2. Neuromuscular Physiology

Topics Covered

HYT 6	Resting membrane potential
HYT 7	Action potential
HYT 8	Strength–duration curve
HYT 9	Neurons and neuroglia
HYT 10	Nerve fibers
HYT 11	Nerve injuries
HYT 12	Neuromuscular junction
HYT 13	Molecular basis of muscle contraction
HYT 14	Physiology of exercise
HYT 15	Smooth muscles
HYT 16	Differences between skeletal, cardiac, and smooth muscles

Clinical Case Study

Myasthenia Gravis

Competencies

PY1.7	Describe the molecular basis of resting membrane potential (RMP) and generation of action potential in a nerve fiber
PY3.1	Describe the structure and functions of a neuron and neuroglia; discuss nerve growth factors
PY3.2	Describe the types, functions, and properties of nerve fibers, including strength–duration curve, chronaxie, and rheobase
PY3.3	Classify nerve injury and discuss the mechanism of degeneration and regeneration in peripheral nerves
PY3.4	Describe the microscopic structure of the neuromuscular junction (NMJ) and the mechanism of neuromuscular transmission
PY3.5	Discuss the applied aspects of the neuromuscular junction: myasthenia gravis, Lambert–Eaton syndrome, and neuromuscular blocking agents
PY3.6	Describe the different types of muscle fibers, their structure, and the physiological basis of action potential
PY3.7	Describe the properties, action potential, and molecular basis of muscle contraction in skeletal muscle
PY3.8	Describe the properties, action potential, and molecular basis of muscle contraction in smooth muscle
PY3.9	Describe the mode of muscle contraction (isometric and isotonic), energy source, muscle metabolism, and gradation of muscular activity
PY3.10	Enumerate and briefly discuss myopathies

HYT 6: Resting Membrane Potential

Q1. Describe the genesis of resting membrane potential (RMP).

Or

Explain why the interior of the resting membrane is electronegative.

Preliminary Concept: Creation of Potential Difference Across Membrane

In the resting state, most of the cations and anions mutually neutralize each other within extracellular fluid (ECF) and intracellular fluid (ICF). Despite this, some unbalanced "+ve" ions exist outside (ECF), while some unbalanced "–ve" ions exist inside (ICF). These unbalanced ions attract each other, resulting in their realignment along their respective membrane surfaces (**Fig. 2.1**). It is the presence of these unbalanced ions that creates a potential difference across the cell membranes.

Note Balanced ions do not contribute toward membrane potential.

Resting Membrane Potential

Resting membrane potential (RMP; or steady-state potential) is the constant potential difference that is recorded across a resting cell membrane. It is normally –70 mV in neurons and –90 mV in skeletal and cardiac muscles. Since its value remains unchanged at rest, it is also known as the steady-state potential. The minus sign signifies the electronegativity of the inner membrane with regard to outside. The recording procedure for RMP is shown in **Fig. 2.2**.

Factors Affecting RMP

- Concentration gradient for ions (Na^+, K^+, Cl^-) across the membrane.
- Permeability of membrane for above ions.
- Activity of Na-K-ATPase.

Note Overall contribution of ions toward RMP: $K^+ > Cl^- > Na^+$.

Genesis of RMP

It is explained in **Table 2.1**.

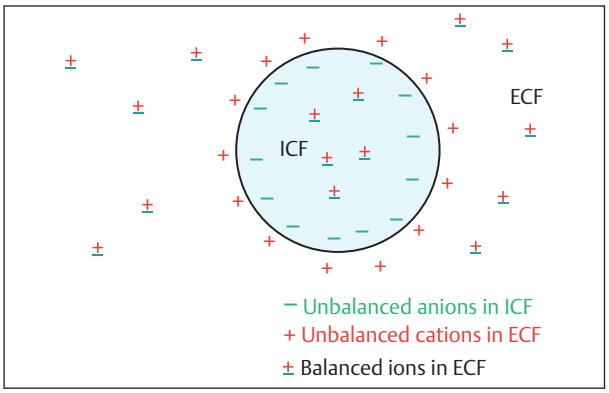


Fig. 2.1 Creation of potential difference across cell membranes. ECF, extracellular fluid; ICF, intracellular fluid.

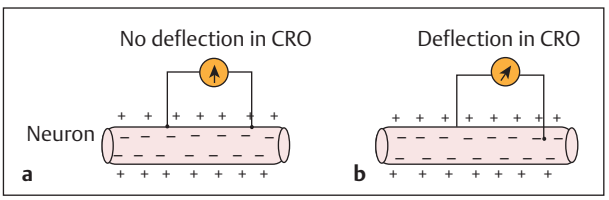


Fig. 2.2 Recording of resting membrane potential (RMP). **(a)** Both microelectrodes are on the cell surface; no deflection is seen. **(b)** One microelectrode is placed in intracellular fluid (ICF); deflection is seen in the recorder (RMP recorded). CRO, cathode ray oscilloscope.

HYT 7: Action Potential

Q2. Define action potential and discuss its ionic basis.

Or

Explain the various changes that occur in ionic permeability during various phases of action potential.

Action Potential

Action potential (AP) is defined as the series of sequential fluctuations recorded in membrane potential of excitable cells (neurons, muscles, gland cells) upon stimulation. AP is due to change in ionic permeability of an excitable membrane, which occurs in response to three types of stimuli (**Table 2.2**).

Ionic Basis of AP and Gating of Ion Channels

The genesis of AP involves participation of Na^+, K^+, and Cl^- channels. Out of these, Na^+ and K^+ channels are voltage sensitive and possess special

Table 2.1 Various factors that contribute toward genesis of RMP

Factor	Contribution	Description
Potassium ions	Maximum, *due to high-concentration gradient and high permeability*	▪ *Concentration gradient:* The ECF:ICF concentration ratio for K^+ is 3.5:150, thus explaining the high concentration gradient, which is directed from ICF → ECF ▪ *Membrane permeability:* Resting membrane is highly permeable to K^+ ions, due to the presence of numerous "leaky channels," through which K^+ ions continuously diffuse from ICF → ECF *Note: Both these factors result in net movement of K^+ toward ECF, thus creating electropositivity outside (and electronegativity inside)*
Chloride ions	Less than K^+ but more than Na^+, *due to large gradient and high permeability*	▪ *Concentration gradient:* The ECF:ICF concentration for Cl^- is 105:5, thus explaining the high-concentration gradient, which is directed from ECF → ICF ▪ *Membrane permeability:* Just like K^+, the resting membrane is also highly permeable to Cl^- ions due to the presence of numerous "leaky channels" through which these ions continuously diffuse from ECF →ICF *Note: Both these factors result in net movement of Cl^- toward ICF, thus creating electronegativity inside (and electropositivity outside)*
Sodium ions	Least, *because only one factor (large-concentration gradient) works in its favor*	▪ *Concentration gradient:* The ECF:ICF concentration ratio for Na^+ is ~145:14.5, thus explaining the high-concentration gradient, which is directed from ECF → ICF ▪ *Membrane permeability:* The resting membrane is totally *impermeable* to Na^+ ions since "leaky channels" for Na^+ ions do not exist and the voltage-gated Na^+ channels are closed at rest. Consequently, there is no movement of Na^+ ions across the resting membrane *Note: Thus, in a resting membrane, only one factor, i.e., concentration gradient, is important for Na^+ ions, and the large-concentration gradient coupled with the impermeability of resting membrane for Na^+ maintains the electropositivity outside*
Na-K-ATPase pump	–	It is an electrogenic pump (3 Na^+ influx: 2 K^+ efflux) whose activity causes net loss of 1 positive charge from cell interior per cycle. This will ultimately result in creation of electronegativity inside and positivity outside the membrane

Abbreviations: ECF, extracellular fluid; ICF, intracellular fluid; RMP, resting membrane potential.

Table 2.2 Types of stimuli that elicit action potentials

Electrical stimulus	Chemical stimulus	Mechanical stimulus
In vivo: Ionic flow via gap junctions within cardiac and smooth muscle cells (e.g., GIT) *In vitro:* Electrical stimulation with currents of predetermined strength and frequencies, applied via microelectrodes	Neurotransmitters, taste, and smell chemicals (tastants, odorants) trigger APs in neurons	Touch, pressure, stretching of membrane, etc., can also trigger APs by mechanically distorting the membranes

Abbreviations: AP, action potential; GIT, gastrointestinal tract.
Note: Electrical stimuli are preferred for experiments because their strength and duration can be precisely controlled, which is not possible with other stimuli.

"gate-like extensions." The voltage-gated Na^+ channel has an activation (M) gate toward ECF and an inactivation (H) gate toward ICF, while the voltage-gated K^+ channel has only a single activation (N) gate toward ICF. These gates respond (i.e., open and close) at specific values of membrane potentials.

Phases of Action Potential

The recording procedure for AP in a giant squid axon is shown in **Fig. 2.3**, while its various phases, their ionic basis, and correlation with channel activity are explained in **Table 2.3** and **Figs. 2.4** and **2.5**.

Concept Connect

Role of Other Factors in Genesis of Action Potential

- **Role of Na-K-ATPase in the genesis of AP:** After termination of AP, the membrane reattains the resting state, but there occurs ionic disequilibrium since Na^+ is now more inside, while K^+ is more outside. In this state,

the next AP cannot occur as Na^+ influx and K^+ efflux will be absent. Na-K-ATPase activity restores ionic balance to the preexcitation state by actively pumping 3 Na^+ ions out, along with 2 K^+ ions inside.

- **Role of calcium ions in genesis of AP:** Even though Ca^{2+} ions do not participate in AP, they influence opening of "M" gates of Na^+ channels. Ca^{2+} ions (in ECF) bind and stabilize these gates, thus modulating their response to voltage changes in membrane. During severe hypocalcemia (hypoparathyroidism), voltage-gated Na^+ channels destabilize and start opening either spontaneously or with low threshold stimuli (<−55 mV), producing signs/symptoms of neuromuscular irritability, i.e., paresthesias, muscle spasms, and epileptic fits.
- **Role of chloride ions in the genesis of AP:** These have no role in AP because there is no change in their membrane permeability when resting membrane is suddenly excited. Reason: Cl^- channels are mainly leak channels, thus allowing a constant passive diffusion of these ions irrespective of the presence of RMP or AP.

Table 2.3 Various phases of action potential

Phase of AP	Potential value	Description	Channel activity	Ionic basis
Latent period (LP)	−70 mV (resting value)	It is an isoelectric phase that represents the time taken by the impulse to travel from the stimulating electrode toward the recording electrode. Measured from the stimulus artifact till the upward deflection point in the AP curve. Duration of LP is: ▪ Directly proportional to the distance between stimulating and recording electrodes ▪ Inversely proportional to the speed of impulse conduction	▪ *Na^+ channel:* M gate closed; H gate open ▪ *K^+ channel:* N gate closed; leaky K^+ channels remain open	Constant K^+ efflux via leak channels maintains the resting potential value
Slow depolarization	−55 mV	Membrane potential undergoes a slow change toward a more positive value	▪ *Na^+ channels* open (some M gates flip open) ▪ *K^+ channels* remain closed	Potential slowly rises toward the firing level due to the small amount of Na^+ influx
Rapid depolarization	+35 mV	Membrane potential instantaneously overshoots the zero level. The transition point from slow to rapid depolarization is called the "firing level," while the membrane potential value of −55 mV is called the threshold potential	"M gates" of all Na^+ channels suddenly open at −55 mV	Sudden, sharp rise in membrane potential due to large Na^+ influx
Rapid repolarization	−40 mV	Membrane potential falls sharply to around −40 mV. Repolarization is 70% complete in this phase *Note: Sudden rise and fall in membrane potential resembles a spike (pointed needle*), due to which rapid depolarization and rapid repolarization phases are collectively known as *"spike potential"*	▪ Many Na^+ channels close instantaneously (H gates slam shut) ▪ Many K^+ channels start opening (N gates open slowly)	Potential value rapidly falls due to sudden stoppage of Na^+ influx and simultaneous K^+ efflux *Note: Opening of the K^+ channel's gates is a slow process*
Slow repolarization	−70 mV	▪ Membrane potential falls slowly thereafter to reattain resting levels ▪ Also called after-depolarization	▪ All Na^+ channels close ▪ All K^+ channels open	Potential slowly falls toward baseline due to K^+ efflux
Hyperpolarization	Below −70 mV	Membrane potential continues its decline despite reaching −70 mV, thus slightly overshooting the negative value. At the end of this phase, potential slowly reattains the resting value	K^+ channels still open (K^+ channels are slow to open and slow to close)	Potential value declines below baseline as "N" gates of K^+ channels take extra time to close completely, resulting in prolonged K^+ efflux

Note: The **stimulus artifact** is an initial small deflection in the baseline that occurs during membrane stimulation due to leakage of current from the stimulating electrode. Although this is an incidental finding (artifact = experimental error), it is very important as it marks this point of stimulation on the cathode ray oscilloscope (CRO).

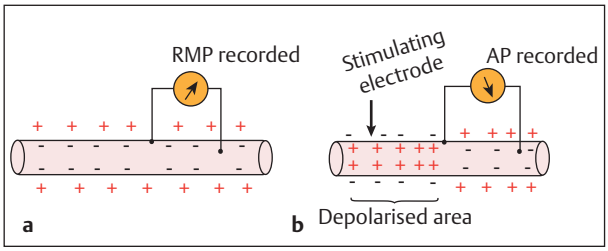


Fig. 2.3 Recording procedure for action potential. **(a)** Membrane at rest. **(b)** Membrane depolarized by an electrical stimulus. RMP, resting membrane potential; AP, action potential.

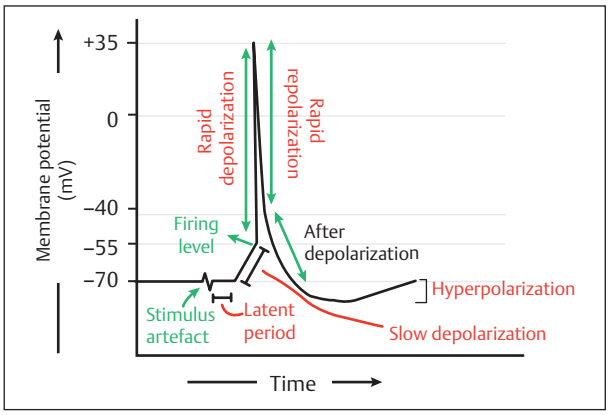


Fig. 2.4 Various phases of action potential. Note: In this figure, the action potential curve is slightly distorted to clearly show all the phases.

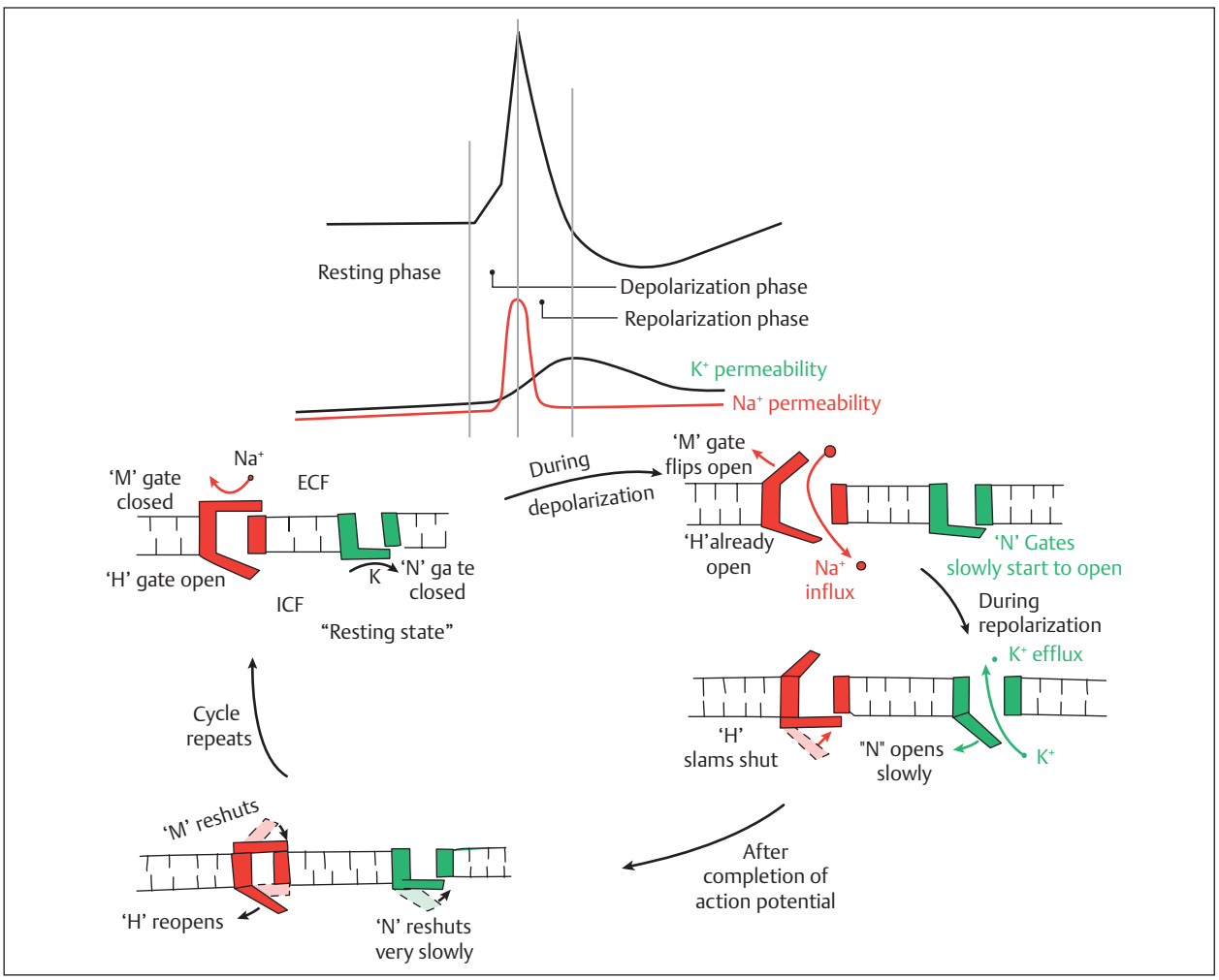


Fig. 2.5 Gating of ion channels and change in ionic permeability during various phases of action potential.

Q3. Describe the properties of action potential.

Or

Write short notes (a) the all-or-none law and (b) refractory period.

The various properties of AP are described in **Table 2.4**.

Q4. Write a short note on electrotonic potentials.

Or

Differentiate between local potentials and action potentials.

Or

Explain why catelectrotonic potentials are depolarizing in nature, while anelectrotonic potentials are hyperpolarizing in nature.

Or

Explain why stimulation occurs at cathode.

Electrotonic (Local) Potentials

Threshold stimuli evoke APs by producing +15 mV potential change. However, subthreshold (weak) stimuli that induce potential changes <15 mV typically evoke local/electrotonic potentials. Some neurons produce only local potentials, instead of APs, e.g., amacrine cells in the retina.

Table 2.4 Properties of action potential (AP)

Property	Description
Threshold (adequate) stimulus	It is the minimum strength of stimulus that produces an action potential when applied for an adequate duration
All-or-none law	"Whenever action potential is generated, it is always at maximal level; otherwise, it is not generated at all." Implications of the all-or-none law are: ▪ There is no such thing as an inadequate AP ▪ Threshold stimuli produce full-fledged AP ▪ If suprathreshold stimulus is given, AP is similar to threshold stimulus (i.e., amplitude of AP does not increase further) **Note: Specific effect of suprathreshold stimuli on AP** *Suprathreshold stimuli do not affect AP amplitude, but they do increase AP frequency due to reduction in duration of latent period*
Conductivity (propagation)	AP travels in all directions away from the stimulation point until the entire membrane is depolarized
Amplitude is constant	Magnitude of AP remains unchanged during conduction, i.e., does not diminish with time
Refractory period *(refractory = nonresponsive)*	With two successive stimuli, the membrane becomes refractory (nonresponsive) to the second stimulus for a brief duration, called the refractory period. Types of refractory period are depicted in **Fig. 2.6** **Absolute refractory period (ARP):** Membrane is completely nonresponsive to even suprathreshold stimuli. ARP lasts from the firing level to one-third completion of repolarization *Ionic basis*: During ARP, all "M" gates of Na^+ channels are open; thus, no "M" gate is left unopened for the second stimulus **Relative refractory period (RRP):** Membrane is responsive only to suprathreshold and nonresponsive to threshold stimuli. RRP lasts from the end of ARP to the end of the hyperpolarization phase *Ionic basis:* During RRP, "H" gates of Na^+ channels are closed and can be opened up by suprathreshold stimuli only **Significance of refractory period:** ▪ Impulse is always conducted from presynaptic to postsynaptic membrane ▪ Traveling impulse does not depolarize the area immediately behind it because it is under ARP
Mnemonic for properties of action potential: ACTOR: **A**mplitude, **C**onductivity, **T**hreshold stimulus, **O**beys the all-or-none law, **R**efractory period	

Types of Local Potentials

These are recorded by applying two electrodes, anode and cathode, across a membrane as shown in **Fig. 2.7**. The types of local potentials and their relationship with the strength of stimulus are given in **Table 2.5**.

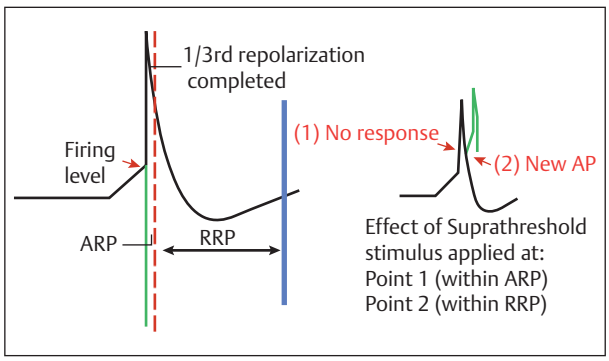


Fig. 2.6 Types of refractory period in the action potential curve. ARP, absolute refractory period; RRP, relative refractory period.

Concept Connect

Membrane Stimulation Normally Occurs at Cathode

Cathode ends (of stimulating electrodes) generate strong electrical fields due to their high electron concentration. This secondarily leads to membrane depolarization by strongly attracting positive ions (cations) toward it, thus stimulating the membrane.

Differences between Local and Action Potentials

The differences are enumerated in **Table 2.6**.

Table 2.5 Types of local potentials

Magnitude of change in membrane potential with subthreshold stimulus	Anelectrotonic potentials (anode is +ve end)	Catelectrotonic potentials (cathode is –ve end)
<7 mV	Graded response is seen, i.e., magnitude of local potentials is directly proportional to the strength of (subthreshold) stimuli	
8–14 mV	Maintain graded response	Potential change is disproportionately larger
≥15 mV		Transform into action potential

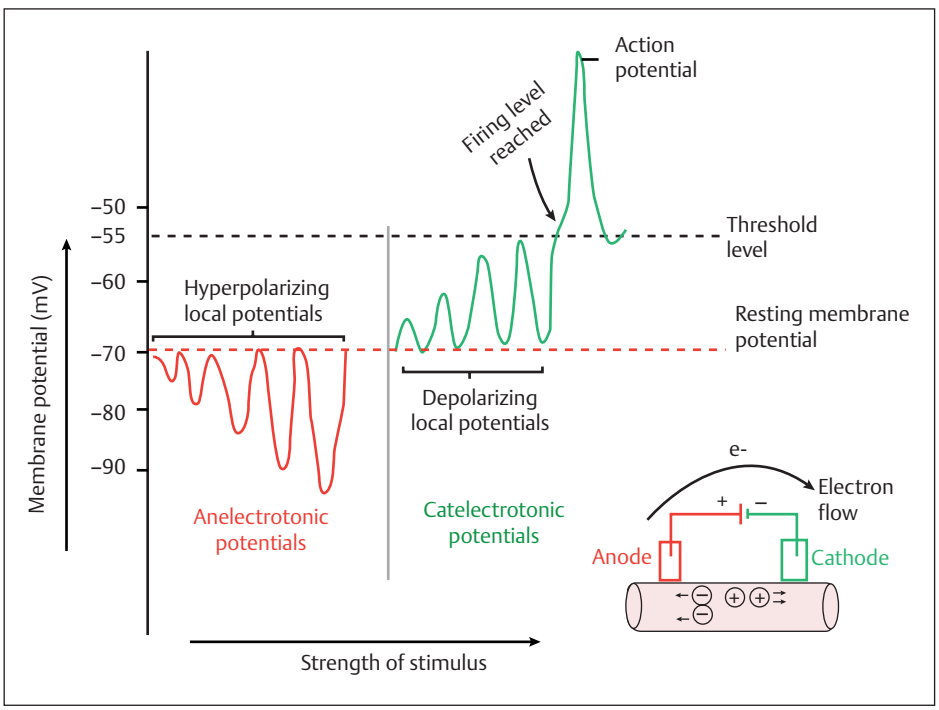


Fig. 2.7 Local potentials.

Table 2.6 Local potentials versus action potentials

Features	Electrotonic potentials	Action potentials
Stimulus strength	Subthreshold	Threshold
Propagation	Not seen; remain confined to the portion of membrane where they are induced (local potentials)	Present
Graded response	Present	Absent
All-or-none law	Do not obey	Obey
Refractory period	Absent	Present
Type of change induced in membrane	Depolarization with cathodic (catelectrotonic) potentials; hyperpolarization with anodic (anelectrotonic) potentials	Depolarization only

HYT 8: Strength–Duration Curve

Q5. Write a short note on the strength–duration curve.

Or

Discuss in brief chronaxie and its clinical importance.

Strength–Duration Curve

This curve depicts the relationship between the strength of stimulus and the duration for which it needs to be applied to elicit an adequate response (i.e., AP; **Fig. 2.8**).

Interpretations of the Curve

From this curve, three indices of membrane excitability have been derived:

- **Rheobase:** The minimum strength of stimulus that needs to be applied for an adequate amount of time to excite the membrane.
- **Utilization time:** Time taken by the rheobase current to sufficiently excite a membrane.
- **Chronaxie:** Time required to stimulate a membrane with a current of twice the rheobase strength.

Mnemonic: Alphabetically, **C**(hronaxie) is with **D**(uration), while **R**(heobase) is with **S**(trength).

Physiological Significance

Chronaxie is a clinical index of membrane excitability. It is estimated in nerve injuries and neuropathies to assess the progress of nerve healing and for the prognosis of an ongoing therapy.

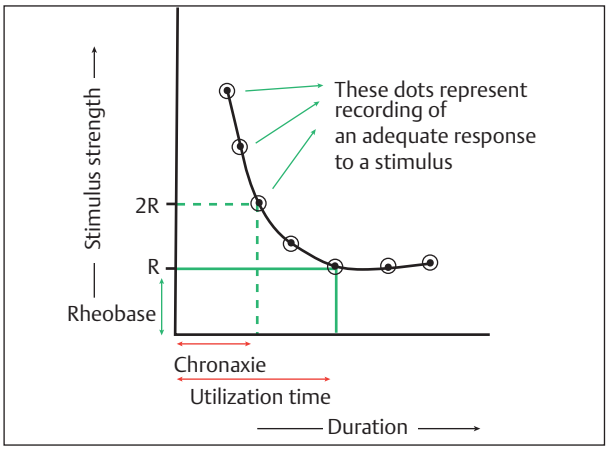


Fig. 2.8 Strength–duration curve.

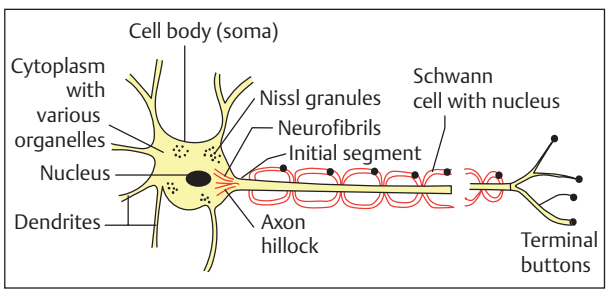


Fig. 2.9 Structure of a neuron.

HYT 9: Neurons and Neuroglia

Q6. Describe the structure and functions of a neuron.

Neurons (~100 billion) are the structural and functional units of the nervous system. The structure and functions of a neuron are explained in **Fig. 2.9** and **Table 2.7**.

Table 2.7 Structure and function of a neuron

Parts	Morphology	Function(s)
Nerve cell body (soma/perikaryon)	Contains: ▪ *Organelles*: Mitochondria, Golgi apparatus, nucleus, endoplasmic reticulum, etc. ▪ *Neurofibrils:* Thread-like structures that form a loose, interconnected network that forms the internal scaffolding for a neuron ▪ *Nissl granules*: Granular vesicles covered with ribonucleoproteins. Their number varies with the physiological state of the cell. They undergo chromatolysis (i.e., disintegrate into fine dust) due to fatigue, toxins, and trauma	▪ Maintains the structural and functional integrity of a neuron ▪ Endoplasmic reticulum synthesizes nerve growth factors and neurotransmitters, which are necessary for neuronal function
Dendrites	These are hair-like, branched processes radiating out from soma	These are like the antennae that receive signals from other neurons and transmit them towards the soma.
Axis cylinder (axon)	Long fibrous extension that arises from the "axon hillock/initial segment" (thickened area of soma). It is covered by the Schwann cell sheath (nonmyelinated neurons) or myelin sheath (myelinated neurons). Nodes of Ranvier are regular interruptions in the myelin sheath, which are placed 1 mm apart	▪ *Initiation of action potential*: Occurs at the axon hillock ▪ *Conduction of nerve impulse*: Occurs in the form of a propagated action potential, which spreads either *orthodromically* (i.e., anterogradely from dendrites→ cell body → axon → terminal ends) or *antidromically* (reverse direction) ▪ *Transport of substances:* Neurotrophins, neurotransmitters, organelles, etc., are transported anterogradely (from soma to terminals) via axoplasmic flow. Retrograde transport occurs in the opposite direction for empty vesicles, viruses, tetanus toxin, etc.
Terminal buttons (synaptic knobs)	At its termination, the axon loses its myelin sheath and divides into many branches with knob-like endings. These contain vesicles with neurotransmitters	Different responses are obtained depending on the type of cells that these endings make contact with: ▪ Impulse conduction (another neuron) ▪ Muscle contraction (motor end plate) ▪ Secretions (glandular cells)

Q7. Explain why action potentials originate at axon hillock.

The neuronal soma has relatively fewer voltage-gated Na^+ channels in its membrane, which makes it difficult to attain the required magnitude of depolarizing potential, which is necessary for initiating an AP. Conversely, the initial segment portion of the neuron has seven times more Na^+ channels than the soma, thus facilitating the initiation of AP in this part. This AP wave propagates in two directions, i.e., downward toward terminal buttons and retrogradely toward the soma. This retrograde firing "*wipes the slate clean*" for subsequent renewal of excitatory and inhibitory activity within the neurons.

Q8. Discuss various types of neuroglia and their significance.

Neuroglia are the second type of cells in the nervous system. They are 10 to 50 times higher in number than the neurons. This is because, unlike the latter, these regenerate due to the presence of centrioles. They do not generate/conduct nerve impulses and mainly have a supportive role. The various glial cells and their functions are described in **Table 2.8**.

Table 2.8 Various neuroglia and their functions

Glial cells within the central nervous system (Fig. 2.10)	
Cells	**Functions**
Astrocytes	▪ Reinforcement of the blood–brain barrier (BBB): Tight junctions between adjacent brain capillary endothelial cells form the BBB, thereby preventing entry of potentially unwanted/toxic agents into the brain via bloodstream. This barrier is further reinforced by podocytes (i.e., foot processes) of adjacent astrocytes, thus making it impermeable to most pathogens/toxins ▪ Synthesize neurotrophins for neuronal growth and survival ▪ Form protective covering on adjacent synapses and neurons ▪ Maintain normal neuronal excitability by taking up excess K^+ from CSF ▪ Provide physical support to neurons ▪ Reuptake and recycle the neurotransmitters released within synaptic cleft
Microglia	Scavenger cells that resemble tissue macrophages in function. Originate from marrow and enter the nervous system via systemic blood
Oligodendrocytes	Myelin sheath formation in CNS neurons
Ependymal cells	Form epithelial lining of ventricles and spinal cord; secrete CSF
Glial cells within the peripheral nervous system	
Cell	**Functions**
Schwann cells	▪ Myelin sheath formation in peripheral nerves ▪ Synthesize neurotrophins (i.e., chemicals needed for growth of neural tissue) ▪ Insulation and protection of the neuromuscular junction of skeletal muscles from surrounding fluids

Abbreviation: CNS, central nervous system; CSF, cerebrospinal fluid.

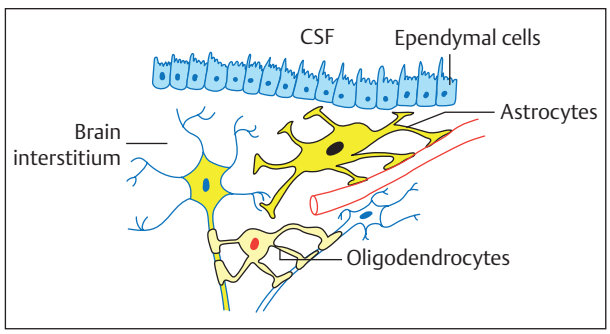


Fig. 2.10 Types of neuroglial cells. CSF, cerebrospinal fluid.

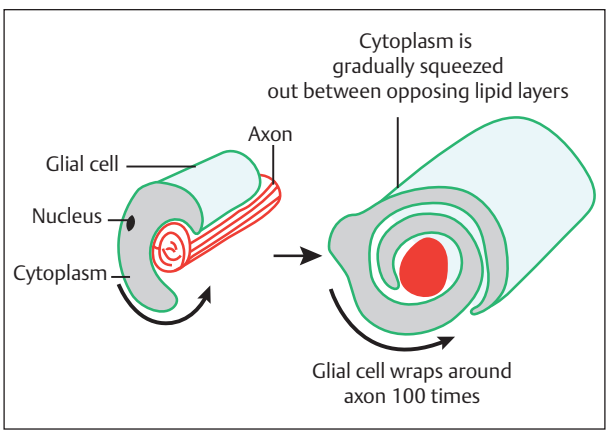


Fig. 2.11 Myelin sheath formation.

HYT 10: Nerve Fibers

Q9. Explain saltatory conduction and its significance.

Preliminary Concept: Myelination

Axons of many neurons acquire a sheath of a protein–lipid complex called myelin, which is formed by oligodendrocytes (in the CNS) and Schwann cells (in peripheral neurons). Myelin is formed when glial cells rotate around the axon 100 times. Cytoplasm gets squeezed out as myelin sheaths are added, such that lipid layers become highly compacted (**Fig. 2.11**).

Structure of Myelinated Axon

The myelin sheath so formed is interrupted regularly at nodes of Ranvier, which are regular 1-µm constrictions placed 1 mm apart. Na^+ channels are abundant at these bare spots.

Advantage of Myelination: Saltatory Conduction

Just like an athlete doing a somersault (acrobatic movement in which a person turns head over heels in the air or on the ground and lands or finishes on the feet), a nerve impulse also "jumps from one node of Ranvier to the next" (**Fig. 2.12**). Myelin sheath is an effective insulator because there is no flow of current through it as its thick lipid layer is impermeable to ions. However, at the bare points on the membrane, i.e., at nodes of Ranvier, there is no insulating layer. There is a high density of Na^+ channels at these nodes. As the nodes are only 1 mm apart, the strong local depolarizing currents can reach from an active (depolarized) node to the next node, before dying out. Consequently, the AP jumps from node to node, effectively skipping the myelinated portions lying in between.

Advantage of Saltatory Conduction

Myelinated nerves can conduct signals extremely rapidly over large distances due to saltatory conduction, almost 50 times faster than unmyelinated fibers. Within the body, the most urgent information is transmitted via myelinated fibers, while the less important information travels via unmyelinated fibers. In unmyelinated nerves, the depolarizing currents have to travel along the entire length of the axon.

In the Clinic

Multiple Sclerosis

It is an autoimmune disorder in which antibodies are produced against myelin sheath components, resulting in progressive demyelination. This significantly reduces the speed of transmission of neural impulses, especially in autonomic nerves. Patients present with features of autonomic dysfunction, such as arrhythmias, paresthesia, BP fluctuations, and hypotonia.

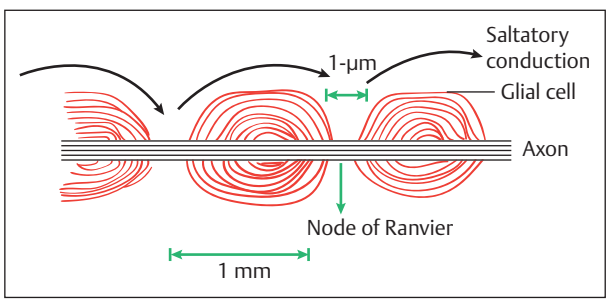


Fig. 2.12 Saltatory conduction.

Q10. Explain the various types of classification of nerve fibers.

There are three main types of classifications for nerve fibers, as explained in **Table 2.9**.

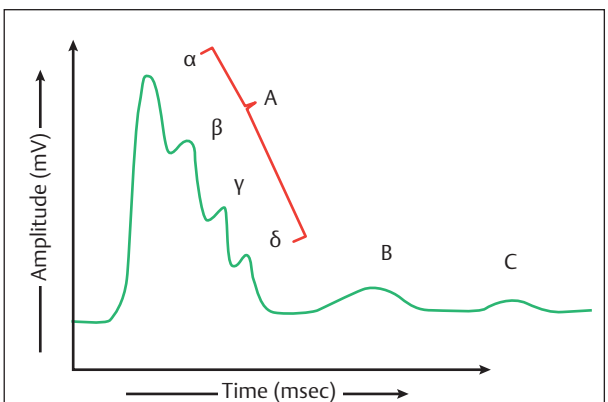
Q11. Write a short note on compound action potential.

Compound Action Potential

Action potential recording obtained from a mixed nerve (containing different types of nerve fibers) consists of multiple peaks, i.e., initial large peak, followed by successively smaller peaks. This recording is known as compound AP.

Recording of Compound Action Potential Curve

A mixed nerve consists of different types of nerve fibers with varying speeds of conduction (as classified by Erlanger and Gasser). When a "maximal stimulus" (i.e., a stimulus that can adequately excite all these nerve fibers) is given, the activity in the fastest conducting fibers (Aα) is recorded earlier than activity in slower ones (B and C). The number and size of peaks vary depending on the type of fibers in that particular nerve (**Fig. 2.13**).



Note: This recording shows a compound action potential recording obtained from a hypothetical mixed nerve containing all types of nerve fibers included in Erlanger and Gasser classification.

Fig. 2.13 Compound action potential.

Table 2.9 Classifications of nerve fibers

Erlanger and Gasser classification					
Type of fiber	**Myelinated**	**Functions**	**Mnemonic**	**Fiber diameter (μm)**	**Conduction velocity (m/s)**
Aα	Yes	**P**roprioception **M**otor to muscle spindle (extrafusal fibers)	**P**rime **M**inister	Thickness of nerves reduces from Aα → C *(Aα is thickest; C is thinnest)*	Speed of impulse conduction reduces from Aα → C *(Aα is fastest; C is slowest)*
Aβ		**P**ressure **T**ouch	**P**ressurized **T**o		
Aγ		**M**otor to muscle spindles (intrafusal fibers)	**M**ake		
Aδ		**F**ast pain **C**old **T**ouch	**F**avorable **C**omments **T**o		
B		**A**utonomic (preganglionic)	**A**bolish		
C	No	**A**utonomic (postganglionic) **W**armth Slow **p**ain **T**ickle and itch	**A**tomic **W**orld **P**ower **T**reaty		

Numerical classification (for sensory nerves only)		
Number	**Fiber type (as per Erlanger and Gasser)**	**Site of origin of sensory nerve**
Ia	Aα	Annulospiral endings on muscle spindle
Ib		Golgi tendon organs
II	Aβ	Flower spray endings on muscle spindle
	Aδ	Touch and pressure receptors
III	C	Fast pain and cold receptors
IV	Aα	Slow pain and warmth receptors

Physioclinical classification	
Stimuli	**Order of susceptibility of nerves**
Hypoxia	B > A > C
Pressure	A > B > C
Local anesthetics	C > B > A

Q12. Enumerate the properties of nerve fibers.

The various properties of nerve fibers are explained in **Table 2.10**.

Q13. Write a short note on neurotrophins.

Neurotrophins

Neurotrophins (NTs) are proteins necessary for optimal growth and survival of neurons (*neuro* = *nerve*; *trophic* = *related with growth*). Examples: Nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), and neurotrophin-3 (NT-3).

Table 2.10 Properties of nerve fibers

Property	Description
Excitability	Nerve cells are excited by electrical/chemical/mechanical stimuli, leading to production of local potentials or action potentials. Excitability depends on various factors (such as strength and duration of stimuli and ECF Ca^{2+} concentration)
All-or-none law	In nerve fibers, only threshold stimuli can evoke action potentials, whereas subthreshold stimuli fail to evoke any response. The response of nerve fibers to suprathreshold stimuli is the same as that seen with threshold stimuli.
Refractory period	When two (or more) stimuli are applied in quick succession, the nerve fibers become transiently nonresponsive to the second stimulus for a brief period known as the refractory period. This brief nonresponsiveness not only ensures that nerve impulses propagate in the forward direction but also limits the frequency of impulses that can be generated within a nerve fiber
Accommodation	Slowly rising currents fail to fire the nerve because the nerve fibers gradually "adapt" to the increasing stimulus intensity Mechanism: With application of slowly rising currents, opening of Na^+ channels is slowed down, and it starts coinciding with K^+ channel opening, resulting in a reduction in the extent of depolarization change
Conductivity	Experimentally, if a nerve fiber is stimulated at its center point, then it conducts the impulse bidirectionally (i.e., along both its ends simultaneously). However, in vivo, intact nerve fibers exhibit only unidirectional conduction (i.e., away from stimulus). Myelinated nerve fibers exhibit faster conduction (saltatory conduction)

Abbreviation: ECF, extracellular fluid.

Sources and Transport

NTs from neuronal soma are transported by axoplasmic flow toward the nerve endings (terminal buttons), while those from astrocytes and muscle cells bind to their receptors on the nerve endings and are then transported retrogradely toward the soma.

Functions of Neutrophins

- Help in synthesis of proteins associated with neuronal growth and development (especially anterogradely transported NTs).
- Maintain integrity of postsynaptic neuron (especially retrogradely transported NTs).
- NGF facilitates survival of central cholinergic neurons by inhibiting apoptosis.

HYT 11: Nerve Injuries

Q14. Describe Seddon's grading of nerve injuries.

Or

Write short notes on (a) motor march and (b) Tinel's sign.

Seddon's grading of nerve injuries is given in **Table 2.11**.

Q15. Describe in detail the various changes occurring during degeneration and regeneration of nerve fibers.

Or

Write a short note on wallerian degeneration.

The various changes are shown in **Fig. 2.14** and explained in **Table 2.12**.

In the Clinic

Neuroma

For successful regeneration, the endoneurium should be intact and the gap between the two cut ends should be <3 mm. Suturing the cut ends together reduces this gap, thus facilitating early regeneration. If the gap is >3 mm or if the endoneurium is also lesioned, then the sprouts from the proximal end form an entangled mass neuroma. This is a very painful condition and is a dreaded complication of the limb amputation procedure.

Q16. Explain denervation hypersensitivity.

Denervation Hypersensitivity

If a nerve is cut and allowed to degenerate, then the excitable cell innervated by that nerve gradually

Table 2.11 Seddon's grading of nerve injuries

Features	Neuropraxia	Axonotmesis	Neurotmesis
Severity	Mildest	Moderate	Severe
Cause	Nerve ischemia	Crush injury	Severe stretching
Nature of defect	There is only a transient interruption of nerve impulse conduction. No anatomical disruption is seen. Motor nerves are affected more by ischemia as compared to sensory nerves (*apraxia = functional impairment*)	There is disruption of nerve axons (*tmesis = sectioning*)	Complete disruption of the neuron, including the axons and their surrounding sheaths, is seen
Nerve sheaths			
Endoneurium	All are intact	Lesioned	All are lesioned
Myelin			
Perineurium		Intact	
Epineurium			
Spontaneous recovery	Complete recovery occurs within hours to days	Recovery is complete but often delayed by a few months	Spontaneous recovery is absent. Surgical intervention is usually required
Motor march *(progressive reinnervation of affected muscles, from proximal to distal direction)*	Absent	Present	Absent
Tinel's sign	Present *(gentle touching of involved nerves evokes paresthesia, i.e., pins and needles sensation in areas supplied by it)*		Absent
Wallerian degeneration	Absent	Present	Present

becomes very sensitive to the neurotransmitter released at the nerve endings. This exaggerated response of the target tissue to nerve injury is known as denervation hypersensitivity. For example, a denervated skeletal muscle becomes hypersensitive to the neurotransmitter acetylcholine (ACh).

Physiological Basis

There are two important mechanisms that increase the sensitivity of denervated structures:

- **Upregulation of receptors:** There is a reduction in neurotransmitter secretion within the synaptic cleft after injury. This deficiency leads to an upregulation of receptors for that neurotransmitter on the postsynaptic membrane. A higher number of receptors results in a greater response to even a slight amount of neurotransmitters.
- **Prolonged availability of neurotransmitter:** Intact nerve terminals can reuptake the released neurotransmitter, thus ensuring its rapid removal away from its receptors. However, denervation blocks this reuptake process, thereby prolonging the availability of neurotransmitter at the synaptic cleft.

Note

This hypersensitivity occurs temporarily and if the nerve does not regenerate within a few days to months, then the corresponding muscle fibers gradually start degenerating (i.e., undergo atrophy) and get replaced with fibrous tissue.

HYT 12: Neuromuscular Junction

Q17. Describe in detail the structure of neuromuscular junction.

Or

Write a short note on synapse-en-passant.

Neuromuscular Junction

The neuromuscular junction (NMJ) is formed between the terminal branch of the motor neuron and motor end plate (thickened portion of muscle fiber).

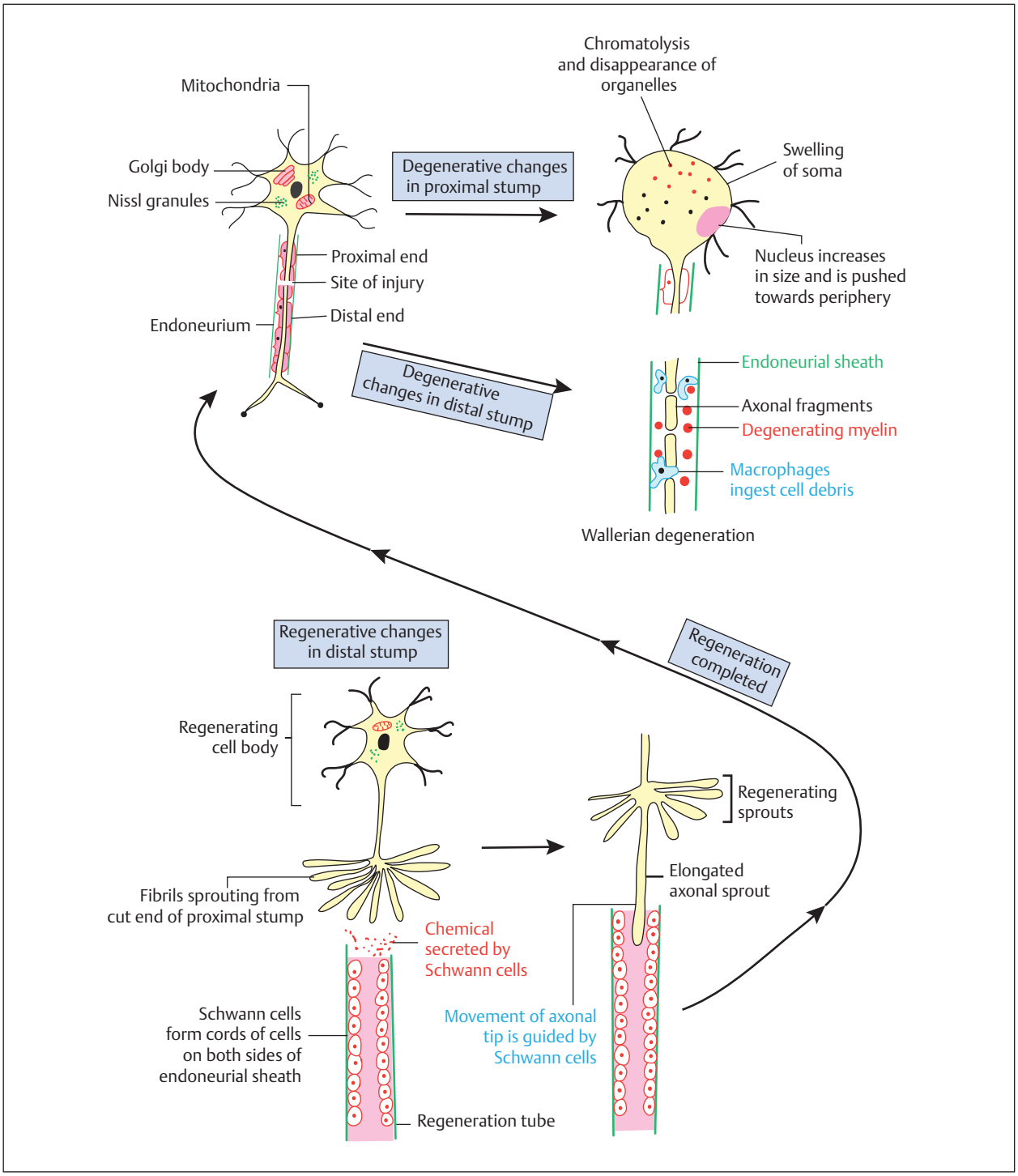


Fig. 2.14 Degeneration and regeneration in nerve fibers.

Table 2.12 Degenerative and regenerative changes in a nerve fiber

Degenerative changes	
Proximal stump	**Distal stump (wallerian degeneration)**
▪ Cell body (soma) becomes swollen and distorted ▪ Chromatolysis (disintegration of Nissl granules) ▪ Fragmentation and disappearance of various organelles, e.g., Golgi body, mitochondria, and neurofibrillae ▪ Nucleus increases in size and gets displaced peripherally	▪ Fragmentation of axon cylinder ▪ Splitting and breakdown of myelin sheath into "oil-drop"-like fragments ▪ Phagocytosis of above fragments by Schwann cells and macrophages, resulting in clearing of debris from the injury site *Note: Wallerian degeneration starts within 24 hr of injury. Impulse conduction can occur till the 3rd day of injury; thereafter, the affected nerve completely loses its conduction ability*
Regenerative changes *Regeneration starts in the proximal stump. Regeneration of the distal stump will succeed only if it has an endoneurial sheath. Hence, regeneration is possible only in neuropraxia and axonotmesis but not in neurotmesis*	
Proximal stump	**Distal stump**
▪ Cell body regains normal size ▪ Nissl granules and other organelles gradually reappear ▪ Nucleus becomes central again ▪ Axonal endings elongate into finger-like projections (fibrils) in various directions until one of them gains entry into the hollow endoneurial tube below, while all other fibrils completely disappear	Endoneurial tubes "get ready" to receive elongating fibrils from above. Schwann cell nuclei divide within endoneurial tubes to form "cord-like processes." Gradually axon refills this endoneurial tube, and Schwann cells re-form the myelin sheath around it

Table 2.13 Parts of the neuromuscular junction (NMJ) in skeletal muscles

Part	Description
Presynaptic terminal	It consists of synaptic knobs (end feet) of nerve terminals and contains: ▪ Synaptic vesicles containing acetylcholine (ACh) ▪ Mitochondria that provide ATP for mobilization and fusion of vesicles with the presynaptic membrane. Schwann cell covers and insulates the NMJ from surrounding fluids ▪ Dense bars (contain calcium channels) ▪ "Active sites," i.e., special zones near dense bars where vesicles fuse to release neurotransmitter
Synaptic cleft/ synaptic space	It is a 20- to 30-nm-wide space between the nerve terminal and motor end plate, where ACh is released; it contains extracellular fluid and an enzyme "acetylcholinesterase" (*which destroys ACh*)
Postsynaptic membrane	Motor end plate invaginates to form the "synaptic trough" (or synaptic gutter) that encloses the knob. Within this trough, muscle membrane is thrown into numerous "junctional folds" (or subneural clefts). ACh receptors, which are ligand-operated Na^+ channels, lie at the mouth of these folds

Skeletal Muscle NMJ

It has three parts, as shown in **Fig. 2.15** and explained in **Table 2.13**.

Smooth Muscle NMJ: Synapse-En-Passant

Unlike the skeletal muscle NMJ, where each neuron ends on a single muscle fiber, in case of smooth muscle, one neuron innervates many smooth muscle cells simultaneously. Here, postganglionic neurons branch extensively upon coming in contact with muscle cells. Multiple branches of these neurons contain numerous nodular swellings (or varicosities). The structure of synapse-en-passant is shown in **Fig. 2.16** and explained in **Table 2.14**.

Cardiac Muscle NMJ

The **NMJ in ventricular muscles** resembles that in smooth muscles since sympathetic nerve fibers lose their myelin sheath near cardiac muscle cells.
The **NMJ in atrial cells and conducting system cells** is still unknown.

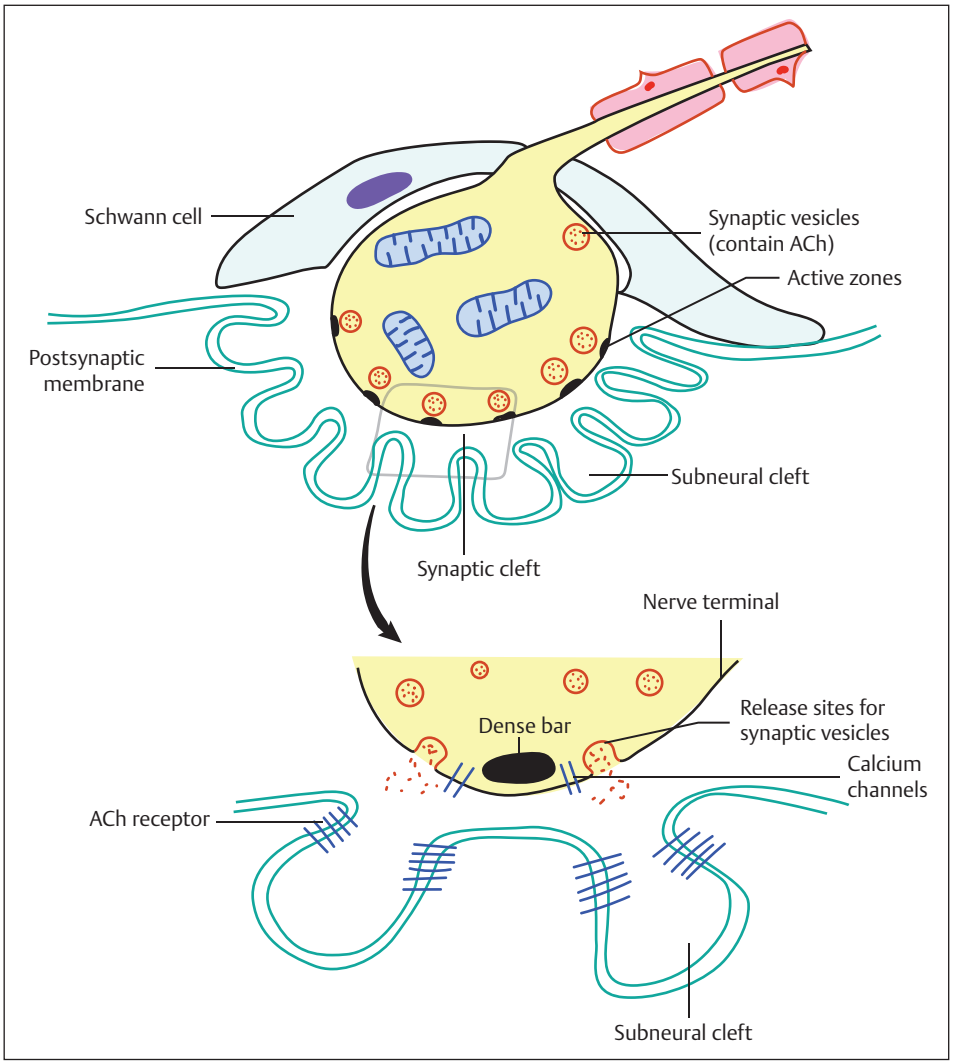


Fig. 2.15 Structure of the neuromuscular junction.

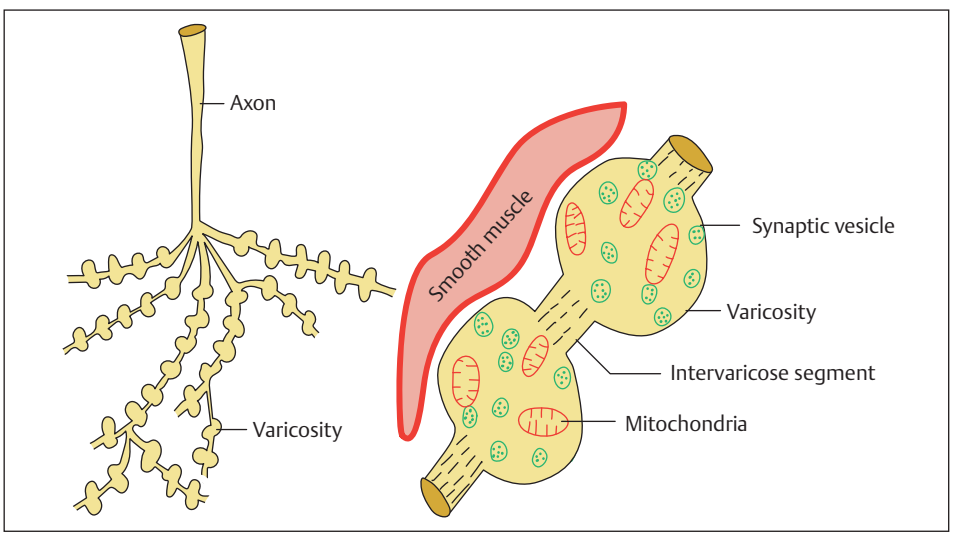


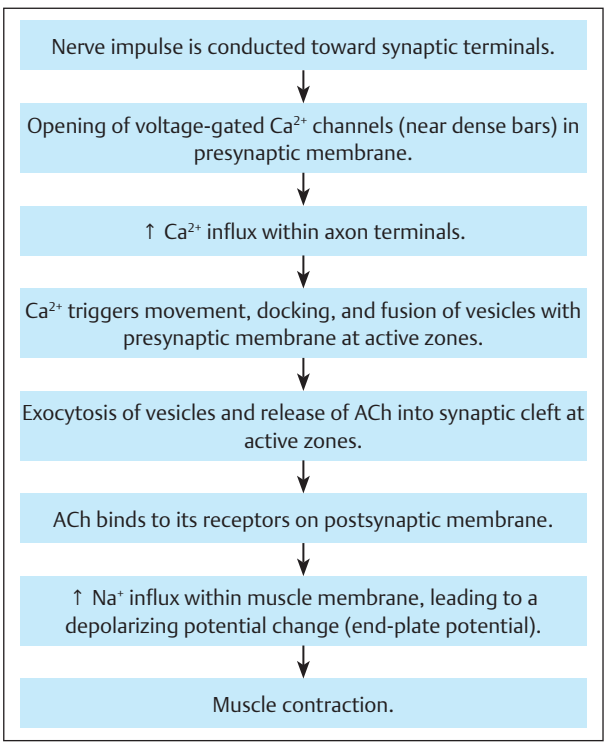
Fig. 2.16 Synapse-en-passant.

Table 2.14 Structure of synapse-en-passant

Part	Description
Presynaptic terminal	It consists of varicosities instead of end feet. Each varicosity contains numerous mitochondria and synaptic vesicles. Synaptic vesicles contain neurotransmitters, which can be either ACh or norepinephrine. In contrast to the skeletal muscle neuromuscular junction (NMJ), here the presynaptic terminal is not covered by Schwann cells
Synaptic cleft	It is not clearly distinguishable. It contains extracellular fluid and enzymes for the breakdown of neurotransmitters
Postsynaptic membrane	In smooth muscles, there are no clearly visible motor end plates or any of the specialized modifications on postsynaptic membrane (such as synaptic gutter/subneural clefts), as seen in skeletal muscles. The nerve terminals simply run parallel and in close proximity to the smooth muscle membrane surface, and at some places may even form a shallow groove on the muscle surface. This is the reason why the smooth muscle NMJ is also referred to as a "synapse-en-passant" since in this case, the neuron forms an NMJ with a smooth muscle cell and then passes on to make similar connections with other smooth muscle cells

Q18. Describe in detail the sequence of events occurring at the NMJ.

The sequence of events that occur at the NMJ on arrival of nerve impulse is depicted in **Flowchart 2.1**.



Flowchart 2.1 Sequence of events at the neuromuscular junction (NMJ). ACh: acetylcholine.

Q19. Write a short note on miniature end-plate potential (MEPP).

Miniature End-Plate Potential

A miniature end-plate potential (MEPP) refers to very-low-voltage local potential changes occurring at postsynaptic membrane, i.e., at motor end plate.

Genesis of MEPP

MEPP is associated with the release of a very minute quantity of ACh from presynaptic terminals, at rest. This phenomenon is referred to as "quantal release of neurotransmitters."

Concept Connect

End-Plate Potentials

When a nerve impulse arrives at the nerve ending, the number of quanta released rises manifold, thus abolishing MEPPs, and instead generating localized depolarizing potentials at motor end plate known as end-plate potentials (EPPs). If EPPs are of adequate magnitude, they are converted into APs.

Safety Factor for Signal Transmission at NMJ

When a nerve impulse reaches the NMJ, around 60 to 125 vesicles containing ACh are released, which are enough to activate 10 times more ACh receptors than those needed to produce an adequate potential at motor end plate. This bestows the NMJ with a large safety factor, ensuring that all nerve impulses are always able to generate an AP, even if they are weak.

Q20. Explain Lambert–Eaton myasthenic syndrome (LEMS).
Or
Write a short note on the Tensilon test.

Lambert–Eaton Myasthenic Syndrome

Lambert–Eaton myasthenic syndrome (LEMS) is a rare disease in which patients experience muscle

weakness and easy fatigability as seen in myasthenia gravis.

Pathophysiology

In LEMS, autoantibodies develop against presynaptic Ca^{2+} channels, thus reducing Ca^{2+} influx. This leads to a substantial reduction in the amount of ACh released within the synaptic cleft.

Clinical Features

Proximal muscles of the upper and lower limbs are mainly affected, producing a waddling (duck-like) gait and difficulty in raising the arms above the shoulder level. However, in sharp contrast to myasthenia gravis, where repeated stimulation worsens the muscle weakness, in LEMS, repetitive nerve stimulation causes a progressive improvement of muscle strength due to progressive accumulation of Ca^{2+} within the nerve terminals.

Tensilon (Edrophonium) Test

It is not possible to clinically differentiate between the patients of LEMS and those of myasthenia gravis since the symptoms are exactly the same. An edrophonium test is thus used to differentiate between these two conditions.

Procedure

Two milligrams (2 mg) of edrophonium is administered intravenously. It blocks acetylcholinesterase enzyme, thus providing symptomatic relief from muscle weakness within 30 seconds. If no improvement is seen after 30 seconds, the procedure is repeated until muscle weakness improves.

Inference

Myasthenia patients report improvement in muscle weakness, but patients with LEMS show no improvement in their symptoms. This is because in myasthenia, ACh receptors are fewer in number, and edrophonium can sufficiently stimulate them by prolonging the availability of ACh. However, in LEMS, this drug is ineffective since ACh receptors are normal.

Note The tensilon test is mostly obsolete now and has been replaced by electromyography (EMG).

HYT 13: Molecular Basis of Muscle Contraction

Q21. Describe in detail the structure of sarcomere in skeletal muscle.

Or

Sarcomere is the structural and functional unit of muscles. Explain.

Sarcomere

Each myofibril consists of multiple sarcomeres lying close together. Each sarcomere consists of light and dark bands that impart a striated look to skeletal muscle. Each sarcomere comprises an area enclosed within two Z lines.

1 sarcomere = ½ I band + 1 A band + ½ I band.

Morphological Features

Sarcomere consists of light and dark bands, as explained in **Table 2.15** and **Fig. 2.17**.

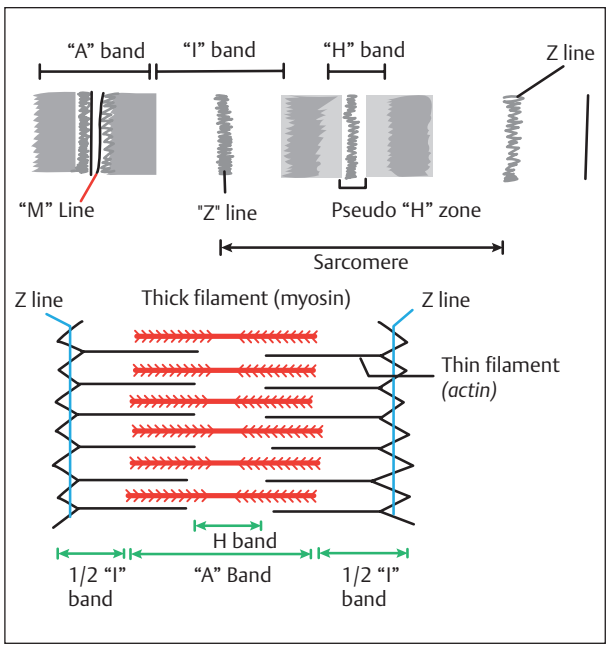


Fig. 2.17 Structure of sarcomere.

Table 2.15 Gross structural characteristics of sarcomere

Light bands ("I" bands)	Dark bands ("A" bands)
▪ Allow polarized light to pass through (isotropic) ▪ Each "I" band has a "Z line" at its center	▪ Do not allow light to pass through (anisotropic) ▪ Each "A" band has an "M" line in its center ▪ Lighter area on either side of M line constitutes "H band"
▪ "I" band represents an area (of sarcomere) where actin does not overlap myosin	▪ A band corresponds to the length of myosin filaments ▪ H band represents an area (of sarcomere) where myosin does not overlap actin

Table 2.16 Parts of the myosin molecule

Part	Morphology	Function
Tail	Two heavy chains are wrapped around each other into a double helical spiral	Anchors each myosin molecule to others within a thick filament
Head	Each of the heavy chains is folded bilaterally at its other end to form two heads per myosin molecule	Interacts with actin during muscle contraction
Arm/neck	Part of the myosin molecule that hangs to one side, along with the head, forms an arm or neck that extends outward from the rest of myosin. These protruding arms and heads are together known as "cross-bridges"	Acts as a pivot to cause movement of the myosin head

Sarcomere Proteins

Myosin

Thick filaments (1 myosin filament = 200 myosin molecules) are placed between two adjacent thin filaments. Each myosin molecule is "golf club" shaped. The three parts of a myosin molecule are discussed in **Table 2.16** and shown in **Fig. 2.18**.

Important Morphological Features of Myosin

- Two light chains associate with each head, resulting in four light chains per myosin molecule.
- Myosin head contains two binding sites, i.e., one for actin and the other for adenosine triphosphate (ATP). The second site has adenosinetriphosphatase (ATPase) activity (i.e., ATP → adenosine diphosphate [ADP] + inorganic phosphate [Pi]).
- Each cross-bridge is flexible (i.e., it bends) at two hinge joints, one where the arm leaves the tail and the other where the head attaches to the arm.
- Within each myosin filament, myosin molecules are arranged in such a way that their heads protrude outward in various directions, due to which no cross-bridges are formed in the center.

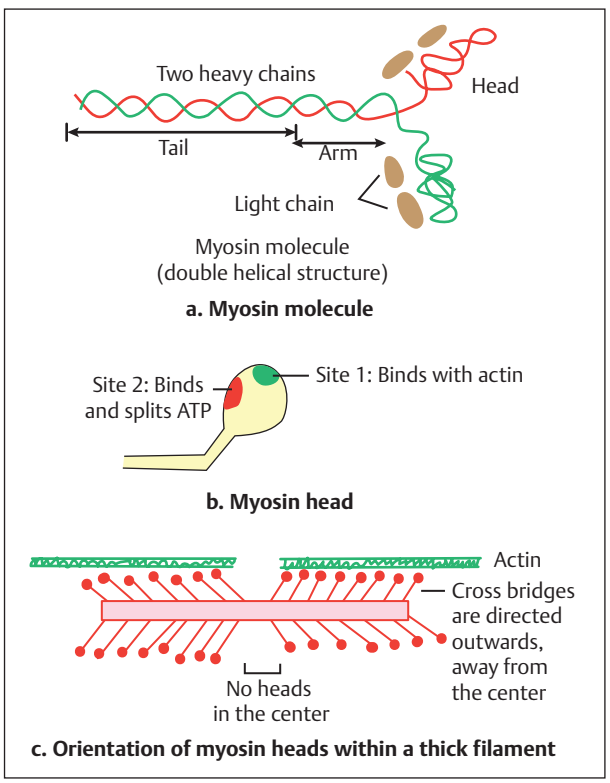


Fig. 2.18 Structure of myosin.

Actin

Actin acts as a "molecular rope" that is pulled by myosin heads during contraction. Actin is synthesized as a globular protein (G-actin) that polymerizes into a filamentous form (F-actin). F-actin contains intertwined helical chains (**Fig. 2.19**). Each G-actin molecule contains an "active site" that interacts with the myosin head (myosin binding site) during cross-bridge formation. F-actin filament, along with troponin and tropomyosin molecules, forms "thin

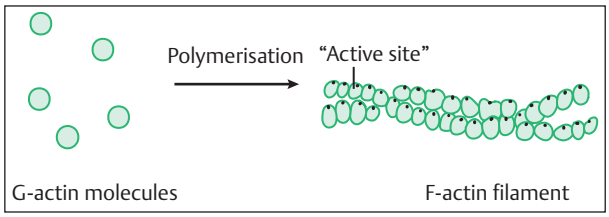


Fig. 2.19 Structure of actin.

filaments." The base of actin filaments is inserted into Z lines, while their tips protrude to lie suspended between myosin filaments.

Tropomyosin and Troponin

- *Tropomyosin* comprises two identical filamentous subunits entwined around actin filament such that they cover active sites on actin molecules when muscle is at rest (**Fig. 2.20**).
- *Troponin* is a complex of three proteins/subunits attached intermittently along tropomyosin.
  - Troponin C (TnC): Binds Ca^{2+} ions.
  - Troponin I (TnI): Binds actin and inhibits actin–myosin interaction.
  - Troponin T (TnT): Attaches the troponin complex to tropomyosin.

Mnemonic for components of Troponin Complex
C = **C**alcium; **I** = **I**nteracts, **T** = **T**ethers (attaches).

Concept Connect

Additional Supportive Proteins Present within Sarcomere

- **Actinin:** Binds thin filaments to Z lines.
- **Titin:** Largest protein that attaches to the Z line on one end and myosin filament on the other. Acts as a "molecular tape" by limiting the extent to which sarcomere can be pulled.
- **Desmin:** Binds Z lines to sarcolemma.
- **Dystrophin:** Connects thin filaments with sarcolemma, thus providing a scaffolding.
- **Nebulin:** A "molecular foot-ruler" that decides the length of thin filaments during their assembly.

Q22. Discuss the length–tension (LT) relationship in skeletal muscles.

Preliminary Concept

Some important terminologies that need to be understood before discussing the LT relationship are given in **Table 2.17**.

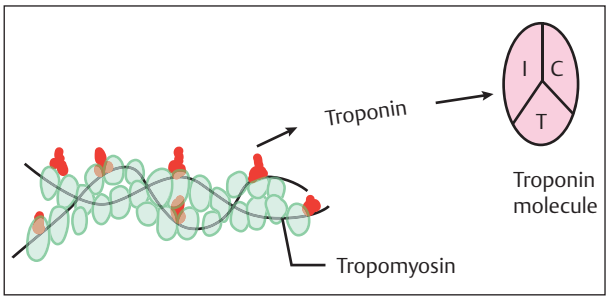


Fig. 2.20 Troponin and tropomyosin.

Table 2.17 Terminologies related to muscle length and tension

Terminology	Definition
Initial length	Length of intact muscle fiber (or sarcomere) just prior to contraction *Note: Resting length is a similar term used in case of isolated muscle fibers*
Optimum length	Length of muscle fiber (or sarcomere) at which the maximum number of cross-bridges can form
Active tension	Tension developed in muscle fiber due to cross-bridge formation
Passive tension	Tension developed in muscle fiber due to stretching
Total tension	Algebraic sum of active and passive tension in a muscle fiber

Molecular Basis of LT Relationship in Skeletal Muscle

This is illustrated in **Fig. 2.21**.

Note
L0 = resting length; N = optimum length; and 2N = twice the optimal length. Thus, 2N represents the elastic limit and if muscle is stretched beyond this limit, it ruptures. Interpretations of this curve are given in **Table 2.18**.

Q23. The sarcotubular system is essential for the excitation–contraction coupling mechanism in skeletal muscles. Justify.

Or

Write a short note on triad.

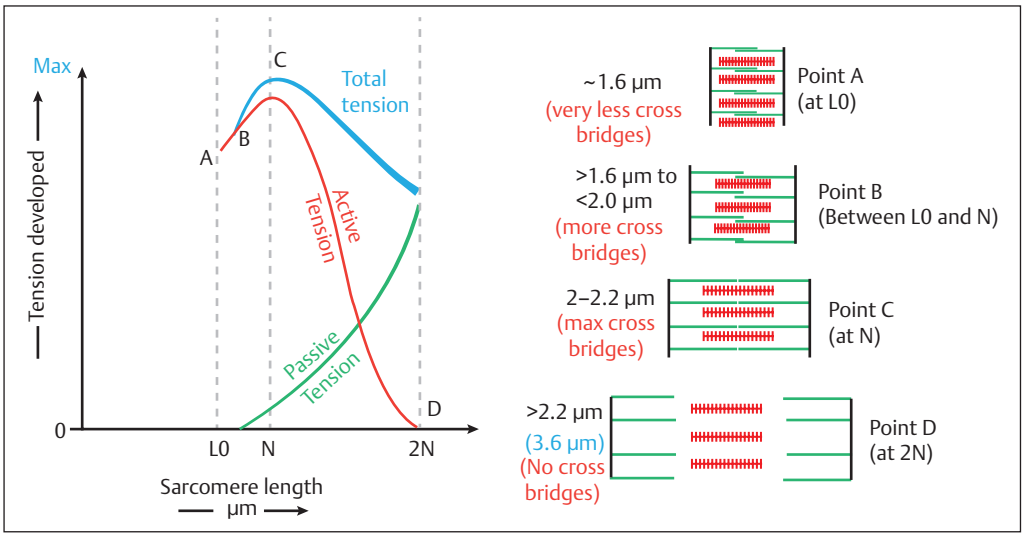


Fig. 2.21 Length–tension curve in skeletal muscle and its molecular basis.

Table 2.18 Interpretations of the LT curve in skeletal muscle

Length at which muscle is stimulated	Corresponding sarcomere length	Number of cross-bridges formed	Tension developed in muscle
At L0 *(resting length)*	≤1.6 µm	Least	▪ Some amount of active tension ▪ No passive tension ▪ Total tension curve follows the active tension curve
Between L0 and N *(between the resting and optimum lengths)*	1.6–2.0 µm	Slightly more	▪ Active tension goes on increasing ▪ Passive tension also develops (since muscle starts getting stretched) ▪ Total tension curve is the sum of active and passive tension curves and thus overshoots the active tension curve
At N *(optimum length)*	2.0–2.2 µm	Maximum	▪ Active tension is maximum ▪ Some more amount of passive tension develops ▪ Total tension curve reaches peak
Between N and 2N *(between optimum length and elastic limit)*	≥2.2 µm	Less	▪ Active tension decreases ▪ Passive tension increases ▪ Total tension curve comes down and deviates toward the passive tension curve
At 2N *(elastic limit)*	~3.6 µm	Zero	▪ Active tension is zero ▪ Passive tension is maximum ▪ Total tension curve joins the passive tension curve, since at this point total tension is contributed only by the passive tension component

Sarcotubular System

The sarcotubular system (or triad) is a specialized structure in skeletal muscles that ensures that every sarcomere gets activated simultaneously by a nerve impulse.

Components of Triad

The components of triad are described in **Fig. 2.22**.

- **Transverse (T) tubules:** Tube-like invaginations of sarcolemma that extend deep within muscle fibers that are filled with ECF and branch repeatedly, thus making contact with all myofibrils enclosed by that sarcolemma. There are two T tubules per sarcomere in skeletal muscles.
- **Sarcoplasmic reticulum:** It is formed by extensively branched modifications of the endoplasmic reticulum that enwraps myofibrils. It has two subparts:
  - *Terminal cisterns:* Large, terminal chambers that abut T-tubules. They act as the storehouse of Ca^{2+} ions. Since each T-tubule forms a junction with

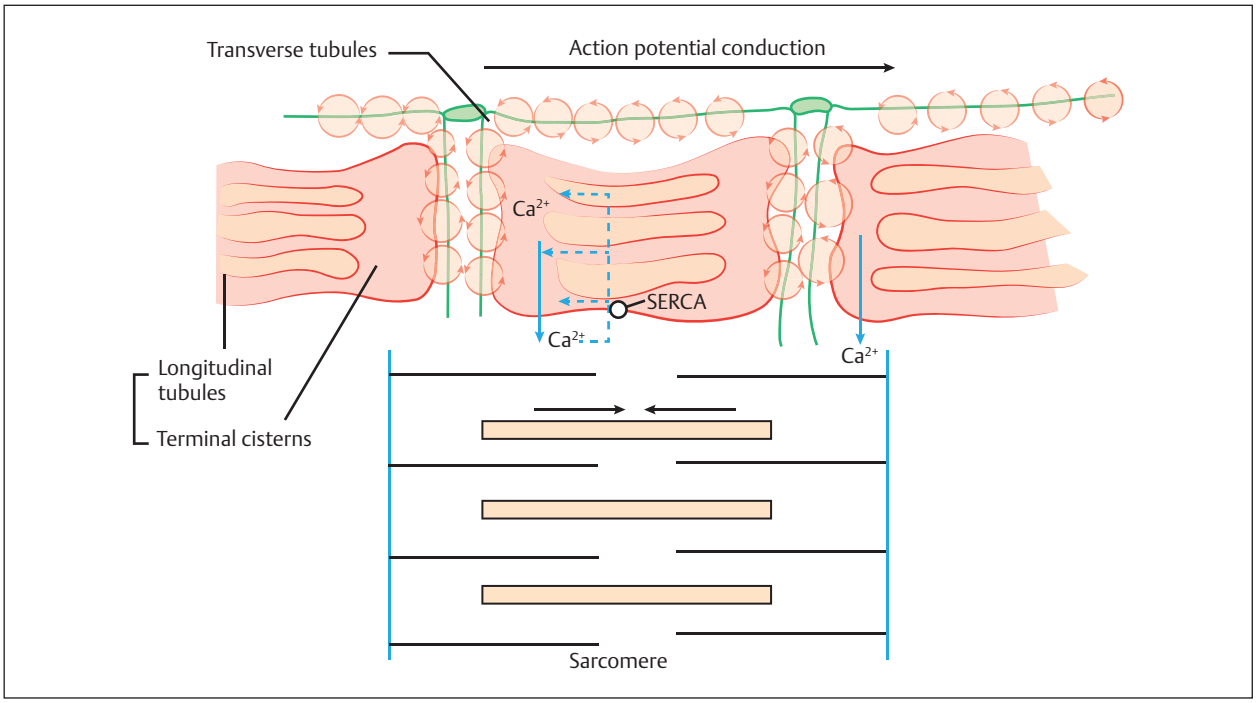


Fig. 2.22 Sarcotubular system. SERCA, sarcoendoplasmic reticulum calcium ATPase.

two terminal cisterns, the sarcotubular system is also called triad.

- *Longitudinal tubules*: Elongated sac-like structures that surround myofibrils from all sides.

Function of Triad

The sarcotubular system establishes a functional link between muscle excitation and contraction (excitation–contraction coupling) by releasing Ca^{2+} ions into muscle cytosol in response to muscle membrane depolarization. After contraction is over, Ca^{2+} is pumped back into the sarcoplasmic reticulum by sarcoendoplasmic reticulum calcium ATPase (SERCA) and gets stored as bound form with calsequestrin.

Mechanism of Calcium Release from Sarcoplasmic Reticulum

Sarcolemmal depolarization wave spreads inward along T-tubule membrane to activate dihydropyridine receptors (DHPRs). This "lifts off" the blockade on ryanodine receptors (RyRs) (Ca^{2+} release channels on terminal cisterns of the sarcoplasmic reticulum), thus causing Ca^{2+} influx within sarcoplasm (refer to Fig. 4.11, Chapter 4).

Concept Connect

- **Calsequestrin:** As soon as Ca^{2+} is pumped back into the sarcoplasmic reticulum, it immediately binds with a protein called calsequestrin and gets stored. This is a reversible process.
- **Triad in cardiac and smooth muscles:**
  - *Cardiac muscles:* T-tubules are well developed (5 times wider than those in skeletal muscles), but the sarcoplasmic reticulum is less developed.
  - *Smooth muscles:* Both T-tubules and the sarcoplasmic reticulum are poorly developed.

Q24. Explain the molecular basis of skeletal muscle contraction.

Or

Discuss the sliding filament theory of muscle contraction.

Sliding Filament Theory of Muscle Contraction

The sliding filament theory (*or walk-along theory or ratchet theory*) is the most widely accepted theory that proposes that muscle contractions are due to

sliding of thin filaments over thick filaments, which is facilitated by the formation of cross-bridges between actin and myosin (**Fig. 2.23**).

During Resting State of Muscle

Opposing tips of actin filaments barely touch each other. Active sites on actin molecules are covered by the tropomyosin–troponin complex, and myosin heads lie in the "cocked-up" position.

During Muscle Contraction

Thin filaments are pulled inward over thick filaments due to the formation of cross-bridges. During this process, the tips of thin filaments begin to touch and overlap each other.

Concept Connect

Changes Occurring within Sarcomere during Muscle Contraction

- Width of I band decreases.
- Width of H band also reduces.
- Width of A band remains constant.
- Z lines come closer.
- Length of thick or thin filaments is unchanged throughout contraction.

During Muscle Relaxation

When Ca^{2+} is no longer available, the troponin–tropomyosin complex slides back into place to again cover all active sites. Consequently, cross-bridges are no longer formed.

Q25. ATP is required not only for muscle contraction but also for muscle relaxation. Justify.

Or

Explain why muscle relaxation is also an active process.

Or

Explain why rigor mortis occurs earlier in violent deaths.

Role of ATP in Muscle Relaxation

It is understood that ATP is vital for muscle contraction since energy released by splitting ATP is used for movement of myosin heads. However, it is also important to note that ATP also has an important role in muscle relaxation because relaxation can

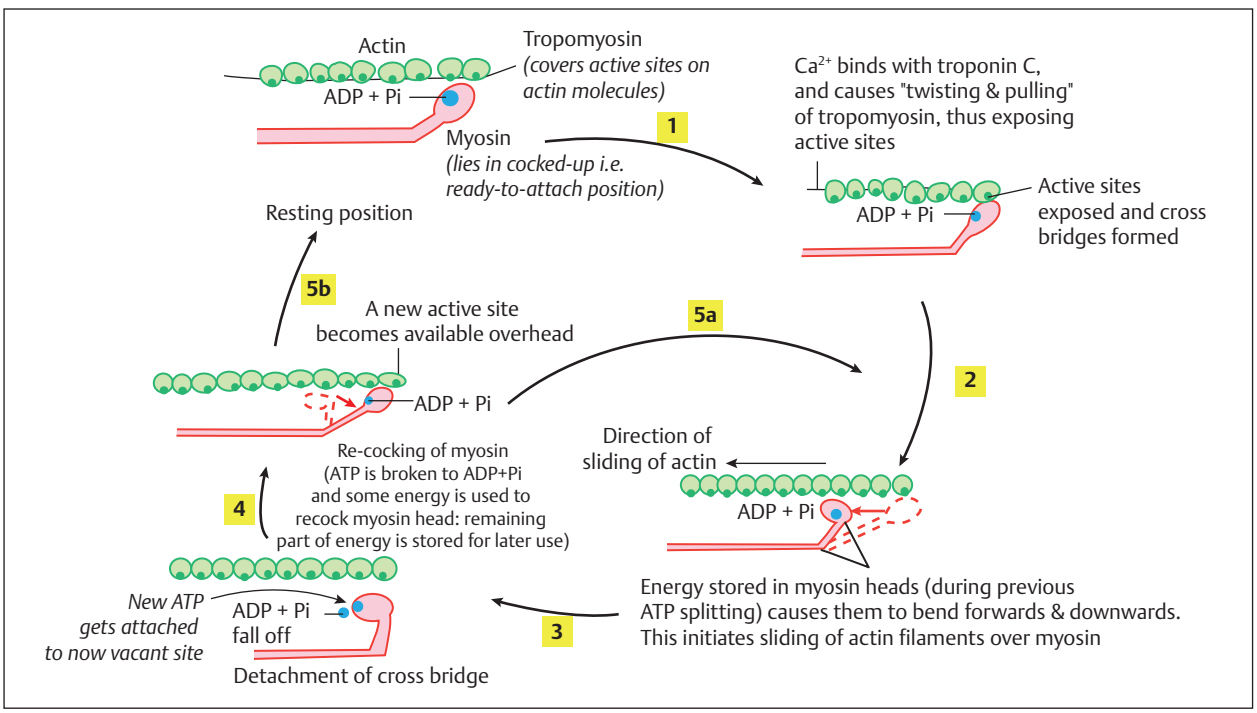


Fig. 2.23 Sliding filament theory of muscle contraction. Steps: 1. Cross-bridge formation; 2. Initiation of power stroke; 3. Detachment of cross-bridges; 4. Re-cocking of myosin heads; 5a. Formation of new cross-bridges; 5b. Reattainment of resting position.

occur only when cross-bridges have detached, and this will happen when a new ATP molecule binds to the myosin head (*that is already attached to actin*). Thus, if ATP gets depleted, then the already attached myosin heads will not detach and relaxation will not occur.

In the Clinic

Rigor Mortis Occurs Earlier in Violent Deaths as Compared to Silent Deaths

Rigor mortis (*rigor = spasms*; *mortify = death*) is characterized by generalized, severe muscle contractures within few hours after death due to ATP deficiency. After death, no new ATPs are synthesized; thus, myosin heads do not get detached; moreover, SERCA pumps are also unable to function, thus increasing Ca^{2+} availability. Due to both these effects, muscles remain in a spasmodic state. Rigor mortis occurs earlier if there is active muscle contraction (due to struggle) just before death, e.g., in hunted animals and homicidal deaths.

Q26. Define a motor unit and discuss its various properties.

Or

Write a short note on (a) recruitment of motor units and (b) gradation of motor response.

Motor Unit

A single motor neuron and all the muscle fibers that it innervates are known as a motor unit (**Fig. 2.24**). The properties of a motor unit are explained in **Table 2.19**.

HYT 14: Physiology of Exercise

Q27. Differentiate between slow and fast muscle fibers.

The differences between these two types of muscle fibers are listed in **Table 2.20**.

Q28. Differentiate between isometric and isotonic contractions.

The important differences between these two contractions are given in **Table 2.21** and **Fig. 2.25**.

Q29. Exercising muscles undergo oxygen debt. Explain.

Preliminary Concept: O_2 Stores in Body

Around 2 L of O_2 is stored within blood (Hb), muscles (Mb), lungs (alveolar air), and plasma (in dissolved form).

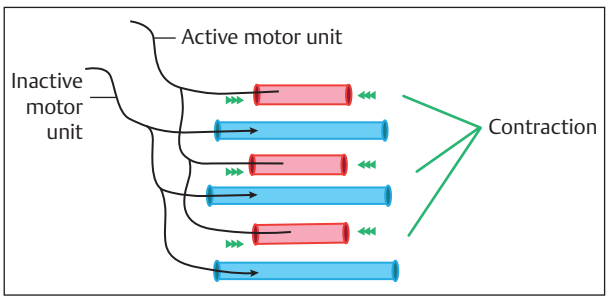


Fig. 2.24 Motor unit.

Table 2.19 Properties of a motor unit

Property	Description
Type of muscle fibers	All muscle fibers in a given motor unit are of a similar type
Number of muscle fibers	It depends on the type of motor activity being executed by that muscle fiber
Size principle	Small-size motor neurons (conduct slowly) innervate slow (red) muscle fibers, while large-size motor neurons (conduct rapidly) innervate fast (white) muscle fibers
Recruitment of motor units	Progressive rise in load/voluntary contraction results in activation of more and more motor units (in response to increasing frequency of signals from the motor cortex). This recruitment phenomenon of motor units is responsible for gradation of muscle strength, ensuring energy efficiency of muscle contraction
Asynchronous firing	During an ongoing voluntary contraction, the newly recruited motor units fire at slightly different time periods with respect to each other, thereby ensuring optimum and prolonged contraction *Note: Synchronous firing of activated motor units results in only a short-lasting burst of contraction that is followed by sudden relaxation. This is not useful in daily life scenarios, as it would result in sudden dropping of loads after they have been picked up*

Table 2.20 Slow versus fast muscle fibers

Features	Slow muscle fibers	Fast muscle fibers
Also known as	Red fibers	White (pale) fibers
Myoglobin content	High	Very low
Mitochondria	Numerous	Less
Oxidative metabolism	High	Low
Glycolysis	Low	High
Vascularity	Extensive	Less extensive
Diameter	Thin	Thick
Twitch duration	Long (~100 msec)	Very short (~7 msec)
Fatigue tendency	Not fatigued easily	Easily fatigued
Physical activity for which these muscles are more specialized	Gross, sustained movements, e.g., running, jumping, climbing, and standing	Fine, rapid, skilled movements, e.g., reading, writing, and speaking
Location of muscles	Legs, arms, abdomen, etc.	Eyes, hands, fingers, etc.

Table 2.21 Differences between isometric and isotonic contraction

Features	Isometric contraction	Isotonic contraction
Definition	Muscle length remains unchanged despite change in muscle tension (iso: same; metric: refers to length)	Muscle tension remains unchanged despite change in muscle length (iso: same; tonic: refers to tension)
Experimental setup	Isolated muscle is firmly attached at both ends. No load is attached	Isolated muscle is fixed at one end, while load is attached to the other end such that muscle detects load only during contraction
Work done	Zero (since length is unchanged)	Yes (due to change in length)
Joint movement	Absent; since muscle contraction occurs without muscle shortening	Present; since muscle contraction occurs along with muscle shortening
Applied load	Much more than contractile power of muscles (very heavy loads)	Usually less than or equal to contractile power of muscles (moderately heavy, light loads)
Utility in real life	Helps in "holding" already lifted objects; muscle strengthening (in athletes)	Helps in lifting various objects
Examples	Pushing against a wall, holding a lifted weight	Running, cycling, weightlifting

Note *Mixed contractions:* In most daily life scenarios, both types of contractions coexist. For example, lifting a stone from the ground is an isotonic contraction, but if it is held in the hand thereafter, then it is an isometric contraction.

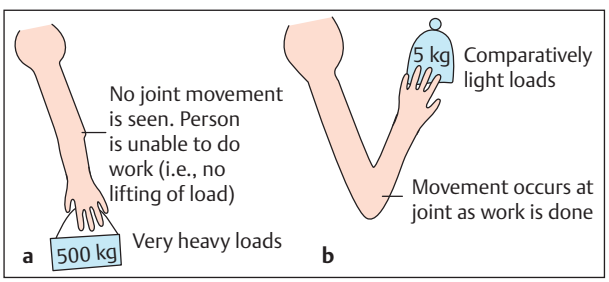


Fig. 2.25 **(a)** Isometric contractions. **(b)** Isotonic contractions.

Creation of O_2 Debt

Oxygen demand rises considerably during *prolonged, heavy exercise* because of its increased utilization for ATP synthesis. This leads to a compensatory rise in respiratory rate, but despite this O_2 supply is still inadequate. To overcome this shortage, some O_2 is extracted from its reserves so as to match O_2 supply with its (high) demand. It is this borrowing of oxygen that creates O_2 debt during heavy exercise!

Repayment of O_2 Debt

When exercise is stopped (due to fatigue or voluntary stopping), some extra amount of O_2 is breathed for a prolonged period and gradually O_2 uptake returns to baseline values. This extra O_2 being inhaled for repaying O_2 debt is ~11.5 L (i.e., *9.5 L more than what was taken originally from O_2 stores*). It is completed in the following two phases, as shown in **Fig. 2.26**:

- **Repayment of nonlactic oxygen debt:** Initial 3.5 L of oxygen is used for replenishment of ATP stores, O_2 stores, and phosphocreatine system.
- **Repayment of lactic acid oxygen debt:** The remaining 8 L is used for lactic acid disposal (mainly) and replenishment of muscle glycogen stores (slightly).

Q30. Define muscle fatigue and explain its genesis.

Or

Explain why the site of fatigue varies depending upon whether it is elicited in vivo or in vitro.

Fatigue is a temporary loss of strength and energy as a result of vigorous physical activity. Various probable sites of fatigue and their associated mechanisms are explained in **Table 2.22**.

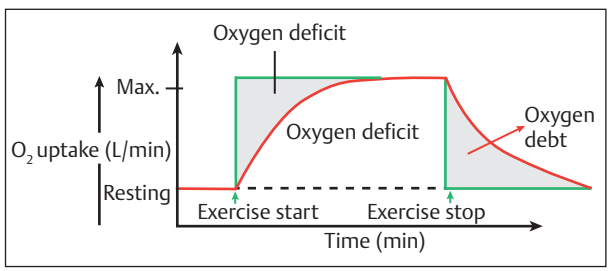


Fig. 2.26 Oxygen debt.

Q31. Describe various energy sources for exercising skeletal muscles.

Or

Write a short note on the phosphagen system and its significance.

Exercising muscles depend on three metabolic systems for providing an uninterrupted ATP supply. These are explained in **Table 2.23**.

HYT 15: Smooth Muscles

Q32. Differentiate between single-unit and multiunit smooth muscles.

The differences between these two types of smooth muscles are listed in **Table 2.24**.

Q33. Discuss the unique properties of smooth muscles.

Or

Write short notes on (a) latch bridge mechanism and (b) smooth muscle plasticity.

Or

Smooth muscles are more energy efficient than skeletal muscles. Why?

There are four unique characteristics of smooth muscles as given in **Table 2.25**.

Table 2.22 Sites of fatigue

Site of fatigue	Scenario	Mechanism of fatigue
Brain/central synapses	Normal humans	Fatigue is purely psychological *Supportive evidence*: During an ongoing exercise, if a tired person is motivated to perform better, then the person can significantly improve performance despite feeling exhausted
Neuromuscular junction (NMJ)	Isolated nerve muscle preparation	Exhaustion of neurotransmitter ACh at the NMJ Note: *In intact organisms, ACh is continuously synthesized and is thus never exhausted completely*
Muscles	Intact laboratory animals; humans (*second most common site*)	Depletion of muscle metabolic systems, leading to failure of adequate ATP replenishment Inhibition of muscle metabolic enzymes due to lactic acid accumulation

Note: Nerves/neurons do not exhibit fatigue.

Table 2.23 Muscle metabolic systems in exercise

Metabolic system	Description	Moles of adenosine triphosphate (ATP) replenished	Duration for which energy is provided
Phosphagen system (phosphocreatine–ATP system)	Phosphocreatine, like ATP, is a high-energy compound (*releases 10,300 calories per mole as compared with 7,300 calories per mole from ATP*). Phosphocreatine and ATP together constitute the phosphagen system	4/min (fastest)	8–10 s
Glycogen–lactic acid system	Muscle glycogen stores are metabolized via glycolysis to yield pyruvic acid (*in aerobic conditions*) or lactic acid (*in anaerobic conditions*), along with ATP synthesis	2.5/min	~1.5 min
Aerobic system	In this, various nutrients (glucose, fatty acids, and amino acids) after initial processing combine with oxygen (*inside mitochondria of muscle cells*) to release tremendous amounts of energy to replenish ATP stores	1/min (slowest)	As long as nutrients last

Table 2.24 Differences between single- and multiunit smooth muscles

Features	Single-unit smooth muscle	Multi-unit smooth muscle
Other name	Visceral/solitary/phasic smooth muscle	Tonic smooth muscle
Gross morphology (**Fig. 2.27**)	Individual muscle fibers are arranged such that if one of them is stimulated, all other fibers contract together as a single unit	Individual muscle fibers contract independently from each other
Functional syncytium	Present, i.e., muscles follow the principle of "stimulate one; stimulate all"	Absent
Gap junctions	Present; permit rapid transfer of ions between muscle cells, resulting in simultaneous excitation of all muscle cells	Absent
Type of contraction	Undergo sustained contraction	Undergo graded contractions for precise control of muscle function
Neuromuscular junction (NMJ) density	Less *(due to the presence of gap junctions)*	Numerous *(due to the absence of gap junctions)*
Location	Stomach, intestine, ureters, uterus, and male reproductive tract	Sphincters (in the gut and urinary tract), bronchi, eye, etc.

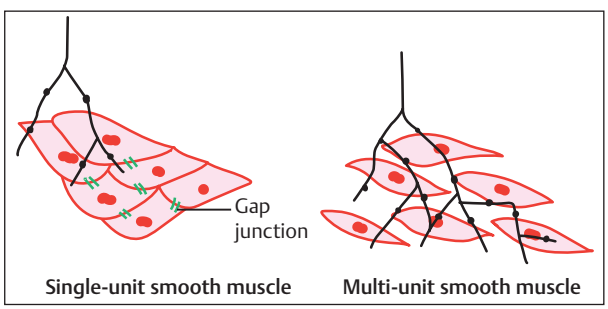


Fig. 2.27 Types of smooth muscles.

HYT 16: Differences between Skeletal, Cardiac, and Smooth Muscles

Q34. Explain the various differences between skeletal, cardiac, and smooth muscles.

The differences are enumerated in **Table 2.26**.

Table 2.25 Unique characteristics of smooth muscles

Characteristics	Description
Plasticity	No resting length can be assigned to visceral smooth muscles since they exert variable tension at any length, thus behaving as viscous, malleable masses. For example, if a piece of visceral smooth muscle is stretched, initially it exerts increased tension, but if it is held at that increased length, tension gradually falls back to resting levels. This property of plasticity enables viscera (alveoli, vessels, bladder) to accommodate large amounts of content without altering their muscle tone significantly **Probable mechanism: length adaptation** During stretching, smooth muscle cells probably replicate sarcomeres and insert new sarcomeres in series with existing sarcomeres. But when muscle returns to its normal length, it readapts by removal of these additional sarcomeres and/or by shortening of preexisting ones
Unipolar cross-bridges (**Fig. 2.28**)	Sarcomere of smooth muscles contains many actin filaments of variable length that radiate from dense bodies. However, only one among them is long enough to make cross-bridges till the far end of the myosin filaments. This unique arrangement is known as unipolar/side polar arrangement of cross-bridges, and it allows a myosin filament to pull two actin filaments in opposite directions simultaneously, till the last point on myosin filaments. This arrangement ensures: ▪ Contraction of even fully filled viscera ▪ About 80% shortening, enabling viscera to empty almost entirely, as compared with only 30% in skeletal muscles ▪ Formation of more cross-bridges, resulting in higher contractile strength
Latch bridge mechanism	A special feature of smooth muscle is that they undergo *slow and sustained* contraction because of the slow cycling rate of cross-bridges (i.e., very few cross-bridges are formed at each instant due to the slow activity of myosin ATPase). Consequently, myosin heads remain "latched" to actin for prolonged periods of time before getting detached. This mechanism makes smooth muscle more energy efficient by providing: ▪ Prolonged contraction with less ATP consumption ▪ High fatigue resistance, since ATPs are available for a longer duration **Physiological significance:** ▪ *High energy efficiency of smooth muscles:* The latch mechanism makes smooth muscles highly energy efficient, i.e., they can generate a higher force of contraction despite using very less ATP. This mechanism also ensures that cross-bridges remain attached for some extra time, thereby maintaining contractile force for that extra time. It is especially important in sphincters; otherwise, much of body's energy would have been spent in maintaining tonic constriction of sphincter muscles ▪ *Improved energy efficiency of nerves supplying smooth muscles:* Since cross-bridges remain attached for a long duration, there is no need of giving repeated nerve signals to smooth muscles for achieving constant contractile force. Consequently, the nerves innervating these muscles also utilize less ATP
Mechanism of muscle contraction	Overall steps are the same as those for skeletal muscles except that troponin is absent. Released Ca^{2+} ions bind to calmodulin (in sarcoplasm), which further activates myosin light chain kinase (MLCK). MLCK then phosphorylates myosin heads to initiate cross-bridge cycling. The whole process is explained in **Flowchart 2.2** and illustrated in **Fig. 2.29**.

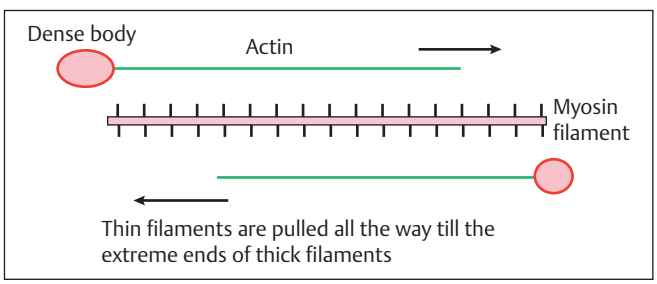


Fig. 2.28 Unipolar cross-bridges in smooth muscles.

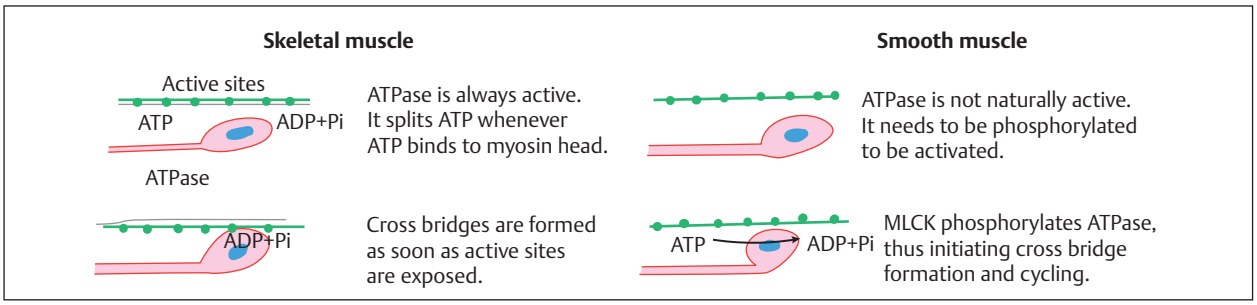
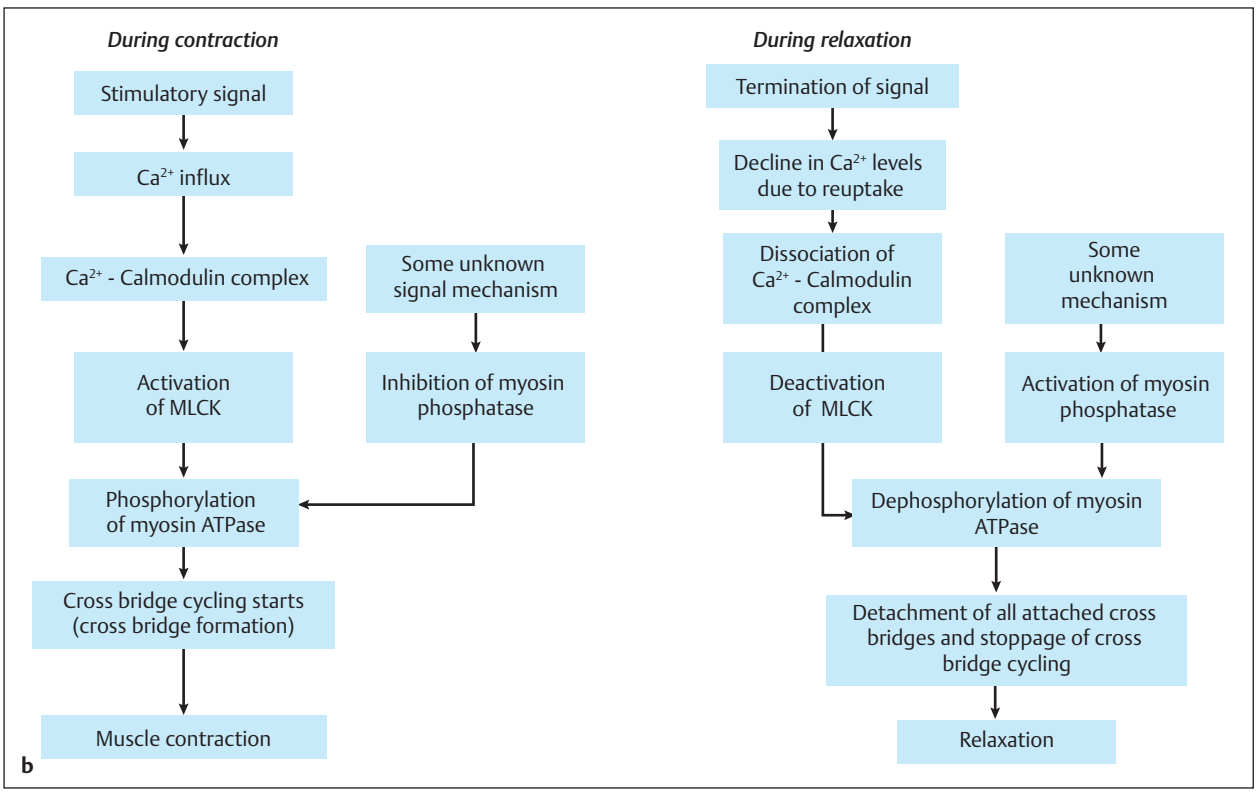


Fig. 2.29 Cross-bridge formation in skeletal versus smooth muscles.



Flowchart 2.2 Sequence of events during contraction and relaxation in smooth muscles. MLCK, myosin light chain kinase.

Table 2.26 Differences between skeletal, cardiac, and smooth muscles

Features	Skeletal muscle	Cardiac muscle	Smooth muscle
Gross morphology			
Location	Fixed to the skeleton	Confined to the heart only	Found in hollow viscera (gallbladder, stomach, gut, etc.), skin, and eyes. Genitourinary tract and blood vessels
Function	Movement of joints and locomotion	Pumping of blood	Site-specific function
Types	Slow (red) and fast (white) muscle fibers	Contractile and noncontractile (conducting) fibers	Single-unit and multiunit fibers
Striations	Present	Present	Absent
Functional syncytium	Absent	Present; due to intercalated discs	Present in single-unit muscle fibers due to gap junctions and dense plaques; absent in multiunit fibers
Control and innervation	Voluntary, somatic innervation	Involuntary, autonomic innervation	Involuntary, autonomic innervation
Effects of denervation	Muscular atrophy occurs	Muscle continues to function	Muscle continues to function
Neuromuscular junction (NMJ)	Typically located at the midpoint of each muscle fiber	Exact structure is still unknown	Synapse-en-passant
Muscle sarcomere			
Contractile proteins	Actin, myosin, troponin, and tropomyosin	Same as skeletal muscle, except that cardiac troponins T and I (cTnT and cTnI) are different in structure from skeletal muscle	Same as skeletal muscle, except that troponin is absent
Length of thick and thin filaments	Fixed lengths. Myosin is 1.6 μm long	Fixed lengths	Thin filaments are of variable length, while thick filaments are quite long (2.2–2.6 μm)
Z lines	Present	Present	Absent; instead, dense bodies are present
Arrangement of cross-bridges	Bipolar	Bipolar	Unipolar/side polar
Initiator of cross-bridge cycling	Formation of the Ca^{2+} troponin C complex → exposure of active sites on actin filaments	Same as skeletal muscle	Formation of the Ca^{2+} calmodulin complex → MLCK activation → myosin head phosphorylation
Sarcotubular system			
T-tubules	Less developed, narrow diameter	Well-developed; the diameter is 5 times more than that in skeletal muscle	Very poorly developed. Represented by caveolae
Sarcoplasmic reticulum	Well developed	Less well developed	Poorly developed; lies around caveolae
Location	Lie at the AI junction (2 per sarcomere, i.e., triad)	Lie at Z lines (1 per sarcomere, i.e., diad)	Not present
DHPR and RyR	DHPRs: Voltage sensors RyRs: Mechanically operated Ca^{2+} channels	DHPRs: Voltage-gated Ca^{2+} channels RyRs: Ca^{2+}-gated Ca^{2+} channels	Both are absent. Sarcolemma contains L-type voltage-gated Ca^{2+} channels instead

(Continued)

Table 2.26 *(Continued)*

Features	Skeletal muscle	Cardiac muscle	Smooth muscle
Source of Ca^{2+} for muscle contraction	Sarcoplasmic reticulum	Mainly ECF contained within T-tubules Slightly from the sarcoplasmic reticulum as well	Mainly from ECF surrounding the muscle membrane Very slightly from the sarcoplasmic reticulum
Electrical properties			
RMP value	−90 mV	−90 mV	Variable for different smooth muscles. It is unstable (−50 to −60 mV) for smooth muscles with pacemaker activity (e.g., in the GIT)
Appearance of action potential	Action potential appears with a spike	Action potential contains a plateau phase	Action potential is absent in multiunit smooth muscles. Here, junctional potentials are seen In single-unit smooth muscles, action potentials may have a spike or a plateau or may be superimposed on a slow wave rhythm
Ions involved in depolarization	Na^+	Na^+ and Ca^{2+}	Ca^{2+}
Duration of ARP	1–2 ms	~250 ms	Not defined
Type of excitatory stimulus	Neural only	Self-stimulation (pacemaker activity); neural (autonomic)	Neural (autonomic); non-neural (stretch/hormones/paracrines/self-stimulation)
Mechanical properties			
Cross-bridge cycling rate	Rapid	Rapid	Slow (due to latch bridge mechanism)
Extent of contraction	Up to 30% of the initial length	Not defined	Up to 80% of the initial length
Duration of single contraction	Short (maximum value is 100 ms)	Long (~300 ms)	Very long (can reach up to 3,000 ms in some cases)
Force of contraction	3–4 kg/cm^2	Not defined	4–6 kg/cm^2
Fatigue	Easily fatigued	Never fatigued	Quite resistant to fatigue, usually never fatigued in physiological conditions
Tetanus	Present	Absent (since some amount of relaxation always occurs within long ARP)	Difficult to demonstrate
LT relationship	Bell-shaped curve for active tension The passive tension curve is linear (till the elastic limit)	Same as skeletal muscle	Variable tension exerted at the given length, i.e., plasticity
Metabolic properties			
O_2 consumption	Moderate	High	Low
Mitochondrial density	Moderate	High	Low
Nutrients consumed during activity	Carbohydrates → 60% Fats → 20% Proteins → 20%	Carbohydrates → 60% Fats → 35% Proteins→ 5%	Mainly fats

Abbreviations: ARP, absolute refractory period; DHPRs, dihydropyridine receptors; ECF, extracellular fluid; GIT, gastrointestinal tract; LT, length–tension; MLCK, myosin light chain kinase; RMP, resting membrane potential; RyRs, ryanodine receptors.

Clinical Case Study

Myasthenia Gravis

Mrs. Gupta, a 25-year-old woman, comes to the physician with complaints of easy fatigability and generalized weakness for the past few months. She reveals that she has difficulty combing her hair and climbing stairs. Her vision has also started to blur and her arms start to ache even while carrying shopping bags from the market. The doctor observes that there is no significant abnormality in the patient and all her vitals are normal. He suspects some neuromuscular disorder and administers the drug Tensilon, which provides prompt relief to the patient. Based on this case history, answer the following questions:

a. What is the probable diagnosis?
b. Discuss the pathophysiology of this condition.
c. Why did the doctor give Tensilon?
d. Explain the physiological basis of the treatment of this condition. Add a note on other drugs acting on the neuromuscular junction (NMJ).

Case Discussion

Probable Diagnosis

Myasthenia gravis.

Pathophysiology

Myasthenia gravis is an autoimmune condition occurring due to the destruction of postsynaptic acetylcholine (ACh) receptors by anti-ACh antibodies. This causes a severe reduction in the amount of Na^+ influx, which leads to failure in the development of action potential at the motor end plate (skeletal muscles). In this condition, the morphology of the NMJ is grossly disturbed, i.e., synaptic clefts become sparse, shallow, and abnormally wide (or may even be severely obliterated) as seen in **Fig. 2.30**.

Tensilon Test

This test involves administration of the drug edrophonium (marketed as Tensilon) and is used to differentiate between two clinically similar conditions, i.e., myasthenia gravis and Lambert–Eaton myasthenic syndrome (LEMS). Edrophonium promptly blocks acetylcholinesterase, thus providing symptomatic relief *only* in myasthenia gravis (by prolonging removal of ACh within the synaptic cleft) but not in LEMS (because in LEMS presynaptic Ca^{2+} channels are involved, but ACh receptors are unaffected).

Note

Edrophonium (Tensilon) is used only for diagnosis and not for treatment of myasthenia gravis because of its ultrashort half-life (starts acting within 30 seconds but is effective for only 5–10 minutes) as compared with other similarly acting drugs such as physostigmine and neostigmine, which have longer duration of action and thus are preferred for treatment.

Drugs Acting on NMJ

These are explained in **Table 2.27.**

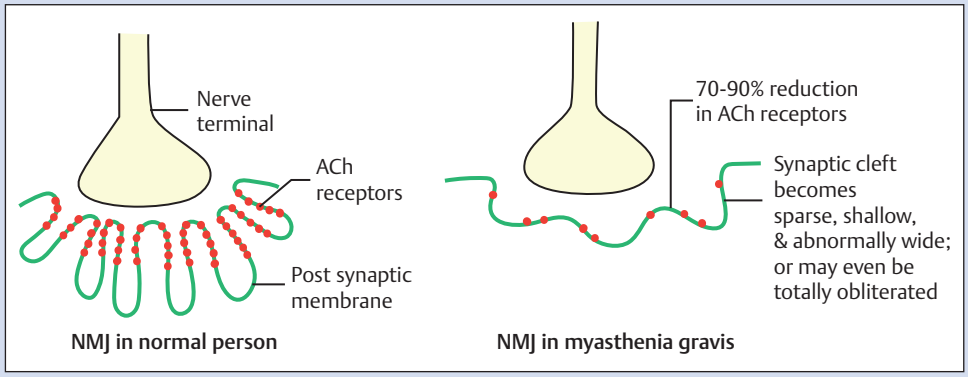


Fig. 2.30 Neuromuscular junction (NMJ) in myasthenia gravis. ACh acetylcholine.

Table 2.27 Drugs acting on the neuromuscular junction

Name of drug	Mechanism of action
Acetylcholinesterase inhibitors *(e.g., physostigmine, neostigmine, edrophonium)*	These are the drugs of first choice for the treatment of myasthenia. They act by inhibiting acetylcholinesterase, thus prolonging ACh action within the synaptic cleft. Consequently, with each successive nerve impulse, ACh keeps accumulating resulting in stronger muscle contraction
Cholinomimetics	These mimic the ACh action of stimulating nicotinic cholinergic receptors. They have prolonged effect because they are destroyed very slowly (by pseudocholinesterase)
D-Tubocurarine (Curare)	Competitive inhibitor of ACh (curare blocks ACh receptors). African pygmies use it as arrowhead poison during hunting. *Note: Bungarotoxin present in cobra venom acts just like curare*
Botulinum toxin (Botox)	Toxin of *Clostridium botulinum* bacteria inhibits fusion of synaptic vesicles at active zones, thus reducing the overall amount of ACh released at the NMJ

Disclaimer: All the names of the patients/persons and other case details (e.g., investigations, treatment) that have been included in case studies are fictional and are intended for educational/representational purposes only. They DO NOT represent the medical condition of any living person.

Extra Edge

- **Nernst (equilibrium) potential** (for an ion): It represents the magnitude of electrical force that (when applied toward inside of membrane) exactly counterbalances the concentration gradient for that ion, thus achieving equilibrium. The Nernst potential value (of an ion) is calculated as follows: **Ei = 61/z log (Co/Ci)**, where E_i is the equilibrium potential for an ion at 37°C, Z = valence of ion, and C_o/C_i is the ionic concentration gradient, since C_i is ionic concentration in ICF (in mM) and C_o is ionic concentration in ECF (in mM).
- **Goldman–Hodgkins–Katz equation:** It is derived from the Nernst equation and is used to calculate the RMP values by taking into consideration both concentration differences across membranes as well as membrane permeability for Na^+, K^+, and Cl^-.
- **Biphasic AP:** If both recording electrodes are placed on the outer surface of membrane and thereafter membrane is stimulated, then two deflections are obtained in the AP curve (initial upward, later downward), with an intervening isoelectric period between them. For example, electrocardiogram (ECG; heart), electroencephalogram (EEG; brain), electroretinogram (ERG; retina), and electromyogram (EMG; skeletal muscles).
- **Coverings of nerve fibers:**
  - *Endoneurium:* Connective tissue sheath, which loosely wraps the individual axons. Several such endoneurium-wrapped axons are bundled together to form a nerve fiber/fascicle.
  - *Perineurium:* Covering sheath around nerve fibers.
  - *Epineurium:* Outermost layer that encloses several perineurium-covered fibers.
- **Structure of unmyelinated axons:** These are surrounded by Schwann cells (i.e., Schwann cell sheath) without any multiple wrapping layers.

- **Nicotinic cholinergic receptor:** It is composed of five protein subunits, i.e., 2 α, 1 β, 1 γ, and 1 δ; that enclose an ion channel between them; that allows Na^+ and K^+ ions to pass through it. However, remember that the negatively charged Cl ions and HCO_3 ions are repelled by strong electronegativity of these subunits. Note: *K^+ efflux is not witnessed since electronegativity of muscle membrane interior holds them from moving out through this channel.*
- **Atropine** is an anticholinergic drug, but it still does not act as a blocker of the NMJ because it acts exclusively on muscarinic cholinergic receptors. It has no effect on nicotinic cholinergic receptors, which are present at the NMJ in skeletal muscles.
- **Auxotonic contractions:** The muscle tension keeps increasing as the muscle shortens during contraction. For example, pulling a bowstring while shooting an arrow and stretching a rubber band.
- **Electromyography (EMG):** It is a procedure used to record the electrical activity of skeletal muscles using surface/needle electrodes. *Principle:* Electrical activity is induced in muscle membrane using electrical stimulus.
- **Patterns of EMG activity:**
  - *At rest*, miniature end plate potentials i.e., MEPPs are recorded from motor end plate.
  - *During exercise*, motor action potentials (MAPs) are recorded due to the activation of motor units.
  - *In myopathies/motor neuropathies*, abnormal patterns are recorded, i.e., fibrillations and fasciculations.
- **Summation of muscle contractions** results in two patterns: (1) **tetanus** i.e., sustained muscle contraction without any intermittent relaxation and (2) **clonus** i.e., successive contractions separated by intermittent relaxation periods.
- **Congenital muscle dystrophies:** *Duchenne's:* Occurs due to complete absence of dystrophin; *Becker's:* Occurs due to mild to moderate deficiency of dystrophin.
- In each neuronal terminal, **300,000 vesicles** are present, and a single vesicle contains up to **10,000 molecules of neurotransmitters**.
- **Edrophonium** is used exclusively for Tensilon test but not for treatment of myasthenia patients because of its ultrashort half-life (its effect starts within 30 seconds and stays only till 5–10 minutes) as compared to physostigmine/neostigmine.