

Muscle

BME 5010 - Engineering Physiology

Objectives - Skeletal Muscle

- ◆ Define the function of skeletal muscle
- ◆ Discuss the hierarchical structure of skeletal muscle
- ◆ Describe the mechanism of contraction at a molecular level, including the role of ATP and calcium
- ◆ List the steps in neural stimulation of muscle contraction
- ◆ Define the three types of muscle fiber contraction
- ◆ Discuss the following relationships:
 - Frequency-muscle tension
 - Length-muscle tension
 - Load-shortening velocity

Objectives - Skeletal Muscle

- ◆ Discuss the three types of energy metabolism which occur in muscle
- ◆ Define muscle fatigue and give theories for its occurrence
- ◆ Define the three types of muscle fibers
- ◆ Discuss how whole-muscle tension and shortening velocity is regulated by the nervous system
- ◆ Explain how exercise or lack of activity affects muscle
- ◆ Describe the benefits and drawbacks of the lever system of movement based on muscle and bone

Skeletal Muscle

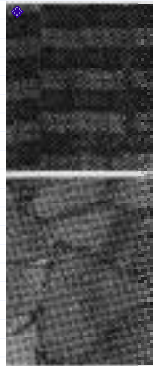
- ◆ Most are attached to bone
- ◆ Responsible for supporting and moving the skeleton
- ◆ Generally voluntary control

Skeletal Muscle Structure

- ◆ Myoblasts (undifferentiated, mononucleated cells) fuse during fetal development to form a single, cylindrical, multi-nucleated cell called a muscle fiber which is no longer able to divide
 - Muscle fibers are between 10 and 100 μm in diameter and up to 20 cm long
- ◆ Muscle fibers are grouped into cylindrical bundles and eventually a whole muscle by connective tissue
- ◆ Muscles are connected to bones by tendons
- ◆ Destroyed muscle fibers are replaced by undifferentiated satellite cells located in the connective tissue surrounding muscle cells

Muscle Microstructure

- ◆ Skeletal and cardiac muscle show a striated structure under the microscope
- ◆ Striated pattern is due to the arrangement of thick and thin filaments into myofibrils which run the length of muscle fiber within the cytoplasm
- ◆ One unit of repeating pattern within a muscle cell is called a sarcomere



Muscle Microstructure

- ◆ See Figure 11-4 in Vander, Sherman, and Luciano
- ◆ Thick filaments: myosin
 - Located in the middle of the sarcomere
 - Wide, dark band of myosin called the A band
 - Held together by proteins within the cytoplasm (not free-floating)
- ◆ Thin filaments: actin along with troponin and tropomyosin
 - Located at either end of the sarcomere, with one end of each filament anchored to the Z line and the other end overlapping the myosin filaments

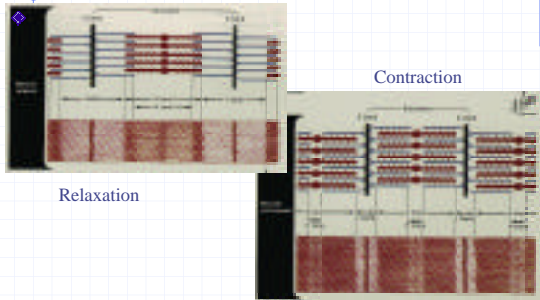
Muscle Microstructure

- ◆ Sarcomeres are bounded by Z-lines on both ends
- ◆ The light bands of the muscle fiber contain only thin filaments
 - Called the I band
 - Divided in half by a Z-line

Molecular Mechanism of Contraction

- ◆ Contraction: turning on of cross-bridges within muscle fibers
- ◆ Relaxation: turning off of cross-bridges, reducing tension
- ◆ In order for muscle shortening to occur, the cross-bridge induced force must exceed an external, opposing force
- ◆ The current theory of muscle contraction is called the sliding filament mechanism

Sarcomeres in Contraction and Relaxation



Sliding Filament Theory

- ◆ Myosin is a linear molecule with a globular end
 - All myosin molecules have their linear portion directed parallel to the myofibril axis and towards the center of the sarcomere
 - The globular end has a binding site for actin and a second site for ATPase (an enzyme that breaks down ATP)
 - ◆ This globular portion is termed the cross-bridge
- ◆ Actin is a globular molecule that forms a double helix
 - Actin is wrapped by a molecule of tropomyosin which covers binding sites for the cross-bridges
 - The tropomyosin is held in this blocking position by molecules of troponin, which have a binding site for calcium

Sliding Filament Mechanism*

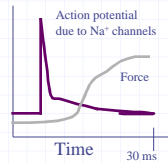
- ◆ (1) Calcium is released by the sarcoplasmic reticulum of the muscle cells
- ◆ (2) Calcium ion binds to troponin molecule of thin filament
- ◆ (3) Troponin moves tropomyosin molecule away from cross-bridge binding sites of actin
- ◆ (4) ATP molecules bound to myosin are hydrolyzed by ATPase to produce an energized myosin molecule
 - $M \cdot \text{ATP} \rightarrow M^* \cdot \text{ADP} \cdot \text{P}_i$

Sliding Filament Mechanism

- ◆ (5) The cross-bridge of the energized myosin molecule binds to actin and triggers the release of the energy stored in the myosin
 - $A + M \cdot ADP \cdot P_i \rightarrow A \cdot M \cdot ADP \cdot P_i \rightarrow A \cdot M + ADP + P_i$
- ◆ (6) Energy release corresponds to movement of bound cross-bridge in a rowing motion, bringing the actin molecules towards the center of the sarcomere
- ◆ (7) An ATP molecule binds to the myosin molecule and releases the cross-bridge attachment
 - $A \cdot M + ATP \rightarrow A + M \cdot ATP$
- ◆ (8) Myosin molecule is then ready to bind to another actin site and steps 4 through 7 are repeated as long as calcium is present

Excitation-Contraction Coupling

- ◆ Sequence of events by which an action potential at the plasma membrane leads to cross-bridge activity
- ◆ Skeletal muscle plasma membrane is excitable and capable of generating and propagating action potentials in a similar way to nerve cells
- ◆ A muscle action potential lasts 1 to 2 ms and is followed by 100 ms or more of mechanical activity within the muscle due to an increase in cytosolic calcium



Action Potential and Calcium Concentration

- ◆ In resting muscles, the cytosolic calcium concentration is very low (10^{-7} mol/L)
- ◆ Following an action potential, there is a rapid increase in cytosolic calcium due to release of calcium stores from the cellular sarcoplasmic reticulum
- ◆ Within a muscle fibre, the myofibrils are surrounded by sleeves of sarcoplasmic reticulum (SR) (See Fig 11-15)
 - At the end of each segment of SR are enlarged regions called lateral sacs or terminal cisternae which contain the stored calcium

Action Potential and Calcium Concentration

- ◆ A transverse tubule (or T tubule) crosses a muscle fiber even with each A-I junction, between adjacent lateral sacs, and connects to the plasma membrane
 - Action potentials along the plasma membrane are conducted into the center of the cell by the T tubules
- ◆ When an action potential passes a lateral sac, calcium channels are opened and calcium is released into the cytosolic fluid surrounding the myofibrils
- ◆ A positive feed-back loop is set-up, as initially released calcium binds to calcium channels of the lateral sacs and causes more channels to open
- ◆ As Ca^{2+} concentration rises, Ca^{2+} binds to lower affinity sites on the channels and causes them to close and end ion release

Calcium Concentration and Muscle Relaxation

- ◆ Contraction of myofibrils will continue as long as there is an elevated cytosolic calcium concentration and binding to troponin
- ◆ Calcium is returned to the SR by active transport in the presence of ATP
 - The time required to remove the calcium determines the length of time of mechanical activity, not the duration of the action potential
 - Note: this a third role for ATP in muscle contraction

Muscle Membrane Excitation

- ◆ Activated by stimulation of nerve fibers to a skeletal muscle (**motor neurons**)
- ◆ The axon of a motor neuron branches into multiple branches, with each forming a single junction with a muscle fiber
 - A single motor neuron innervates many muscle fibers, but each muscle fiber is controlled by only one motor neuron
- ◆ A **motor unit** is defined as a motor neuron plus the muscle fibers it innervates
 - Muscle fibers in a single motor unit are scattered throughout a single muscle
 - An action potential produced in a motor neuron causes all of the muscle fibers in its motor unit to contract

Muscle Membrane Excitation

- ◆ The area of the plasma membrane under the terminal portion of an axon is the motor end plate
- ◆ The junction of the axon with the motor end plate is called the neuromuscular junction

Muscle Membrane Excitation Mechanism*

- ◆ (1) An action potential arriving at an axon terminal opens calcium channels in the axon, allowing calcium to diffuse into the axon
- ◆ (2) The calcium triggers the release by exocytosis of acetylcholine into the extracellular cleft separating the axon terminal and the motor end plate
- ◆ (3) Acetylcholine binds to receptor sites on the motor end plate, opening ion channels which allow sodium ions to enter and potassium ions to exit
- ◆ (4) Ion movement results in a local depolarization of the membrane, triggering an action potential which propagates along the membrane
- ◆ (5) Acetylcholinesterase breaks down acetylcholine, ion channels close, and the membrane repolarizes

Single Fiber Contraction

- ◆ Whether or not muscle contraction leads to muscle shortening depends on the relationship between muscle tension and external loads
- ◆ Note that muscle fibers only shorten when stimulated -- there are no inhibitory impulses nor any mechanisms to actively lengthen the fibers
 - Lengthening occurs when an external force is greater than the generated muscle force

Single Fiber Contraction

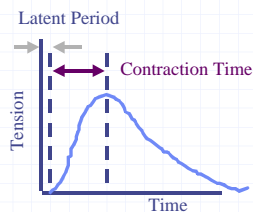
- ◆ **Isometric contraction:** muscle develops tension but does not shorten or lengthen
 - Occurs when: (1) a muscle supports a load in a constant position; or (2) attempts to move a load that is greater than the muscle tension and that is externally supported
 - Cross-bridges generate a tension but are not able to shorten myofibrils
- ◆ **Isotonic contraction:** load on muscle remains constant but the muscle is shortening
 - ie. lifting an object
 - Cross-bridges cause tension and myofibril shortening

Single Fiber Contraction

- ◆ **Lengthening contraction:** muscle lengthens while constant tension is being maintained
 - Occurs when an unsupported load on a muscle is greater than the generated tension, such as lowering an object
 - While bound to the actin, the cross-bridges are pulled towards the ends of the sarcomere instead of stroking towards the middle

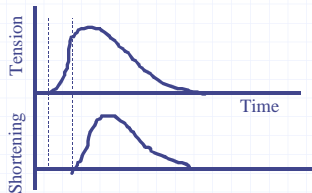
Single Fiber Contraction

- ◆ **Twitch:** response of a muscle fiber to a single action potential
- ◆ **Latent period:** time between action potential and initial generation of tension (isometric) or shortening (isotonic)
- ◆ **Contraction time:** time between initial generation of tension and generation of peak tension
 - Contraction time can differ between muscle fibers, ranging from 10 ms for fast fibers to 100 ms or more for slow fibers



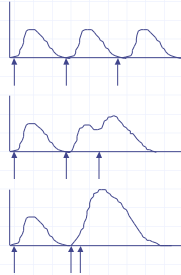
Single Fiber Contraction

- ◆ Tension often increases before shortening occurs, as the tension must first overcome any external load (including that of bones, etc.)



Single Fiber Contraction - Tension:Frequency

- ◆ Due to time difference between the duration of an action potential and the duration of mechanical response in the myofibrils, multiple action potentials can be applied to a muscle fiber before relaxation occurs
- ◆ The mechanical activity of a muscle fiber is subject to summation
 - A subsequent action potential can result in a generated tension higher than the peak tension of a single action potential



Single Fiber Contraction - Tension:Frequency

- ◆ Maintained contraction resulting from a repetitive stimulus is called tetanus
 - This occurs when the frequency of stimulation is such to not allow complete relaxation of the muscle in between action potentials
 - A maximal tetanic tension exists for each muscle fiber, which is approximately 3 to 5x greater than the isometric twitch tension
- ◆ The tension produced by each sarcomere at any time depends on the number of cross-bridges which are bound to actin and are "rowing"
- ◆ A single action potential releases enough calcium to saturate the troponin molecules

Single Fiber Contraction - Tension:Frequency

- ◆ Almost immediately after the action potential, calcium is pumped back into the SR and the Ca^{2+} concentration decreases resulting in fewer actin sites being available for binding
- ◆ Maximal tension takes time to develop as there is a finite time required for the molecular reactions and responses
- ◆ During a single twitch, the maximal number of actin sites does not stay available long enough for the time lags to be overcome and maximal tension to be developed
- ◆ During tetanic contraction, successive action potentials release calcium before the concentration can be returned to resting levels, allowing the maximal number of actin sites to be made available for contraction and maximum tension develops

Single Fiber Contraction - Tension:Length

- ◆ See Figure 11-25
- ◆ The length of the muscle fiber before contraction influences the maximal contraction that can be developed
 - The length at which a muscle fiber generates its maximal tetanic tension is termed the optimal length
- ◆ When the fiber length is less than 60 percent of its optimal length, no tension is developed on stimulation
 - The actin molecules cannot move further towards the center of the sarcomere
- ◆ When the fiber length is greater than 175 percent of its optimal length, no tension is developed on stimulation
 - The actin and myosin fibrils no longer overlap

Single Fiber Contraction - Tension:Length

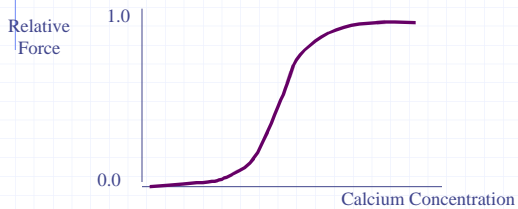
- ◆ At rest, most skeletal fibers are near their optimal lengths
- ◆ Length of a relaxed fiber can be altered by externally applied loads or the contraction of other muscles
 - Due to limits caused by the attachment of muscles to bone, muscle fiber length rarely varies by more than 30 percent from optimal
 - Muscles can therefore always contract

Single Muscle Contraction - Load:Velocity

- ◆ The velocity at which a muscle shortens while undergoing maximal tetanic stimulation decreases with increasing loads
 - Maximum velocity at zero load
 - Zero velocity when external load is equal to maximal isometric tension
 - At loads greater than maximal isometric tension, the fiber will lengthen at a velocity which increases with increasing load and at very high loads fibers will break
- ◆ Shortening velocity is determined by the rate at which individual cross-bridges cycle
 - Increasing the load decreases the rate at which the cross-bridge "rows" and generates force

Single Fiber Contraction - Calcium Concentration

- ◆ The generated force in a single muscle fiber is dependent on the cytosolic Ca^{2+} concentration in a sigmoidal fashion



Energy Metabolism

- ◆ ATP performs three functions related to muscle contraction and relaxation
- ◆ For contraction to be maintained, ATP must be supplied at a rate equal to that at which it is broken down
- ◆ ATP is generated through phosphorylation of ADP by three mechanisms within muscle cells
 - (1) Through creatine phosphate
 - (2) Through oxidation in the mitochondria
 - (3) Through glycolysis in the cytosol

Energy Metabolism - Creatine Phosphate

- ◆ Rapid means of forming ATP at the beginning of contraction
- ◆ Chemical bond between creatine and phosphate is broken, the energy released is the same as needed by ADP to attract the free phosphate group and form ATP
 - $CP + ADP \rightleftharpoons C + ATP$
- ◆ Reversible reaction
- ◆ During rest, muscle concentrations of CP build up to 5x the concentration of ATP
- ◆ After contraction, mass action favors formation of ATP
- ◆ Amount of ATP formed by this mechanism is limited by the initial concentration of creatine phosphate in the cell
- ◆ Beyond a few seconds of contraction, additional sources of ATP are required to maintain contraction

Energy Metabolism - Oxidation

- ◆ Requires fuel plus oxygen
- ◆ Predominant mechanism of ATP production during moderate muscular activity
- ◆ Energy provided by muscle glycogen during first 5 to 10 minutes of muscle contraction
- ◆ For following 30 minutes or so, glucose and fatty acids brought by the blood supply contribute equally to fuel supply
- ◆ In sustained activity, fatty acids become progressively dominant as the fuel for oxidation

Energy Metabolism - Glycolysis

- ◆ Requires fuel but no oxygen
- ◆ Contributes increasingly more to ATP production when the intensity of exercise exceeds 70 percent of maximal rate of ATP breakdown
- ◆ Produces lactic acid, which results in muscle burn

Energy Metabolism

- ◆ Replenishment of glycogen and creatine phosphate within the cytosol after contraction has stopped requires additional energy to be supplied
- ◆ Results in continued use of oxygen
 - Evidenced by continued deep and/or rapid breathing for a period after activity has finished
- ◆ The longer and more intense the exercise, the longer it takes to replenish the stores

Muscle Fatigue

- ◆ With repeated stimulation, fiber tension, contraction velocity, and the rate of relaxation eventually slow
- ◆ Rest allows the muscle to regain its ability to contract
- ◆ The onset of muscle *fatigue*, its rate of development, and rate of recovery depend on the type of muscle fiber and the intensity and duration of contraction
 - Muscle fatigue following weight lifting (short-duration, high-intensity) can develop quickly but recovers rapidly
 - Fatigue that develops slowly with low-intensity, long-duration exercise such as long distance running may take up to 24 hours to recover completely

Muscle Fatigue - High Frequency Stimulation

- ◆ Fatigue is partly caused by the increase in inorganic phosphate concentration (from ATP breakdown) and hydrogen ion concentration (from lactic acid build-up)
- ◆ P_i and H^+ concentration inhibit portions of the cross-bridge cycle, leading to decreased force production
 - Accounts for 50 percent of force reduction
- ◆ Additional fatigue is due to decreased release of calcium ions from the SR

Muscle Fatigue

- ◆ Fatigue from long-term, continuous activity is due to changes in activity of proteins: calcium channels, Ca-ATPase pumps in the SR, troponin, tropomyosin, actin, and myosin
- ◆ Fatigue may provide a protective mechanism
 - It occurs at a time when ATP breakdown exceeds ATP formation
 - Without fatigue, ATP concentration would decrease to a level resulting in continued binding of cross bridges in rigor

Skeletal Muscle Fibers

- ◆ Fibers can be identified based on
 - Maximal velocity of shortening: fast vs. slow
 - Major ATP forming pathway: oxidative vs. glycolytic
- ◆ Three types of fibers
 - Slow-oxidative fibers
 - Fast-oxidative fibers
 - Fast-glycolytic fibers
- ◆ Fast fibers: contain myosin with high ATPase activity
- ◆ Slow fibers: contain myosin with low ATPase activity

Skeletal Muscle Fibers

- ◆ Oxidative fibers
 - Contain numerous mitochondria
 - Surrounded by numerous blood vessels
 - Large amounts of myoglobin which increases the rate of oxygen diffusion and makes muscle fibers red
- ◆ Glycolytic fibers
 - Few mitochondria but high levels of glycolytic enzymes
 - Large store of glycogen but little myoglobin
 - Surrounded by few blood vessels, larger diameter than oxidative fibers
 - More overall myofibrils allow generation of higher fiber tension

Skeletal Muscle Fibers

- ◆ Fast-glycolytic fibers fatigue rapidly
- ◆ Slow-oxidative fibers fatigue slowly
- ◆ Fast-oxidative fibers have an intermediate capacity to resist fatigue

Whole Muscle

- ◆ Muscles are made up of many muscle fibers organized into motor units
- ◆ All fibers of a single motor unit are of a single fiber type
- ◆ Most muscles are composed of all three motor unit types mixed together
 - Proportion of the three fiber types determines the muscle's maximum contraction speed, strength, and fatigability
 - Back and Legs: slow-oxidative fibers predominate to support an upright posture for extended periods
 - Arms: fast-glycolytic fibers in greater proportion to produce large amounts of tension over short times

Muscle Tension

- ◆ Depends on the amount of tension developed by each fiber and the number of fibers contracting at any time
- ◆ Nervous system controls both factors to determine muscle tension and shortening velocity
- ◆ The number of fibers contracting depends on the the number of fibers in each motor unit and the number of active motor units
 - Muscles requiring fine control (eye and hand) have motor units with very few fibers -- as few as 13 -- so that activating a new motor unit generates a small increase in tension
 - Coarsely controlled muscles (back and legs) have motor units with hundreds or thousands of fibers

Muscle Tension

- ◆ Motor unit recruitment generally occurs in the following order
 - Slow-oxidative
 - Fast-oxidative
 - Fast-glycolytic
- ◆ Moderate levels of exercise will thus generally not include high numbers of fast-glycolytic fibers
 - These last motor units are generally recruited after the intensity of contraction exceeds about 40 percent of the maximal tension of the muscle
- ◆ Tension in a motor unit is governed by the frequency of neural stimulation

Muscle Shortening Velocity

- ◆ Recruitment also affects shortening velocity
 - The type of motor units recruited play a role in shortening velocity
 - An increased number of active motor units results in less load being carried by each motor unit (and fiber) thus allowing for higher shortening velocities

Adaptation to Exercise

- ◆ Muscle reduction can occur due to:
 - Denervation atrophy: if the neurons to a muscle are destroyed, the diameter of the denervated fibers and number of contractile proteins will decrease
 - Disuse atrophy: loss of muscle diameter and contractile proteins due to lack of use (ie. casting)
- ◆ Increased levels of activity can produce muscle hypertrophy as well as changes in the chemical composition of the of the fibers
- ◆ Muscle atrophy and hypertrophy is not through changes in the number of fibers, but through the metabolic capability and size of each fiber

Adaptation to Exercise

- ◆ Increased aerobic exercise
 - Produces an increased number of mitochondria in oxidative fibers
 - Causes an increase in the number of capillaries around the fibers
- ◆ Increased "strength training"
 - Causes an increase in the diameter of fast-glycolytic fibers through the production of more actin and myosin filaments
 - Increases the synthesis of glycolytic enzymes in fast-glycolytic fibers

Adaptation to Exercise

- ◆ Changes in muscle occur slowly over time in response to repeated exercise
- ◆ Stopping exercise will cause muscles to return to the original state, again slowly

Lever Action of Muscles

- ◆ Muscles exert tensile forces on the lever arms of bones through tendons
- ◆ Muscles act as antagonists through this tensile force
 - One set of muscles acting on a limb will cause flexion (bending) while a paired set will cause extension (straightening)
- ◆ Muscles and applied external forces exert moments on a lever arms about a joint (fulcrum)

Lever Action of Muscles

- ◆ Lever system amplifies the velocity of movement at the end of the lever
 - ie. A 1 cm shortening of the bicep produces a 7 cm movement of the hand in the same amount of time
- ◆ Short lever arm of muscles compared to supported weight requires much greater muscle tension to overcome the external load

Smooth Muscle

BME 5010 - Engineering Physiology

Objectives

- ◆ Discuss the function of smooth muscle
- ◆ Describe the structure of smooth muscle and how this relates to its function
- ◆ Explain the mechanism of contraction and its control
- ◆ List the types of smooth muscle and their differentiating features

Smooth Muscle

- ◆ Most smooth muscle surrounds hollow organs

Structure

- ◆ Smooth muscle fibers are spindle-shaped cells with diameters from 2 to 10 μm
- ◆ Single nucleated cells that retain their ability to divide
- ◆ Contain two types of filaments:
 - Thick, myosin containing filaments
 - Thin, actin containing filaments
- ◆ Actin filaments are anchored to either the plasma membrane or to structures in the cytoplasm known as dense bodies
 - Dense bodies function similarly to Z-lines in skeletal muscle

Structure

- ◆ Filaments are oriented diagonally with respect to cell axis
- ◆ Thick and thin filaments are not organized into myofibrils or sarcomeres
 - No striated pattern
- ◆ Actin of thin filaments is not bound to the regulatory molecule, troponin

Contraction

- ◆ Calcium triggered cross-bridge activation is mediated by a calcium-regulated enzyme that phosphorylates myosin
- ◆ The phosphorylated myosin is then capable of binding to actin and undergoing cross-bridge cycling
- ◆ Smooth muscle contraction involves calcium-induced changes in the thick filaments, whereas skeletal muscle regulation was through the thin filaments

Contraction Mechanism

- ◆ (1) Rise in cytosolic calcium
- ◆ (2) Calcium binds to calmodulin (a calcium binding protein)
- ◆ (3) Calcium-calmodulin complex binds to myosin light-chain kinase (a protein kinase) which activates the enzyme
- ◆ (4) Activated myosin light-chain kinase uses ATP to phosphorylate the myosin
- ◆ (5) Myosin cross-bridge binds to actin and goes through remainder of cross-bridge cycle (see skeletal muscle steps 5 to 8)

Contraction

- ◆ Smooth muscle has a low rate of ATP degradation, thus a low cycling rate and a slow contraction rate
- ◆ An overall low rate of ATP use contributes to lack of fatiguability in smooth muscle
- ◆ Isometric contraction of smooth muscle can be maintained with a very low rate of ATP use
- ◆ Smooth muscle relaxes when myosin is dephosphorylated
 - Dephosphorylation occurs at a slower rate than phosphorylation during contraction
 - When cytosolic calcium decreases, dephosphorylation exceeds the rate of phosphorylation and the muscle relaxes

Smooth Muscle Tension

- ◆ A length:tension relationship exists which is qualitatively similar to that of skeletal muscle
 - Range of muscle lengths over which smooth muscle can generate tension is greater
 - Hollow organs undergo changes in volume which also change the muscle length

Cytosolic Calcium

- ◆ In smooth muscle calcium enters the cytosol from both the SR and the extracellular fluid
 - Extracellular calcium enters through calcium channels
- ◆ The ratio of supply from these two sources depends on the type of smooth muscle
- ◆ There is no defined arrangement of the SR around the filaments and no T-tubules
- ◆ Calcium release is triggered by action potentials reaching SR located near the surface of the plasma membrane and by second messengers

Cytosolic Calcium

- ◆ Voltage-sensitive calcium channels in the plasma membrane open in response to an action potential and allow fast diffusion of ions
- ◆ Calcium is returned to the SR and the extracellular fluid by active transport
 - Active transport is much slower than in skeletal muscle, allowing single twitches to last for several seconds
- ◆ A single action potential does not activate all cross-bridges in smooth muscle
 - Allows tension to be graded by cytosolic calcium concentration and therefore the degree of electrical stimulation
- ◆ Some smooth muscle maintains a smooth muscle tone without external stimuli
 - Due to a normal cytosolic calcium concentration which maintains some cross-bridge activation

Membrane Activation

- ◆ Cytosolic calcium concentration is governed by a combination of mechanisms
 - Spontaneous electrical activity in the plasma membrane
 - Neurotransmitters of the autonomic nervous system
 - Hormones
 - Local changes in extracellular fluid composition
 - Stretch
- ◆ Not all smooth muscle membranes are capable of generating action potentials
- ◆ Graded membrane potentials, in addition to action potentials, can govern cytosolic calcium concentration
 - Graded potentials can increase or decrease calcium

Membrane Activation -- Spontaneous Electrical Activity

- ◆ Some smooth fibers generate action potentials in the absence of neural or hormonal input
- ◆ Membrane does not maintain a resting potential, but gradually depolarize until reaching a threshold and producing an action potential
 - Repolarization starts process again
- ◆ Potential change between the end of repolarization and the depolarization that reaches a threshold is termed the pacemaker potential

Membrane Activation - Nerves

- ◆ Autonomic nerve endings release neurotransmitters
- ◆ Smooth muscle does not have specialized motor end-plate regions
- ◆ Axons enter the region of smooth muscle fibers and branch, with each branch containing swollen varicosities
 - Neurotransmitters are released from vesicles in the varicosities in response to an action potential
- ◆ Varicosities from a single axon can be located along several muscle fibers
- ◆ A single muscle fiber can be located near varicosities belonging to both sympathetic and parasympathetic neurons

Membrane Activation - Nerves

- ◆ Some neurotransmitters cause depolarization of the membrane and increase in cytosolic calcium
- ◆ Some neurotransmitters cause hyperpolarization of the membrane and a decrease in cytosolic calcium, thus reducing contraction
- ◆ The type of response depends not only on the type of neurotransmitter, but also on the type of smooth muscle cell
 - Norepinephrine contracts muscle in blood vessels but inhibits the spontaneous activity of intestinal smooth muscle

Membrane Activation - Hormones

- ◆ Smooth muscle plasma membrane contains receptors for
- ◆ Membrane-bound hormones can open or close ion channels that change the membrane potential or release second messengers that affects release of SR calcium
 - Second messenger effects can occur without a change in membrane potential

Membrane Activation - Local Factors

- ◆ Local factors can affect cytosolic calcium concentration
 - paracrine agents
 - acidity
 - oxygen concentration
 - osmolarity
 - ion composition of fluid
- ◆ Stretching opens mechanosensitive ion channels in some smooth muscle
 - Leads to depolarization
 - Resulting contraction resists force of stretching

Types of Smooth Muscle

- ◆ Smooth muscles can be placed in one of two groups according to the excitability characteristics of the plasma membrane and the conduction of electrical activity between the muscle fibers
- ◆ Single-unit smooth muscles:
 - membranes propagate action potentials from cell to cell through gap junctions
 - may exhibit spontaneous action potentials
- ◆ Multi-unit smooth muscles:
 - little, if any, propagation of action potential from cell to cell
 - contraction dominated by neural stimulation

Single-Unit Smooth Muscle

- ◆ Include muscles of intestinal tract, uterus, and small diameter blood vessels
- ◆ Whole muscle responds to stimulation as a single unit
 - Gap junctions allow an action potential occurring in one cell to propagate to remaining cells of muscle
- ◆ Some of cells in muscle will act as pacemaker cells
- ◆ Regulation mechanisms often target pacemaker cells
- ◆ Contraction can often be induced by stretching the muscle
 - ie. uterine contraction is in response to the increase in volume of the hollow structure

Multi-Unit Smooth Muscle

- ◆ Include large airways of the lung, larger arteries, hair follicles of skin
- ◆ Each muscle fiber responds independently of its neighbors
- ◆ High levels of autonomic nerve stimulation
- ◆ Contractile response of whole muscle depends on number of fibers activated and the frequency of stimulation
- ◆ Stretch does not induce contraction
