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EXCITABLE TISSUE

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Introduction

- Nerves and muscle are excitable tissue b/c they have the ability to respond to stimuli.
- Nerve and muscle cells are excitable tissues developed a specialized use for the membrane potential.
- Nerve and muscle cells are capable of producing electrical signals when excited.
- Action potentials are brief reversals of membrane potential brought about by rapid changes in membrane permeability.
- Once started, action potentials are propagated throughout an excitable cell.

Membrane Potential

- All plasma membranes are polarized electrically. It means separation of electric charges across the membrane.
- A separation of charges across the membrane is referred to as membrane potential.
- It is primarily due to differences in the distribution and membrane permeability of sodium, potassium and large intracellular anions.
- All living cells have a slightly excess of positive charges outside and a corresponding slight excess of negative charges on the inside of its membrane.

Table : Concentration and permeability of ions responsible for membrane potential in a resting nerve cell

Ion	Extra cellular Conc(mmol /L)	Intra cellularConc(mmol/L)	Relative permeability
Sodium	150	15	1
Potassium	5	150	50-100
Anion(A-)	0	65	0

Effect of sodium-potassium pump on membrane potential

- About 20% of membrane potential is contributed by the Na+ K+pump. This pump generates unequal transport for both positive ions, that creates a membrane potential with the outside becoming more positive than the inside.
- This active transport mechanism pumps three sodium ions out for two potassium ions pumped in.
- However, most of the potential (80%) is caused by passive diffusion of potassium and sodium ions down their gradients.

Concurrent potassium and sodium effects on membrane potential

- As potassium is more permeable at rest, it influences the resting membrane potential to a greater extent than does sodium. RMP of nerve is -70 mV.
- It is slightly less than potassium equilibrium potential because of the weak influx of sodium.
- Nerve and muscle use the membrane potential for their specialized advantages.
- They are capable of rapidly and transiently alter the permeability of these ions in response to appropriate stimulation, thereby bringing about fluctuations in membrane potential.

NEURONS

- The nervous system consists of cells that are called neurons.
- The neuronal cell contains a cell body and processes that are arranged to the cell to receive, conduct and transmit stimuli to other cells.

Glial cells

- The neurons gain efficiency through special glial cells.
- These surround the neuron, adhering to their surface and helping to remove problem of resistance to the conduction of excitation

Components of the nervous system

1. Neurons: The original neuron is "nerve cell"

- Cells best equipped to sense and react to the chemical and physical change occurring in their surrounding environment.
- They are present in the entire human body and communicate with each other regarding their conditions and reactions.
- Primary neural functions include reception, conduction and transmission.
- Nerve cells grow 2 types of processes from their cell bodies - axons and dendrites.

Components of the nervous system…

- **Dendrites:** are those processes that are concerned with reception of stimuli from environment.
- **Axons**: are those processes that are concerned with conduction and transmission of the stimuli-signal to another cell or cells.
- The axon gives out collateral branches when the target consists of many cells.

Various Functions of Glial Cells

- Mechanical supportive elements of neurons
- Insulator of neuron
- Phagocytic defense mechanism
- Secretory
- Modifiers of electrical activity in neuron
- Regulation of metabolism in neuron
- Development assistance in neuronal circuitry
- Producers of myelin sheath

N.B Glial cells retain the ability to divide throughout life.

Terminals in peripheral nervous system (PNS):

- **Sensory endings**: The sensory endings pick up a stimulus either directly from the environment as simple receptors or indirectly through specialized cells, as encapsulated receptor organs.
  - A receptor is a biologic transducer which picks up one form of energy or stimulus and transforms it into another form of energy.
  - All peripheral sensory endings are receptors either directly or indirectly.
- **Motor endings** are neural endings that transmit impulses to the effector cells.
  - Effectors are cells in organs that respond to impulses from the NS. Muscles and glands are effectors.

Classification of sensory endings or receptors:

1. Exteroreceptors: Localized in the body surface; receive information from the external environment

- Sight, hearing, smell
- Pick up distant stimuli (teleoreceptors)
- Touch, pressure, temperature
- Stimulation by contact

2. Proprioceptors: Localized in the locomotion apparatus (muscles, tendons, joints). Receive information regarding posture, movements

3. Interoreceptors (visceroreceptors): Visceral activity (digestion, excretion, circulation) Located in Viscera and blood vessels

Sensory endings or receptors

- **Free nerve endings**: Most free nerve endings arborize between the tissue cells; other surround the hair follicles.
- **Nerve fibers**: The axons are covered by glial cells. Only the sites of synapses are free from the glial lining.
- The axons in the CNS are covered by oligodendrocytes and the PNS by Shawn cells.
- An axons with its glial covering is called nerve fiber.
- Fibers are classified as myelinated or nonmyelinated.
- **Electric signal in nerve**: The nervous system controls body's muscular and glandular activities that are mostly directed towards maintaining homeostasis

Electric signal in nerve:

- Nerve and muscle able to develop rapid and transient change in their membrane potentials. These fluctuations serve as signal / impulse in two forms

1. **Graded potentials-** serving as short distance signals
2. **Action potentials-** which serve as a long distance signals without any change**.**

Graded potentials

- Graded potentials die out over short distances.
- Local membrane potentials (Changes occur in varying grades of magnitude or strength).
  - ✓ For example, RMP of -70 mV may become -60 mV or -50 mV.
- This magnitude is related to the magnitude of the triggering event, i.e. the stronger the triggering event, the larger the graded potential.
- Triggering event may be
  - Stimulus - such as light stimulating photoreceptors on the retina
  - Interaction of chemical with a receptor on a nerve or muscle cell membrane (neurotransmitter).
  - Spontaneous change of potential caused by imbalance in the leak-pump cycle

Characteristics of Graded potential

- Graded potential change: magnitude varies with the magnitude of triggering event
- Decremental conduction: magnitude diminishes with distance from initial site
- Passive spread to nearby inactive areas of membrane
- No refractory period
- Can be summed (temporal and spatial)
- Can be depolarized or hyperpolarized
- Triggered by stimulus, combination of neurotransmitter with receptor or by spontaneous shift in leak-pump cycle.
- Occurs in specialized regions of membrane designed to respond to triggering event:
  - e.g. end plate potential, receptor/ generator potential, excitatory postsynaptic potentials, inhibitory postsynaptic potentials

The Action Potential

❑ Characteristics:

- All or none membrane response, magnitude of the triggering event coded in frequency rather than amplitude of action potential
- Propagated through out membrane in undiminished fashion
- Self-generation in nearby inactive areas of membrane
- Refractory period present
- Summation impossible
- Always depolarization to threshold through spread of graded potential
- Occurs in regions of membrane with abundance of voltage-gated sodium channels

Initiation of the Action Potential

- Action potential is generated when an axon is stimulated by sufficient strength electric current
- As soon as the critical level of depolarized, the threshold is reached, any further increase in the strength of the applied current do not affect size of the potential.
- It is all- or- none response.
- The action potential crosses the zero line it is moving from -80 to +30 mV inside the membrane.
- The action potential is propagated along the whole length of the fiber membrane with a constant speed and amplitude.

Monophasic and diphasic action potential

- When one electrode is kept inside and the other is outside, potential changes across the membrane can be measured and if properly amplified and electrodes connected to a cathode ray oscilloscope, they can be recorded as the monophasic action potentials.
- Using 2 surface electrodes on the nerve or muscle, a diphasic action potential can be seen on the screen and recorded

Phases of the action potential

Resting membrane potential (RMP): Voltage difference between inside and outside of cell in absence of excitatory or inhibitory stimulation.

Threshold potential: Membrane potential to which excitable membrane must be depolarized to incite an action potential

Upstroke or rising phase: This is a very rapid period of change, when the cell is losing its negative resting potential, and becomes depolarized (zero potential) and shows reversal of the membrane potential so that the inside of the membrane is transiently positive.

Phases of the action potential..cont

Overshoot: The short positive phase is known as overshoot and is usually of about +30 mV- +40 mV in amplitude.

Repolarization phase: The down stroke of the potential change is the repolarization, a slower process than the initial phase of depolarization.

Depolarization after potentials: The membrane potential for a brief period becomes more positive than the resting membrane potential and the cell, therefore, is slightly more excitable than normal.

Hyperpolarization after potentials: some cells reflect a fall in the membrane potential below the RMP for a brief period following the action potential. During this time, the cell is less excitable than normal.

Duration of the Action Potential

- Though the peak of the action potential or the overshoot is about the same for most excitable cells, the duration of the action potential varies significantly.
- Action potentials for nerves are very brief, lasting only about 2-3 milliseconds, and the nerve cell is almost instantly ready again to conduct the next potential.
- Cardiac muscle cells, on the contrary, have long action potential more than 200 milliseconds, and these cells are not ready to respond to another stimulus until the cell membrane has almost returned to its original polarized state of RMP.

Ionic basis of the action potential

- The different phases of the action potential are correlated with the following changes in ionic influxes:
- The initial depolarization of the plasma membrane leads to an increase in the permeability of the membrane to sodium ions (**sodium conductance)**
- The sodium conductance rises very steeply by self-propagating (positive feedback) mechanism, because the more sodium enters, the greater the depolarization and the greater the increase in sodium conductance up to the peak of the impulse.
- This is the basis of the all or none character of the action potential. During this period the sodium channels are open.

Ionic basis of the action potential…

- The potassium channels/gates open a little latter than the sodium gates /channels and stay open for long. Consequently, the increase in potassium conductance / permeability starts a little later and lasts longer.
- The outward flow of the potassium ions slows the rise of the potential, then causes it to fall to its initial level by negative feedback mechanism, the membrane regains its original permeability and is ready to conduct another impulse.
- There is a very small period of less than 1 millisecond during which time the sodium gates are closing and the potassium gates are still open.

Ionic basis of the action potential…

- During this time the nerve fiber is unresponsive to a depolarizing current and, therefore, cannot conduct an impulse.
- This is the absolute refractory period.
- This interval is very brief (2 millisecond) and the nerve fibers can carry very fast frequency of impulses.
- The absolute refractory period is followed by a recovery of excitability during which time the threshold of the nerve is higher than normal, and so only stimuli of very great strength can evoke a propagated impulse, which is it self smaller and slower.
- This recovery phase is called relative refractory period. It lasts another 2 milliseconds after the end of the absolute refractory period.

Conduction of the Action Potential

- The action potential is conducted along the nerve fibers by the ionic mechanism of the plasma membrane
- There exists self regenerative sodium conductance of the stimulated membrane, which changes the initial depolarization to the all or none full-sized action potential that is propagated without loss of amplitude along the entire length of the fiber.
- Unmyelinated fibers are thin, slow conducting nerves often called "C" fibers on the basis of their diameter of less than 1 micron.
- Myelinated fibers have the nodes of Ranvier at regular intervals of 1-2 mm. iameter

Saltatory conduction

- Myelinated fibers are often classified as "A" fibers with diameters of 3-13 μm. The addition of myelin sheath allows an enormous increase in conduction velocity with a relatively small increase in fiber d
- Inefficient electrical characteristic are compensated by the wrapping of the axon in concentric layers of myelin, which acts as **insulating** sheath that increases the resistance and **greatly speed up** velocity action potential by nodes of Ranvier at 1 mm distance that lifts the attenuated signals.

The stimulus

- A stimulus is any change that can alter the energy state of a tissue sufficiently to depolarize the membrane. A nerve can be stimulated by mechanical, thermal, chemical, osmotic or electrical stimulation.
- These various stimuli are converted or transduced by the nerve to an electrical response, i.e. an action potential.

Excitability

- Excitability may be defined as the ability of a cell to respond to a stimulus with an action potential.
- A stimulus must fulfill to evoke response.
  - Strength of the stimulus
  - Duration of the stimulus
  - Rate of rise of the stimulus intensity

Neuromuscular junction / synapse

- The neuromuscular junction is the specialized region of contact between nerve and muscle.
- Each skeletal muscle fiber receives only one of the many terminal branches of the nerve fiber.
- All movements are composites of contraction of muscle unit, the motor neuron, its axon, and all the muscle fibers it innervates.
- The resulting contraction of each muscle fiber of the motor unit is all or nothing. Increase in the strength of muscle contractions are obtained through the recruitment of greater number of motor units.
- **Motor unit**: Motor nerve and all the muscle(s) innervated by the nerve.

Neuromuscular junction / synapse

- **Functional anatomy of neuromuscular Junction**

1. Presynaptic Structure

- The axon terminals in knobs on the membrane surface do not fuse with it. The knob terminals have the spherical synaptic vesicles (40-200 nm diam.) containing acetylcholine, and the many mitochondria needed for synthetic processes occurring in the terminals. There are active zones of the presynaptic membrane, where transmitter release occurs. The presynaptic membranes have selective ionic gates, voltage gated Ca++ channels.
- **The synaptic Cleft:** The cleft is a gap of about 40 mm separating the axon terminal and the muscle membrane.

Neuromuscular junction / synapse

2. Postsynaptic Structure

- At the junction area, there is an enlargement of the sarcoplasm of the muscle fiber, known as the end plate. This is the postsynaptic region where depolarization occurs to give rise to the end-plate potential (EPP).
- The postsynaptic surface area is markedly increased by deep functional folds.
- The postsynaptic membrane is both structurally and physiologically different from the rest of the muscle membrane. The postsynaptic region responds only to chemical stimulation or inhibition. The region of the muscle surface membrane under the nerve terminal is sensitive to acetylcholine.

Physiology of Neuromuscular Junction

- The EPP is graded in size and at a critical level of depolarization- about -50 mV.
  - it triggers an impulse that travels along the muscle membrane.

Mechanism of Action of Acetylcholine

- **Release:** The action potential reaching the nerve terminal depolarizes the membrane to about 30 mV to open the calcium channels permitting the influx of ionic calcium down the steep electrochemical gradient. This triggers the release of Ach from the synaptic vesicles by exogenous Ca++.
- **Recycling of vesicles:** The disrupted vesicles are modified and same vesicles are pinched off and filled. These vesicles store Ach.

Mechanism of Action of Acetylcholine

Ach activity of the end plate

- At the motor end plate, Ach combines with a muscle receptor that results in opening of the ionic gates to cause depolarization, and also it combines with a hydrolytic enzyme - Ach estrase (AchE) which rapidly inactivates it, after its role is over. The Ach receptor is a protein; its conformation changes when Ach binds to it, resulting in the opening of the ionic gates and a change in permeability.
- Curare also binds to receptor protein but alters it to an inactive form, which does not result in depolarization. Snake venom containing bungarotoxin binds very tightly and specifically to Ach receptor. The receptor density is very high (3x 107) per end plate, which is enough for the 104 quanta of Ach released.

Inactivation of acetylcholine

- There are 12,000 -21,000 molecules of Ach per quanta packed in to one vesicle.
- The concentration of Ach at the end plate remains high briefly for it is hydrolyzed rapidly by the enzyme AchE into choline and acetate.

Synapse and neuronal integration

- A neurotransmitter transmits the signal across a synapse. A neuron terminal ends at a muscle, gland or another neuron. The junction between the 2 neurons is a synapse. Classically, a neuron to neuron synapse is a junction between an axon terminal of one neuron and the dendrites or cell body of a second neuron. Some neurons within the CNS receive as many as 100,000 synaptic inputs.

Inhibitory and excitatory synapses

- Some synapses excite the post synaptic neuron whereas others inhibit it, so there are 2 types of synapses depending on the permeability changes in the post synaptic neuron by the binding of neurotransmitter with receptor site.
- At an excitatory synapse, the neurotransmitter receptor combination opens sodium and potassium channels within the subsynaptic membrane, increasing permeability to both ions. Both ions move simultaneously in opposite directions as per their gradients.

Chemical Neurotransmitter

Chemical Neurotransmitter (rapidly acting molecules)

- Acetylcholine (Ach),
- dopamine,
- epinephrine, norepinephrine,
- serotonin, histamine,
- glycine, glutamate, aspartate, gamma-aminobutyric acid:

Neuropeptides (large, slow-acting molecules)

- Beta-endorphin, ACTH, MSH, TRH, GnRH,
- somatostatin, VIP, CCK, gastrin, substance P,
- neurotensin, leucine, enkephalin, methionine
- enkephalin, motilin, insulin, glucagons, angiotensin-II,
- bradykinin, vasopressin, oxytocin, carnosine, bombesin.

Removal of neurotransmitter

- It is important that neurotransmitter be inactivated or removed after it has produced desired response in the postsynaptic neuron, leaving it ready to receive additional message from the same or other neuron inputs. The neurotransmitter may diffuse away from the cleft, be inactivated by specific enzyme within the subsynaptic membrane, or be actively taken back up in to the axon terminal by transport mechanism in the presynaptic neuron for storage and release at another time.

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Characteristics of chemical transmission

- Chemical transmission is unidirectional
- Chemical transmission is graded, with the amount of transmission chemical released dependent on the frequency of stimulation of the presynaptic neuron.
- The effect of chemical transmitter can be summed so that the final state of the postsynaptic potential will depend on the amount of excitatory transmitter reaching the postsynaptic membrane.(temporal and spatial summation)
- There is delay at the synapse

Characteristics of chemical transmission…

- There are means of inactivating the transmitter by enzyme
- There has to be rapid, efficient means of synthesizing the NT at the nerve terminals.
- Chemical transmission is variable, susceptible to change in physiological conditions such as fatigue and disease

Skeletal Muscle

- Body's skeletal muscles play a major role in producing food, breathing, heat generation for maintenance of body temperature and diverse movements including movement away from harm; thus, this contribute to homeostasis by their versatile movements.
- Skeletal muscles attached to the bones contract allowing the body to perform a variety of motor activities; these activities are needed for acquisition, chewing and swallowing of food, and that move the chest for breathing. They also contract in defending the body by protective movements. Smooth muscles are present in all hollow organs and the vascular conduits.

Skeletal Muscle

- Regulated contractions of smooth muscles make the blood flow through the vessels, food through the GIT, air through the respiratory passages, and urine to the out side. Cardiac muscle pumps life sustaining blood throughout the body.
- The muscle cells are the real specialists having contractile proteins present in skeletal, cardiac and smooth muscle cells. They are capable of shortening and developing tension that enables them to produce movement and do work.
- Muscles in response to electric signals convert chemical energy (ATP) into mechanical energy that helps in purpose movement of the body: driving a car or moving a piece of furniture.

Skeletal Muscle…

- Skeletal muscle is the largest body tissue accounting for almost 40% of the body weight in men and 32% in women.
- Smooth muscles and skeletal muscles account about 10% of the total weight.
- Muscles are categorized as striated and non-striated/ smooth muscles and also typed as voluntary and involuntary subject to innervations by somatic or autonomic nerves and whether subject to voluntary or not subject to voluntary control.

Microstructure of Skeletal muscle

- Skeletal muscles contract in response to signals from its innervating somatic nerve that releases acetylcholine at its terminals that starts the muscle action potentials.
- A muscle fiber is fairly large, elongated and cylindrical shaped ranging from 10-100 μm in diameter and up to 2.5 feet in length.
- A muscle is made up of a number of muscle fibers arranged parallel to each other and wrapped by connective tissue as a bundle.
- A single muscle cell is multi-nucleatd with abundant number of mitochondria to meet its high energy demands.

Microstructure of Skeletal muscle…

- Each cell has numerous contractile myofibrils, constituting about 80% of volume of muscle fibers extending the entire length.
- Each myofibril consists of the thick myosin filaments (12-18 nm diameter) and thin actin filaments (1.6 nm in diameter).
- A relaxed muscle shows alternating dark bands (A band) and light bands (I band) due to slight overlapping of thick and thin filaments under the microscope.
- H zone does not have the thin filaments. The "I" band contains only thin actin filaments. In the middle of each I band is a dense vertical Z line, actually a flattened disc like cytoskeletal protein that connects the thin actin filaments of 2 adjoining sarcomers. Relaxed sarcomere is about 2.5 μm in width.

Excitation - Contraction Coupling…cont

- When an action potential travels down the T- tubules, the local depolarization activates the voltage-gated dihydropyridine receptors.
- Activated T- tubules receptors in turn trigger the opening of the Ca++ channels (ryanodine receptors) in the adjacent lateral sacs of the sarcoplasmic reticulum.
- Calcium is released from lateral sacs. Tropomyosin-troponin complex is repositioned; the released Ca++ binds with troponin C exposing the binding sites on the actin molecule so that they can attach with the myosin cross bridges at their specific sites.

Excitation - Contraction Coupling…cont

- Calcium is the link between muscle excitation and contraction. Excitation - Contraction Coupling refers to the sequence of events linking muscle excitation to mechanical contraction.
- At neuro-muscular junction of skeletal muscle neurotransmitter Ach released from innervating motor neuron results in muscle contraction.
- The surface membrane dips in to the muscle fiber to form a 'transverse tubule' which runs from the cell membrane surface in to the central portion of the muscle fiber.
- The T- tubule also has receptors where it contracts the ryanodine receptors. These T- tubule receptors are known as dihydropyridine receptors.

Excitation - Contraction Coupling…cont

- A myosin cross bridge has an actin binding site and an ATPase site. In skeletal muscle, Mg++ must be attached to ATP before myosin ATPase can split the ATP yielding energy in the process.
- It is to be noted that fresh ATP must attach to myosin to permit the cross bridges link between myosin and actin to be broken down at the end of the cycle. The necessity for ATP for separation of myosin and actin is well evidenced by rigor mortis.
- This stiffness of death is a generalized locking in place of skeletal muscle beginning 3-4 hours after death and completed in about 12 hours.

Excitation - Contraction Coupling…cont

- A single action potential in skeletal muscle fiber lasts only 1-2 msec.
- The onset of the resultant contraction response lags behind the action potential because the excitation- contraction coupling process must occur before cross bridges activity begins.
- As a matter of fact, the action potential ends before the contraction mechanism even becomes operational.
- This time delay of a few msec between stimulation and onset of contraction is known as the 'latent period’.
- This is also needed for generating tension within the muscle fiber. The contraction time lasts about 50 msec, although it varies with the type of muscle fiber.

Excitation - Contraction Coupling…cont

- **Muscle twitch** Contraction of a whole muscle can be of varying strength.
- A twitch, which is too short and too weak for any use in the body, is produced as a result of a single action potential in a muscle fiber.
- Muscle fibers are arranged into a whole muscle and function with cooperation producing contraction of varying grades of strength stronger than a twitch.
- Two factors accomplish gradation of whole muscle tension. The number of muscle fibers contracting within a muscle The tension developed by each contracting fiber**.**

Excitation - Contraction Coupling…cont

- **Motor unit:** Each whole muscle is innervated by a number of different motor neurons.
- One motor neuron innervates a number of muscle fibers, but each muscle fiber is supplied by only one motor neuron.
- On activation of a motor neuron, all of the supplied fibers are stimulated to contract simultaneously - the team of concurrently activated component is a 'motor unit’.
- For stronger contraction, motor units are recruited or stimulated to contract.

Excitation - Contraction Coupling…cont

- Muscles producing very precise, delicate movement such as extraocular eye muscles and the hand digit muscles contain a few dozen muscle fibers.
- These small motor units allow a very fine degree of control over muscle fibers.
- Muscles designed for powerful, coarsely controlled movement such as those of legs, a single motor unit may have 1500-2000 muscle fibers.

1. Isometric contraction

- As a result of cross bridge activity and the resultant sliding of filaments, a tension is developed internally within the sacromere.
- This tension generated by the contractile elements is transmitted to the bone via the connective tissue and tendon before the bone can be moved. Intracellular components of the muscle such as the elastic fiber proteins and connective tissue collagen fibers have a certain degree of passive elasticity.
- These non-contractile elements are the ‘series-elastic-components' of the muscle, behaving like a spring placed between the tension generating contractile proteins and the bone that is to be moved against an external lead.
- Shortening of the sarcomere stretches the 'series- elastic-component' and the muscle tension is passed to the bone by their tightening. This tension application moves the bone against a load. There are 2 primary types of movement depending on whether the muscle changes length during contraction.

2. Isotonic contraction

- This type, muscle tension remains constant as the muscle changes length.
- Isometric contraction: In this type, the muscle is prevented from shortening, so tension developed at constant muscle length.
- The same internal events occur in both types of contractions. Isotonic contractions are used for body movements and for moving external objects.
- The submaximal isometric contractions are important for maintaining posture and for supporting the object in a fixed position.
- During a given movement, a muscle may shift between Isotonic and isometric contractions.

Steps of Excitation-contraction coupling

1. Ach released from a motor neuron terminal initiates an action potential in the muscle cell that is conducted over the entire surface of the muscle cell membrane.
2. The surface electrical activity is carried in to the central portion of the muscle fiber by the T-tubule.
3. Spread of the action potential down the T- tubules triggers the release of Ca++ ions from the adjacent lateral sacs of sarcoplasmic reticulum.
4. Released of Ca++ binds with troponin and changes its shape so that the tropomyosin-troponin complex is pulled aside, exposing actin's cross bridge binding site.

Steps of Excitation-contraction coupling…

5. Exposed actin binding site bind with myosin cross bridges which have previously been energized by the splitting of ATP in to ADP+ Pi+ energy by the myosin ATPase site on the cross bridge.
6. Binding of actin and myosin at a cross bridge causes the cross bridge to bond producing a power stroke that pulls the thin filament
7. ADP and Pi are released from the cross bridge during the power stroke.
8. Attachment of a new molecule of ATP permits detachment of the cross bridge, which returns to its original conformation.
9. Splitting of the fresh ATP molecule by myosin ATPase energizes the cross bridge once again.
10. If Ca++ is still present so that the tropomyosin-troponin complex remains pulled aside.

Steps of Excitation-contraction coupling…

Contractile state:

- The invading action potential to T-Tubule → Ca^{2+} released from SR → binds to troponin C → binding of troponin I to actin is weakened → tropomyosin moves laterally → uncovers binding sites for myosin heads → contraction (*in the presence of ATP).*
- Seven myosin-binding sites are uncovered for each molecule of troponin that binds a Ca^{2+}.

Skeletal muscle metabolism

Three steps in the contractile process require ATP

1. Splitting of ATP by myosin ATPase providing energy for the power stroke of the cross bridge
2. Binding of a fresh molecule of ATP to myosin permitting detachment of the cross bridge from actin at the end of the power stroke so that the cycle could be repeated.
   - This ATP provides energy for the next stroke of the cross bridge.
3. The active transport of Ca++ ions back in to the sarcoplasmic reticulum, is energy dependent.

- Therefore, ATP must be continuously supplied for contraction activity to continue.
- The muscle has small and limited source of ATP for its immediate needs. Three pathways provide additional ATP needed during muscle contraction.

1. Creatinine phosphate transfers high energy phosphate bonds to ADP
2. Oxidative phosphorylation - the citric acid cycle (Kreb's cycle) and electron transport system
3. Glycolysis - aerobic and anaerobic

Smooth and Cardiac Muscle

- Smooth muscle shares some basic properties with skeletal muscle and also have some distinctive properties.
- The same is true for cardiac muscle.
- Common features of the 3 muscles:
  - All have specialized contractile proteins and made up of actin and myosin that slide past in response to rise in cytosolic calcium to achieve contraction
  - All use ATP for cross bridge cycling Different features:
  - Structure variation as well as excitation
  - The means by which excitation - contraction is coupled.
  - There are distinct contractile responses.

Smooth muscle

- The majority of these muscles are present in the walls of hollow organs, blood vessels and tubular structures in the body.
- Their contraction exerts pressure on the contents and regulates the forward movement of contents of these structures.
- Smooth muscles are spindle-shaped, have 1 nucleus and are much smaller in size (2-10 μm in diameter and 50-100 μm in length).
- Groups of smooth muscles are typically arranged in sheets.

Smooth muscle….

- Three types of filaments present in smooth muscles are
  1. Thin actin filaments, which have tropomyosin but lack troponin
  2. Thick myosin filaments, longer than those found in skeletal muscles.
  3. Filaments of intermediate size - serve as part of the cytoskeleton framework that supports the shape of the cell, but does not directly participate in contraction.
- Smooth muscles do not form myofibril and are not arranged in sarcomere pattern of skeletal muscle.
- Smooth muscles don’t display striation

Calcium dependent phosphorylation of myosin

- Smooth muscles do not have troponin and tropomyosin and do not block actin's cross bridge blocking sites, yet actin and myosin are prevented from binding in the resting state.
- Smooth muscle myosin interacts with actin only when the myosin is phosphorylated.
- During excitation, cytosolic Ca++ increases, that acts as an intracellular messenger, initiating a series of biochemical events that result in phosphorylation of myosin.
- In Smooth muscles Ca++ binds with calmodulin and intracellular protein similar to troponin in structure.
- This calcium- calmodulin complex binds to and activates another protein, myosin kinase, which in turn phosphorylats myosin.
- Phosphorylated myosin then binds with actin thin filament starting cross bridge cycle.

Multi-Unit and Single Unit Smooth Muscle

Multi- unit smooth muscle

- Multi- unit are discrete units that function independently of each other and separately contract, similar to skeletal muscle motor units.
- Contraction activity is neurogenic
- Innervated by autonomic nerves
- These types of smooth muscles are found in the large body vessels, in large airways to the lung, in ciliary muscles (the eye), that adjust the lens for near or far vision, in the iris of the eye, base of hair follicles.

Multi-Unit and Single Unit Smooth Muscle

Single- unit smooth muscle (visceral smooth muscles)

- Found in the walls of hollow organs/viscera - digestive, reproductive, urinary tract and small blood vessels.
- Single-unit is self excitable rather than needing nerve stimulation for contraction
- Cluster of cells show spontaneous electrical activity, undergoing action potential without any external stimulation
- Have 2 major types of spontaneous depolarization;
    1. Pacemaker activity
    2. Slow wave potential

Slow contractile response of smooth muscle

- A smooth muscle contractile response is slower than of muscle twitch.
- A single smooth muscle contraction may last as long as 3 sec (3000 msec) compared to the maximum of 100 msec for a single contraction response skeletal muscle.
- Smooth muscle also relax slowly because of slower rate of calcium removal.

Cardiac Muscle

- Cardiac muscle shares structural and functional characters with both skeletal and single unit smooth muscle.
- It is striated like skeletal muscle with highly organized actin and myosin in regularly banding pattern
- Cardiac muscle contain tropomyosin and troponin providing the site for calcium
- Have abundant mitochondria, myoglobin and T-tubules like skeletal muscles
- Like smooth muscles Ca++ enters both ECF and SR. It has pacemaker activity but not slow wave action like single unit smooth muscle
- Cardiac muscle has gap junction for enhancing the spread of action potential throughout the heart
- Innervated by both ANS components.