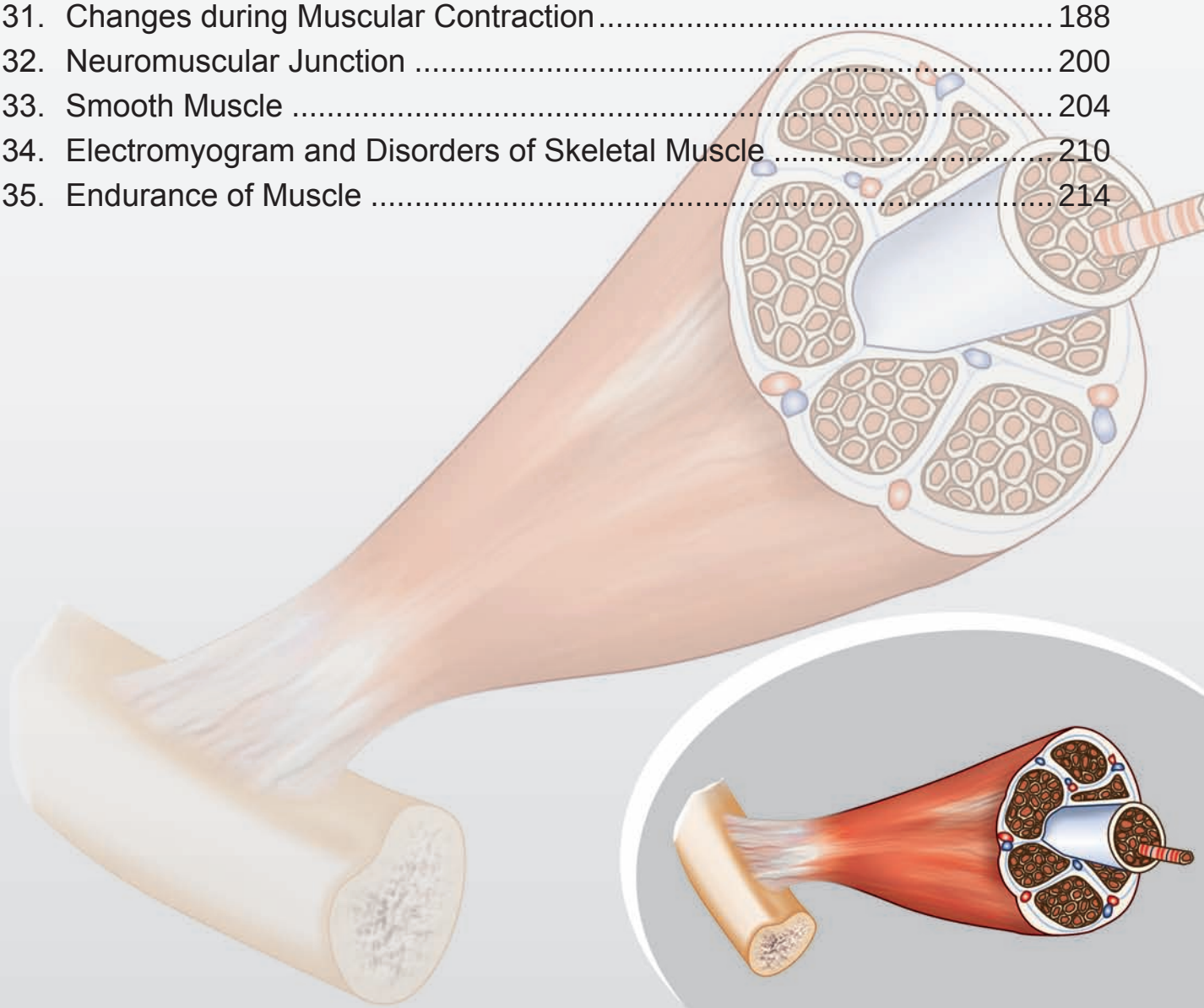
Section 3

Muscle Physiology



Classification of Muscles

Chapter 28

- 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 29

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.**

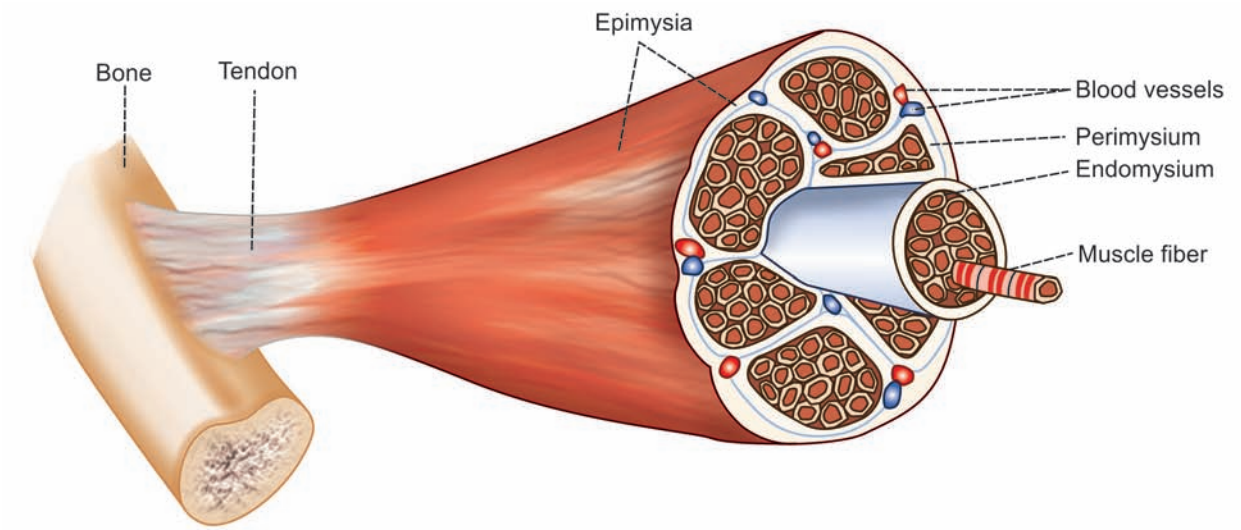


FIGURE 29.1: Structure of a skeletal muscle

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.

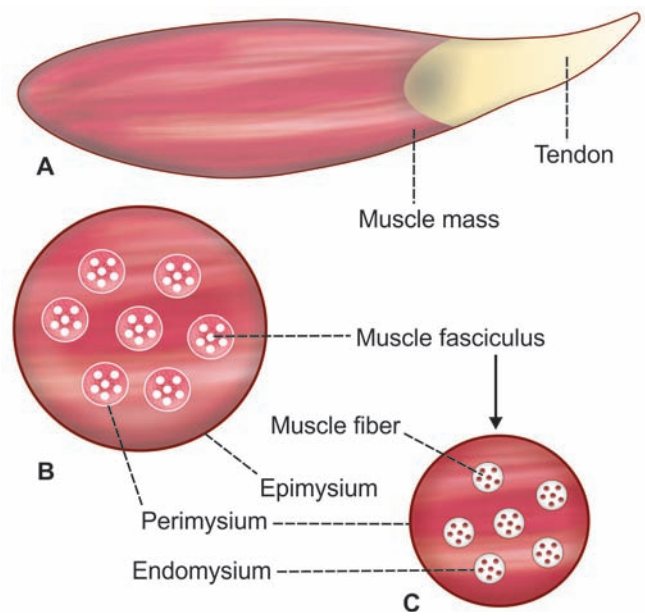


FIGURE 29.2: Diagram showing. **A.** Skeletal muscle mass; **B.** Cross-section of muscle; **C.** One muscle fasciculus.

■ 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.

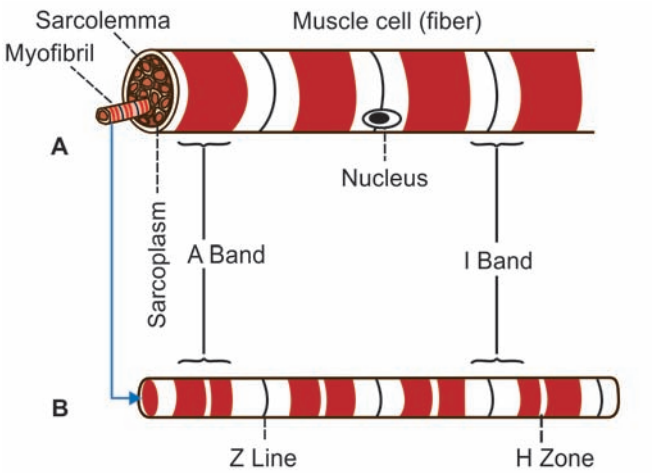


FIGURE 29.3: A. One muscle cell; **B.** One myofibril.

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.

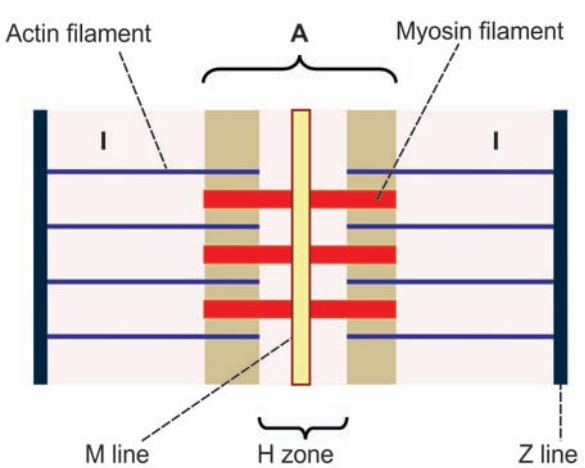


FIGURE 29.4: Sarcomere. A = A band, I = I band.

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.

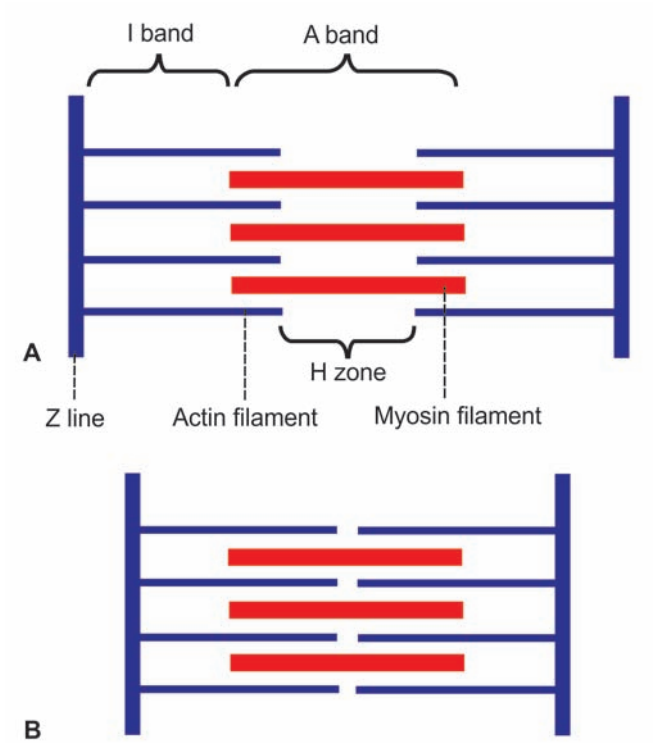


FIGURE 29.5: Sarcomere in resting muscle **A.** Contracted muscle; **B.** During contraction; Z lines come close, H zone and I band are reduced and no change in A band.

■ 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).

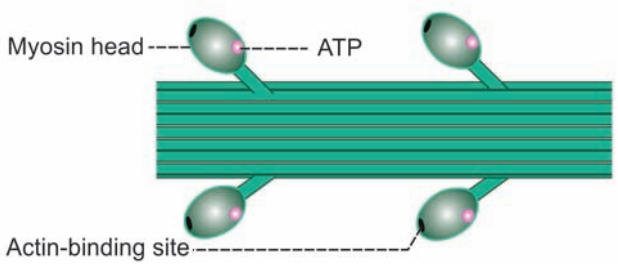


FIGURE 29.6: Diagram showing myosin filament. ATP = Adenosine triphosphate.

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.

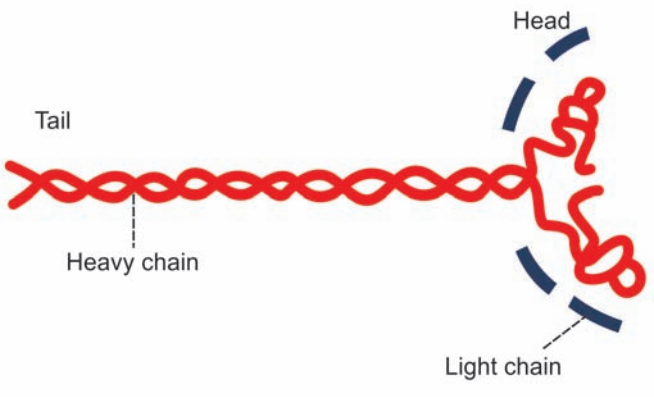


FIGURE 29.7: Myosin molecule formed by two heavy chains and four light chains of polypeptides

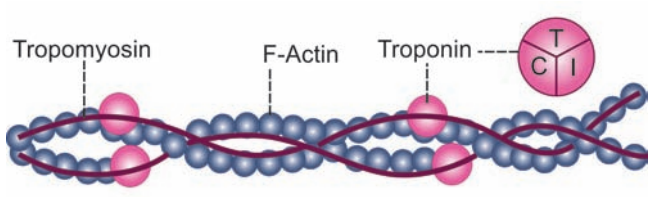


FIGURE 29.8: Part of actin filament. Troponin has three subunits, T, C and I.

■ 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.

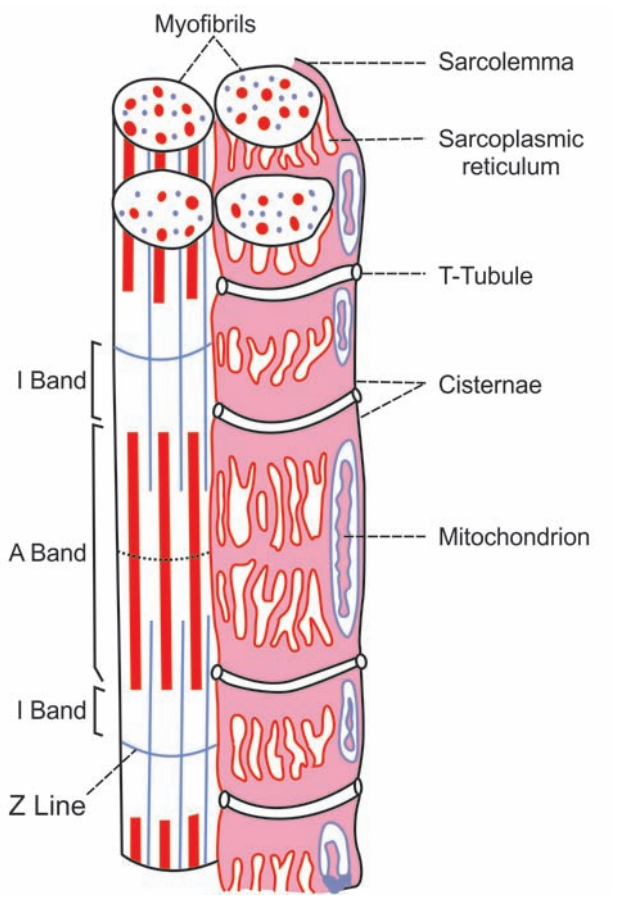


FIGURE 29.9: Diagram showing the relation between sarcotubular system and parts of sarcomere. Only few myofilaments are shown in the myofibril drawn on the right side of the diagram.

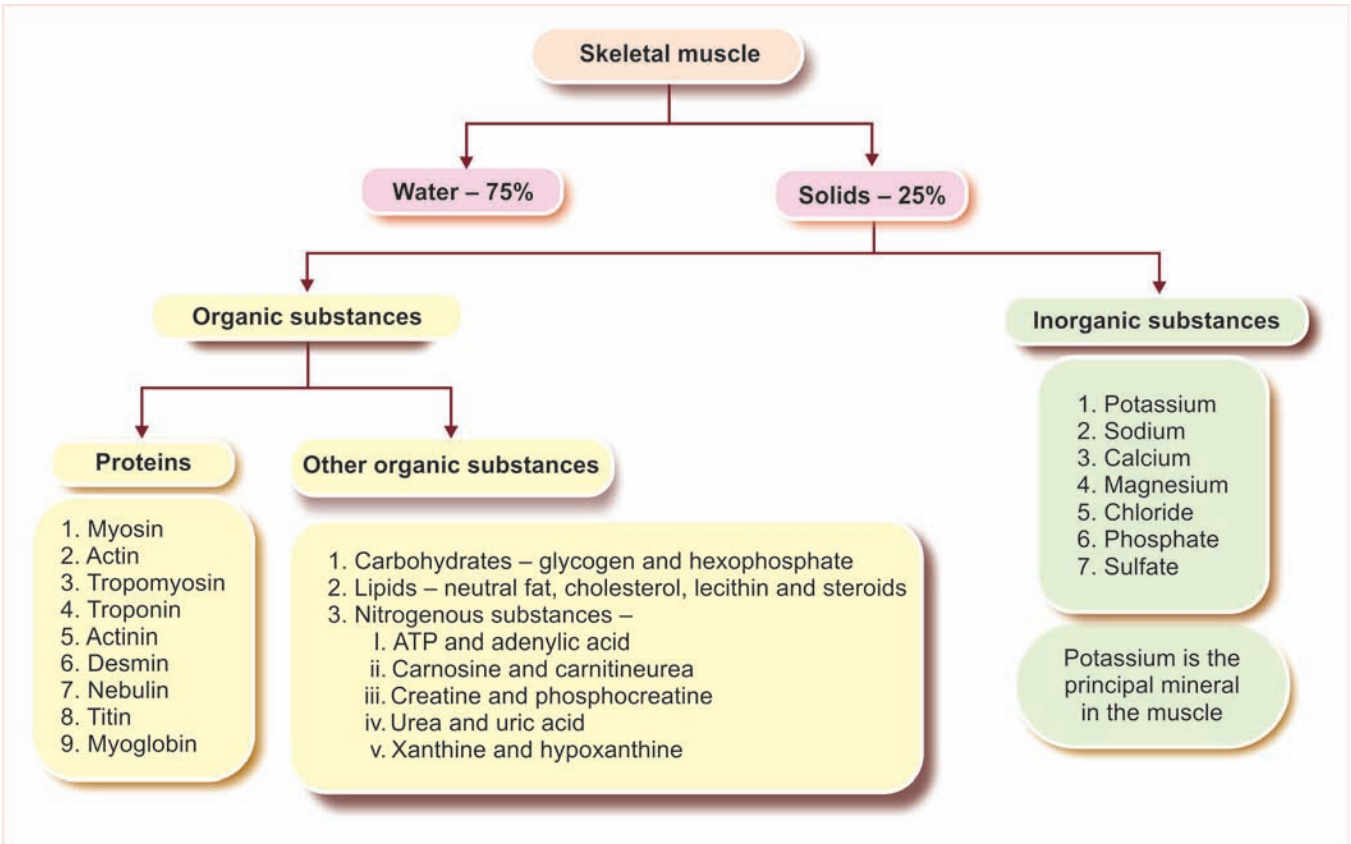


FIGURE 29.10: Composition of skeletal muscle

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 (Chapter 31).

■ 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 30

- EXCITABILITY
  - DEFINITIONS
  - TYPES OF STIMULUS
  - QUALITIES OF STIMULUS
  - EXCITABILITY CURVE OR STRENGTH-DURATION CURVE
- CONTRACTILITY
  - TYPES OF CONTRACTION
  - SIMPLE MUSCLE CONTRACTION OR TWITCH OR CURVE
  - CONTRACTION TIME – RED MUSCLE AND PALE MUSCLE
  - FACTORS AFFECTING FORCE OF CONTRACTION
  - LENGTH-TENSION RELATIONSHIP
  - REFRACTORY PERIOD
- MUSCLE TONE
  - DEFINITION
  - MAINTENANCE OF MUSCLE TONE
  - APPLIED PHYSIOLOGY – ABNORMALITIES OF MUSCLE TONE

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).

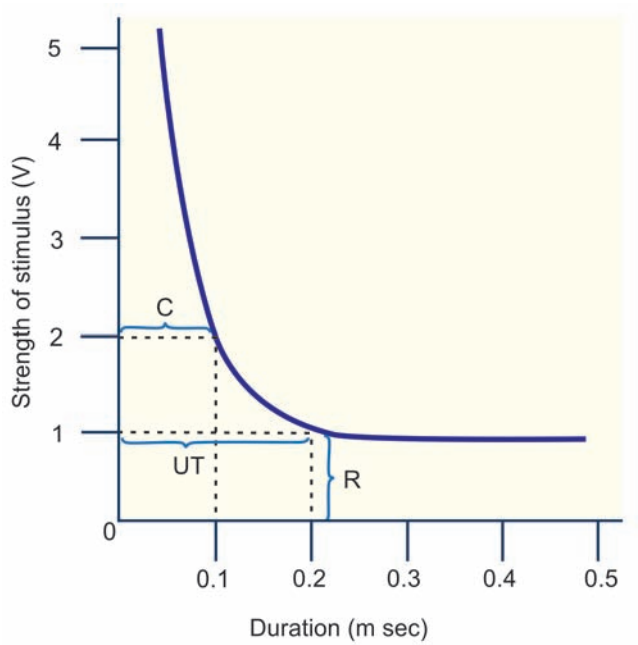


FIGURE 30.1: Strength–duration curve. R = Rheobase, UT = Utilization time, C = Chronaxie.

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.

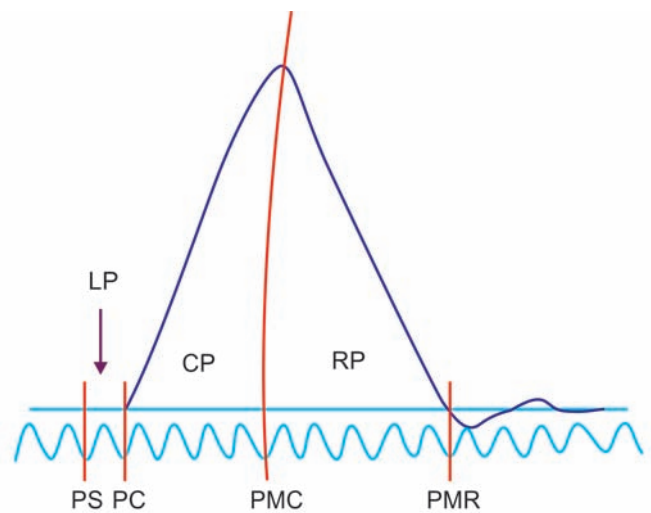


FIGURE 30-2: Isotonic simple muscle curve
PS = Point of stimulus
PC = Point of contraction
PMC = Point of maximum contraction
PMR = Point of maximum relaxation
LP = Latent period (0.01 sec)
CP = Contraction period (0.04 sec)
RP = Relaxation period (0.05 sec)

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.

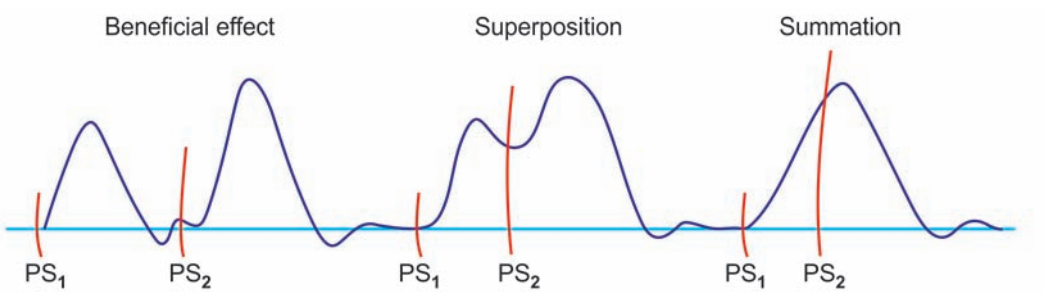


FIGURE 30.3: Effects of two successive stimuli. PS_1 = Point of first stimulus, PS_2 = Point of second stimulus.

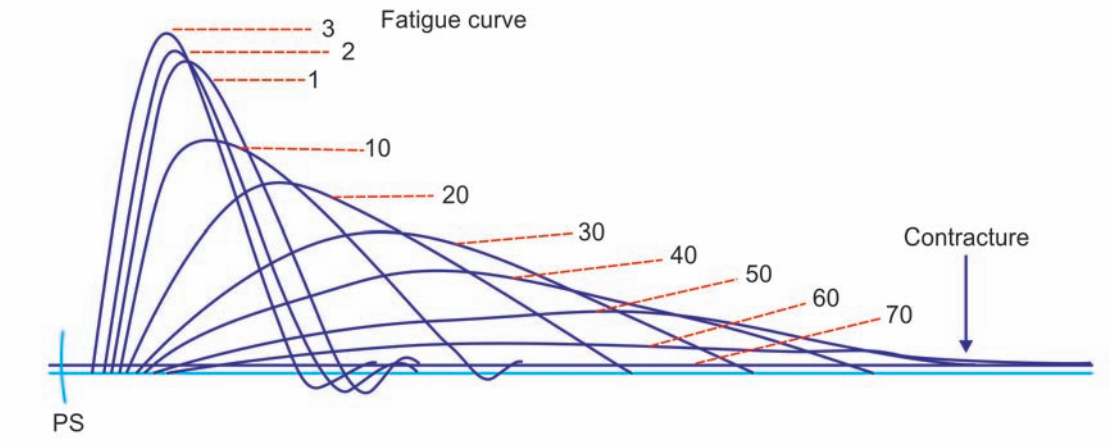


FIGURE 30.4: Fatigue curve. PS = Point of stimulus.

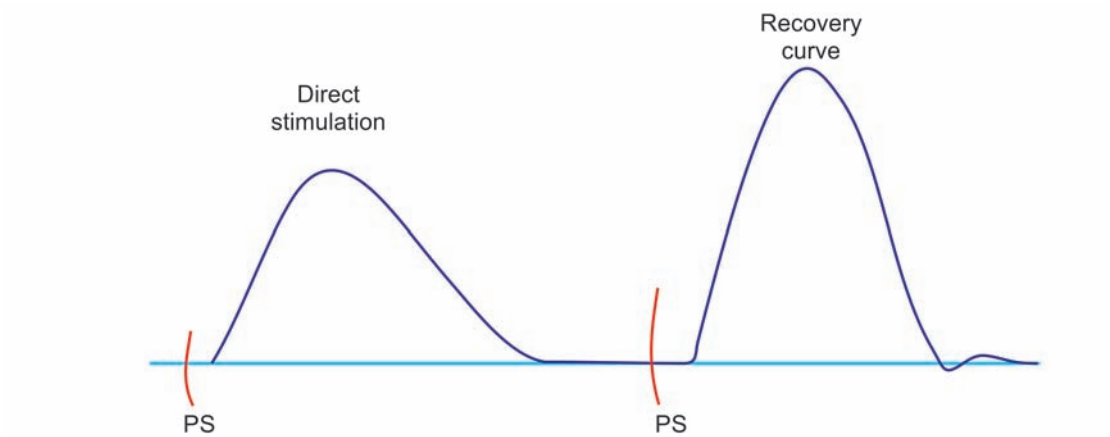


FIGURE 30.5: Recovery curve. PS = Point of stimulus.

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

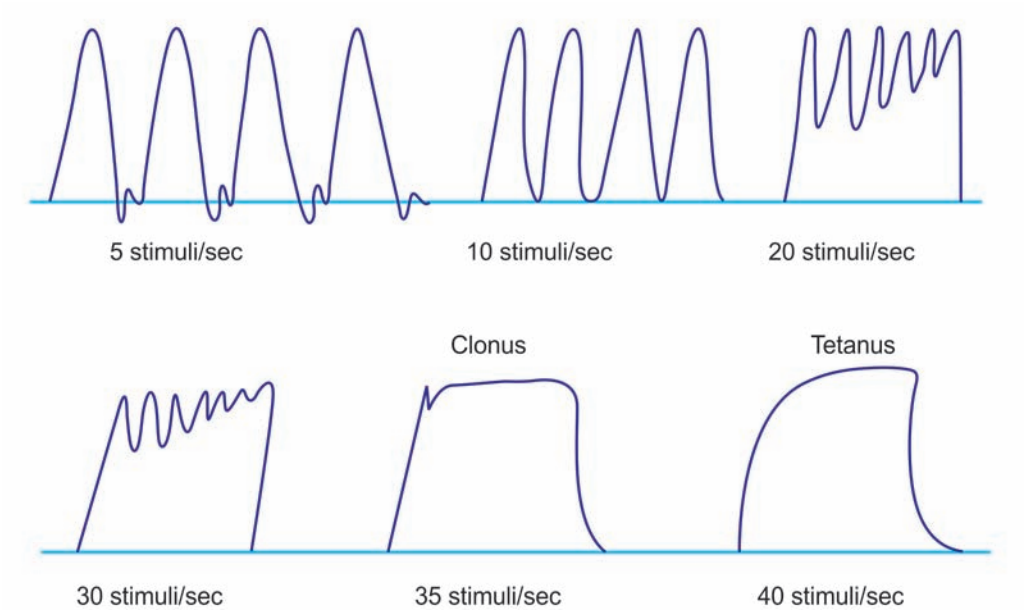


FIGURE 30.6: Genesis of tetanus and tetanus curves

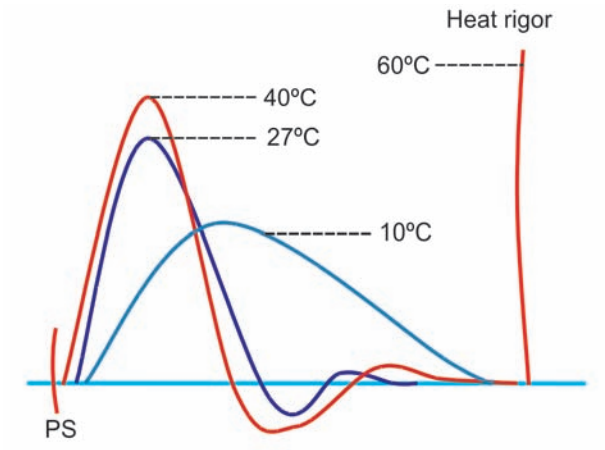


FIGURE 30.7: Effects of variations of temperature

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.**

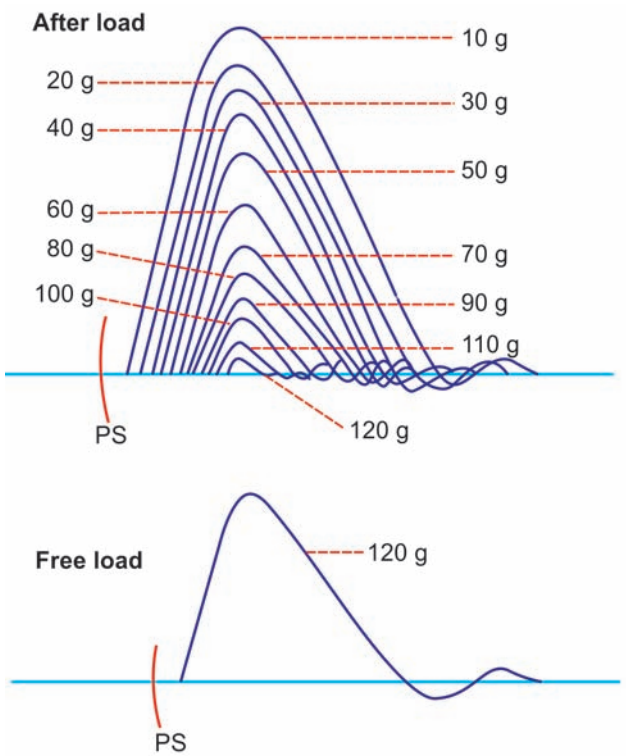


FIGURE 30.8: Effect of after load and free load. PS = Point of stimulus. In free-loaded condition, the force of contraction is greater than in after-loaded condition with the same weight.

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.

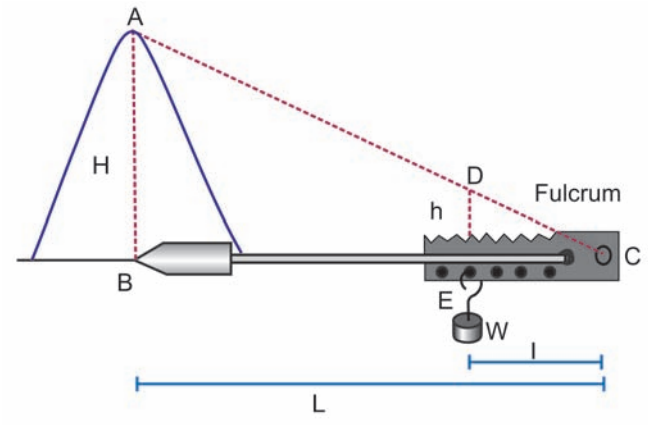


FIGURE 30.9: Work done by the muscle

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.

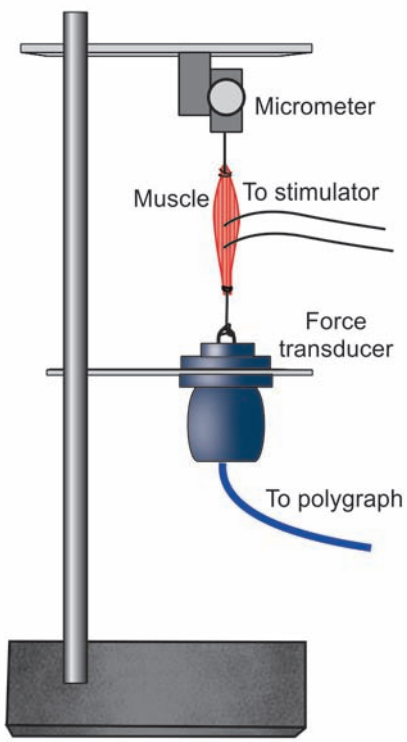


FIGURE 30.10: Experimental setup to measure the tension developed in the muscle

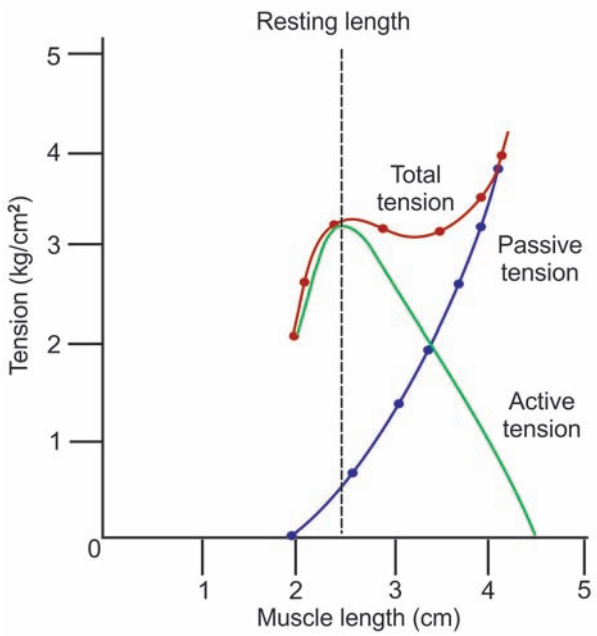


FIGURE 30.11: Length-tension curve

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 Chapter 157.

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 (Chapter 157).

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.

Refer Chapter 34 for details.

Changes during Muscular Contraction

Chapter 31

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

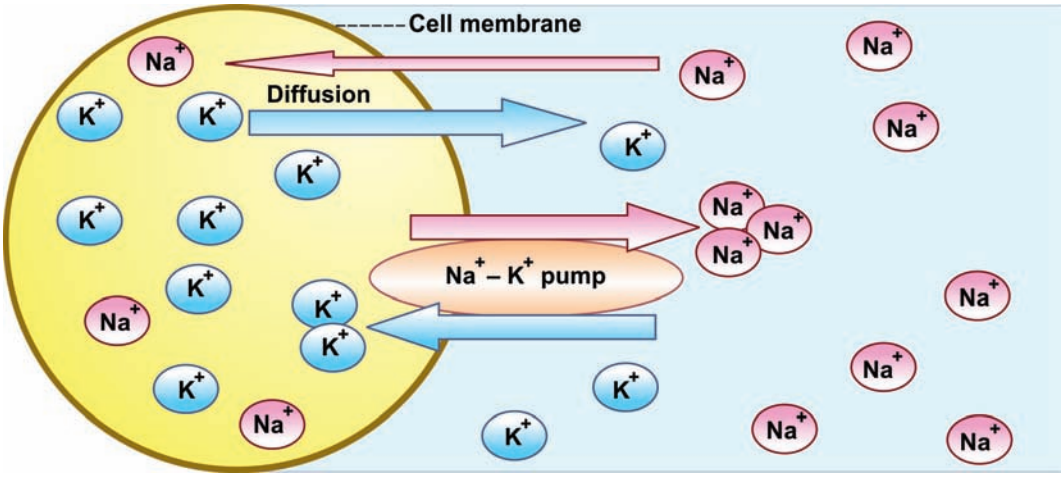


FIGURE 31.1: Development of resting membrane potential by sodium-potassium (Na^+-K^+) pump and diffusion of ions. Na^+-K^+ pump actively pumps three Na^+ outside and two K^+ into the cell. However, the diffusion of K^+ out of the cell is many times greater than the diffusion of Na^+ inside the cell because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

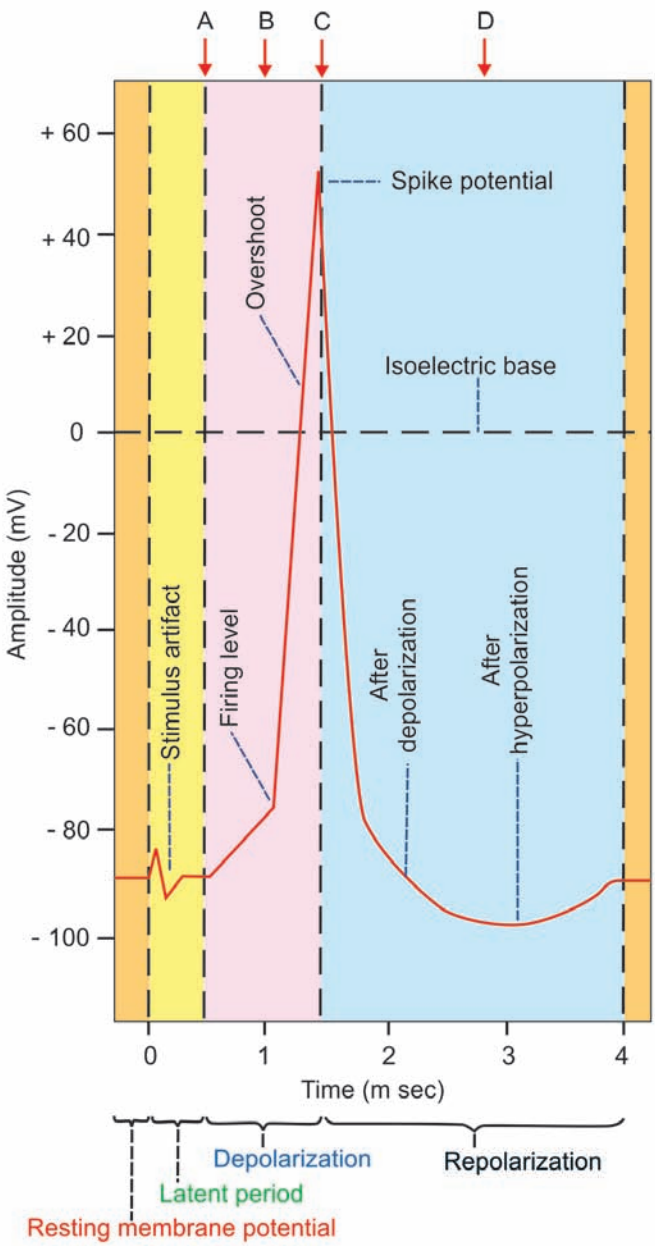


FIGURE 31.2: Action potential in a skeletal muscle
A = Opening of few Na^+ channels
B = Opening of many Na^+ channels
C = Closure of Na^+ channels and opening of K^+ channels
D = Closure of K^+ channels

■ 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).

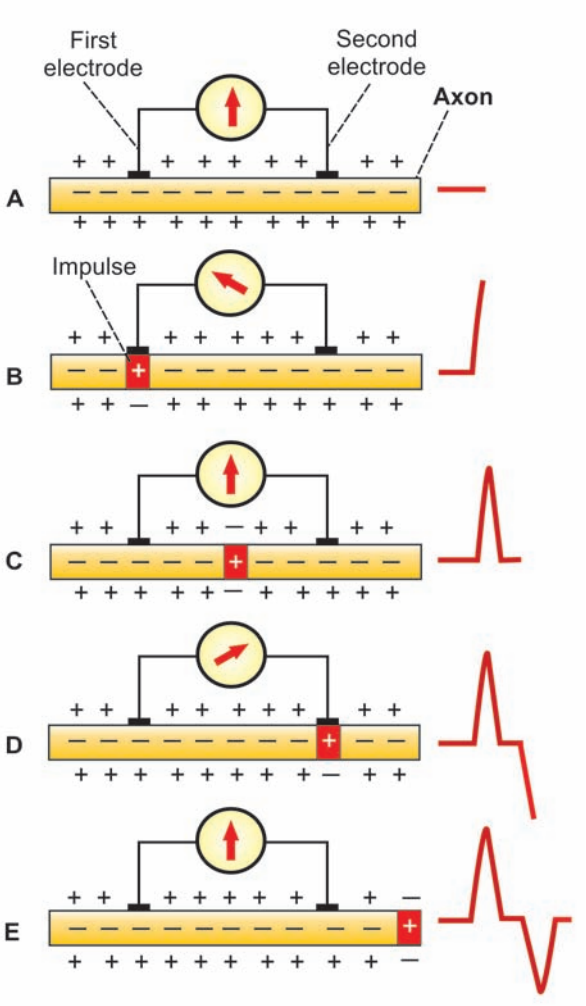


FIGURE 31.3: Biphasic action potential in an axon recorded by placing both the electrodes outside the axon
A = Resting state – zero potential
B = Depolarization of membrane under first electrode
C = Repolarization of membrane under first electrode followed by zero potential
D = Depolarization of membrane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

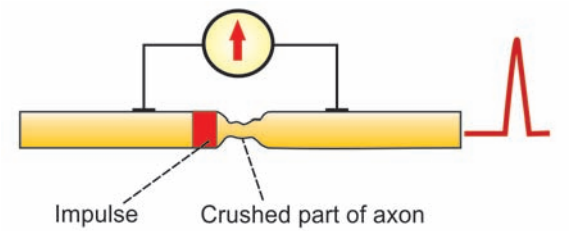


FIGURE 31.4: Monophasic action potential in a crushed axon

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: Chapter 140).

Different Graded potentials

1. End plate potential in neuromuscular junction (Chapter 32)
2. Electronic potential in nerve fibers (Chapter 136)
3. Receptor potential (Chapter 139)
4. Excitatory postsynaptic potential (Chapter 140)
5. Inhibitory postsynaptic potential (Chapter 140).

■ 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 (Chapter 136).

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 Configurations

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

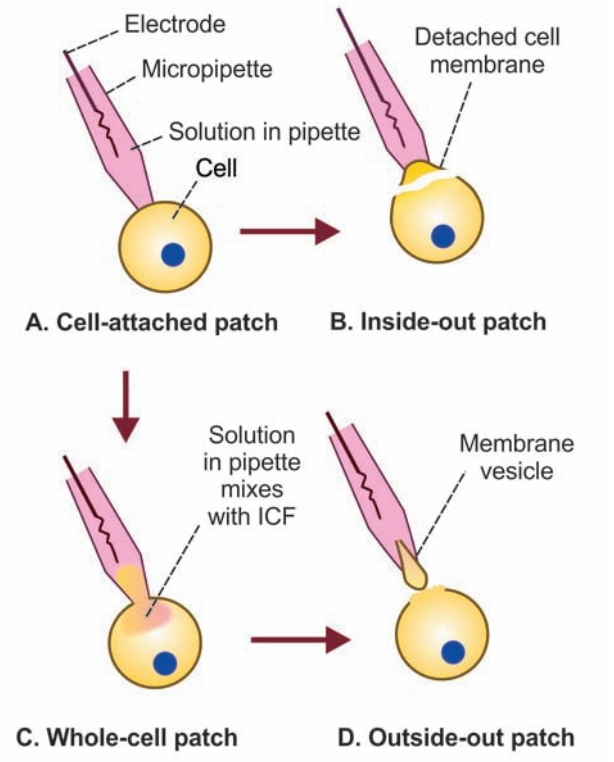


FIGURE 31.5: Patch-clamp configurations

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.

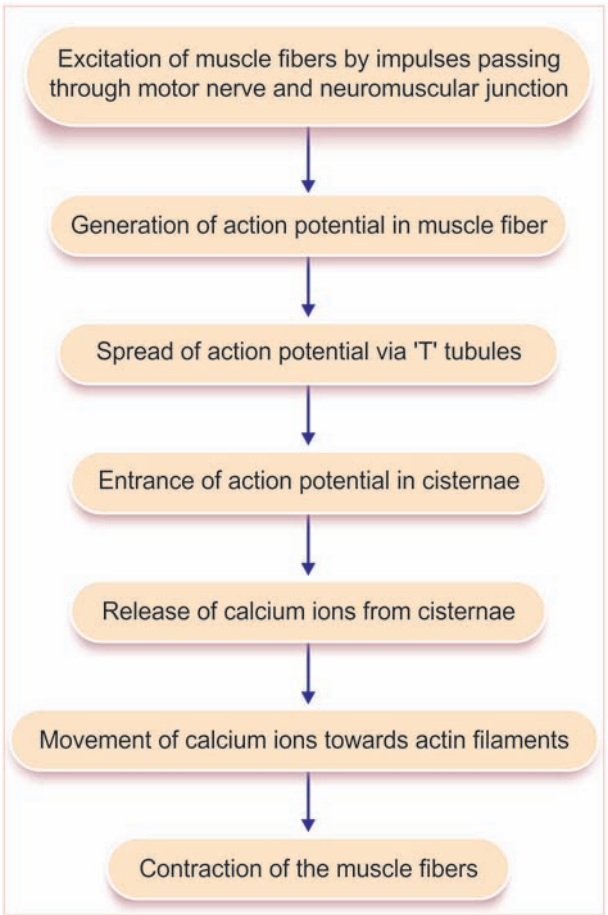


FIGURE 31.6: Excitation-contraction coupling

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

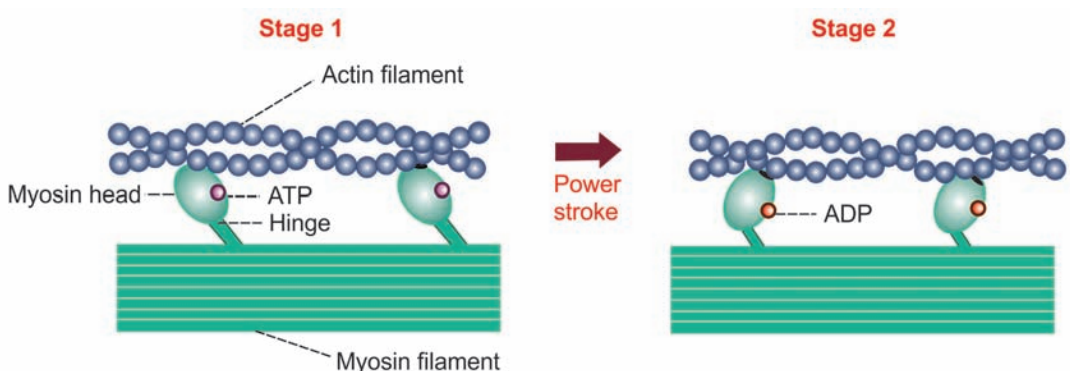


FIGURE 31.7: Diagram showing power stroke by myosin head.
Stage 1: Myosin head binds with actin; Stage 2: Tilting of myosin head (power stroke) drags the actin filament.

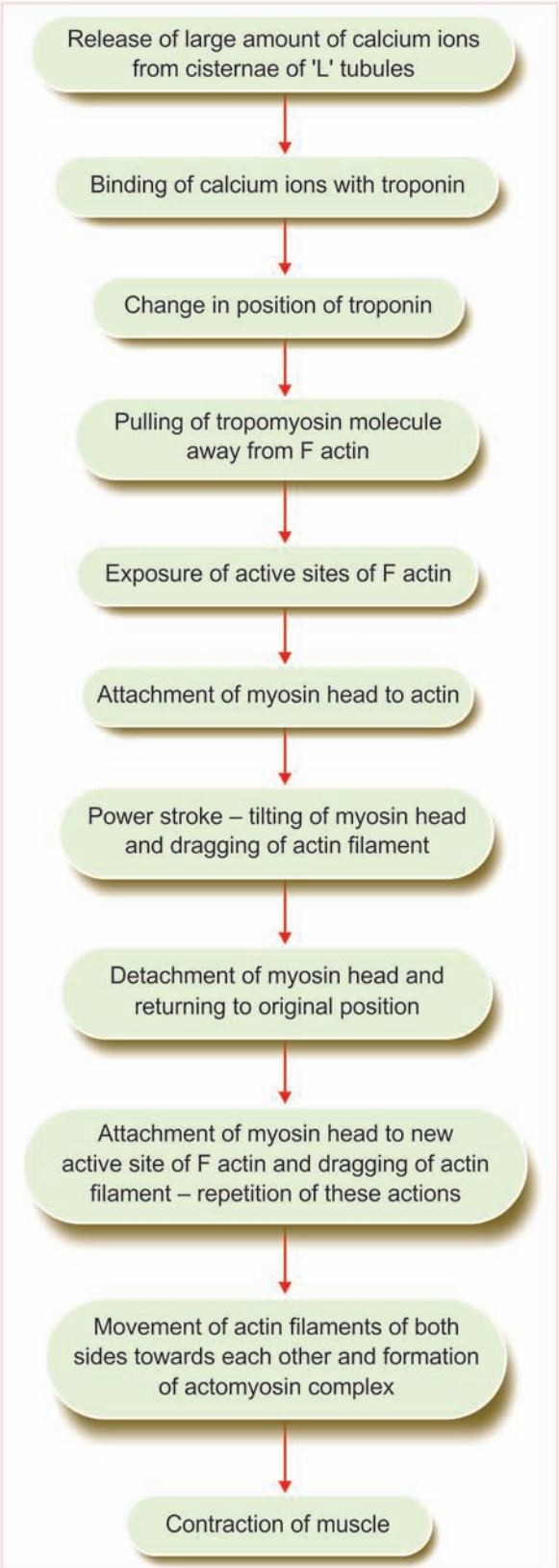


FIGURE 31.8: Sliding mechanism

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

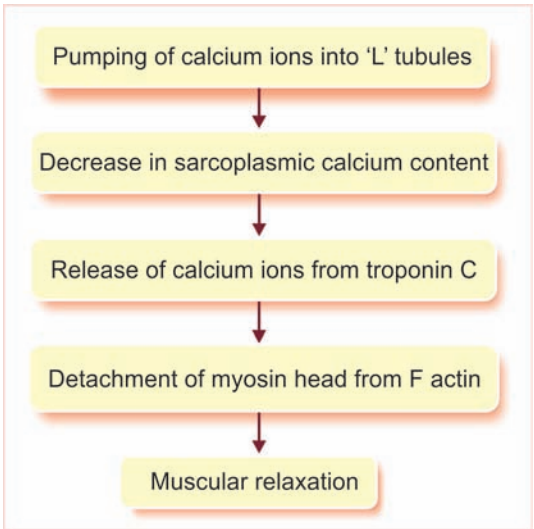


FIGURE 31.9: Sequence of events during muscular relaxation

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).

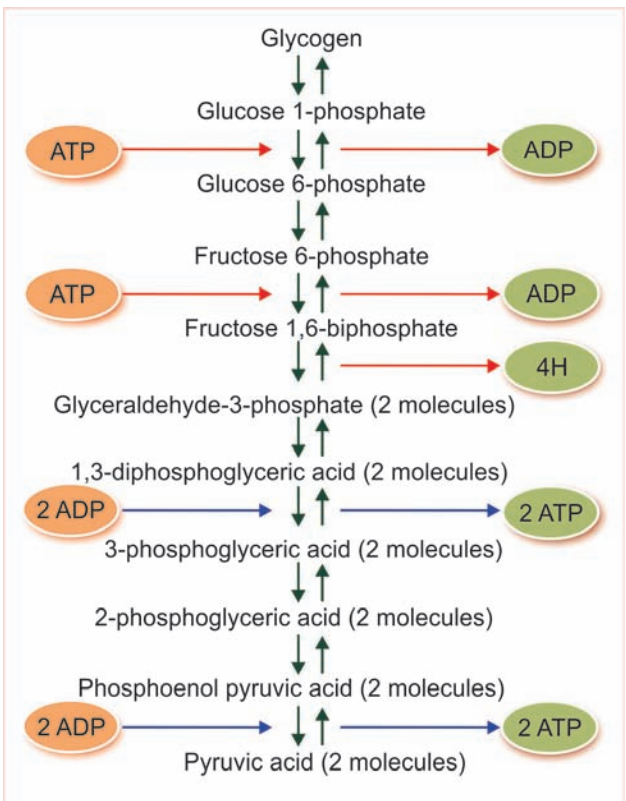


FIGURE 31.10: Glycolysis/Embden-Meyerhof pathway
Number of ATP molecules formed in this pathway:
Total ATP formed = 4 molecules
Loss of ATP during phosphorylation = 2 molecules
Net ATP formed during glycolysis = 2 molecules

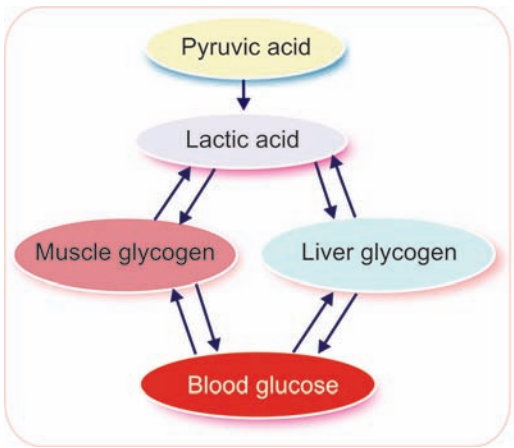


FIGURE 31.11: Cori cycle

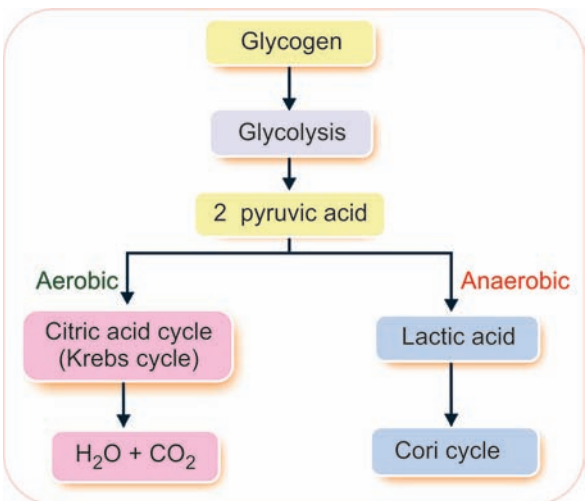


FIGURE 31.12: Schematic diagram showing carbohydrate metabolism in muscle

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 32

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

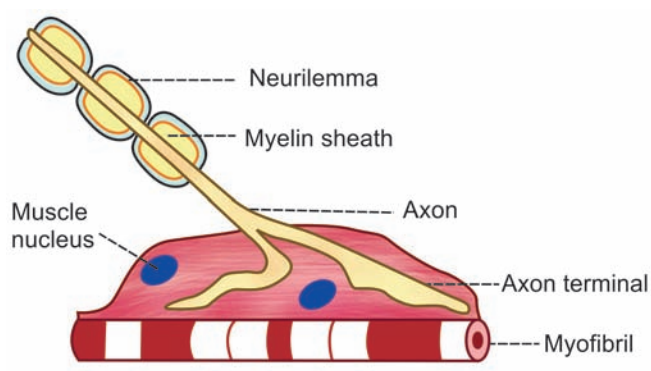


FIGURE 32.1: Longitudinal section of neuromuscular junction

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.

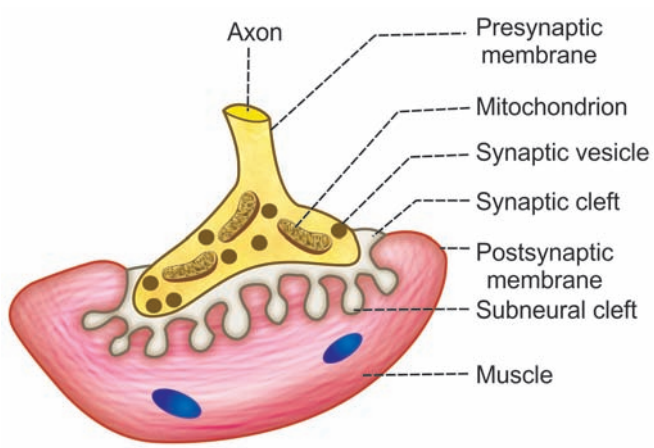


FIGURE 32.2: Structure of neuromuscular junction

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 (Chapter 31) and it is not action potential. Refer Table 31.1 for the properties of graded potential.

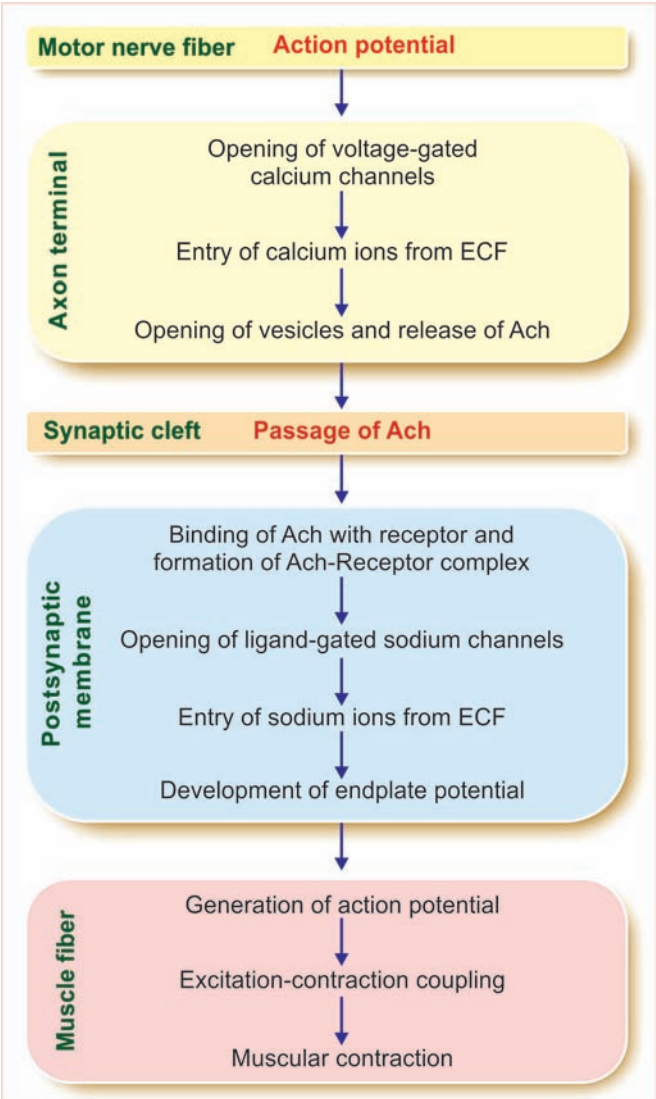


FIGURE 32.3: Sequence of events during neuromuscular transmission. Ach = Acetylcholine, ECF = Extracellular fluid.

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. Refer Chapter 34 for details.

■ 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. Refer Chapter 34 for details.

Chapter 33

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

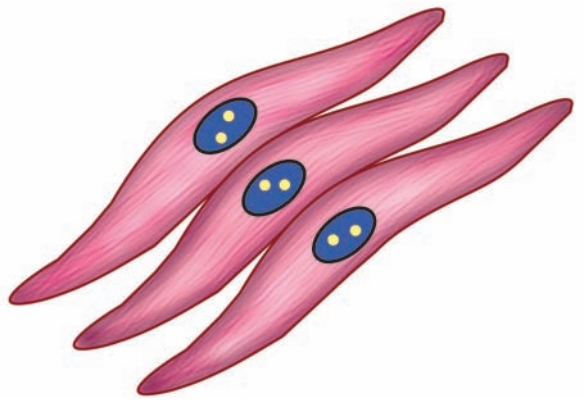


FIGURE 33.1: Smooth muscle fibers

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.

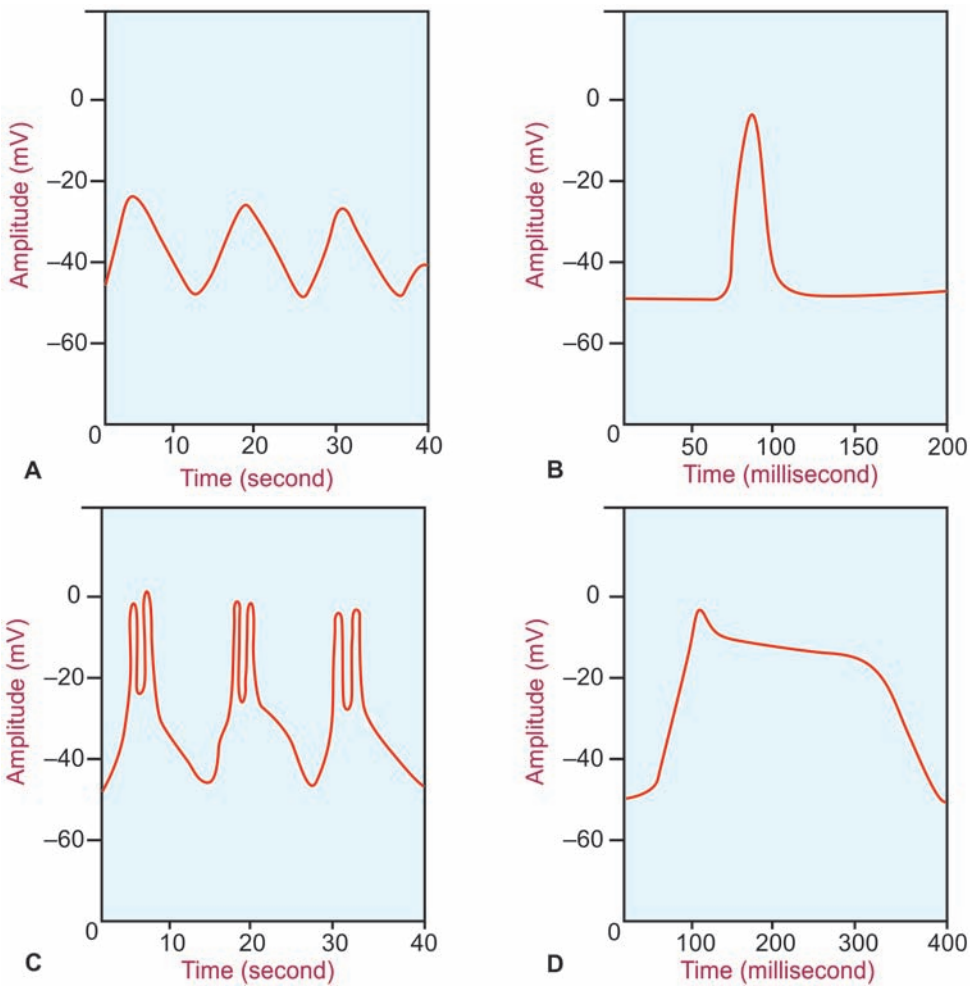


FIGURE 33.2: Electrical activities in smooth muscle
A = Slow-wave rhythm of resting membrane potential
B = Spike potential
C = Spike potential initiated by slow wave rhythm
D = Action potential with plateau

■ 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

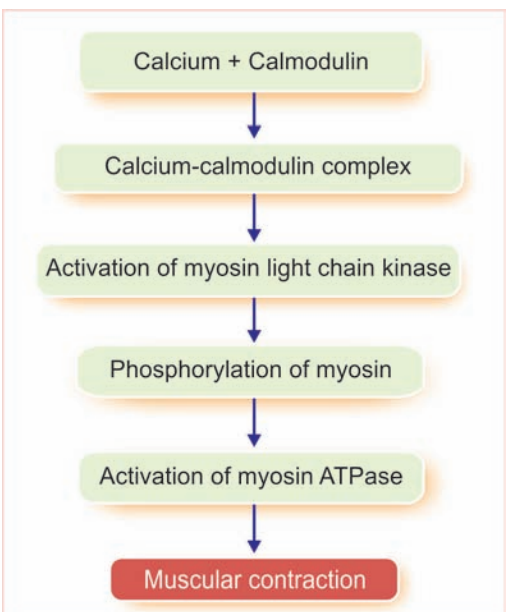


FIGURE 33.3: Molecular basis of smooth muscle contraction

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).

Electromyogram and Disorders of Skeletal Muscle

Chapter 34

- 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 neuromuscular diseases such as motor neuron lesions, peripheral nerve injury and myopathies.

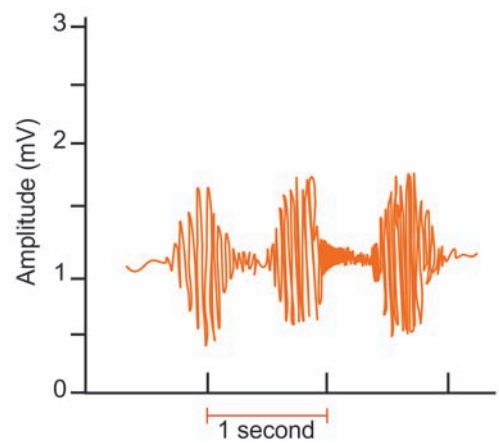


FIGURE 34.1: Electromyogram during alternate contraction and relaxation of biceps muscle

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 (Chapter 144). 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 (Chapter 144). 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 (Chapter 17). 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.

Endurance of Muscle

Chapter 35

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.