Electrical and Molecular Changes during Muscular Contraction

When the muscle is in resting condition, the electrical potential is called resting membrane potential. When the muscle is stimulated, electrical changes occur which are collectively called action potential.

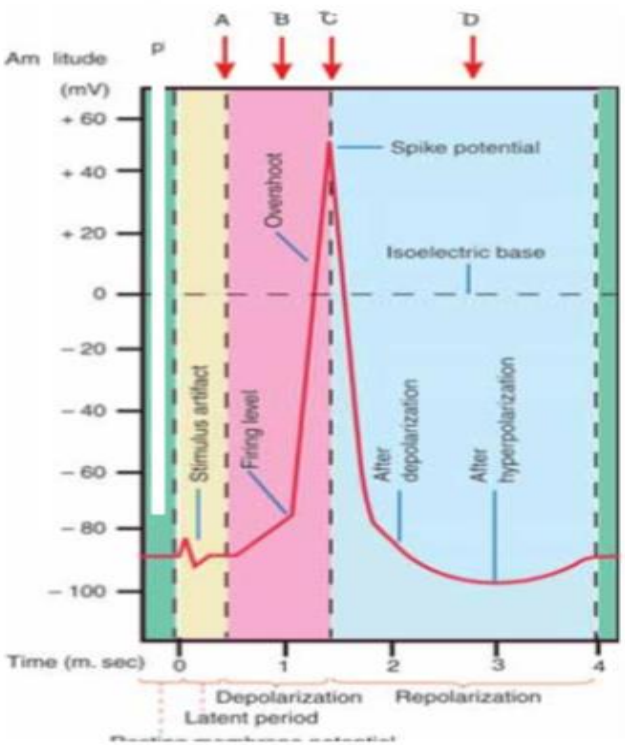
RESTING MEMBRANE POTENTIAL is the electrical potential difference (voltage) across the cell membrane (between inside and outside of the cell) under resting condition. It is also called membrane potential, transmembrane potential, transmembrane potential difference or transmembrane potential gradient. Resting muscle shows negativity inside and positivity outside. The condition of the muscle during resting membrane potential is called polarized state. In human skeletal muscle, the resting membrane potential is –90 mV.

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

1. Depolarization 2. Repolarization.

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

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



Action potential in a skeletal muscle

A= Opening of few Na+ channels **B** = Opening of many Na+ channels

C = Closure of Na+ channels and opening of K+ channels **D** = Closure of K+ channels.

IONIC BASIS OF ELECTRICAL EVENTS

Resting Membrane Potential: The development and maintenance of resting membrane potential in a muscle fiber or a neuron are carried out by movement of ions, which produce ionic imbalance across the cell membrane. This results in the development of more positivity outside and more negativity inside the cell. The ionic imbalance is produced by two factors:

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

1. **Sodium-potassium pump:** Sodium and potassium ions are actively transported in opposite directions across the cell membrane by means of an electrogenic pump called sodium-potassium pump. It moves three sodium ions out of the cell and two potassium ions inside the cell by using energy from ATP.

Since more positive ions (cations) are pumped outside than inside, a net deficit of positive ions occurs inside the cell. It leads to negativity inside and positivity outside the cell.

2. Selective permeability of cell membrane: The permeability of cell membrane depends largely on the transport channels. The transport channels are selective for movement of some specific ions. Most of the channels are gated channels and the specific ions can move across the membrane only when these gated channels are opened.

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

Channels for ions In addition, the channels for three important ions, sodium, chloride and potassium also play an important role in maintaining the resting membrane potential.

Action Potential during the onset of depolarization, voltage gated Na+ channels open resulting in slow influx of Na+. When depolarization reaches 7 to 10 mV, the voltage gated Na+ channels start opening at a faster rate. It is called Na+ channel activation. When the firing level is reached, the influx of Na+ is very great and it leads to overshoot. But the Na+ transport is short-lived. This is because of rapid inactivation of Na+ channels.

Electrical and Molecular Changes during Muscular Contraction

Thus, the Na+ channels open and close quickly. At the same time, the K+ channels start opening. This leads to efflux of K+ out of the cell, causing repolarization. Unlike the Na+ channels, the K+ channels remain open for longer duration. These channels remain opened for few more milliseconds after completion of repolarization. It causes efflux of more number of K+ producing more negativity inside. It is the cause for hyperpolarization.

GRADED POTENTIAL: is a mild local change in the membrane potential that develops in receptors, synapse or neuromuscular junction when stimulated. It is also called graded membrane potential or graded depolarization.

In most of the cases, the graded potential is responsible for the generation of action potential. However, in some cases the graded potential hyperpolarizes the membrane potential (more negativity than resting membrane potential). The graded potentials include:

1. End plate potential in neuromuscular junction
2. Receptor potential.
3. Excitatory postsynaptic potential.
4. Inhibitory postsynaptic potential.

MOLECULAR CHANGES DURING MUSCULAR CONTRACTION ACTOMYOSIN COMPLEX

In the relaxed state of the muscle, the thin actin filaments from the opposite ends of the sarcomere are away from each other leaving a broad 'H' zone. During the contraction of the muscle, the actin (thin) filaments glide over the myosin (thick) filaments and form actomyosin complex.

MOLECULAR BASIS OF MUSCULAR CONTRACTION The molecular mechanism is responsible for formation of actomyosin complex that results in muscular contraction. It includes three stages:

1. Excitation contraction coupling

2. Role of troponin and tropomyosin

3. Sliding mechanism

1. Excitation Contraction Coupling: is the process that occurs in between the excitation and contraction of the muscle. This process involves series of activities which are responsible for the contraction of the excited muscle.

Stages of excitation contraction coupling: When the impulse passes through a motor neuron and reaches the neuromuscular junction, acetylcholine is released from motor endplate. Acetylcholine causes opening of ligand gated sodium

channels. So, sodium ions enter the neuromuscular junction. It leads to the development of endplate potential. Endplate potential causes generation of action potential in the muscle fiber. The action potential spreads over sarcolemma and also into the muscle fiber through the 'T' tubules. The 'T' tubules are responsible for the rapid spread of action potential into the muscle fiber. When the action potential reaches the cisternae of 'L' tubules, these cisternae are excited. Now, the calcium ions stored in the cisternae are released into the sarcoplasm. The calcium ions from the sarcoplasm move towards the actin filaments to produce the contraction. Thus, the calcium ion forms the link or coupling material between the excitation and the contraction of muscle. Hence, the calcium ions are said to form the basis of excitation contraction coupling

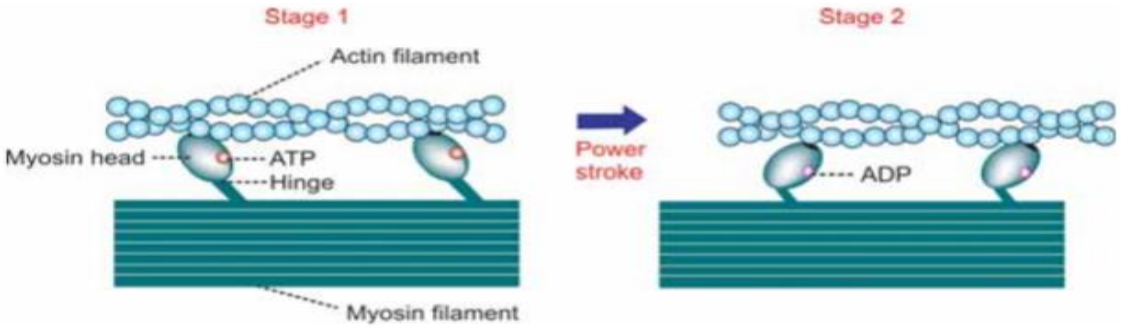


Diagram showing power stroke by myosin head. Stage 1: Myosin head binds with actin; Stage 2: Tilting of myosin head (power stroke) drags the actin filament

2. Role of Troponin and Tropomyosin Normally, the head of myosin molecules has a strong tendency to get attached with active site of F actin. However, in relaxed condition, the active site of F actin is covered by the tropomyosin. Therefore, the myosin head cannot combine with actin molecule. Large number of calcium ions, which are released from 'L' tubules during the excitation of the muscle, bind with troponin C. The loading of troponin C with calcium ions produces some change in the position of troponin molecule. It in turn, pulls tropomyosin molecule away

from F actin. Due to the movement of tropomyosin, the active site of F actin is uncovered and immediately the head of myosin gets attached to the actin.

3. Sliding Mechanism and Formation of Actomyosin Complex – Sliding Theory
Sliding theory explains how the actin filaments slide over myosin filaments and form the actomyosin complex during muscular contraction. It is also called ratchet theory or walk along theory. Each cross bridge from the myosin filaments has got three components namely, a hinge, an arm and a head. After binding with active site of F actin, the myosin head is tilted towards the arm so that the actin filament is dragged along with it. This tilting of head is called power stroke. After tilting, the head immediately breaks away from the active site and returns to the original position. Now, it combines with a new active site on the actin molecule. And, tilting movement occurs again. Thus, the head of cross bridge bends back and forth and pulls the actin filament towards the center of sarcomere. In this way, all the actin filaments of both the ends of sarcomere are pulled. So, the actin filaments of opposite sides overlap and form actomyosin complex. Formation of actomyosin complex results in contraction of the muscle. When the muscle shortens further, the actin filaments from opposite ends of the sarcomere approach each other. So, the 'H' zone becomes narrow. And, the two 'Z' lines come closer with reduction in length of the sarcomere. However, the length of 'A' band is not altered. But, the length of 'I' band decreases. When the muscular contraction becomes severe, the actin filaments from opposite ends overlap and, the 'H' zone disappears. Thus, during the contraction of the muscle, the following changes occur in the sarcomere:

1. The length of all the sarcomeres decreases as the 'Z' lines come close to each other

2. The length of the 'I' band decreases since the actin filaments from opposite side overlap

3. The 'H' zone either decreases or disappears

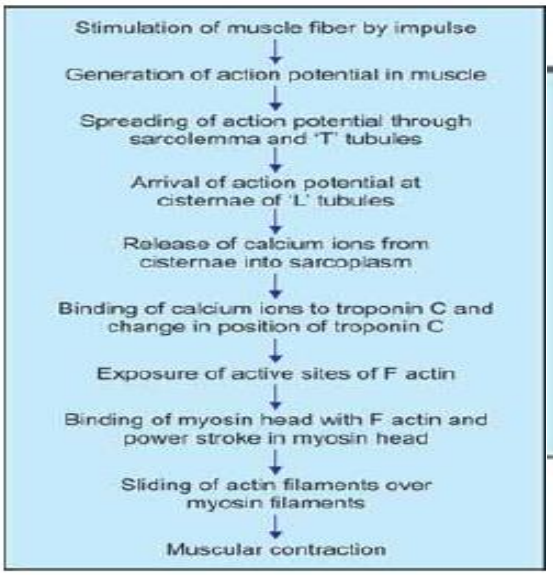
4. The length of 'A' band remains the same.

Energy for Muscular Contraction

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

The head of myosin has a site for ATP. Actually, the head itself can act as the enzyme ATPase and catalyze the breakdown of ATP. Even before the onset of contraction, an ATP molecule binds with myosin head. When tropomyosin moves to expose the active sites, the head is attached to the active site. Now ATPase cleaves ATP into ADP and Pi, which remains in head itself. The energy released during this process is utilized for contraction. When head is tilted, the ADP and Pi are released and a new ATP molecule binds with head. This process is repeated until the muscular contraction is completed.

Relaxation of the Muscle: occurs when the calcium ions are pumped back into the L tubules. When calcium ions enter the L tubules, calcium content in sarcoplasm decreases leading to the release of calcium ions from the troponin. It causes detachment of myosin from actin followed by relaxation of the muscle. The detachment of myosin from actin obtains energy from breakdown of ATP. Thus, the chemical process of muscular relaxation is an active process although the physical process is said to be passive.



Sequence of events during muscular contraction

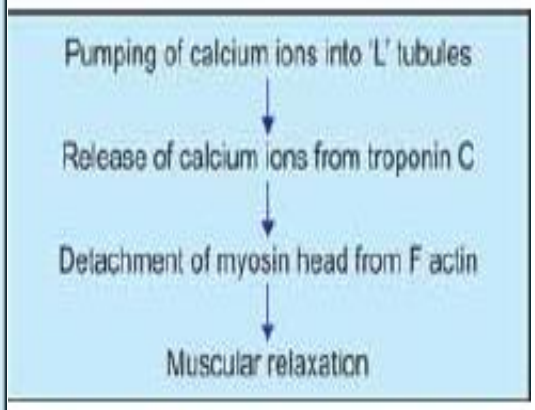


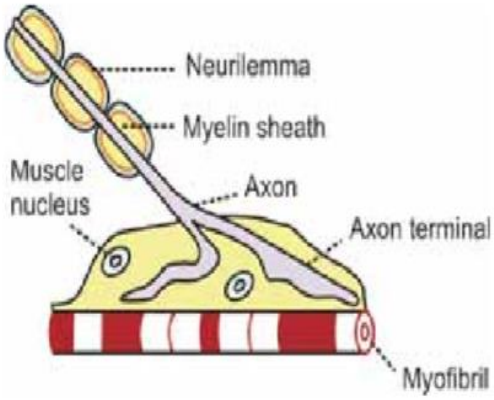
FIGURE 23-4: Sequence of events during muscular relaxation

Sequence of events during muscular relaxation

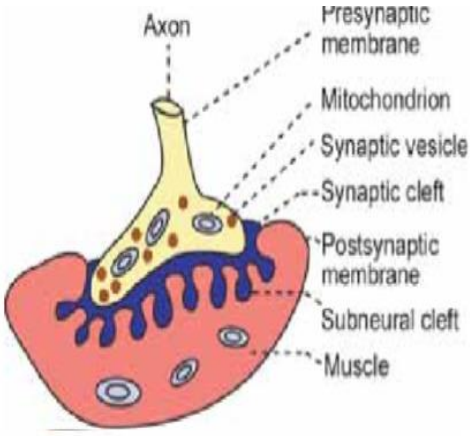
Neuromuscular Junction

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

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



Longitudinal section of neuromuscular junction



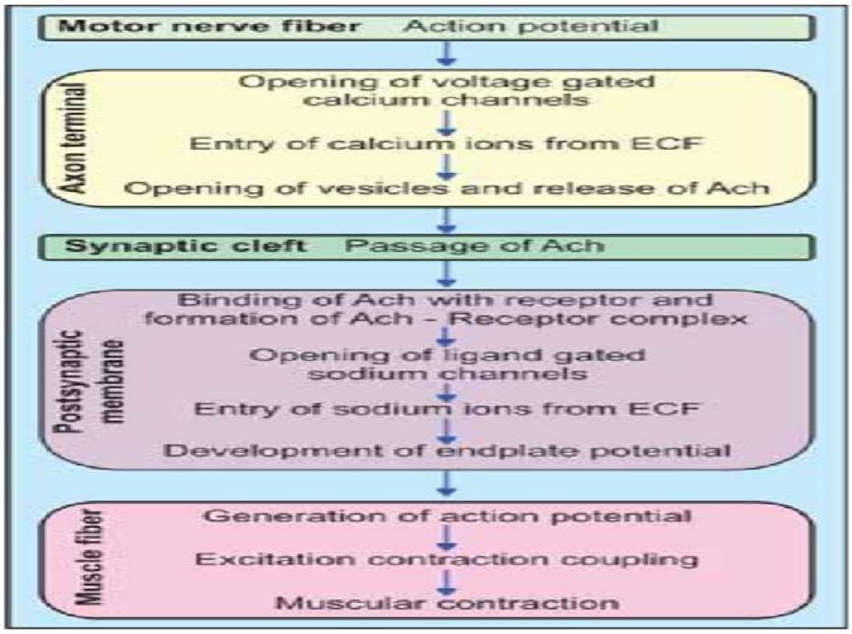
Structure of neuromuscular junction

Axon Terminal and Motor Endplate Terminal branch of nerve fiber is called axon terminal. When the axon comes close to the muscle fiber, it loses the myelin sheath. So, the axis cylinder is exposed. This portion of the axis cylinder is expanded like a bulb which is called motor endplate. The axon terminal contains mitochondria and synaptic vesicles. The synaptic vesicles contain the neurotransmitter substance, acetylcholine. The acetylcholine is synthesized by mitochondria present in the axon terminal and stored in the vesicles. The mitochondria contain ATP which is the source of energy for the synthesis of acetylcholine.

Synaptic Cleft: The membrane of the nerve ending is called the presynaptic membrane. The membrane of the muscle fiber is called postsynaptic membrane. The space between these two is called synaptic cleft. The synaptic cleft contains basal lamina. It is a thin layer of spongy reticular matrix through which, the extracellular fluid diffuses. Large quantity of an enzyme called acetylcholinesterase is attached to the matrix of basal lamina.

Sub neural Clefts: The postsynaptic membrane is the membrane of the muscle fiber. It is thrown into numerous folds called sub neural clefts. The postsynaptic membrane contains the receptors called nicotinic acetylcholine receptors

NEUROMUSCULAR TRANSMISSION: is defined as the transfer of information from motor nerve ending to the muscle fiber through neuromuscular junction. It is the mechanism by which the motor nerve impulses initiate muscle contraction. A series of events take place in the neuromuscular junction during this process.



Sequence of events during neuromuscular transmission. Ach = Acetylcholine. ECF=Extracellular fluid

1. Release of acetylcholine

2. Action of acetylcholine

3. Development of endplate potential

4. Development of miniature endplate potential

5. Destruction of acetylcholine.

1. RELEASE OF ACETYLCHOLINE: When the action potential reaches the axon terminal, it opens the voltage gated calcium channels in the membrane of the axon terminal. Calcium ions enter the axon terminal from extracellular fluid and cause bursting of the vesicles. Now, acetylcholine is released from the vesicles and diffuses through presynaptic membrane and enters the synaptic cleft. Each vesicle

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

2. ACTION OF ACETYLCHOLINE: After entering the synaptic cleft, the acetylcholine molecules bind with nicotinic receptors present in the postsynaptic membrane and form the acetylcholine–receptor complex. It opens the ligand gated channels for sodium in the postsynaptic membrane. Now, sodium ions from extracellular fluid enter the neuromuscular junction through these channels. And there, the sodium ions produce an electrical potential called the endplate potential.

3. ENDPLATE POTENTIAL: is the change in the resting membrane potential when an impulse reaches the neuromuscular junction. The resting membrane potential at the neuromuscular junction is –90 mV. When sodium ions enter inside, slight depolarization occurs up to –60 mV which is called endplate potential. The endplate potential is a graded potential and it is not action potential. It is no propagative. But it causes the development of action potential in the muscle fiber.

4. MINIATURE ENDPLATE POTENTIAL: Miniature endplate potential is a weak endplate potential in neuromuscular junction that is developed by the release of a small quantity of acetylcholine from axon terminal. And, each quantum of this neurotransmitter produces a weak miniature endplate potential. The amplitude of

this potential is only up to 0.5 mV. Miniature endplate potential cannot produce action potential in the muscle. When more and more quanta of acetylcholine are released continuously, the miniature endplate potentials are added together and finally produce endplate potential resulting in action potential in the muscle.

5. FATE OF ACETYLCHOLINE: Acetylcholine released into the synaptic cleft is destroyed very quickly within one millisecond by the enzyme, acetylcholinesterase. However, the acetylcholine is so potent, that even this short duration of 1 millisecond is sufficient to excite the muscle fiber. The rapid destruction of acetylcholine is functionally significant because it prevents repeated excitation of the muscle fiber and allows the muscle to relax.

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

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

APPLIED PHYSIOLOGY – DISORDERS OF NEUROMUSCULAR JUNCTION

The disorders of neuromuscular junction includes:

1. Myasthenia gravis

2. Eaton-Lambert syndrome.

1. MYASTHENIA GRAVIS is an autoimmune disorder of neuromuscular junction caused by antibodies to cholinergic receptors. It is characterized by grave

weakness of the muscle due to the inability of neuromuscular junction to transmit impulses from nerve to the muscle.

3. **EATON-LAMBERT SYNDROME** is also an autoimmune disorder of neuromuscular junction. It is caused by antibodies to calcium channels in axon terminal. This disease is characterized by features of myasthenia gravis. In addition the patients have blurred vision and dry mouth.

Smooth Muscle

DISTRIBUTION OF SMOOTH MUSCLE Smooth muscles are nonstriated (plain) and involuntary muscles present in almost all the organs in the form of

sheets, bundles or sheaths around other tissues. These muscles form the major contractile tissues of various organs. Smooth muscle fibers are present in the following structures:

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

STRUCTURE OF SMOOTH MUSCLE

Smooth muscle fibers are fusiform or elongated cells. The nucleus is single and elongated and it is centrally placed. Normally, two or more nucleoli are present in the nucleus. Smooth muscle fibers are generally very small, measuring 2 to 5 μ in diameter and 50 to 200 μ in length. Smooth muscle fibers are covered by connective tissue. But the tendons are absent.

Myofibrils and Sarcomere Well: are absent in smooth muscles. So, the alternate dark and light bands are absent. Absence of dark and light bands gives the nonstriated appearance to the smooth muscle.

Myofilaments and Contractile Proteins: The contractile proteins in smooth muscle fiber are actin, myosin and tropomyosin. But troponin or troponin like substance is absent. Thick and thin filaments are present in smooth muscle. However, these

filaments are not arranged in orderly fashion as in skeletal muscle. Thick filaments are formed by myosin molecules and have more number of cross bridges than in skeletal muscle. Thin filaments are formed by actin and tropomyosin molecules.

Dense Bodies Dense bodies are the special structures of smooth muscle fibers to which the actin and tropomyosin molecules of thin filaments are attached.

Sarcotubular System: in smooth muscle fibers is in the form of network. 'T' tubules are absent and 'L' tubules are poorly developed.

TYPES OF SMOOTH MUSCLE FIBERS Smooth muscle fibers are of two types:

1. Single unit or visceral smooth muscle fibers

2. Multiunit smooth muscle fibers.

SINGLE UNIT OR VISCERAL SMOOTH MUSCLE FIBERS Single unit smooth muscle fibers are the fibers with interconnecting gap junctions. The gap junctions allow rapid spread of action potential throughout the tissue so that all the muscle fibers show synchronous contraction as a single unit. Single unit smooth muscle fibers are also called visceral smooth muscle fibers.

The features of single unit smooth muscle fibers:

i. The muscle fibers are arranged in sheets or bundles
ii. The cell membrane of adjacent fibers fuses at many points to form gap junctions. Through the gap junctions, ions move freely from one cell to the other. Thus a functional syncytium is developed. The syncytium contracts

as a single unit. In this way, the visceral smooth muscle resembles cardiac muscle more than the skeletal muscle. The visceral smooth muscle fibers are in the walls of the organs such as gastrointestinal organs, uterus, ureters, respiratory tract, etc.

MULTIUNIT SMOOTH MUSCLE FIBERS: The multiunit smooth muscle fibers are the muscle fibers without interconnecting gap junctions.

These smooth muscle fibers resemble the skeletal muscle fibers in many ways. The features of multiunit smooth muscle fibers:

i. the muscle fibers are individual fibers
ii. Each muscle fiber is innervated by a single nerve ending
iii. iii. Each muscle fiber has got an outer membrane made up of glycoprotein, which helps to insulate and separate the muscle fibers from one another
iv. The control of these muscle fibers is mainly by nerve signals
v. These smooth muscle fibers do not exhibit spontaneous contractions. The multiunit muscle fibers are in ciliary muscles of the eye, iris of the eye, nictitating membrane (in cat), arrector pili, and smooth muscles of the blood vessels and urinary bladder.

ELECTRICAL ACTIVITY IN SINGLE UNIT SMOOTH MUSCLE

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

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

plateau in smooth muscles. The calcium ions play an important role during the contraction of the muscle

ELECTRICAL ACTIVITY IN MULTIUNIT SMOOTH MUSCLE

The electrical activity in multiunit smooth muscle is different from that in the single unit smooth muscle. The electrical changes leading to contraction of multiunit smooth muscle are triggered by nervous stimuli. The nerve endings secrete the neurotransmitters like acetylcholine and noradrenaline. The

neurotransmitters depolarize the membrane of smooth muscle fiber slightly leading to contraction. The action potential does not develop. This type of depolarization is called local depolarization of junctional potential. The local depolarization travels throughout the entire smooth muscle fiber and causes contraction. The local depolarization is developed because the multiunit smooth muscle fibers are too small to develop action potential.

CONTRACTILE PROCESS IN SMOOTH MUSCLE: Compared to skeletal muscles, in smooth muscles, the contraction and relaxation processes are slow.

CONTROL OF SMOOTH MUSCLE: Smooth muscle fibers are controlled by:

NERVOUS FACTORS Smooth muscles are supplied by both sympathetic and parasympathetic nerves, which act opposite to each other in controlling the activities of smooth muscles. However, these nerves are not responsible for the initiation of any activity in smooth muscle.

HUMORAL FACTORS The activity of smooth muscle is also controlled by humoral factors which include hormones, neurotransmitters and other humoral factors**.**

Smooth muscle:

There are significant differences between the two types of muscles, smooth and skeletal, in the way in which Ca^{+2}exerts its effects on cross-bridge activity and in the mechanisms by which stimulation leads to alterations in Ca^{+2} concentration:

1-The thin filaments in smooth muscle do not have the Ca^{+2}-binding protein troponin but they have calmodulin, Ca-binding protein.

1. Cross-bridge cycle in smooth muscle is controlled by a Ca^{+2}-regulated enzyme that phosphorylates myosin.

2. Only the phosphorylated form of smooth muscle myosine is able to bind to actine and undergo cross-bridge cycling.

The following sequence of events occurs after a rise in cytosolic Ca^{+2} in smooth muscle fiber:

1. Ca^{+2} binds to calmodulin

2. The Ca^{+2}-calmodulin complex binds to a protein kinase, myosin light-chain kinase, thereby activating the enzyme.

3. The activate protein kinase then uses ATP to phosphorylate myosin light chain in the globular head of myosin. Hense, cross-bridge activity in smooth muscle is turned on by calcium-mediated changes in the thick filaments, whereas in striated muscle, calcium mediates changes in the thin filaments.

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Cardiac Muscle:

The contract mechanism in the cardiac muscle is same in the skeletal only there are functional differences between cardiac muscle and skeletal muscle:

1. Since skeletal muscle is more extensible than the cardiac muscle, the passive extension force of cardiac muscle at rest is greater than that of skeletal muscle.

2. Action potentials in cardiac muscle are of much longer duration than those in skeletal because K temporarily decreases and Ca increases after rapid in activation of Na channels. This allows the slow influx of Ca^{2+}, causing the action potential. As a result, the refractory period does not end until a contraction has almost subsided, therefore, tetanus cannot be evoked in cardiac muscle.

3. Unlike skeletal muscle, cardiac muscle has no motor units. Instead, the stimulus spreads across all myocardial fibers of atria and subsequently of the ventricles generating an all-or-none contraction of both atria and, thereafter, both ventricles.

4. In cardiac muscle but not in skeletal muscle, the duration of an action potential can change the force of contraction, which is controlled by the variable influx of Ca^{2+} into the cell.