CHAPTER

10

Nerve and Muscle Physiology

NEURON

Structural and functional unit of nervous system is called neuron. The term neuron is used to describe the nerve cell and its processes, the dendrites and the axon (Fig. 10.1). It is specialized for the function of reception, integration and transmission of information in the body. The basic structure of neuron is best studied in a spinal motor neuron.

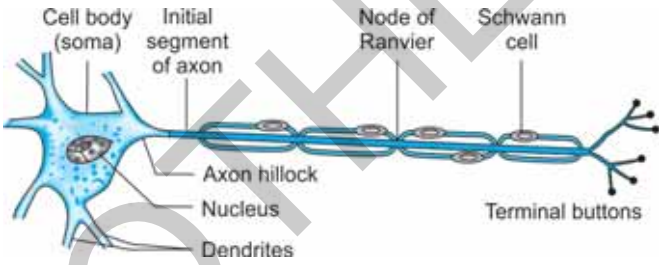


Fig. 10.1: Structure of neuron

Structure

Nerve Cell Body (Soma or Perikaryon)

They are of various size and forms: stellate, round, pyramidal, fusiform, etc. Its principal constituents are similar to a generalized cell. However, after fixation with special stains its cytoplasm also reveals the presence of:

Nissl granules/bodies

Nissl bodies are large granular body found in neuron. They are present in all over the soma (body), except in axon hillock and they extend to some extent in the dendrities, but not within the axon. These granules are rough endoplasmic reticulum (RER) with free ribosomes and are the site of protein synthesis. They are thought to be involved in the synthesis of neurotransmitter such as acetylcholine. Nissl bodies are basophilic granules. Chromatolysis (disappearance of nissl bodies) is an important histological sign of neuronal injury.

Neurofibrillae

These are fine threads 6–10 nm in diameter and of variable length. They traverse the cytoplasmic matrix forming a loose framework of fibrils in the cytoplasm.

Note

There is no centriole which indicate that the highly specialized nerve cell lost its power of division. Nerve cell once destroyed are replaced merely by neuroglia, cells which support the nerve cell.

Dendrites

These are 5–7 processes extending out from the cell body and arborize extensively after they leave the cell. They also contains nissl granule, mitochondria and neurofibrillae. They are the receptive processes of the neuron. Impulse can be transmitted from one dendrite to another in the CNS.

Axon (Axon Cylinder or Nerve Fiber)

It originates from a thickened area of the cell body called axon hillock, in which there is no nissl granules. The first portion of the axon is called initial segment. In a motor neuron, the axon hillock and the initial segment of the axon have the lowest threshold for excitation. This is because they have a much higher density of voltage gated sodium channels. The cytoplasmic fluid occupying the center of the axon is known as axoplasm. The cell membrane enveloping the cytoplasm is also continued on the axon as axolemma. Axon vary from a few microns in length to as long as 90 cm. Axon is the single elongated cytoplasmic extension with the specialized function of conducting impulses away from the cell body.

Synaptic Knobs (Terminal Buttons or Axon Telodendria)

The axon divides into terminal branches, each ending in a number of synaptic knobs. They contain granules or vesicles in which synaptic transmitter secreted by the nerve is stored.

Functionally speaking, the neuron can be divided into four zones:

1. Dendrites and Soma (cell body)—Receptor zone
2. Axon hillock of body and initial segment of axon—Generator area (Nerve impulse is generated)
3. Axon (main length)—Transmitter zone (Transmits nerve impulse).
4. The nerve terminals (Terminal knobs or buttons)—Release zone (release neurotransmitters).

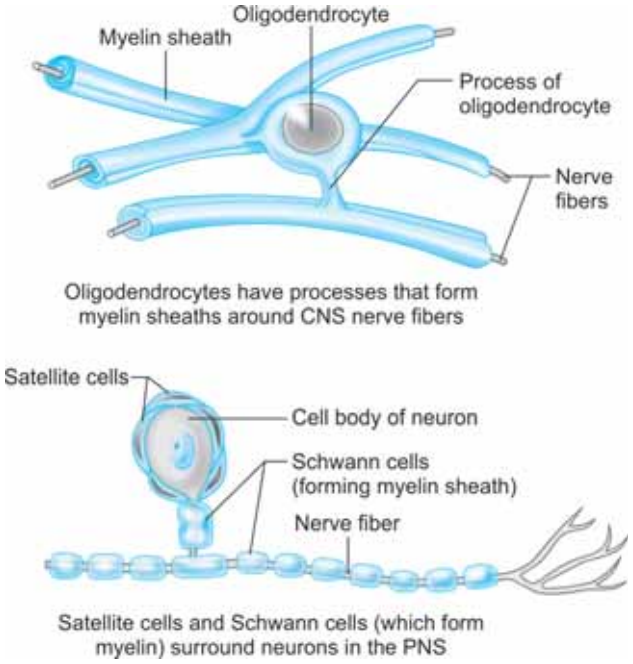


Fig. 10.2: Myelinogenisis

Myelinogenesis

Neurolemma or sheath of Schwann has got a cell, Schwann cell which takes part in the deposition of myelin sheath round the axon, a process called myelinogenesis. Myelination of axons in the CNS system is by the oligodendrocytes. One oligodendrocytes sends processes to up to 40 axons (Fig. 10.2).

Schwann cells are found both in myelinated and nonmyelinated nerve fibers of peripheral nervous system (Table 10.1). In myelinated nerves, Schwann cells provide structural support and form myelin sheath, whereas in nonmyelinated nerves Schwann cells only provide structural support. Schwann cells are derived from neuroectoderm.

Glial Cell (Neuroglia)

Glial cell means glue, these are the cells which support the nerve cells. Glial cells are very numerous. There are approximate ten times as many glial cells as neurons. Unlike the neurons, the glial cells are capable of multiplying by mitosis. Glial cell are of three types:

1. ***Microglia:*** They are phagocytic cells that enter the CNS from meninges and blood vessels.
2. ***Astrocytes:*** They are found throughout the brain joining to the blood vessels and investing synaptic structures, neural bodies and neural processes.

   Function: It plays an important role in support, transport mechanisms, inflammatory and repairative reactions and also helps in forming the blood-brain barrier. They also help in maintaining optimal concentration of ions and neurotransmitter (specially glutamine) in the brain neurons.
3. ***Oligodendrolia:*** These are cells that form myelin around within CNS. The axons in the CNS do not have Schwann cells.

Table 10.1: Differences between myelinated and unmyelinated nerves

Myelinated nerves	Unmyelinated nerves
1. Multiple layers of Schwann cell membrane make myelin, formed by coiling of membrane many times round the axon.	1. Axons are simply surrounded in the Schwann cell without wrap ping of myelin.
2. Faster conduction of nerve impulse (50–100 times) than the unmyelinated fiber because of saltatory conduction, i.e. jumping of impulse from node to node over intersegmental region.	2. Slower conduction of nerve impulses as it is a continuous process due to lack of myelination.
3. For example i. All preganglionic fibers of ANS ii. Nerve fibers in somatic nervous system more than 1 mm in diameter.	3. For example i. All post-ganglionic fibers of ANS ii. Nerve fibers in somatic nervous system less than 1 mm in diameter

Orthodromic and Antidromic Conduction (Fig. 10.3)

Experimentally, an axon can conduct impulse in either direction. When an action potential is initiated in the middle of the axon, the impulse shall travel in both direction, i.e. one along the axon towards its terminal knobs and one in opposite direction, i.e. along the axon towards the cell body (soma) and dendrites. However, in the intact body, i.e. in the natural situation, the impulses are conducted in the one direction only, i.e. from synaptic junction or receptors along axons to their termination. Such conduction is called orthodromic conduction. Conduction in opposite direction is called antidromic conduction, i.e. opposite to physiological direction. However, antidromic conduction is very rare and may be seen only in muscle tissue, sensory nerve supplying the blood vessels. In nerve fibers, the propagation of action potential is unidirectional (orthodromic) because transmission across neuromuscular junction and synapses is unidirectional.

Nerve Fibers Types and Function

Erlanger and Gasser's Classification (Table 10.2)

Nerve fibers have been divided into A, B and C groups. A group is further subdivided into α, β, γ and δ fibers. Only C fibers are nonmyelinated, A and B fibers are myelinated.

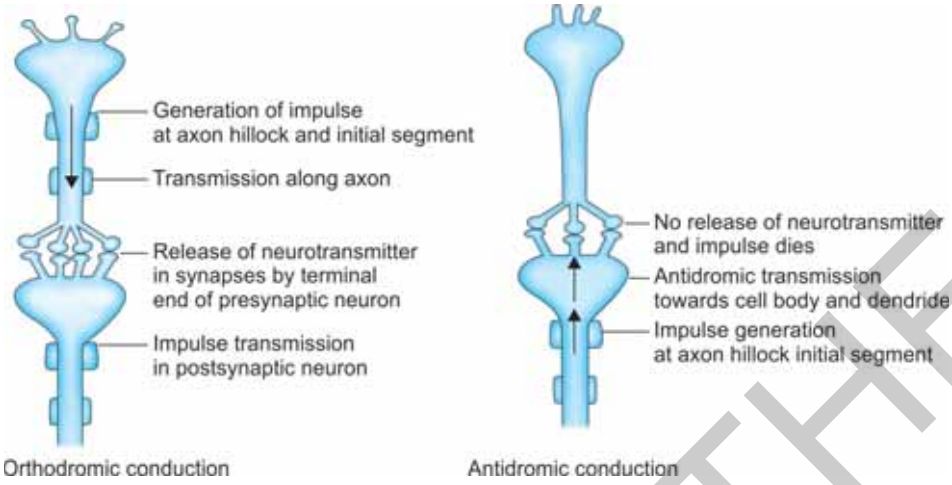


Fig. 10.3: Types of conduction

Table 10.2: Erlanger and Gassers classification

Class of nerve fiber	Diameter of fiber (in µm)	Velocity of conduction (m/s)	Function
A			
Aα	12–20 (Thickest and heavily myelinated)	70–120	Proprioception, somatic motor
Aβ	5–12 (Thinner than a; myelinated)	30–70	Touch, pressure, motor
Aγ	3–6 (Still more thin; slightly myelinated)	15–30	Motor to muscle spindles
Aδ	2–5 (Still thinner)	12–30	Pain, cold, touch
B	<3 (Myelinated)	3–15	Preganglionic fibers of ANS
C			
Dorsal root	0.4–1.2 (Unmyelinated)	0.5–2	Pain, temperature, some mechanoreception, reflex responses
Sympathetic	0.3–1.3 (Unmyelinated)	0.7–2.3	Postganglionic sympathetic

Table 10.3: Numerical classification for sensory neurons

Number	Origin	Fiber Type
Ia	Muscle spindle, annulospiral ending	Aα
Ib	Golgi tendon organ	Aα
II	Muscle spindle, flower-spray ending, touch, pressure	Aβ
III	Pain and temperature receptors, some touch, pressure	Aδ
IV	Pain and other receptors	Dorsal root 'C' fibers

Numerical Classification (Lloyed and Hunt) (Table 10.3)

This is used for sensory neurons and is based on the origin of nerve fibers.

Physio-clinical Classification (Table 10.4)

It has clinical as well as physiological significance and is based on sensitivity to hypoxia, pressure and anesthetic agents.

Important Facts

- Type A fibers have maximum velocity because they are thick and myelinated. Among A fibers, A α have maximum conduction because they are thickest and myelinated.
- Type C fibers have slowest conduction because they are thin and nonmyelinated. Type C fibers are post ganglionic autonomic fibers especially postganglionic sympathetic.
- Type B fibers are preganglionic autonomic fibers, both sympathetic and parasympathetic preganglionic.

Table 10.4: Physio-clinical classification

	Most susceptible	Intermediate	Least susceptible
Sensitivity to 'Hypoxia'	B	A	C
Sensitivity to 'Pressure'	A	B	C
Sensitivity to 'Local anesthetics'	C	B	A

- Thickest fibers are for proprioception. Thinnest fibers are postganglionic sympathetic (C).
- Pain is carried by two types of fibers:
  1. *A δ:* These are relatively fast. Therefore the pain carried by these is fast pain (epicritic pain or first pain).
  2. *C:* These are slow, therefore the pain carries by these is slow pain (protopathic pain or second pain).

Local anesthesia, hypoxia and pressure can block the conduction of nerve impulses. Different fibers have different susceptibility.

- Most susceptible fibers to pressure are A fibers and least susceptible fibers to pressure are C fibers. Amongst the A fibers, A α are most susceptible to pressure.
- Most susceptible fibers to hypoxia are B fibers and least susceptible fibers to hypoxia are C fibers.
- Most susceptible fibers to local anesthesia are C fibers and least susceptible fibers to local anesthesia are A fibers.

Neuronal (Axoplasmic) Transport System

Axoplasmic transport is the physical transport of substances in the axoplasm. Neurons are secretory cells; they release neurotransmitters at the axon terminals. Axoplasmic transport may be slow or fast. Fast transport may be antegrade or retrograde, whereas slow transport is always antegrade.

Fast Axoplasmic Transport

It may be antegrade or retrograde:

- *Fast antegrade transport (400 mm/day):* It occurs along the microtubules and is driven by kinesin. It transports membrane-bounded organelles like ER, mitochondria, golgi derived vesicles, microvesicles containing neurotransmitter, lipid, proteins, actin, myosin and the clathrin used in recycling of synaptic vesicle membrane.
- *Fast retrograde transport (200 mm/day):* It also occurs along the microtubules and is driven by the molecular motor dynein. Materials transported by retrograde transport system include empty (used) microvesicles for recycling or degradation by lysosomes, and nerve growth factors. Some toxins (tetanus toxin) and viruses (herpes and rabies) may reach the CNS by retrograde transport.

Slow Axoplasmic (Slow Antegrade) Transport

Slow transport carries tubulin of microtubules, protein subunits of neurofilaments and soluble enzyme for synthesis of neurotransmitters. Occurs at a rate of 0.5–10 mm/day. It is always anterograde. The mechanism is not clear.

Neuronal Injury

The effects of injury to a nerve depend upon the degree of damage. The injuries can be divided into three types:

1. *Neurapraxia:* There is contusion of the peripheral nerve which causes reversible physiological nerve conduction block. The axis cylinder (i.e. axon with its endoneurium) is preserved. Thus, there is physiological conduction without anatomic disruption. The injury is temporary and recovery is complete. It is seen in crutch palsy, tourniquet palsy, and saturday night palsy. Neurapraxia has best prognosis for recover.
2. *Axonotmesis:* There is injury to axon with myelin sheath, but endoneurium is preserved. Spontaneous recovery is expected in some cases. This is seen in closed fracture and dislocations.
3. *Neurotmesis:* There is complete anatomical section of nerve. No recovery is possible. It is seen in open wound.

Structure of a Peripheral Nerve (Fig. 10.4)

A peripheral nerve consists of masses of axis cylinders (axon), each with a neurilemmal tube. An individual nerve fiber is enclosed in a collagen connective tissue known as *endoneurium*. A bundle of such nerve fibers are further bound together by fibrous tissue to form a fasciculus. Binding fibrous tissue is known as *perineurium*. A number of fasciculi are bound together by a fibrous tissue sheath known as *epineurium*. An individual nerve, therefore, is a bundle of a number of fasciculi.

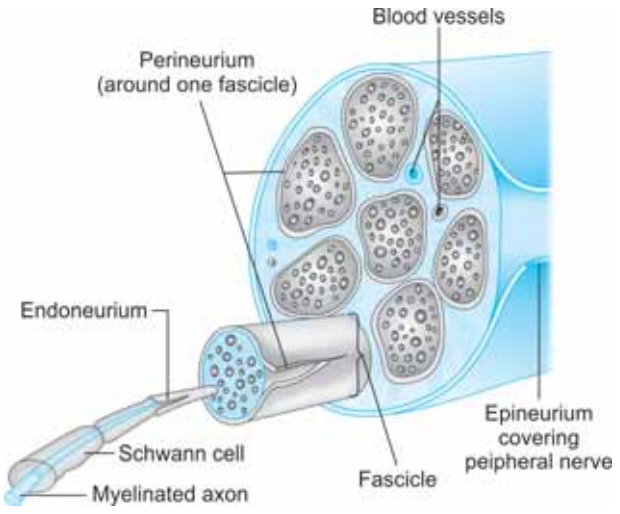


Fig. 10.4: Structure of a peripheral nerve

Degeneration and Regeneration of Nerve Fibers

When a nerve fiber is injured sufficiently, the part distal to the injury dies. Some changes in the proximal part are also seen. The entire process is known as degeneration (also called *Wallerian degeneration*, after Waller who described it).

Common causes of injury

a. Transection
b. Crushing
c. Injection of toxic or poisonous substance into the nerve.
d. Ischemia-interference in blood supply.
e. Hyperpyrexia-increase in body temperature.

Grading of injury (by 'Sunderland')

- *First degree injuries:* Most commonly seen and is secondary to ischemia caused by direct pressure to a nerve for a limited time. Ischemia produces local anoxia with temporary impairment of nerve function. It gets corrected within hours to few weeks, because the axon is not destroyed but merely loses its functional properties for a short time.
- *Second degree injuries:* Prolonged or severe pressure damages the nerve fibers at the pressure point eventually causing death of axon locally and distally.
- *Third degree injuries:* Endoneurial tubes becoming interrupted.
- *Forth degree injuries:* Fascicles becoming disorganized.
- *Fifth degree injuries:* Through and through cutting of nerve fibers, i.e. complete transection.

Degenerative changes occur at three levels

1. Changes in nerve cell body (retrograde changes)
2. Changes in the distal stump
3. Changes at the site of injury.

Series of Degenerative Changes

1. Change in nerve cell body begin within 48 hours of injury
   a. Chromatolysis: Nissl's granule disintegrate.
   b. Golgi apparatus, mitochondria, and neurofibrils are fragmented and disappear.
   c. Cell draws more fluid and become round.
   d. Nucleus increase in size and move to periphery.
2. Change in the distal stump begin within 24 hours of injury
   a. Axis cylinder breaks into short lengths and few days later little debris is left.
   b. Myelin sheath breaks up more slowly than axon into small oily droplets. It occurs in two stages: 1. Physical destruction up to 8–10 days, 2. Chemical destruction starts at 8th day and goes on till 32 days.
   c. Nucleus of Schwann cell start multiplying mitotically, which fill up the endoneurial tubes.

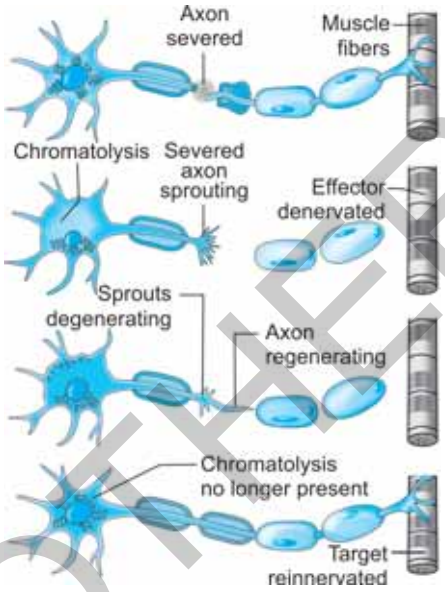


Fig. 10.5: Peripheral nerve damage and repair

   d. Macrophages from endoneurium start phagocytosing debris of axis cylinder and myelin sheath.
   e. Once the debris are cleared, Schwann cell cytoplasm starts proliferating and fills up the endoneurial tubes.
3. Changes in the site of injury
   Schwann cell differentiate into thin enlongated cells, mainly from the distal end and very little from the proximal end. It can bridge up the gap of 3 cm. Rate of progress of growth is 1–2 mm/day.

Regenerative Changes

A degenerated nerve may regenerate, provided there is neurilemmal sheath. In places where the neurilemma is absent, there can be no regeneration. Nerve fibers of CNS therefore, once degenerated, never regenerate as these nerves have no neurilemma. Degenerative and regenerative processes go side by side (Fig. 10.5).

1. Changes in the nerve cell body
It begins in 20 days and is completed in 80 days. Nissl granules and Golgi apparatus gradually reappear, cell regains its normal size and nucleus returns to its central position. Repair of cell may even occur if the axon does not regenerate.

2. Changes in the distal stump and at the site of injury
   a. Axis cylinder from the proximal stump elongates and then grows out in all directions as rounded pseudopod like structures called fibrils towards the distal stump.

b. Each axon gives rise to 50–100 fibrils which are guided by the strands of Schwann cell into the distal ends of the endoneurial tubes.
c. 2–3 weeks after the nerve section the distal endoneurial tube contains varying number of developing fibrils.
d. Eventually all the fibrils re-innervating one tube degenerate except one which thereupon progressively gets enlarged to fill the tube.
e. To begin with, rate of growth is 0.25 mm/day, but once it enters the distal stump, the rate of growth becomes 3–4 mm/day. As it grows deeper down, the rate of growth further increases because mechanical conditions for regeneration are more suitable than those in a cut nerve end.
f. In approx 15 days, Schwann cell filling the endoneurial tube starts laying down myelin sheath round the successful fibril, which is completed by 1 year.
g. Increase in fiber diameter takes place very slowly. Final diameter attained is 80–85% of normal. It is limited by the diameter of the distal tube and the size of the parent nerve cell. Therefore, functional recovery is not full which takes longer time and may be associated with different complications if it does not reach its own cut stump. That is why, for a motor nerve, recovery may be complete but for a mixed nerve it is rarely so.

Denervation Hypersensitivity

When the motor nerve to skeletal muscle is cut and allowed to degenerate, the muscle becomes extremely sensitive to ACh. This phenomenon is referred to as denervation hypersensitivity or supersensitivity and is seen in smooth muscles also. Smooth muscles, unlike skeletal muscle do not atrophy when denervated, but it becomes hyper-responsive to the chemical mediator that normally activates it. Hypersensitivity is limited to the structure immediately innervated by the destroyed neurons. For example, the response of the denervated iris. If the postganglionic sympathetic nerves to one iris are cut in an experimental animal and after several weeks, if norepinephrine is injected intravenously, the denervated pupil dilates widely. A much smaller, less prolonged response is observed on the intact side.

Causes

a. Synthesis and activation of more receptors
b. There is an increase in the area of muscle membrane sensitive to ACh
c. ACh receptors of fetal gamma subunit appears

In orthograde degeneration (Wallerian degeneration), part distal to cut degenerates. Retrograde degeneration of axon is towards nearest collateral (Fig. 10.6).

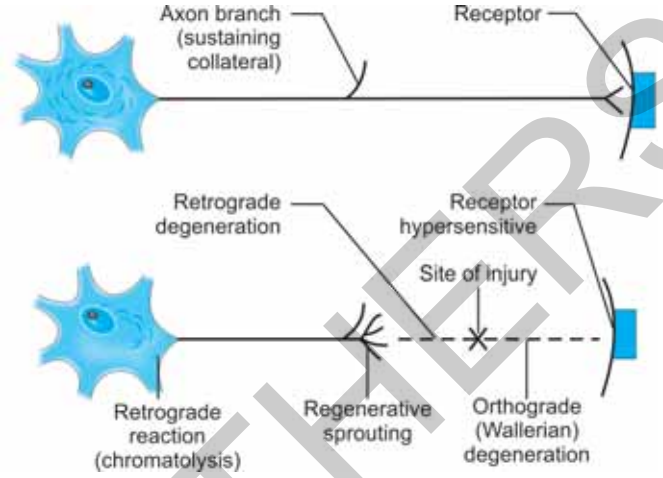


Fig. 10.6: Retrograde degeneration

Clinical Note

CNS neurons do not repair. In the case of peripheral nerves, a Schwann cell myelinates only a small segment of the axon, that is, between the two adjacent nodes of Ranvier. In the case of CNS nerves, oligodendrocytes form the myelin for these neurons; almost 20 axons are myelinated by a single oligodendrocyte. If a peripheral nerve is cut, it can regenerate and repair. The cut axon can regrow along the path that is created by the proliferating Schwann cells. In the CNS, the injured and transected axons make an attempt to regrow. However, there is no definitive path to guide them. This lack of guidance path is attributed to the fact that a single oligodendrocyte myelinates many axons in the CNS.

NEUROMUSCULAR JUNCTION (NMJ)

It is the junction between the motor nerve and skeletal muscle fiber. Nerve membrane which is in close approximation with the muscle membrane is called presynaptic membrane, while the muscle membrane is called postsynaptic membrane. The space between these membranes is called synaptic cleft (50–100 nm wide) which is filled with ECF.

Postsynaptic membrane has many folds of muscle membrane called subneural cleft which increases the surface area for the synaptic transmitter. Axon terminal has many mitochondria (for the synthesis of ACh) and minute vesicles or granules, which contain small packets of chemical transmitter, acetylcholine (ACh) responsible for synaptic transmission. An enzyme specific acetylcholinesterase is found in high concentration in postsynaptic clefts, which destroys the ACh.

Synthesis Storage and Release of ACh

Acetylcholine is synthesized within the mitochondria from 'choline' in the presence of enzyme choline acetyltransferase

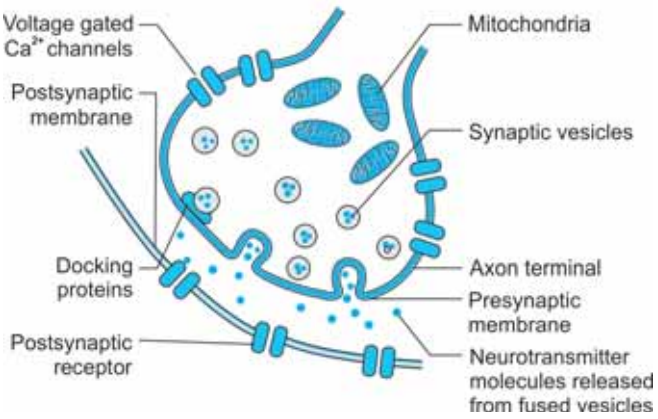


Fig. 10.7: Neuromuscular junction

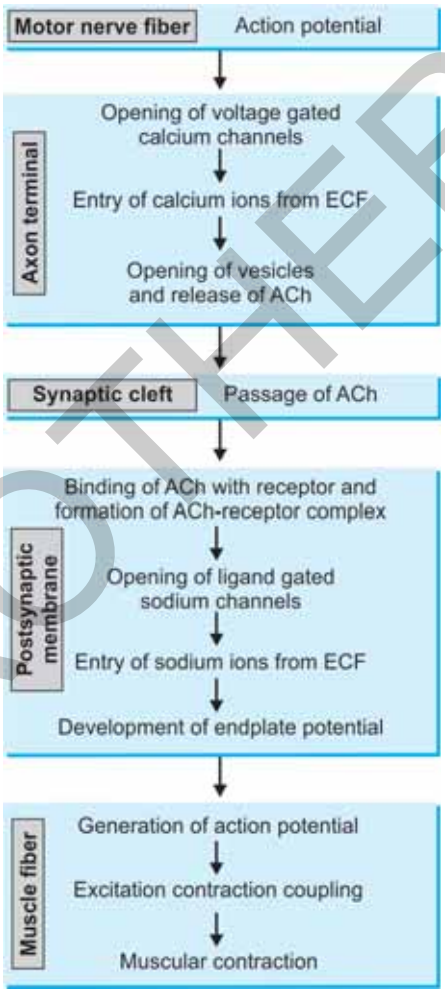
(choline acetylase). In addition, it requires acetyl Co-enzyme A, ATP and glucose. With the exception of choline all components required for synthesis of ACh are present within mitochondria or gain ready access to them.

Acetylcholine once formed is temporarily stored in minute vesicles (synaptic vesicles) (Fig. 10.7). Nerve impulse causes fusion of vesicles with membrane of terminal nerve fiber by increasing permeability of Ca^{2+}. Ca^{2+} in ECF helps in fusion by changing ionic composition and thereby decreasing the flow of axoplasm, therefore, vesicles easily come in contact with the membrane. Mg^{2+} decreases this process. The amount of transmitter released is directly proportional to the Ca^{2+} influx.

Sequence of Events (Flowchart 10.1)

In response to a stimulus, sodium ions enter the axon of motor neuron leading to depolarization. This reduces the membrane potential in motor nerve axon. When the impulse reaches the end of axon, it increases the permeability to calcium ions. Calcium ions enter the axon of motor neuron through voltage gated calcium channels. It is this calcium entry that causes exocytosis of acetylcholine stored in motor nerve terminals. Acetylcholine, once released into the synaptic cleft is degraded by the enzyme acetylcholine esterase. Few molecules of Ach which escapes degradation finds its receptor, nicotinic acetylcholine receptor in the muscle. Nicotinic acetylcholine receptor in the muscle is N_M type. Binding of acetylcholine to these receptors increases influx of Na^+ ions leading to a depolarizing potential called the endplate potential. Endplate potential are local potentials. Once they cross the threshold, action potential is fired. In response to the action potential, muscle contracts.

Flowchart 10.1: Sequence of events during nerve impulse transmission



Note

It appears that vesicle breaks with the membrane when VAMP, a vesicle membrane protein connects with syntaxin, a cell membrane protein. The connection occurs in presence of G proteins—a SNAP, b SNAP, SNAP-25 and NSF.

Toxins which blocks neurotransmitter release

a. d-tubocurarine competes with ACh for same nicotinic receptors on the motor endplate.
b. Tetanus and botulinum neurotoxin-b cleaves VAMP
c. Botulinum neurotoxin-b cleave SNAP-25
(Tetanus cause spastic paralysis, botulinum cause flaccid paralysis).

Drug that stimulate neuromuscular junction by inactivating acetylcholinesterase

a. Neostigmine
b. Physostgmine
c. Diisopropyl fluorophosphate.

Disease

Myasthenia Gravis

Autoimmune disease in which patients have developed antibodies against their own ACh-activated ion channels. These antibodies destroy ACh receptors, thereby causing muscle paralysis due to the inability of the neuromuscular junctions to transmit enough signals from the nerve fibers to the muscle fibers. The disease is characterized by rapid onset of fatigue with marked generalized weakness of muscles. The most commonly affected muscle are extraocular muscle, facial, swallowing and mastication muscle. In severe form patient may die with paralysis of respiratory muscles.

Treatment

In myasthenia gravis (autoimmune disorder) antibodies are produced against nicotinic N_M receptors in the NMJ. To prevent the action of the antibody, we have to increase the release of ACh, for that the cholinesterase enzyme has to be inhibited by anticholinesterases such as neostigmine.

Lambert-eaten Syndrome

In this muscle weakness is caused by antibodies against one of the Ca^{2+} channels in the nerve endings at the neuromuscular junction. This decreases the normal Ca^{2+} influx that causes ACh release.

SKELETAL MUSCLE

Skeletal muscle is made up of many long thin cells called muscle fibers. Each muscle fiber is multinucleated, 1–40 mm long, cylindrical, 50–100 μm diameter and surrounded by a cell membrane, the sarcolemma. Muscle fibers are made up of many fibrils called myofibrils. Each myofibril is 1–2 μm in diameter. The cytoplasm in the muscle fibers is called sacroplasm.

Light Microscopic Appearance

The cross striations which are characteristic of skeletal muscle are due to difference in the refractive indices of various parts of muscle fiber. Therefore, the muscle fiber is seen to show alternate dark and light cross bands (Fig. 10.8).

1. The dark band is made of highly refractile material (anisotropic) called A-band (1.5 μm in length).

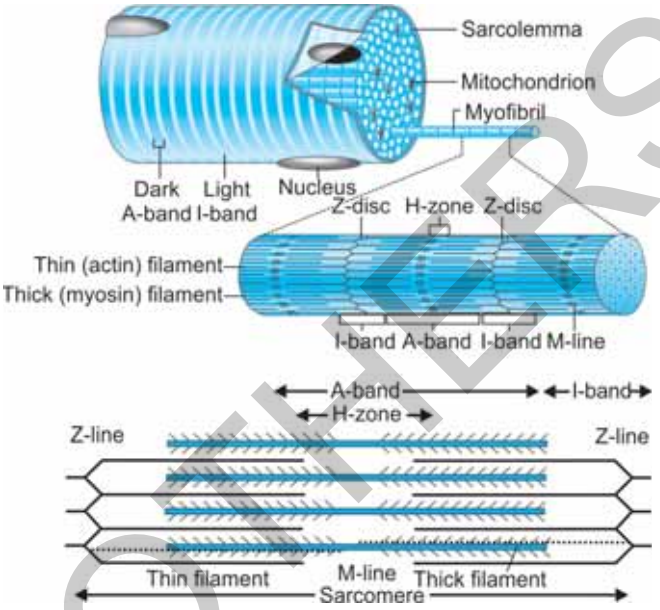


Fig. 10.8: Electron microscopic appearance of skeletal muscle

2. In the center of each A-band is found a slight less refractile region called H-band.
3. M line is seen in the middle of H-band, due to central bulge of A-band.
4. The alternate light band is made of lower refractile material (isotropic), therefore looks lighter and is called I-band (1 μm).
5. In the center of each I-band is found a narrow line of highly refractile material which looks dark called Z-line.
6. Contractile unit of the muscle is the substance between two adjacent Z-lines called sarcomere (2.5 μm).

Electron Microscopic View

The myofibrils are made up of two sets of protein filaments, thick and thin filaments.

1. *Thick filament:* Made out of myosin (cause for A-band). Myosin molecule is made up of 6 polypeptide; 2 heavy chain and 4 light chain. Myosin treated with proteolytic enzyme (trypsin) reveals 2 fragments.
   i. *Short compact head of heavy meromyosin (HMM):* It has 2 important sites: (a) Actin binding site-where myosin comes in contact with actin, (b) ATPase (catalytic) site-that hydrolyses ATP (Fig. 10.9).
   ii. *Long chain of light meromyosin:* It has only structural function and acts as backbone for HMM.
2. *Thin filament:* Made of actin, tropomyosin and troponin. They arrange themselves to form 2 chains of globular units

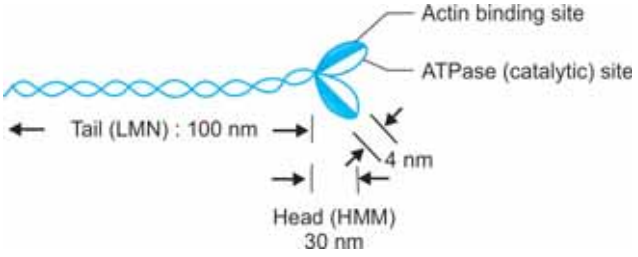


Fig. 10.9: Electron microscopic structure of thick filament

that form a double helix (responsible for I-band formation). Each thin filament contains 300–400 actin molecules and 40–60 tropomyosin molecule.

Actin

It occurs in two forms:

- *G actin:* Each molecule bind with 1 molecule of ATP firmly.
- *F actin:* Formed by polymerization of G actin.

Tropomyosin

It covers the binding site of actin where myosin head comes in contact with actin, i.e. it prevents interaction between actin and myosin.

Troponin

They are small globular proteins. It is made up of 3 subunits:

- Troponin 'T'—binds the other troponin components to tropomyosin
- Troponin 'I'—inhibits the interaction of myosin with actin
- Troponin 'C'—contains binding site for Ca^{2+} that initiates muscle contraction.

Sarcotubular System (Fig. 10.10)

Sacroplasm (cytoplasm of skeletal muscle) contains sacrotubular system. It is highly specialized system of internal conduction of depolarization within the muscle fiber. It is made T-system (transverse tubular system) and a longitudinal sarcoplasmic reticulum (LSR).

T-system

They are inwardly directed extensions of the sarcolemma into the muscle fibers at the junction between 'A' and 'I' bands (A-I junctions). Its function is the rapid transmission of the action potential from the cell membrane to all the fibrils in the muscle. The T-tubule protein is a modified voltage-sensitive Ca^{2+} channel known as the dihydropyridine receptor (so named because it binds the class of drugs called dihydropyridines). The main role of DHP receptor, however, is not to conduct Ca^{2+}, but rather to act as voltage sensor.

LSR

Longitudinally on either side of the tubular system are found the sacs of the dilated LSR. These sacs are called terminal cisternae, which are rich in glycogen and Ca^{2+}. Ca^{2+} channels in sarcotubular reticulum are not voltage gated and allow the release of Ca into the cell. These are called ryanodine receptors. In skeletal muscle, one T tubule is surrounded by two L tubules. This classical arrangement is called triad. But in cardiac muscle, one T tubule is surrounded by one L tubule. This arrangement is called dyad.

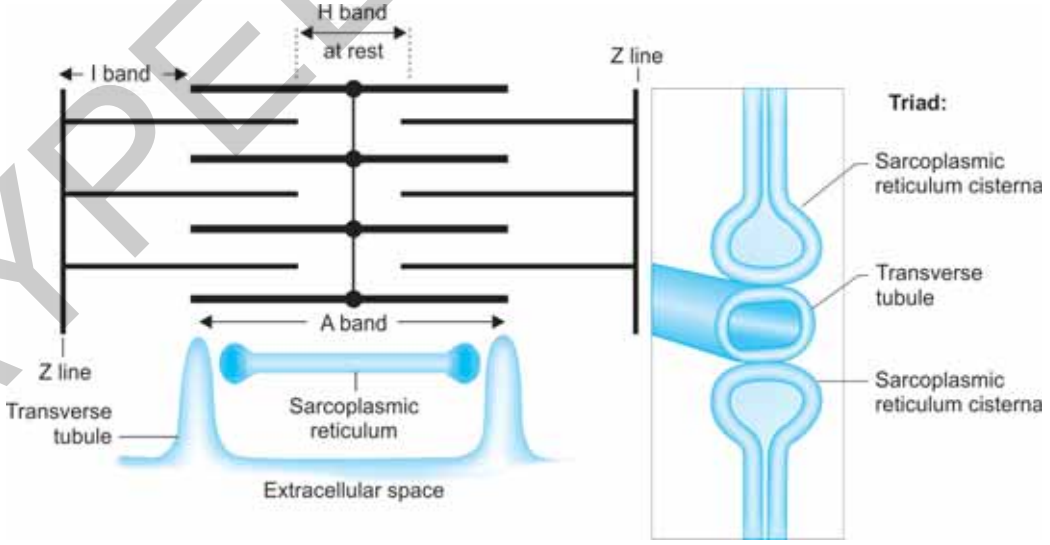


Fig. 10.10: Sarcotubular system

Action

Depolarization of T-tubule cause the DHP receptors to induce a conformational change to open the ryanodine receptors channel. Ca^{2+} is thus released from the lateral sac of sarcoplasmic reticulum. This Ca^{2+} bind with the troponin, removes blocking action of tropomyosin.

Excitation Contraction Coupling

Process by which depolarization of the muscle fiber initiates contraction. Sequence of events in excitation contraction coupling (Fig. 10.11).

Steps in muscular contraction

- Stimulation of motor neuron.
- Release of ACh into synaptic cleft causing generation of endplate potential.
- Depolarization of muscle membrane by increasing its permeability to Na^{+}.
- Generation of action potential in the muscle fiber.
- Inward spread of action potential along the T-system.
- Spread of depolarization to terminal cistern with release of Ca^{+} in the myofibrils.
- Increase of concentration of Ca^{2+} in ICF by 2000 times.
- Muscle contraction.

Role of Ca^{2+}

- Ca^{2+} binds with troponin C causing tropomyosin to move laterally. This exposes the binding sites for the myosin heads on the actin.
- Activates prosthetic group of myosin filament which acts as enzyme (ATPase).

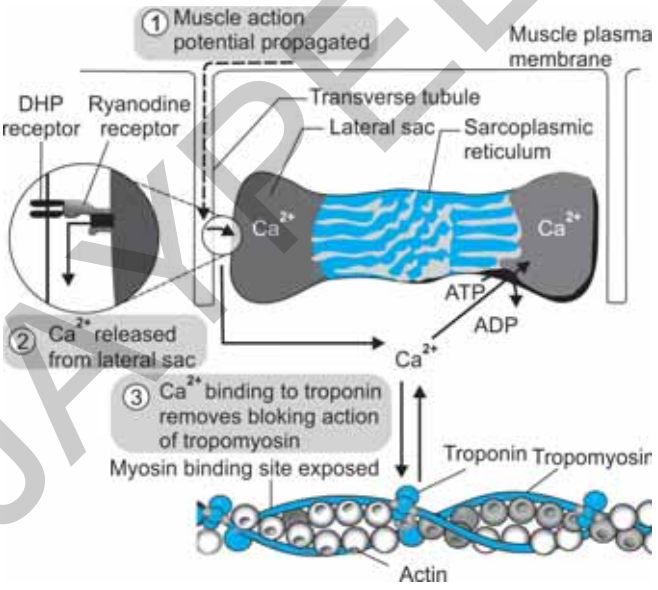


Fig. 10.11: Sequence of events in excitation contraction coupling

Steps in muscular relaxation

A few milliseconds after the action potential is over, sarcoplasmic reticulum begins to reaccumulate Ca^{2+}. The Ca^{2+} ions are actively pumped by Ca^{2+}- Mg^{2+} ATPase into longitudinal portion of the reticulum to terminal cistern for storage.

Molecular Basis of Muscular Contraction

Sliding filament theory (Ratchet theory)

The process by which the shortening of the contractile elements in the muscle is brought about is by sliding of actin filament over the thick (myosin) filaments. The sliding of filaments is brought about by formation of the cross-bridges between the head of myosin and actin molecules.

Events during formation of the cross-bridges

i. In resting muscle no cross-bridges are formed since troponin 'I' is lightly bound to actin and tropomyosin covers the actin sites where myosin bind to actin. Therefore, the troponin–tropomyosin complex constitutes a relaxing protein which inhibits the interaction between actin and myosin.

ii. Ca^{2+} released from the terminal cisterns by the action potential, binds to troponin 'C' and causes.

   a. The binding of troponin 'I' to actin is weakened, this permits tropomyosin to move laterally uncovering the binding sites for myosin heads on actin filaments (Fig. 10.12).

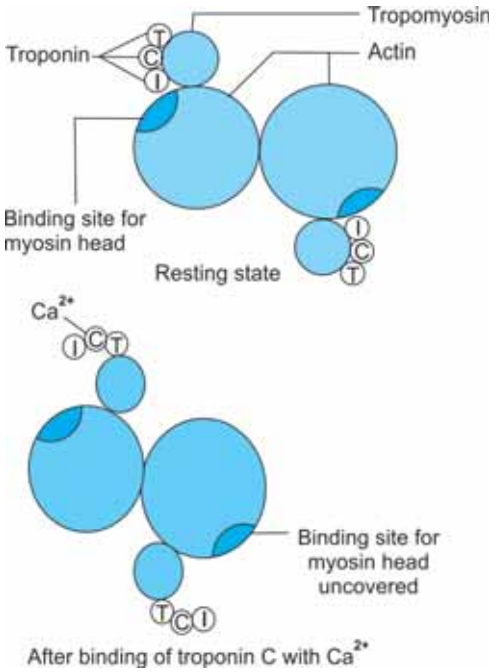


Fig. 10.12: Configurational change in thin filament

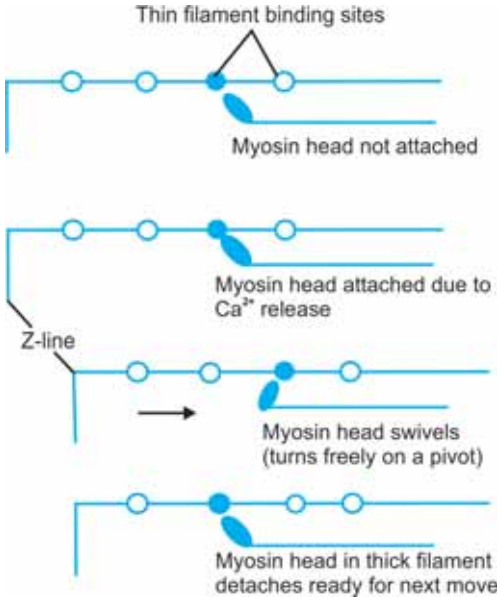


Fig. 10.13: Mechanism of formation of cross-bridges

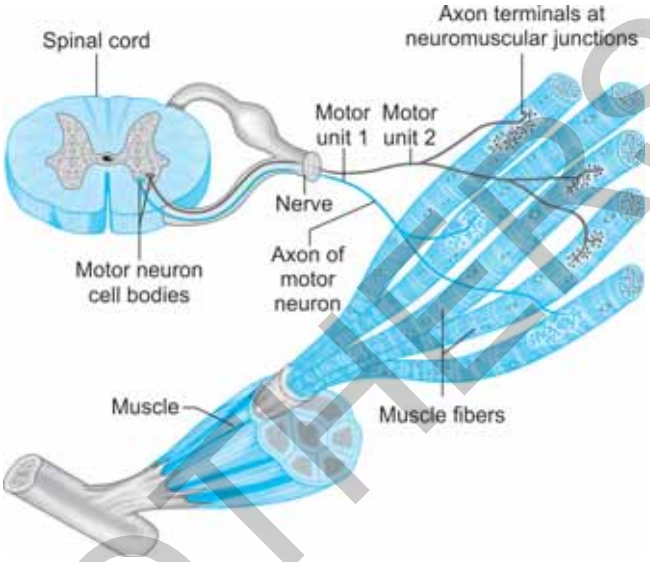


Fig. 10.14: Motor unit

b. Hydrolysis of ATP by ATPase activity in the myosin heads produces energy.

iii. Seven myosin binding sites on actin filaments are uncovered for each molecule of troponin that binds a Ca^{2+}. The heads of the myosin molecules link to the actin, produce movements of myosin on actin by swiveling.

Mechanism of sliding of thin filaments over thick filaments

- The sliding during muscle contraction is produced by breaking and re-forming of cross-bridges between actin and myosin, repeating the process in serial fashion for 5–6 times (Fig. 10.13).
- The width of 'A' bands is constant, whereas the 'Z' move closer together when the muscle contracts.

Motor Unit

Motor unit is the functional unit of muscle contraction in the intact body. It consists of the single motor neuron cell body, its axon fibers and the muscle fibers innervated by it. The cell bodies of the motor neurons supplying the skeletal muscle fibers lie in the ventral horn of the spinal cord or the motor cranial nerve nuclei (Fig. 10.14). In simple words, each single motor neuron and all the muscle fibers it supplies constitutes a motor unit.

Properties of Motor Unit

1. The number of muscle fibers in a motor unit varies inversely with the precision of movements performed by that part.
2. Each motor unit innervates only one type of muscle fiber. In other words, in a single motor unit the muscle fibers supplied by it are of the same type. These are of 2 types- 'red' (Type I) and 'white' (Type II) muscle fibers.
3. All the efferent fibers passing to skeletal muscles are excitatory. There are no efferent nerves which on stimulation produce relaxation of the muscle, i.e. there are no inhibitory efferents to skeletal muscle (as compared to cardiac and smooth muscles where the efferent supply is both excitatory and inhibitory).
4. Depending on the type of muscle fibers they innervate, motor units are of two types, 'slow' and 'fast' motor units.

Applied Aspect

1. When the motor nerve to a skeletal muscle is cut it causes:
   a. Disuse atrophy of the muscle, i.e. shrinkage of muscle fibers, which finally gets replaced by fibrous tissue (fibrous muscle)
   b. Complete paralysis of the muscle
   c. Appearance of fine, irregular contractions of individual fibers called fibrillations:
   d. *Denervation hypersensitivity:* These effects are the classical consequences of LMN (lower motor neuron), i.e. injury to the spinal/cranial motor neurons which directly innervate the muscles.
2. *Muscular dystrophy:* It is a syndrome characterized by progressive muscle weakness due to mutation in dystrophin gene, which results in congenital defect in dystrophin-glycoprotein complex. This is a large protein complex that connects the thin filaments to the transmembrane protein in the sarcolemma and thus provides support and strength to the fibers.

Table 10.5: Difference between white and red muscles

White (fast) muscle fibers	Red (slow) muscle fibers
1. Muscle fibers are large in diameter with high glycogen capacity and ATPase activity. They are called 'white' muscle fibers because they are pale	1. Muscle fibers are of moderate diameter with moderate glycogen capacity and low ATPase activity. They are called 'red' muscle fibers because they are darker than other muscle fibers
2. They are called 'fast' muscle fibers because they are innervated by large, fast conducting motor neurons	2. They are called 'slow' muscle fibers because they are innervated by small, slow conducting motor neurons
3. These muscles get fatigued easily	3. These muscles are resistant to fatigue and are the most used muscles
4. These muscles are specialized for fine rapid and skilled movements and have short twitch durations (7.5 sec). For example, muscles of the hand and extraocular muscles	4. These muscles respond slowly (which duration 100 msec) and have long latency period. They are adapted for sustained, slow and posture maintaining contractions. For example, long muscles of limb and muscles of back
5. They are particularly suited to perform high intensity work that can be sustained for only short period of time	5. They are particularly suited to perform low intensity work over long periods of time such as for athletes, swimmers, etc.

3. *Rigor mortis:* When muscle fibers are completely depleted of ATP and phosphocreatine, they develop a state of extremely rigidity called rigor. When this occurs after death, the condition is called rigormortis. In rigor, almost all of the myosin heads attach to actin but in an abnormal, fixed and resistant way.
4. *Myotonia:* A condition characterized by difficulty and slowness in relaxing muscle after voluntary effort. Various forms of myotonia defined clinically are due to abnormal genes on 7, 17 or 19 chromosomes, which results in abnormalities of Na^+ on Cl^- channels.

Types of Muscle Fibers

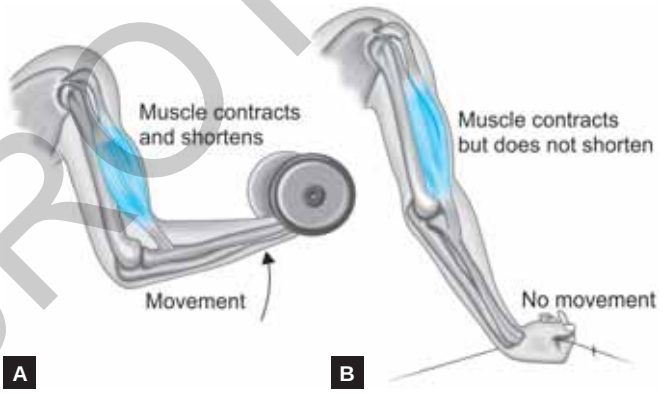
Muscles can be divided into two types: 1. Fast muscles (white muscles), and 2. Slow muscles (red muscles). Fast muscles are pale looking, whereas slow muscles are more red (Table 10.5). This is so because, the slow muscles have greater capillary network. In human beings, most muscles contain a variable mixture of fast and slow muscle fibers. The postural muscles are largely slow muscles.

White Muscles

White muscles constitute 3/4th of the total muscle mass and have greater speed of contractions. They have a resting blood flow of 3 ml/min/100 gm, which may increase to 60–70 ml/min/100 gm in maximal exercise. These muscles are prone to O_2 debt.

Red Muscles

They comprise 25% of the total muscle mass and are concerned with maintenance of posture. Their activity is of the steady prolonged type which requires a relatively low O_2 usage. Their resting blood flow is 20–30 ml/min/100 gm due to low basal myogenic tone. They have vascular bed 3 times the size of white muscles with high flow capacity, approx. 150 ml/min/100 gm. Because of greater surface area of the capillary bed and their lower O_2 requirement, these muscles are unlikely to be exposed to O_2 debt.



Figs 10.15A and B: Isotonic vs isometric contraction

Isotonic Contraction (Fig. 10.15A)

When muscle contraction is associated with change in length at constant tension. The tension is equal to the weight lifted during contraction of the muscle. Here external work is performed, greater amount of energy is used than isometric contraction. Therefore, muscle strength is best increased by isotonic exercise. Exercises one does in the gym are isotonic exercises as muscle length changes in each step but not tension.

Isometric Contraction (Fig. 10.15B)

When muscle contraction is associated with no apparent change in muscle length, but there is increase in tension, the phenomenon is called isometric contraction. The muscle develops tension (tension is the force of the contracting

muscle acting on the object), but does not shorten or lengthen; for example, when somebody is trying to lift a heavy object (when the object is not lifted actually). According to the law of physics, if displacement is zero (position of the object does not change), the work done (force x displacement) is also nil, though force is generated and energy is spent. Thus, in isometric contraction no external work is done.

SMOOTH MUSCLE

Smooth muscle is distinguished anatomically from skeletal and cardiac muscle because it lacks visible cross striations. Actin and myosin-II are present and they slide on each other to produce contraction. However, they are not arranged in regular arrays, as in skeletal and cardiac muscle, and so the striations are absent. Smooth muscle is involuntary. Troponin is absent. Z lines are not there, instead there are dense bodies in the cytoplasm. Actin filament is attached to dense bodies by a protein called α-actinin. T tubules are also absent. Sacroplasmic reticulum is not well-developed. It is rudimentary to moderately developed.

Types

There is considerable variation in the structure and function of smooth muscle in different parts of the body. In general, smooth muscle can be divided into visceral/unitary smooth muscle and multiunit smooth muscle (Table 10.6 and Fig. 10.16).

1. **Single unit (visceral) smooth muscle:** This type of smooth muscle behaves as if the entire muscle mass as single unit, i.e. syncytium. The gap junctions between muscle fibers are so generous that the impulse of activation can spread rapidly from one cell to another. Gap junctions are responsible

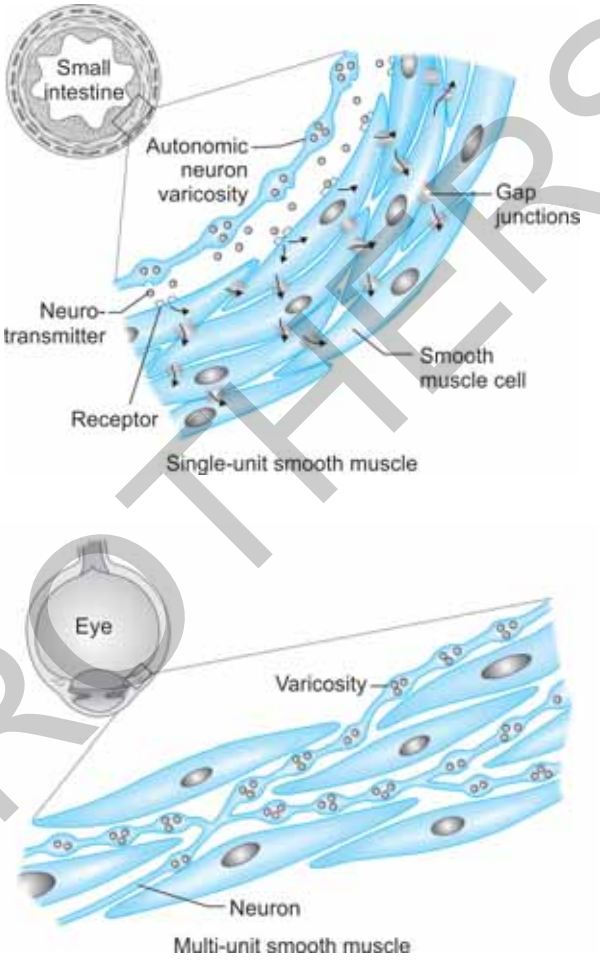


Fig. 10.16: Morphology of smooth muscle fiber

Table 10.6: Difference between single unit and multiunit muscle

Single unit/Visceral smooth muscle	Multiunit smooth muscle
1. It is called single unit smooth muscles because it functions in a syncytial fashion. It occurs in large sheets and has low resistance fashion. Single unit smooth muscles have low resistance bridges between individual muscle cells	1. It is called multiunit smooth muscle because it is made up of individual units without interconnecting bridges, i.e. non-syncytial in character. So its contractions are discrete, fine and localized
2. Location: Wall of hollow viscera, i.e. GIT, ureters, bronchi, uterus and urinary bladder	2. Location: Ciliary muscles of eye, iris, pilomotor muscle of skin and muscles of blood vessels
3. In certain areas the muscles are characterized by appearance of spontaneous activtiy, so called	3. Each muscle fiber of multiunit smooth muscle has its own nerve supply
4. Rhythmic contraction and relaxation of these muscles is independent of their innervation. Innervation has role only in modulating its activity	4. These muscles are sensitive to chemical mediators at the nerve endings (ACh or NE) in response to which muscle contracts. Single stimulus to the nerve causes repeated firing of action potential which produces irregular tetanic contractions rather than a single muscle twitch as seen in skeletal muscle
5. Active tension is produced when the muscle is stretched	5. No response by the muscle to stretch

for syncytial function of single unit smooth muscle. Most of smooth muscle, e.g. that of the gut, ureters, uterus, etc. is of the single-unit type.

2. **Multiunit smooth muscle:** The muscle is composed of discrete muscle fibers. Each muscle fiber is capable of contracting independently and often each fiber is innervated by an individual neuron. Classical examples of this type of smooth muscle are found in the ciliary muscle of the eye; smooth muscle of iris, trachea, bronchi; and piloerector muscles.

   The axons that innervate smooth muscle fibers do not have typical branching end feet of the type in the motor endplate on skeletal muscle fibers. Instead, most of the fine terminal axons have multiple varicosities distributed along their axes.

Electrical and mechanical activity

The electrophysiology of smooth muscle is more complex than that of skeletal muscle, but the basic principles are the same as in other excitable cells. There is no true resting potential in smooth muscle. The smooth muscle membrane is more permeable to ions even at rest than the skeletal muscle membrane. RMP shows rhythmic variations (fluctuations) between –60 mV to –50 mV. RMP is low as compared to skeletal muscle and neuron.

Action potentials in smooth muscle may be brief (spike potential) as in skeletal muscle, or prolonged, with a plateau, as in cardiac muscle. The depolarization phase of action potential is predominantly due to calcium influx and only to a small extent due to sodium influx. Repolarization is due to decrease in the influx of calcium and sodium, and efflux of potassium ions. The entry of calcium during depolarization not only makes a significant contribution to the depolarization but also switches on the contractile process.

Molecular Basis of Smooth Muscle Contraction

Ca^{2+} is involved in the initiation of contraction of smooth muscle. However, visceral smooth muscle generally has a poorly developed sarcoplasmic reticulum and the increase in intracellular Ca^{2+} concentration that initiates contraction is primarily due to Ca^{2+} influx from the ECF via voltage-gated and ligand-gated Ca^{2+} channels.

In addition, the myosin in smooth muscle must be phosphorylated for activation of the myosin ATPase. In smooth muscle, Ca^{2+} binds to calmodulin and the resulting complex activates calmodulin-dependent myosin light chain kinase. This enzyme catalyzes the phosphorylation of the myosin light chain on serine at position 19. The phosphorylation allows the myosin ATPase to be activated and actin slides on myosin, producing contraction. This is in contrast to skeletal and cardiac muscle, where contraction is triggered by the binding of Ca^{2+} to troponin C. Myosin is dephosphorylated by myosin light chain phosphatase in the cell. This enzyme is inhibited when it is phosphorylated and activated by dephosphorylation. It is dephosphorylated by a rho-associated kinase that is activated by ligands which produce inhibition of smooth muscle activity. However, dephosphorylation of myosin light chain kinase does not necessarily lead to relaxation of the smooth muscle. Various other mechanisms such as latch bridge mechanism by which myosin cross-bridges remain attached to actin for sometime after the cytoplasmic concentration falls. This produces sustained contraction with little expenditure of energy, which is especially important in vascular smooth muscle. Relaxation of the muscle presumably occurs when there is final dissociation of the Ca^{2+}-calmodulin complex or when some other mechanism comes into play. The events leading to contraction and relaxation of visceral smooth muscle are summarized.

1. Binding of acetylcholine to muscarinic receptors
2. Increased influx of Ca^{2+} into the cell
3. Ca binds with calmodulin
4. Activation of calmodulin-dependent myosin light chain kinase
5. Phosphorylation of myosin
6. Increased myosin ATPase activity and binding of myosin to actin
7. Contraction
8. Dephosphorylation of myosin by myosin light chain phosphatase
9. Relaxation or sustained contraction due to the latch bridge and other mechanisms.

Note

Latch mechanism facilitates prolonged holding of contraction of smooth muscles. Once smooth muscle contracts, it can maintain its contraction for a prolonged period of time with minimal expenditure of energy. This is because myosin hold on actin filaments like a latch.

CARDIAC MUSCLE

Cardiac muscle fibers are striated like skeletal muscle fibers but the most characteristic histological feature of the cardiac muscle is a syncytium like appearance. But it should be kept in mind that, it looks like a syncytium from a histological point of view, but the heart muscle is not a syncytium. A syncytium is a multinucleated mass of cytoplasm which is

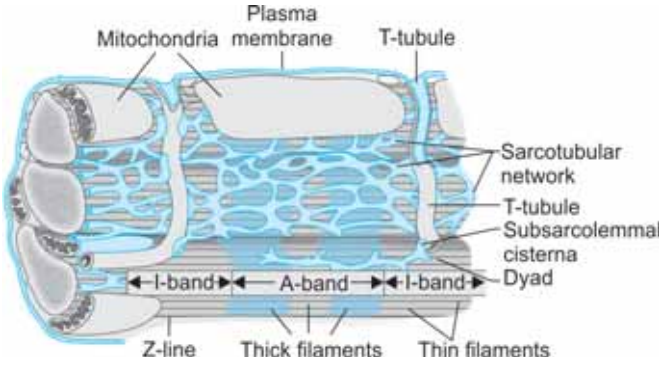


Fig. 10.17: Morphology of cardiac muscle fiber

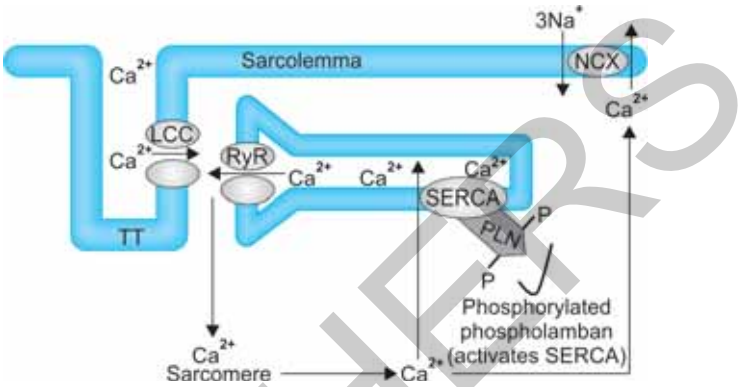


Fig. 10.18: Contraction of cardiac muscle

PLN = Phospholamban; NCX = Na^+ – Ca^{2+} exchanger; LCC = L-type calcium channels; RyR = Ryanodine receptors; TT = T tubule; SERCA = Sarcoendoplasmic reticulum Ca^{2+} – ATPase

not divided by end-membranes into individual cells. Cardiac muscle fibers branch and interdigitate, but each is a complete unit surrounded by cell membrane with a centrally located single nucleus. So, cardiac muscle look like syncytium but histologically is not syncytium (Fig. 10.17).

Each muscle fiber at its end joins with the next cell by intercalated disc. These discs are actually end membranes that separate one muscle cell from another. At the outer border of the intercalated disc, there are gap junctions (connexons) because of which cardiac muscle behaves as a functional syncytium as these gap junctions provide low-resistance bridges for spread of excitation from one fiber to other. So, from a histological point of view, cardiac muscle is not a syncytium. But functionally (electro physiologically) cardiac muscle behave as syncytium.

Contraction of Cardiac Muscle

The cardiac muscle cell contains actin, myosin, the sarcotubular system and other organelles seen in skeletal muscles. However, the T system of cardiac muscle is located at Z lines rather than at A-I junction, where it is located in skeletal muscles. Electrical property (action potential, RMP etc.) of cardiac muscle is explained in cardiovascular system.

Similar to smooth muscles, cardiac muscle contraction is started by Ca^{2+}, i.e. excitation-contraction coupling is caused by Ca^{2+}. In skeletal muscle, intracellular calcium stores are sufficient for contraction. But in cardiac muscle cells, to release calcium from intracellular stores, some calcium must enter cardiac muscle cell to trigger intracellular calcium release. Increase in cytoplasmic (sarcoplasmic) Ca^{2+} cause contraction, similar to smooth muscles. As the action potential develops, it causes Ca^{2+} influx within the cardiac cell via L-type of Ca^{2+} channels in the sarcolemma. This influx of Ca^{2+} ions triggers the release of Ca^{2+} ions from sarcoplasmic reticulum to sarcoplasm via ryanodine receptors. Increase in intracellular Ca^{2+} causes contraction of cardiac muscles, by almost similar mechanism as in smooth muscles. During relaxation, cytoplasmic (sarcoplasmic) Ca^{2+} is lowered by two mechanisms (Fig. 10.18):

1. Sarcoplasmic reticulum calcium pump (SR Ca^{2+} ATPase or SERCA): It pumps back the sarcoplasmic (cytoplasmic) Ca^{2+} into SR.
2. Ca^{2+} $3Na^+$ antiport in sarcolemma: Pumps out the cytoplasmic (sarcoplasmic) Ca^{2+}.

The protein phospholamban is a protein associated with SERCA. Phospholamban typically inhibits SERCA activity. This activity of phospholamban is inhibited by its phosphorylation. Increased level of adrenal medullary epinephrine or increased norepinephrine from sympathetic nerve endings activates β adrenergic receptors on cardiac muscle cells. This in turn activates adenylyl cyclase enzyme resulting in an increase in cAMP. This causes phosphorylation of phospholamban. Phosphorylation of phospholamban by a cAMP dependent protein kinase inhibits the activity of phospholamban. Inhibition of phospholamban causes increased activity of SERCA.

Increased activity of SERCA facilitates: 1. Relaxation of heart because of rapid calcium uptake by SERCA, 2. Increased force of contraction, because more calcium is available for release during the next contraction, and 3. Decreased duration of contraction because of rapid reaccumulation of calcium by sarcoplasmic reticulum.

The features of skeletal muscle, cardiac and smooth muscles are compared in Table 10.7.

Table 10.7: Skeletal muscle, cardiac and smooth muscles compared

Characteristics	Skeletal muscle	Cardiac muscle	Smooth muscle
1. Distribution	Fixed to skeleton	Heart only	Two types: Single and multi
2. Structure	Striated; multi-nucleated; non-syncytial	Striated and branched; single nucleus; syncytial	Unstriated; single nucleus; both synctial and non-syncytial
3. Sarcoplasmic reticulum	Well developed	Well developed	Poorly developed
4. Sarcotubular system	Present at A-I junction	Present at Z-lines	Present but not so characteristic
5. Nerve supply	Via somatic nerve	Via 2 branches of ANS	Via two branches of ANS
6. Control	Voluntary	Involuntary	involuntary
7. Blood supply	3–4 ml/100 gm	80 ml/100 gm/min	1.4 ml/100 gm/min
8. RMP	-90 mV	-80 mV	-55 mV unstable
9. Action potential i. Duration ii. Amplitude	 30-40 msec 120 mV	 250 msec at HR 75 bpm 100 mV	 50 msec 60 mV
10. Absolute refractory period	1–3 msec	180–200 msec	Not defined
11. Phenomenon of tetanus	Present	Not seen	Seen
12. Muscle twitch duration	7.5 msec (fast muscle) 100 msec (slow muscle)	1 1/2 times the total duration of action potential	100 msec
13. Excitation contraction coupling	Rapid process	More rapid process	Very slow process
14. All or none law	Application for single muscle fiber	True for whole of artria or ventricles	True for single muscle fiber
15. Length tension relationship	Maximum active tension at the optimal length	Similar to skeletal muscle	Shows property of plasticity
16. Phenomenon of fatigue	Possible	None	Possible

CLINICAL QUESTIONS

1. **A soldier after death was found in a rigid posture and his limbs could not be disengaged.**
   a. What is the condition called?
   b. What is the cause of the condition?
   c. What is its importance?
2. **A patient came with the complaints of progressive paralysis in muscles. He also had ptosis. On giving injection Neostigmine, patient showed improvement.**
   a. Identify the condition.
   b. What is the cause?
   c. Discuss the action of Neostigmine.
3. **An axon was stimulated with a suprathreshold stimulus within 1 msec and then after 3 msec of firing of the action potential. Response was not observed in the first case but was present in the second case.**
   a. What is this phenomenon known as?
   b. What are the two types?
   c. What is the ionic (molecular) basis of each?
4. **An arrow hit a tourist wandering through the African jungle and he developed skeletal muscle paralysis.**
   a. Which drug may be present in the arrow tip?
   b. What is the mechanism of action of the drug?
5. **A person was brought to the hospital with history of snakebite. On examination patient had ptosis, was unable to lift his neck and his respiratory rate was decreased.**
   a. What is the cause of this condition?
   b. Explain the effects.

Answers for Clinical Questions are given in the Appendix