

“Walk along” theory (“ratchet” theory) of contraction

- ATP molecule is present bound with heads of the cross-bridges of myosin molecule.
- Myosin head has ATPase activity which hydrolyses ATP to ADP and inorganic phosphate (Pi).
- The head extends perpendicular to the actin filament but does not bind with actin.
- The troponin - tropomyosin complex binds with Ca^{2+} ions. Active sites on the actin filaments are uncovered.
- The bond between the head of the cross-bridges and the active sites of the actin cause a conformational change in the head.
- The head tilt towards the arm of the cross-bridge. This tilting of the head is known as the **“power-stroke”**; this pulls the actin filament which slide over the myosin filament.
- Energy required for the power-stroke is provided by splitting the ATP attached with the head of the cross bridges.
- Once the head of the cross-bridge is tilted, the ADP and Pi attached to the head are released.

- When the ADP is released, a new molecule of ATP binds with the head of cross-bridge. This binding of ATP to cross-bridge head detaches the head from the active site.
- The cross bridge head bound with new ATP begin the next cycle leading to another power-stroke, i.e. the detached head is **'cocked'** to its perpendicular position ready to begin another power-stroke cycle again.
- During rapid contraction of skeletal muscle, each myosin head undergoes 5 cycles/sec. Each myosin molecule hydrolyses 5-10 ATP molecules every sec.
- When the cocked head with its stored energy binds with a new active site on the actin filament, it becomes **'uncocked'** and repeats the power-stroke and the actin filament is pulled to one more step.
- Similar repeated back and fourth movements of the cross bridge makes the heads walk along the actin filament step by step thus pull the actin filament towards the centre of the sarcomere, until the z-membrane reaches the ends of the myosin filaments.

Role of Ca^{2+} Ions in Muscle Contraction

- Stimulus applied on the muscle fibre creates an action potential on the sarcolemma. This causes the flow of electrical current through the entire sarcoplasmic reticulum. The impulses spread through the 'T' tubules to the interior of the muscle fibre.
- When the current flow through the cisternae of T tubules, it causes the release of Ca^{2+} ions into the surrounding sarcoplasm. The Ca^{2+} ions diffuse to the interior of the myofibrils and bind with troponin 'C' to catalyse chemical reactions causing an allosteric change in the troponin 'I' of tt- complex. This reaction helps to expose the active binding site of the actin filament to myosin head.

Role of Ca²⁺ Ions in Muscle Relaxation

- The Ca²⁺ ion does not remain in the myofibrils for more than few milliseconds. As the electrical current caused by the action potential is over, the SR almost immediately reabsorb the Ca²⁺ ions from the sarcoplasm, and again stored in the cisternae.
- When the Ca²⁺ ion concentration drops in the sarcoplasm, the strong affinity of Ca²⁺ ions for troponin 'C' is lost.
- This activates the tropomyosin molecule to move up to its original position thus cover the active binding site of the actin filament; this causes relaxation of the muscle.

Electromyogram

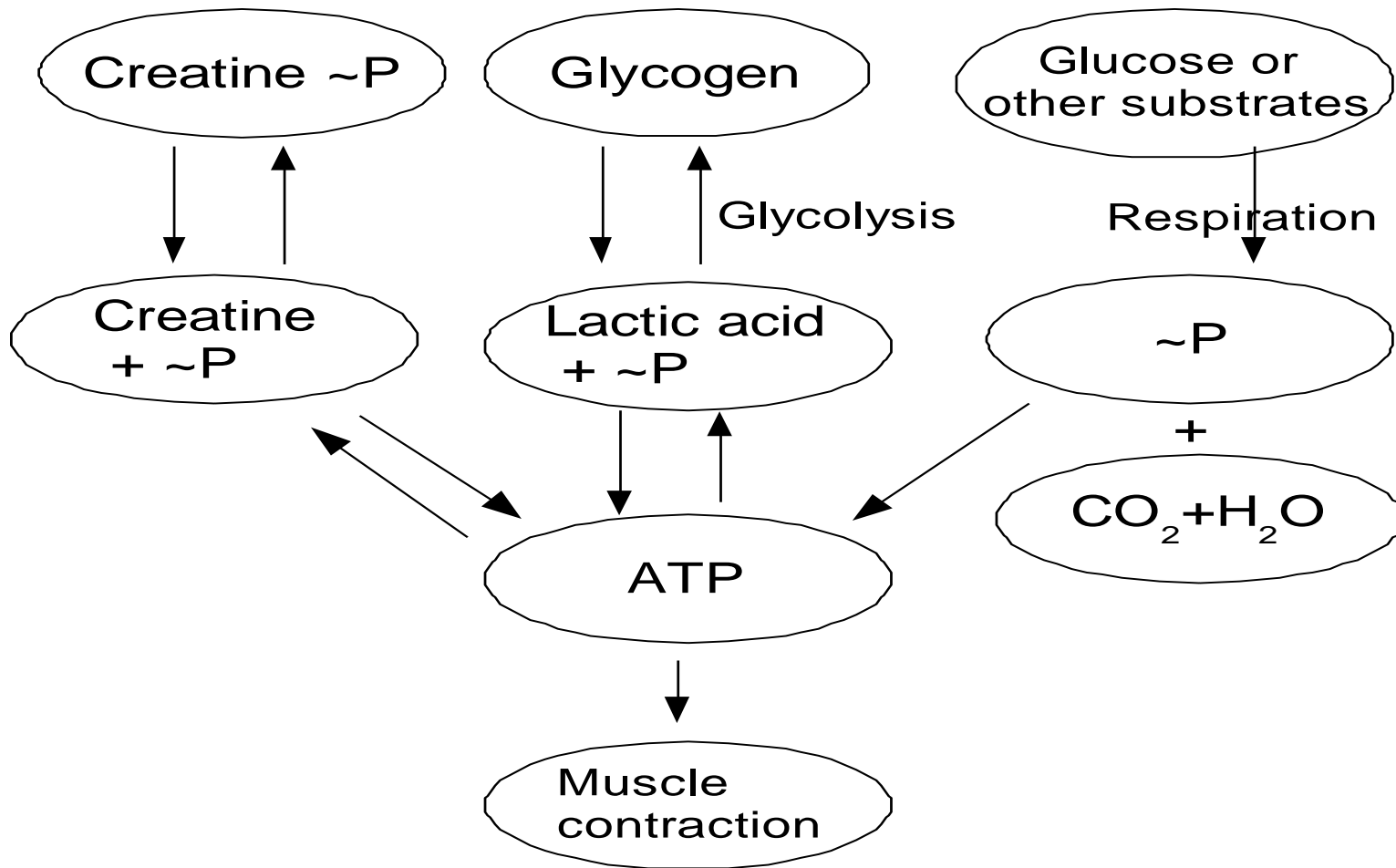
- When an action potential spreads along a muscle fibre, a small part of the electrical current generated spreads away from the fibre which can reach the overlying skin. Electrodes placed on the skin or inserted into the muscle fibre can record the electrical potential when the muscle contracts. Such a measurement is called *electromyogram*.
- EMG helps to identify whether a weakness or paralysis in a muscle is due to disease in the skeletal muscle, neuromuscular junction, motor neuron or CNS.

ENERGY FOR MUSCLE ACTIVITY

- ***Energy is required by the muscle for the following functions***
 - Energy from the hydrolysis of ATP is converted to mechanical work that causes myosin head to bend
 - ATP is required for breaking the myosin head attachment with actin filament
 - Energy is required to remove Ca^{2+} from cytosol to terminate contraction
 - To maintain Na^+ - K^+ pump
 - The immediate source of energy for muscle contraction is provided by ATP.
- The sarcoplasm contains about 4mM of ATP, which is sufficient to maintain contraction for 1-2 seconds. Once the ATP is broken into ADP and energy (Pi), the ADP is rephosphorylated to form a new ATP within a fraction of a second in the muscle.
- There are several sources of energy for this rephosphorylation.
- First source of energy is the **phosphocreatine**.

Creatine Phosphate (Phosphocreatine)

- Its concentration in the muscle fibre is 4 to 8 times more than ATP. Similar to ATP, each molecule of creatine phosphate carries a high-energy phosphate bond, but with little more energy (9500 cal) while compared with ATP (8000 cal) per bond.
- The creatine phosphate is instantly cleaved and releases $\sim\text{P}_i$, which binds with ADP derived from ATP breakdown to reconstitute a new ATP. The enzyme **creatine kinase** (*phosphokinase* or *phosphocreatine kinase*) catalyzes this reaction.
- **The creatine phosphate in the muscle is referred to as *ATP sparer* or *energy buffer of the muscle*.**
- The combined energy of both the stored ATP and the creatine phosphate in the muscle causes maximal contraction for not more than **5-8 seconds**.
- During muscle contraction, concentration of creatine phosphate decreases which must be regenerated to sustain contraction. This occurs through cellular oxidation by *glycolysis* when muscle contraction proceeds for up to 2 min.
- For sustained contraction beyond 2 minutes, *oxidative metabolism* is used to provide energy.



Rigor Mortis

- **When muscle fibres are completely depleted of ATP and creatine phosphate, they develop a state of rigidity called *rigor*.**
- Immediately following contraction, the cytoplasmic Ca^{2+} is pumped back into SR. If this pumping is inhibited, relaxation of muscle cannot occur even though there is no action potential.
- Muscle remains in sustained contraction (i.e. contraction without the presence of action potential) which is known as ***contracture***.
- The rigor that develops 5 to 6 h after death is called ***rigor mortis***.
- It is characterised by the failure of separation of the cross-bridges from the actin filaments of the contracted muscle due to lack of ATP. **The loss of cell function and failure of replenishing the ATP after death are the principal causes of rigor mortis.**

- Ca^{2+} pumps run out of ATP
- Ca^{2+} cannot be removed from cytoplasm
- remains in continuous contraction
- The muscle remains in rigor as long as the contractile proteins are intact.
- The putrefaction of decomposition is usually caused by autolysis by the enzymes of the lysosomes, which are released in about 15 to 25 hours after death.
- They denature or destroy the proteins and the dead body becomes flaccid.

Efficiency of Muscle Contraction

- Out of the total energy liberated by the hydrolysis of ATP in a contracting muscle, only 40-45% can be converted into work energy and the rest is evolved as heat; i.e. the efficiency of muscle contraction is about 45%. (Efficiency is the percentage of energy input that is converted into work instead of heat).
- In mechanical engines, the efficiency of energy is only 20% with 80% energy is released as heat.

Heat production in muscle

- When a muscle contracts, work is performed and energy is utilized.
- **The greater the amount of work performed by the muscle, greater the amount of ATP that is cleaved and larger the amount of heat released. This is called *Fenn effect*.**
- Of the total energy liberated from ATP, the muscle utilises 40 to 50% energy in performing work and the rest is liberated as heat. This helps to maintain body temperature.
- Heat produced in the muscle is classified as:
- ***Resting heat:*** Heat produced in muscle at rest. It indicates heat released by basal metabolic processes.
- ***Initial heat:*** It is produced both at initiation and during the course of muscle contraction. It consists of
 - ***Activation heat:*** Heat produced in a muscle when it begins contraction process. It is due to electrical events and mechanical actions associated with initiation of contraction
 - ***Shortening heat:*** Heat liberated by sliding process; when muscle lifts load and does external work
- ***Maintenance heat:*** Heat liberated in a muscle that is stimulated but does not lead to physical work (isometric contraction); it is proportional to duration of contraction and tension developed during contraction.
- ***Recovery heat:*** Heat liberated after contraction of muscle fibre. It is due to pumping of Ca^{2+} ions back into the tubules and resynthesis of creatine phosphate and ATP and other processes that restore the muscle to precontraction state. .

Isometric Contraction	Isotonic Contraction
Contraction between two fixed points	Contraction between one fixed and the other moveable points
No sliding movements no shortening in length	Shows sliding movements shortening in length
Manifestation of the process of contraction last throughout the period of contraction	Manifestation of the process of contraction last longer even after the completion of contraction of the muscle
No work performance	Work is performed
Less energy release, low Fenn effect"	More energy release, high "Fenn effect"

Contractions of Muscle in the Body

- In the body, most of the muscular contractions are a mixture of both isometric and isotonic contractions.
- During standing posture the quadriceps shows isometric contraction, thus tighten the knee joint to keep the legs stiff.
- Contraction of the biceps is isotonic when the hand lifts the weight.
- Alternate isometric and isotonic contractions of the quadriceps and gastrocnemius (calf muscle) help to effect running or walking. The quadriceps contracts isometrically when the foot hit the ground, while the calf muscle contracts isotonicly when the foot is lifted off the ground.

Series Elastic Component of a Muscle

- The muscle functionally consists of contractile elements arranged *in parallel* with the elastic components (sarcolemma, connective tissue etc) and *in series* with a second set of elastic components called ***series elastic components*** viz. tendons, connective tissue linking muscle fibres to tendons and cross bridge elements.
- The SEC components stretch slightly as tension increases. Consequently, the contractile unit must shorten an extra 3-5% to make up for the stretch of these elements. ***These elements of the muscle that stretch during contraction are known as series elastic components of the muscle.***
- During isometric contraction, these SEC develop greater tension that opposes the contraction of the myofibrils. Hence the contraction becomes zero, but the tension is very high.
- In isotonic contractions, the contractile elements shorten and stretch the series elastic components. This causes the tension to rise just to exceed the force of contraction due to the effect of the weight. Thereafter the tension in the muscle remains constant.

- **Types of Muscle fibres**
- Based on the velocity of contraction, the *muscle fibres are classified as*
- slow (tonic) or Type I fibres
- fast or phasic (twitch) or Type II fibres
- Every muscle in the body is composed of slow and fast muscle fibres.
- Comparison between slow and fast muscle fibres

	Slow Muscle Fibres /Red Muscles/ oxidative fibres	Fast Muscle Fibres/ White Muscles/ Glycolytic fibres
1.	Smaller fibres	Much larger fibres
1.	Innervated by small nerve fibres	Innervated by comparatively large nerve fibres
1.	Have extensive blood supply, hence referred as "Red muscle", shows prolonged performance of work (Long contraction time).	Have less blood supply, hence called as "White muscle", shows quick and repetitive contractions (Short contraction time).
1.	Increased number of sarcosomes	Fewer sarcosomes
1.	Muscle metabolism by aerobic or oxidation of glucose, fatty acids and amino acids, causes the release of 38 molecules of ATP.	Glycolysis or anaerobic type of metabolism liberating 2 molecules of lactic acid and 2 molecules of ATP.
1.		
6.	Large amount of myoglobin in sarcoplasm.	Lack of myoglobin.
1.	Less sarcoplasmic reticulum and less Ca ion release.	Extensive sarcoplasmic reticulum and rapid Ca ion release.
1.	Has large motor units (More muscle fibres/neuron), no fine degree of control.	Has few motor units (less muscle fibres/ neuron), higher degree of fine control.
1.	Adapted for prolonged, continued muscle activity– like support of the body against gravity	Adapted for rapid and powerful muscle contractions – like jumping, running

Fast twitch – type II Fibres

- Fast twitch – type II - fibres produce high amount of force, contract very quickly, and contain less myoglobin and few mitochondria. The fast twitch fibres (*white muscle*) are further grouped into two subgroups - Type IIA and IIB fibres.
- **Type II A Fibres**
 - These fibres, also called ***fast twitch or fast oxidative glycolytic fibres (FOG,)*** have a very high capacity for generating ATP by oxidative metabolic processes, split ATP at a very rapid rate, have a fast contraction velocity and are resistant to fatigue.
- **Type II B Fibres**
 - These fibres, also called ***fast twitch or fast glycolytic (FG) fibres,*** contain relatively few blood capillaries and large amounts glycogen. Type II B fibres produce the highest amount of force, generate ATP by anaerobic glycolytic processes, not able to supply skeletal muscle fibres continuously with sufficient ATP, fatigue easily, split ATP at a fast rate and have a fast contraction velocity.

- **Motor Units of the Muscle**
- Each motor neuron leaves the ventral horn of the spinal cord and innervates many muscle fibres.
- All the muscle fibres in a muscle that are innervated by a single motor neuron (all the muscle fibres supplied by a single motor neuron) are called as ***motor unit***.
- The ratio of motor nerve to the number of muscle fibres innervated in a given skeletal muscle is called ***innervation ratio***.
- The number of muscle fibres per motor unit differs as per the function for which the muscle is used in the body.
- Small muscles which act rapidly and which require finer control of movement have an innervation ratio of **1:2 to 1:4**.
- Large muscles that do not require finer control have an innervation ratio of **1:800 or more**.

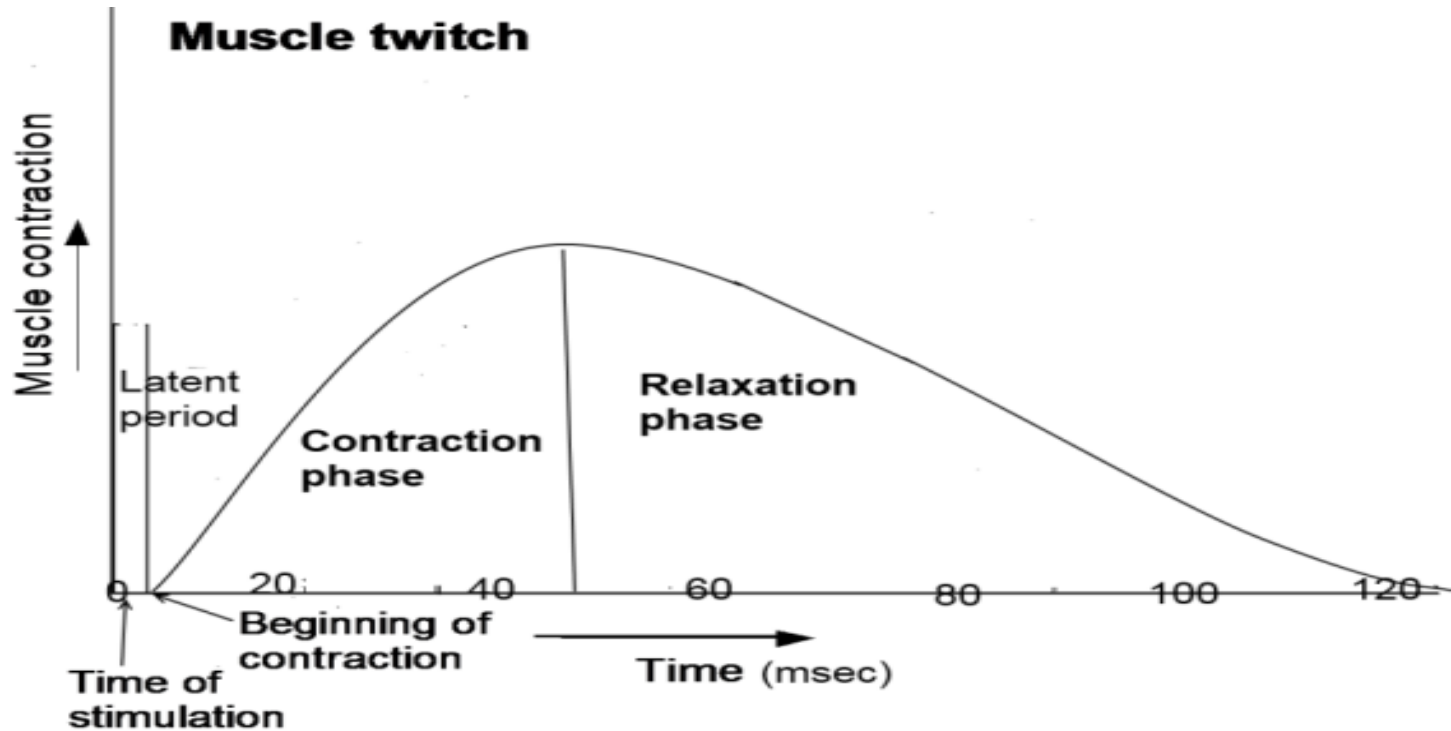
- *Electrical Stimulation of Muscle:* When a muscle is stimulated with a single electric stimulus of sufficient intensity, it responds with a contraction, immediately followed by relaxation to its original length is known as ***muscle twitch.***

MECHANICAL CHARACTERISTICS OF MUSCLE CONTRACTION

- **Stimulus**
- It is an external agent, when applied to an excitable tissue provoke change in membrane potential or a visible response.
- ***Types of Stimuli*** (Based on strength)
 - *Sub threshold*: (sub minimal) low intensity, unable to produce a visible response
 - *Threshold*: minimum intensity, strong enough to initiate an action potential
 - *Sub maximal*: higher threshold strength
 - *Maximal*: highest threshold strength
 - *Supra maximal*: destructive to tissues
- **Classification of Stimulus**
- *Mechanical*: pain, pressure, and touch;
- *Chemical*: acid, alkali;
- *Thermal*: warmth, cold
- *Osmotic*: Hypertonic solution, hypotonic solution

- **All or none law**
- When a muscle fibre is stimulated by minimal or maximal effective stimuli, the whole fibre contracts to the maximum or it will not contract at all.
- In skeletal muscles, this law is applicable to single motor unit (motor nerve and all the muscle fibres it supplies).
- Whole cardiac muscle acts in all or none manner due to the presence of functional syncytium

Simple Muscle Contraction: (SIMPLE TWITCH)



- Application of single threshold level of stimulus (electrical stimulation) causes a single muscle contraction followed by relaxation. The time taken for the simple twitch is 100 -120 msec. The single muscle twitch has 3 phases.
- ***Latent period***
- It is the period between the application of stimulus and beginning of contraction (**about 10msec**). It is due to the time it takes from the arrival of action potential at T tubules up to the build-up of Ca^{2+} concentration in the cytosol to a level enough to initiate a contraction
- ***Period of contraction***
- This period indicates the actual shortening (about 40msec).
- ***Period of relaxation***
- It is the period between the point of maximum contraction and the period of complete relaxation (about 50msec).

Refractory Period

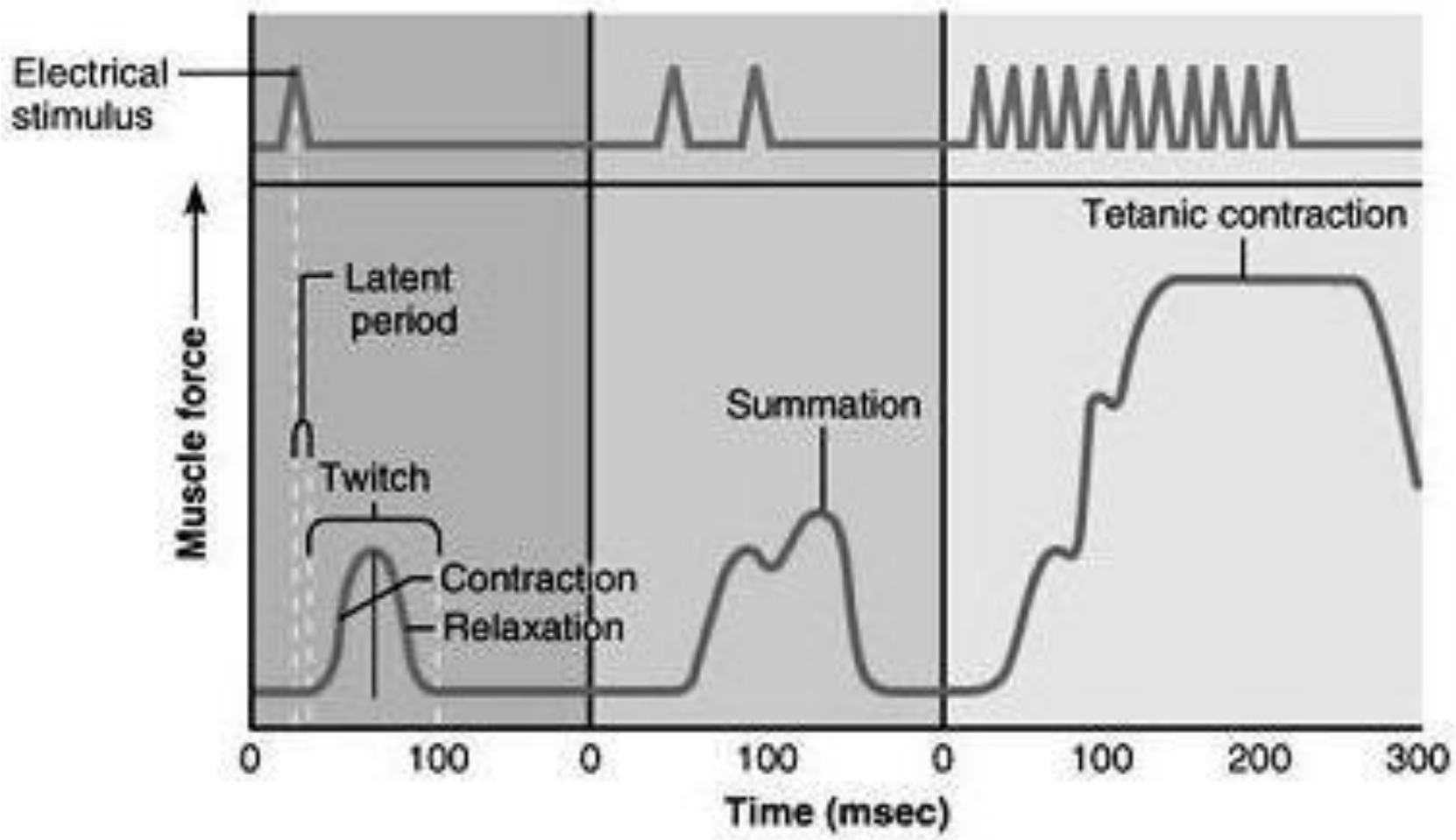
- It is a brief period during which a muscle undergoing contraction for a first stimulus is unable to respond to a second stimulus. It is of two types.
- *Absolute refractory period*
- It is the time interval between two impulses (less than 3 msec) during which the muscle cannot be stimulated even by stronger stimuli. This is due to the rising phase of the action potential when Na^+ ion conductance to the interior of the cell is high.
- *Relative refractory period*
- It is the period of reduced excitability which requires increased intensity of second stimulation to generate another action potential. It is characterised by after depolarization stage of action potential during which the K^+ ion permeability is very high and Na^+ channels are recovering their excitability.

Treppe: (*Staircase phenomenon*)

- When a stimulus of constant strength and duration is repeated (below tetanising frequency) once or twice per second, it causes increased contractions during the first few stimulations, which finally reach a constant response.
- This is due to development of physical and chemical changes i.e. reduced viscosity of the sarcoplasm, increased heat production, increased Ca^{2+} ion availability for binding with troponin during first few contractions; these changes are referred to as ***beneficial effects***.

Summation of Muscle Contraction

- ***Multimotor unit summation (Spatial summation)***
- The strength or the force of contraction of a muscle increases progressively with increasing number of contracting motor units *by increasing the strength of stimulation.*
- ***Wave summation (Temporal summation)***
- By increasing the frequency of stimulation to motor units, successive stimuli will stimulate additional motor units during its contraction phase.
- When a motor unit is excited repeatedly by a rapid succession of weak stimuli, it may evoke stronger contraction.

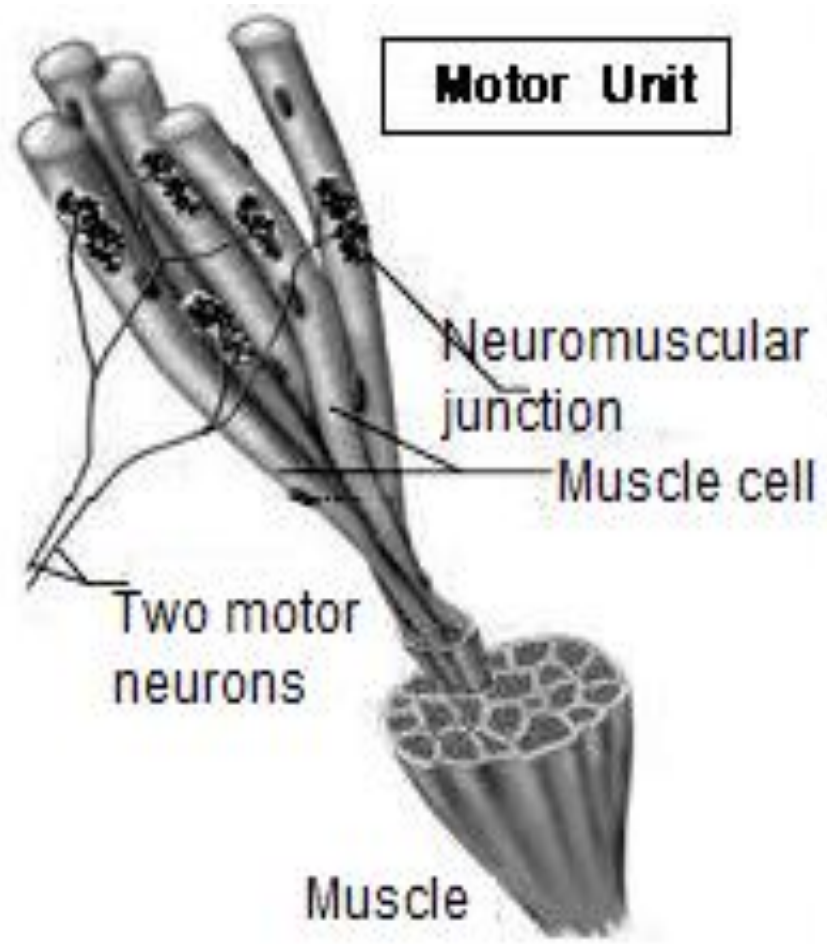


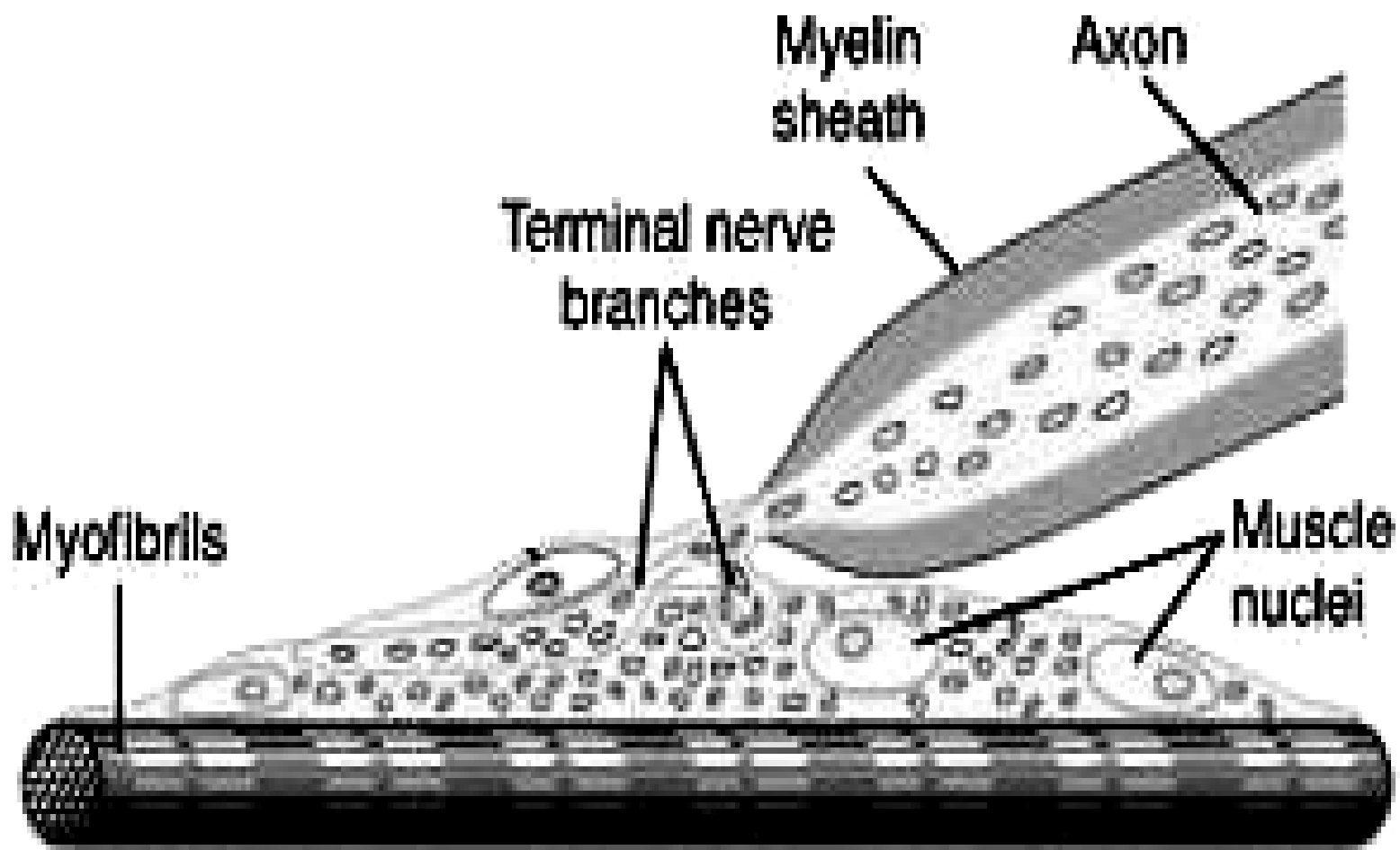
Muscle Fatigue

- Fatigue is the decrease in the working capacity of a muscle or tiredness of the muscle when it is continuously stimulated.
- It is characterised by diminished force of contraction, increased latent period and contraction period and prolonged relaxation period. The relaxation is incomplete i.e., the muscle is in a state of *contracture*. At this stage the muscle cannot be excited nor do any more work.
- In the locomotor system of skeletal muscles, there are three sites, which are easily fatigued.
 - **Synapses of CNS.**
 - **Neuromuscular junction.**
 - **The muscle.**

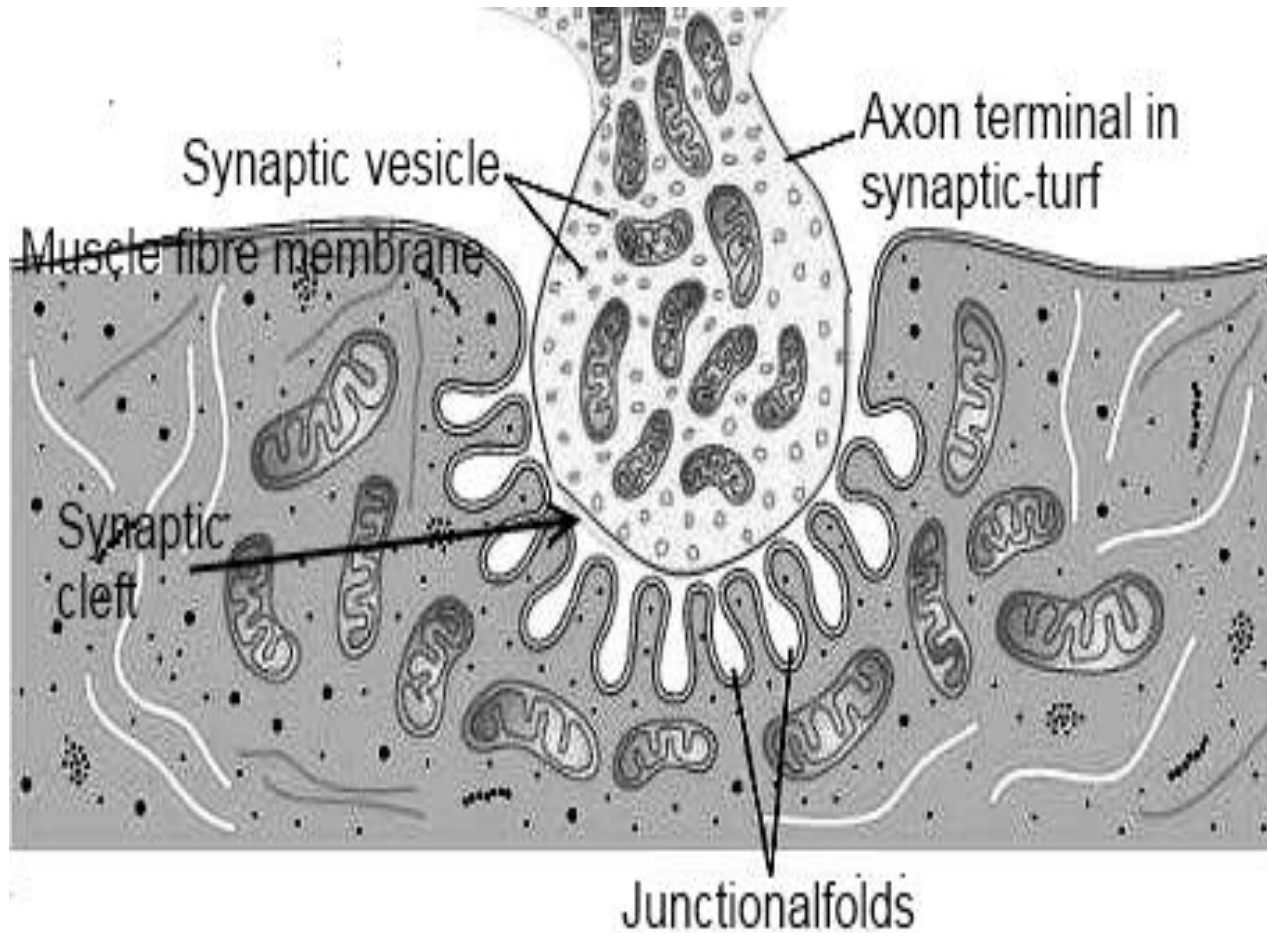
Myoglobinuria (Monday-morning disease) in horses:

- When a well-fed horse is subjected to strenuous physical activity after several days of complete rest, myoglobinuria occurs. During heavy exercise, muscle cell membranes are damaged and cell contents are partly released into blood. Myoglobin being smaller in size is filtered through glomerulus and appears in urine imparting a deep red or brownish red colour to urine – myoglobinuria.





NEUROMUSCULAR JUNCTION



Abnormal signal transmission across neuromuscular synapse

- Organophosphorus insecticides and physostigmine inhibit the action of acetylcholinesterase. A single nerve stimulus can lead to several impulses and the muscles are thrown into tetanic convulsions.
- D-tubocurarine, the active component of curare, a plant-derived arrow poison used by South American Indians and toxin from cobra venom, blocks the effect of acetylcholine by binding to Ach receptors. Skeletal muscles of affected animals are paralysed and the animal may die of respiratory arrest due to paralysis of respiratory muscles.
- Botulinum toxin released by soil bacteria *Clostridium botulinum* under anaerobic condition blocks Ach release and causes **botulism** –a form of food poisoning. Unhygienic condition in preparation of food produces botulism. It can produce skeletal muscle paralysis and death due to respiratory arrest. Cat and dog are resistant to botulism but ruminants are affected

- ***Myasthenia gravis*** is a neuromuscular disorder in which autoantibodies are produced against Ach receptors. Hence, neuromuscular transmission is impaired and leads to paralysis. The condition can be treated with acetylcholinesterase inhibitors

Effect of Temperature in the Muscle

- An increase of temperature shortens the latent and contraction periods. The gradient of contraction is increased and height decreased. Relaxation is not much affected.
- A decrease of temperature has the opposite effect – latent and contraction period are increased and relaxation period is prolonged.
- When temperature exceeds a few degrees above 40°C, irreversible changes take place in the sarcoplasm.
- There is a minimum temperature for muscle contraction, below which the muscle fibres fail to respond to stimulation; but the loss of excitation is reversible. The minimum temperature is near zero.
-