine** and **cysteine proteases.**

■ ACTIONS OF GLUCAGON

Actions of glucagon are antagonistic to those of insulin (Table 69.1). It increases the blood glucose level, peripheral utilization of lipids and the conversion of proteins into glucose.

1. *On Carbohydrate Metabolism*

Glucagon increases the blood glucose level by:

i. Increasing glycogenolysis in liver and releasing glucose from the liver cells into the blood.

TABLE 69.1: Differences between insulin and glucagon

Features	Insulin	Glucagon
Source of secretion	β-cells of islets of langerhans	α-cells of islets of langerhans
Action on carbohydrate metabolism	*Decreases blood glucose level by:* 1. Facilitating transport and uptake of glucose by all cells except liver cells 2. Increasing peripheral utilization of glucose 3. Increasing glycogenesis in liver and muscle 4. Preventing glycogenolysis 5. Preventing gluconeogenesis	*Increases blood glucose level by:* 1. Facilitating glucose transport into liver cells 2. Increasing glycogenolysis 3. Increasing gluconeogenesis
Action on protein metabolism	1. Facilitates amino acid transport 2. Accelerates protein synthesis 3. Prevents protein catabolism 4. Prevents conversion of proteins into glucose	1. Increases transport of amino acids into liver cells 2. Increases utilization of amino acids for gluconeogenesis
Action on fat metabolism	1. Increases synthesis and storage of fat 2. No ketogenic effect	1. Increases lipolysis 2. Promotes ketogenesis
Blood fatty acids	Decreases	Increases
Hypersecretion leads to	Hypoglycemia	Hyperglycemia
Hyposecretion leads to	Diabetes mellitus	Hypoglycemia

Glucagon does not induce glycogenolysis in muscle

ii. Increasing gluconeogenesis in liver by:
   a. Activating the enzymes, which convert pyruvate into phosphoenol pyruvate
   b. Increasing the transport of amino acids into the liver cells. The amino acids are utilized for glucose formation.

2. *On Protein Metabolism*

Glucagon increases the transport of amino acids into liver cells. The amino acids are utilized for gluconeogenesis.

3. *On Fat Metabolism*

Glucagon shows lipolytic and ketogenic actions. It increases lipolysis by increasing the release of free fatty acids from adipose tissue and making them available for peripheral utilization. The lipolytic activity of glucagon, in turn promotes ketogenesis (formation of ketone bodies) in liver.

4. *Other Actions*

Glucagon:

i. Inhibits the secretion of gastric juice
ii. Increases the secretion of bile from liver.

■ MODE OF ACTION OF GLUCAGON

On the target cells (mostly liver cells), glucagon combines with receptor and activates adenyl cyclase via G protein. Adenyl cyclase causes the formation of cyclic adenosine monophosphate (AMP) which brings out the actions of glucagon. Glucagon receptor is a peptide with a molecular weight of 62,000.

■ REGULATION OF GLUCAGON SECRETION

Secretion of glucagon is controlled mainly by glucose and amino acid levels in the blood.

1. *Role of Blood Glucose Level*

Important factor that regulates the secretion of glucagon is the decrease in blood glucose level. When blood glucose level decreases below 80 mg/dL of blood, α-cells of islets of Langerhans are stimulated and more glucagon is released. Glucagon, in turn increases the blood glucose level. On the other hand, when blood glucose level increases, α-cells are inhibited and the secretion of glucagon decreases.

2. *Role of Amino Acid Level in Blood*

Increase in amino acid level in blood stimulates the secretion of glucagon. Glucagon, in turn converts the amino acids into glucose.

3. *Role of Other Factors*

Factors which increase glucagon secretion:

i. Exercise
ii. Stress
iii. Gastrin

iv. Cholecystokinin (CCK)
v. Cortisol.

Factors which inhibit glucagon secretion:

i. Somatostatin
ii. Insulin
iii. Free fatty acids
iv. Ketones.

SOMATOSTATIN

SOURCE OF SECRETION

Somatostatin is secreted from:

1. Hypothalamus
2. D cells (δ-cells) in islets of Langerhans of pancreas
3. D cells in stomach and upper part of small intestine.

CHEMISTRY AND HALF-LIFE

Somatostatin is a polypeptide. It is synthesized in two forms, namely somatostatin-14 (with 14 amino acids) and somatostatin-28 (with 28 amino acids). Both the forms have similar actions. Half-life of somatostatin is 2 to 4 minutes.

SYNTHESIS

Somatostatin is synthesized from the precursor prosomatostatin. Prosomatostatin is converted mostly into somatostatin-14 in the D cells of islets in pancreas. However, in the intestine, large amount of somatostatin-28 is produced from prosomatostatin.

METABOLISM

Somatostatin is degraded in liver and kidney.

ACTIONS OF SOMATOSTATIN

1. Somatostatin acts within islets of Langerhans and, inhibits β and α cells, i.e. it inhibits the secretion of both glucagon and insulin
2. It decreases the motility of stomach, duodenum and gallbladder
3. It reduces the secretion of gastrointestinal hormones gastrin, CCK, GIP and VIP
4. Hypothalamic somatostatin inhibits the secretion of GH and TSH from anterior pituitary. That is why, it is also called **growth hormone-inhibitory hormone** (GHIH).

MODE OF ACTION OF SOMATOSTATIN

Somatostatin brings out its actions through cAMP.

REGULATION OF SECRETION OF SOMATOSTATIN

Pancreatic Somatostatin

Secretion of pancreatic somatostatin is stimulated by glucose, amino acids and CCK. The tumor of D cells of islets of Langerhans causes hypersecretion of somatostatin. It leads to hyperglycemia and other symptoms of diabetes mellitus.

Gastrointestinal Tract Somatostatin

Secretion of somatostatin in GI tract is increased by the presence of chyme-containing glucose and proteins in stomach and small intestine.

PANCREATIC POLYPEPTIDE

SOURCE OF SECRETION

Pancreatic polypeptide is secreted by F cells or PP cells in the islets of Langerhans of pancreas. It is also found in small intestine.

CHEMISTRY AND HALF-LIFE

Pancreatic polypeptide is a polypeptide with 36 amino acids. Its half-life is 5 minutes.

SYNTHESIS

Pancreatic polypeptide is synthesized from pre-prohormone precursor called **prepropancreatic** polypeptide in the PP cells of islets.

METABOLISM

Pancreatic polypeptide is degraded and removed from circulation mainly in kidney.

ACTIONS OF PANCREATIC POLYPEPTIDE

Exact physiological action of pancreatic polypeptide is not known. It is believed to increase the secretion of glucagon from α-cells in islets of Langerhans.

MODE OF ACTION OF PANCREATIC POLYPEPTIDE

Pancreatic polypeptide brings out its actions through cAMP.

REGULATION OF SECRETION

Secretion of pancreatic polypeptide is stimulated by the presence of chyme containing more proteins in the small intestine.

REGULATION OF BLOOD GLUCOSE LEVEL (BLOOD GLUCOSE LEVEL)

NORMAL BLOOD GLUCOSE LEVEL

In normal persons, blood glucose level is controlled within a narrow range. In the early morning after overnight **fasting,** the blood glucose level is low ranging between 70 and 110 mg/dL of blood. Between first and second hour after meals **(postprandial),** the blood glucose level rises to 100 to 140 mg/dL. Glucose level in blood is brought back to normal at the end of second hour after the meals.

Blood glucose regulating mechanism is operated through liver and muscle by the influence of the pancreatic hormones – insulin and glucagon. Many other hormones are also involved in the regulation of blood glucose level. Among all the hormones, insulin is the only hormone that reduces the blood glucose level and it is called the **antidiabetogenic hormone.** The hormones which increase blood glucose level are called **diabetogenic hormones** or **anti-insulin hormones.**

Necessity of Regulation of Blood Glucose Level

Regulation of blood glucose (sugar) level is very essential because, glucose is the only nutrient that is utilized for energy by many tissues such as brain tissues, retina and germinal epithelium of the gonads.

ROLE OF LIVER IN THE MAINTENANCE OF BLOOD GLUCOSE LEVEL

Liver serves as an important **glucose buffer system.** When blood glucose level increases after a meal, the excess glucose is converted into glycogen and stored in liver. Afterwards, when blood glucose level falls, the glycogen in liver is converted into glucose and released into the blood. The storage of glycogen and release of glucose from liver are mainly regulated by insulin and glucagon.

ROLE OF INSULIN IN THE MAINTENANCE OF BLOOD GLUCOSE LEVEL

Insulin decreases the blood glucose level and it is the only antidiabetic hormone available in the body (Refer the actions of insulin on carbohydrate metabolism in this Chapter).

ROLE OF GLUCAGON IN THE MAINTENANCE OF BLOOD GLUCOSE LEVEL

Glucagon increases the blood glucose level (Refer actions of glucagon on carbohydrate metabolism in this Chapter).

ROLE OF OTHER HORMONES IN THE MAINTENANCE OF BLOOD GLUCOSE LEVEL

Other hormones which increase the blood glucose level are:

1. Growth hormone
2. Thyroxine
3. Cortisol
4. Adrenaline

Thus, liver helps to maintain the blood glucose level by storing glycogen when blood glucose level is high after meals; and by releasing glucose, when blood glucose level is low after 2 to 3 hours of food intake. Insulin helps to control the blood glucose level, especially after meals, when it increases. Glucagon and other hormones help to maintain the blood glucose level by raising it in between the meals.

APPLIED PHYSIOLOGY

HYPOACTIVITY – DIABETES MELLITUS

Diabetes mellitus is a metabolic disorder characterized by high blood glucose level, associated with other manifestations. **'Diabetes'** means **'polyuria'** and **'mellitus'** means **'honey'.** The name 'diabetes mellitus' was coined by Thomas Willis, who discovered sweetness of urine from diabetics in 1675.

In most of the cases, diabetes mellitus develops due to deficiency of insulin.

Classification of Diabetes Mellitus

There are several forms of diabetes mellitus, which occur due to different causes. Diabetes may be primary or secondary. Primary diabetes is unrelated to another disease. Secondary diabetes occurs due to damage or disease of pancreas by another disease or factor.

Recent classification divides primary diabetes mellitus into two types, Type I and Type II. Differences between the two types are given in Table 69.2.

Type I Diabetes Mellitus

Type I diabetes mellitus is due to deficiency of insulin because of destruction of β-cells in islets of Langerhans. This type of diabetes mellitus may occur at any age of life. But, it usually occurs before 40 years of age and the persons affected by this require insulin injection. So it is also called **insulin-dependent diabetes mellitus (IDDM).** When it develops at infancy or childhood, it is called juvenile diabetes.

Type I diabetes mellitus develops rapidly and progresses at a rapid phase. It is not associated with **obesity,** but may be associated with **acidosis** or ketosis.

Causes of type I diabetes mellitus

1. Degeneration of β-cells in the islets of Langerhans of pancreas
2. Destruction of β-cells by viral infection
3. Congenital disorder of β-cells
4. Destruction of β-cells during autoimmune diseases. It is due to the development of antibodies against β-cells (Refer Chapter 17 for details).

Other forms of type 1 diabetes mellitus

1. **Latent autoimmune diabetes in adults (LADA):** LADA or slow onset diabetes has slow onset and slow progress than IDDM and it occurs in later life after 35 years. It may be difficult to distinguish LADA from type II diabetes mellitus, since pancreas takes longer period to stop secreting insulin.
2. **Maturity onset diabetes** in young individuals **(MODY):** It is a rare inherited form of diabetes mellitus that occurs before 25 years. It is due to hereditary defects in insulin secretion.

Type II Diabetes Mellitus

Type II diabetes mellitus is due to insulin resistance (failure of insulin receptors to give response to insulin). So, the body is unable to use insulin. About 90% of diabetic patients have type II diabetes mellitus. It usually occurs after 40 years. Only some forms of Type II diabetes require insulin. In most cases, it can be controlled by oral hypoglycemic drugs. So it is also called **noninsulin-dependent diabetes mellitus (NIDDM).**

Type II diabetes mellitus may or may not be associated with ketosis, but often it is associated with obesity.

Causes for type II diabetes mellitus

In this type of diabetes, the structure and function of β-cells and blood level of insulin are normal. But insulin receptors may be less, absent or abnormal, resulting in insulin resistance.

Common causes of insulin resistance are:

1. Genetic disorders (significant factors causing type II diabetes mellitus)
2. Lifestyle changes such as bad eating habits and physical inactivity, leading to obesity
3. Stress.

Other forms of type II diabetes mellitus

1. Gestational diabetes: It occurs during pregnancy. It is due to many factors such as hormones secreted during pregnancy, obesity and lifestyle before and during pregnancy. Usually, diabetes disappears after delivery of the child. However, the woman has high risk of development of type II diabetes later.
2. **Pre-diabetes:** It is also called **chemical, subclinical, latent** or **borderline diabetes.** It is the stage between normal condition and diabetes. The person does not show overt (observable) symptoms of diabetes but there is an increase in blood glucose level. Though pre-diabetes is reversible, the affected persons are at a high risk of developing type II diabetes mellitus.

TABLE 69.2: Differences between type I and type II diabetes mellitus

Features	Type I (IDDM)	Type II (NIDDM)
Age of onset	Usually before 40 year	Usually after 40 year
Major cause	Lack of insulin	Lack of insulin receptor
Insulin deficiency	Yes	Partial deficiency
Immune destruction of β-cells	Yes	No
Involvement of other endocrine disorders	No	Yes
Hereditary cause	Yes	May or may not be
Need for insulin	Always	Not in initial stage May require in later stage
Insulin resistance	No	Yes
Control by oral hypoglycemic agents	No	Yes
Symptoms appear	Rapidly	Slowly
Body weight	Usually thin	Usually overweight
Stress-induced obesity	No	Yes
Ketosis	Yes	May or may not be

Secondary Diabetes Mellitus

Secondary diabetes mellitus is rare and only about 2% of diabetic patients have secondary diabetes. It may be temporary or may become permanent due to the underlying cause.

Causes of secondary diabetes mellitus

1. Endocrine disorders such as gigantism, acromegaly and Cushing's syndrome.
   Hyperglycemia in these conditions causes excess stimulation of β-cells. Constant and excess stimulation, in turn causes burning out and degeneration of β-cells. The β-cell exhaustion leads to permanent diabetes mellitus.
2. Damage of pancreas due to disorders such as chronic pancreatitis, cystic fibrosis and hemochromatosis (high iron content in body causing damage of organs)
3. Pancreatectomy (surgical removal)
4. Liver diseases such as hepatitis C and fatty liver
5. Autoimmune diseases such as celiac disease
6. Excessive use of drugs like antihypertensive drugs (beta blockers and diuretics), steroids, oral contraceptives, chemotherapy drugs, etc.
7. Excessive intake of alcohol and opiates.

Signs and Symptoms of Diabetes Mellitus

Various manifestations of diabetes mellitus develop because of three major setbacks of insulin deficiency.

1. Increased blood glucose level (300 to 400 mg/dL) due to reduced utilization by tissue
2. Mobilization of fats from adipose tissue for energy purpose, leading to elevated fatty acid content in blood. This causes deposition of fat on the wall of arteries and development of atherosclerosis
3. Depletion of proteins from the tissues.

Following are the signs and symptoms of diabetes mellitus:

1. *Glucosuria*

Glucosuria is the loss of glucose in urine. Normally, glucose does not appear in urine. When glucose level rises above 180 mg/dL in blood, glucose appears in urine. It is the renal threshold level for glucose.

2. *Osmotic diuresis*

Osmotic diuresis is the diuresis caused by osmotic effects. Excess glucose in the renal tubules develops osmotic effect. Osmotic effect decreases the reabsorption of water from renal tubules, resulting in diuresis. It leads to polyuria and polydipsia.

3. *Polyuria*

Excess urine formation with increase in the frequency of voiding urine is called polyuria. It is due to the osmotic diuresis caused by increase in blood glucose level.

4. *Polydipsia*

Increase in water intake is called polydipsia. Excess loss of water decreases the water content and increases the salt content in the body. This stimulates the thirst center in hypothalamus. Thirst center, in turn increases the intake of water.

5. *Polyphagia*

Polyphagia means the intake of excess food. It is very common in diabetes mellitus.

6. *Asthenia*

Loss of strength is called asthenia. Body becomes very weak because of this. Asthenia occurs due to protein depletion, which is caused by lack of insulin. Lack of insulin causes decrease in protein synthesis and increase in protein breakdown, resulting in protein depletion. Protein depletion also occurs due to the utilization of proteins for energy in the absence of glucose utilization.

7. *Acidosis*

During insulin deficiency, glucose cannot be utilized by the peripheral tissues for energy. So, a large amount of fat is broken down to release energy. It causes the formation of excess **ketoacids,** leading to acidosis.

One more reason for acidosis is that the ketoacids are excreted in combination with sodium ions through urine **(ketonuria).** Sodium is exchanged for hydrogen ions, which diffuse from the renal tubules into ECF adding to acidosis.

8. *Acetone breathing*

In cases of severe ketoacidosis, acetone is expired in the expiratory air, giving the characteristic acetone or fruity breath odor. It is a **life-threatening** condition of severe diabetes.

9. *Kussmaul breathing*

Kussmaul breathing is the increase in rate and depth of respiration caused by severe acidosis.

10. *Circulatory shock*

Osmotic diuresis leads to dehydration, which causes circulatory shock. It occurs only in severe diabetes.

11. *Coma*

Due to Kussmaul breathing, large amount of carbon dioxide is lost during expiration. It leads to drastic

reduction in the concentration of bicarbonate ions causing severe acidosis and coma. It occurs in severe cases of diabetes mellitus.

Increase in the blood glucose level develops hyperosmolarity of plasma which also leads to coma. It is called **hyperosmolar coma.**

Complications of Diabetes Mellitus

Prolonged hyperglycemia in diabetes mellitus causes dysfunction and injury of many tissues, resulting in some complications. Development of these complications is directly proportional to the degree and duration of hyperglycemia. However, the patients with well-controlled diabetes can postpone the onset or reduce the rate of progression of these complications.

Initially, the untreated chronic hyperglycemia affects the blood vessels, resulting in vascular complications like atherosclerosis. Vascular complications are responsible for the development of most of the complications of diabetes such as:

1. Cardiovascular complications like:
   i. Hypertension
   ii. Myocardial infarction
2. Degenerative changes in retina called diabetic retinopathy
3. Degenerative changes in kidney known as diabetic nephropathy
4. Degeneration of autonomic and peripheral nerves called diabetic neuropathy.

Diagnostic Tests for Diabetes Mellitus

Diagnosis of diabetes mellitus includes the determination of:

1. Fasting blood glucose
2. Postprandial blood glucose
3. Glucose tolerance test (GTT)
4. Glycosylated (glycated) hemoglobin.

Determination of glycosylated hemoglobin is commonly done to monitor the glycemic control of the persons already diagnosed with diabetes mellitus.

Abnormal response in diagnostic tests

Abnormal response in diagnostic tests occurs in conditions like **pre-diabetes** (see above). There is an increased fasting blood glucose level or impaired (decreased) glucose tolerance.

Treatment for Diabetes Mellitus

Type I diabetes mellitus

Type I diabetes mellitus is treated by exogenous insulin. Since insulin is a polypeptide, it is degraded in GI tract if taken orally. So, it is generally administered by subcutaneous injection.

Type II diabetes mellitus

Type II diabetes mellitus is treated by oral hypoglycemic drugs. Patients with longstanding severe diabetes mellitus may require a combination of oral hypoglycemic drugs with insulin to control the hyperglycemia.

Oral hypoglycemic drugs are classified into three types.

1. *Insulin secretagogues:* These drugs decrease the blood glucose level by stimulating insulin secretion from β-cells. Sulfonylureas (tolbutamide, gluburide, glipizide, etc.) are the commonly available insulin secretagogues
2. *Insulin sensitizers:* These drugs decrease the blood glucose level by facilitating the insulin action in the target tissues. Examples are biguanides (metformin) and thiazolidinediones (pioglitazone and rosiglitazone)
3. *Alpha glucosidase inhibitors:* These drugs control blood glucose level by inhibiting α-glucosidase. This intestinal enzyme is responsible for the conversion of dietary and other complex carbohydrates into glucose and other monosaccharides, which can be absorbed from intestine. Examples of α-glucosidase inhibitors are acarbose and meglitol.

■ HYPERACTIVITY – HYPERINSULINISM

Hyperinsulinism is the hypersecretion of insulin.

Cause of Hyperinsulinism

Hyperinsulinism occurs due to the tumor of β-cells in the islets of Langerhans.

Signs and Symptoms of Hyperinsulinism

1. *Hypoglycemia*

Blood glucose level falls below 50 mg/dL.

2. *Manifestations of central nervous system*

Manifestations of central nervous system occur when the blood glucose level decreases. All the manifestations are together called **neuroglycopenic symptoms.**

Initially, the activity of neurons increases, resulting in nervousness, tremor all over the body and sweating. If not treated immediately, it leads to **clonic convulsions** and **unconsciousness.** Slowly, the convulsions cease and **coma** occurs due to the damage of neurons.

Cardiovascular Adjustments during Exercise

Chapter 37

INTRODUCTION

During exercise, there is an increase in metabolic needs of body tissues, particularly the muscles.

Various adjustments in the body during exercise are aimed at:

1. Supply of various metabolic requisites like nutrients and oxygen to muscles and other tissues involved in exercise
2. Prevention of increase in body temperature.

TYPES OF EXERCISE

Exercise is generally classified into two types depending upon the type of muscular contraction:

1. Dynamic exercise
2. Static exercise.

Cardiovascular changes are slightly different in these two types of exercise.

DYNAMIC EXERCISE

Dynamic exercise primarily involves the **isotonic muscular contraction.** It keeps the joints and muscles moving. Examples are swimming, bicycling, walking, etc. Dynamic exercise involves **external work,** which is the shortening of muscle fibers against load.

In this type of exercise, the heart rate, force of contraction, cardiac output and systolic blood pressure increase. However, the diastolic blood pressure is unaltered or decreased. It is because, during dynamic exercise, peripheral resistance is unaltered or decreased depending upon the severity of exercise.

■ STATIC EXERCISE

Static exercise involves **isometric muscular contraction** without movement of joints. Example is pushing heavy object. Static exercise does not involve **external work.**

During this exercise, apart from increase in heart rate, force of contraction, cardiac output and systolic blood pressure, the diastolic blood pressure also increases. It is because of increase in peripheral resistance during static exercise.

■ AEROBIC AND ANAEROBIC EXERCISES

Based on the type of metabolism involved, exercise is classified into two types:

1. Aerobic exercise
2. Anaerobic exercise.

The terms aerobic and anaerobic refer to the energy producing process during exercise. Aerobic means **'with air'** or **'with oxygen'.** Anaerobic means **'without air'** or **'without oxygen'.** Both aerobic and anaerobic exercises are required to maintain physical fitness.

■ AEROBIC EXERCISE

Aerobic exercise involves activities with lower intensity, which is performed for longer period. The energy is obtained by utilizing nutrients in the presence of oxygen and hence it is called aerobic exercise. At the beginning, the body obtains energy by burning glycogen stored in liver. After about 20 minutes, when stored glycogen is exhausted the body starts burning fat. Body fat is converted into glucose, which is utilized for energy.

Aerobic exercise requires large amount of oxygen to obtain the energy needed for prolonged exercise.

Examples of aerobic exercise:

1. Fast walking
2. Jogging
3. Running
4. Bicycling
5. Skiing
6. Skating
7. Hockey
8. Soccer
9. Tennis
10. Badminton
11. Swimming
12. Rowing.

■ ANAEROBIC EXERCISE

Anaerobic exercise involves exertion for short periods followed by periods of rest. It uses the muscles at high intensity and a high rate of work for a short period. Body obtains energy by burning glycogen stored in the muscles without oxygen hence it is called anaerobic exercise.

Burning glycogen without oxygen liberates lactic acid. Accumulation of lactic acid leads to fatigue. Therefore, this type of exercise cannot be performed for longer period. And a recovery period is essential before going for another burst of anaerobic exercise. Anaerobic exercise helps to increase the muscle strength.

Examples of anaerobic exercise:

1. Pull-ups
2. Push-ups
3. Weightlifting
4. Sprinting
5. Any other rapid burst of strenuous exercise.

■ METABOLISM IN AEROBIC AND ANAEROBIC EXERCISES

When a person starts doing some exercise like jogging, bicycling or swimming, the muscles start utilizing energy. In order to have quick energy during the first few minutes, the muscles burn glycogen stored in them. During this period, fat is not burnt. Only glycogen is burnt and it is burnt without using oxygen. This is called **anaerobic metabolism.** Lactic acid is produced during this period. Presence of lactic acid causes some sort of burning sensation in the muscles particularly the muscles of arms, legs and back.

Muscles burn all the muscle glycogen within 3 to 5 minutes. If the person continues the exercise beyond this, glycogen stored in liver is converted into glucose, which is transported to muscles through blood. Now the body moves into **aerobic metabolism.** The glucose obtained from liver is burnt in the presence of oxygen. No more lactic acid is produced. So the burning sensation in the muscles disappears. Proper breathing is essential during this period so that adequate oxygen is supplied to the muscles to extract the energy from glucose. The supply of glucose from liver in combination with adequate availability of oxygen allows the person to continue the exercise.

Utilization of all the glycogen stored in liver is completed by about 20 minutes. If the exercise is continued beyond this, the body starts utilizing the fat. The stored fat called body fat is converted into carbohydrate, which is utilized by the muscles. This allows the person to do the exercise for a longer period.

■ SEVERITY OF EXERCISE

Cardiovascular and other changes in the body depend upon the severity of exercise also. Based on severity, the exercise is classified into three types.

1. MILD EXERCISE

Mild exercise is the very simple form of exercise like slow walking. Little or no change occurs in cardiovascular system during mild exercise.

2. MODERATE EXERCISE

Moderate exercise does not involve strenuous muscular activity. So, this type of exercise can be performed for a longer period. Exhaustion does not occur at the end of moderate exercise. The examples of this type of exercise are fast walking and slow running.

3. SEVERE EXERCISE

Severe exercise involves strenuous muscular activity. The severity can be maintained only for short duration. Fast running for a distance of 100 or 400 meters is the best example of this type of exercise. Complete exhaustion occurs at the end of severe exercise.

EFFECTS OF EXERCISE ON CARDIOVASCULAR SYSTEM

1. ON BLOOD

Mild hypoxia developed during exercise stimulates the juxtaglomerular apparatus to secrete erythropoietin. It stimulates the bone marrow and causes release of red blood cells. Increased carbon dioxide content in blood decreases the pH of blood.

2. ON BLOOD VOLUME

More heat is produced during exercise and the thermoregulatory system is activated. This in turn, causes secretion of large amount of sweat leading to:

i. Fluid loss
ii. Reduced blood volume
iii. Hemoconcentration
iv. Sometimes, severe exercise leads to even dehydration.

3. ON HEART RATE

Heart rate increases during exercise. Even the thought of exercise or preparation for exercise increases the heart rate. It is because of impulses from cerebral cortex to medullary centers, which reduces vagal tone.

In moderate exercise, the heart rate increases to 180 beats/minute. In severe muscular exercise, it reaches 240 to 260 beats/minute. Increased heart rate during exercise is mainly because of **vagal withdrawal.** Increase in sympathetic tone also plays some role.

Increased heart rate during exercise is due to four factors:

i. Impulses from proprioceptors, which are present in the exercising muscles; these impulses act through higher centers and increase the heart rate
ii. Increased carbon dioxide tension, which acts through medullary centers
iii. Rise in body temperature, which acts on cardiac centers via hypothalamus, increased temperature also stimulates SA node directly
iv. Circulating catecholamines, which are secreted in large quantities during exercise.

4. ON CARDIAC OUTPUT

Cardiac output increases up to 20 L/minute in moderate exercise and up to 35 L/minute during severe exercise. Increase in cardiac output is directly proportional to the increase in the amount of oxygen consumed during exercise.

During exercise, the cardiac output increases because of increase in heart rate and stroke volume. Heart rate increases because of **vagal withdrawal.** Stroke volume increases due to increased force of contraction. Because of vagal withdrawal, sympathetic activity increases leading to increase in rate and force of contraction.

5. ON VENOUS RETURN

Venous return increases remarkably during exercise because of muscle pump, respiratory pump and splanchnic vasoconstriction.

6. ON BLOOD FLOW TO SKELETAL MUSCLES

There is a great increase in the amount of blood flowing to skeletal muscles during exercise. In resting condition, the blood supply to the skeletal muscles is 3 to 4 mL/100 g of the muscle/minute. It increases up to 60 to 80 mL in moderate exercise and up to 90 to 120 mL in severe exercise.

During the muscular activity, stoppage of blood flow occurs when the muscles contract. It is because of compression of blood vessels during contraction. And in between the contractions, the blood flow increases.

Sometimes the blood supply to muscles starts increasing even during the preparation for exercise. It is due to the sympathetic activity. Sympathetic nerves cause vasodilatation in muscles. The sympathetic nerve fibers causing vasodilatation in skeletal muscle are called **sympathetic cholinergic fibers** since these fibers secrete **acetylcholine** instead of noradrenaline.

Several other factors also are responsible for the increase in blood flow to muscles during exercise. All such factors increase the amount of blood flow to muscles by means of dilatation of blood vessels of the muscles. Such factors are:

i. Hypercapnea
ii. Hypoxia
iii. Potassium ions
iv. Metabolites like lactic acid
v. Rise in temperature
vi. Adrenaline secreted from adrenal medulla
vii. Increased sympathetic cholinergic activity.

■ 7. ON BLOOD PRESSURE

During moderate isotonic exercise, the systolic pressure is increased. It is due to increase in heart rate and stroke volume. Diastolic pressure is not altered because peripheral resistance is not affected during moderate isotonic exercise.

In severe exercise involving isotonic muscular contraction, the systolic pressure enormously increases but the diastolic pressure decreases. Decrease in diastolic pressure is because of the decrease in peripheral resistance. Decrease in peripheral resistance is due to vasodilatation caused by metabolites.

During exercise involving isometric contraction, the peripheral resistance increases. So, the diastolic pressure also increases along with systolic pressure.

Blood Pressure after Exercise

Large quantities of metabolic end products are produced during exercise. These substances accumulate in the tissues, particularly the skeletal muscle. Metabolic end products cause vasodilatation. So, the blood pressure falls slightly below the resting level after the exercise. However, the pressure returns to resting level quickly as soon as the metabolic end products are removed from muscles.

QUESTIONS IN CARDIOVASCULAR SYSTEM

LONG QUESTIONS

1. Define cardiac cycle. Describe various events of cardiac cycle with pressure and volume changes.
2. Define electrocardiogram. Describe the waves, segments and intervals of normal ECG. Add a note on ECG leads.
3. Give the definitions, normal values and variations of cardiac output. Explain the factors regulating cardiac output.
4. What is cardiac output? Enumerate the various methods to measure cardiac output and explain the measurement of cardiac output by applying Fick principle.
5. Describe the innervation of heart and the regulation of heart rate.
6. Define arterial blood pressure. Describe the nervous regulation of arterial blood pressure.
7. Describe renal mechanism of (long term) regulation of arterial blood pressure.
8. What is the normal blood flow through coronary circulation? Explain the phasic changes, measurement and regulation of coronary blood blow.
9. Give an account of cerebral circulation.
10. Define hemorrhage. Explain various effects of hemorrhage.
11. Describe the cardiovascular and respiratory changes during exercise.

SHORT QUESTIONS

1. Action potential in cardiac muscle.
2. Pacemaker.
3. Pacemaker potential.
4. Conductive system in heart.
5. All-or-none law.
6. Refractory period in cardiac muscle.
7. Isometric contraction period.
8. Atrial pressure changes during cardiac cycle.
9. Ventricular pressure changes during cardiac cycle.
10. Ventricular volume changes during cardiac cycle.
11. Ejection fraction.
12. Heart sounds.
13. First and second heart sounds.
14. Phonocardiogram.
15. Cardiac murmurs.
16. Waves of normal ECG.
17. ECG leads.
18. Mean QRS vector.
19. Vectorcardiogram.
20. Sinus arrhythmia.
21. Heart block.
22. Extrasystole.
23. Stokes-Adams syndrome.
24. Abnormal pacemaker.
25. Current of injury.
26. Effect of electrolyte changes on heart.
27. Venous return.
28. Peripheral resistance.
29. Fick principle.
30. Cardiac catheterization.
31. Cardiac function curves.
32. Cardiac centers.
33. Nerve supply to heart.
34. Vagal tone.
35. Marey reflex.
36. Sinoaortic mechanism.
37. Buffer nerves.
38. Baroreceptors.
39. Chemoreceptors.
40. Bainbridge reflex.
41. Streamline and turbulent flow of blood.
42. Windkessel effect.
43. Mean volume of blood flow.
44. Velocity of blood flow.
45. Circulation time.
46. Autoregulation.
47. Determinants of arterial blood pressure.
48. Vasomotor center.
49. Vasomotor tone.
50. Nerve supply to blood vessels.
51. Renal regulation of blood pressure.
52. Vasoconstrictor substances.
53. Vasodilator substances.
54. Renin-angiotensin mechanism.
55. Hypertension.
56. Venous pressure.
57. Capillary pressure.
58. Arterial pulse.
59. Phlebogram.
60. Phasic changes in coronary blood flow.
61. Regulation of coronary circulation.
62. Coronary occlusion.
63. Myocardial infarction.
64. Angina pectoris.
65. Physiological shunt in heart.
66. Measurement of cerebral blood flow.

67. Regulation of cerebral blood flow.
68. Cushing reflex.
69. Stroke or cardiovascular accident.
70. Capillary circulation (microcirculation).
71. Shunt in capillaries.
72. Cutaneous circulation.
73. Vascular responses of skin.
74. Lewis triple response.
75. Fetal circulation.
76. Neonatal circulation.
77. Hemorrhage.
78. Manifestations of circulatory shock.
79. Syncope or fainting.
80. Vasovagal syncope.
81. Cardiovascular changes in moderate exercise.
82. Effect of exercise on blood pressure.