Muscle physiology

I. Introduction.

A. Muscle types.

1. Skeletal muscle.

2. Smooth muscle.

3. Cardiac muscle.

B. Functional characteristics of muscle.

1. Excitability (irritability).

2. Contractility.

3. Extensibility.

4. Elasticity.

II. Skeletal muscle.

A. Gross anatomy: muscles as organs.

1. Connective tissue coverings.
- loose areolar connective tissue sheath surrounding each individual muscle fiber (cell), endomysium.
- several ensheathed muscle fibers grouped into fascicle by collagenic sheath, perimysium.
- several fascicles together with blood vessels and nerves wrapped by a fibrous connective tissue layer, epimysium.
- all these three CT sheaths are continuous with one another and often extend beyond the muscle itself forming a tendon or aponeurosis.

2. Muscle is richly vascularized, has extensive innervation; each individual muscle fiber is innervated by an axon terminal of a motor neuron; capillaries wrap themselves around individual muscle fibers.

3. Attachments
- muscles attached to bone at origin or insertion; attachments can be direct (epimysium/periosteum fusion) or indirect (through tendons).

B. Microscopic anatomy of a muscle fiber: the reductionist ladder.

- general characteristics: long, cylindrical, multinucleate, sarcolemma with a system of invaginations, well developed endoplasmic (sarcoplasmic) reticulum; however most visible structures are the myofibrils.

1. Myofibrils.
- rod-like, run length of cell, contractile elements of muscle fiber; composed of an orderly, repetitive arrangement of thick and thin filaments (myofilaments) that gives skeletal muscle its characteristic striated pattern.
- point where adjacent thin filaments attach to one another, Z-line; the area of myofibril between two adjacent Z-lines, sarcomere, the basic structural/functional unit of skeletal muscle, the contractile unit of skeletal muscle.
- the I-band is a light band, area of only thin filaments, bisected by Z-line, thus I-band involves two adjacent sarcomeres.
- the A-band, a dark band is an area that contains both thick and thin filaments.
- the H-zone is a lighter area in the center of the A-band, its is a central area that contains only thick filaments as opposed to the rest of A-band that contains both thick and thin filaments.
- M-line is a dense line that bisects the H-zone, represents a more dense part of the thick filaments.

2. Ultrastructure/molecular composition of myofilaments.

a. Thick filaments

- made up of myosin; myosin molecule has long tail, two globular heads.

- molecule made up of two heavy chains and four light chains; the light chains and the N-terminal portions of the heavy chains combine to form the globular heads; the shaft comprised of intertwined area of the heavy chains.

- N-terminus of each heavy chain contains an ATP binding site and an actin binding site

- high energy conformation vs. low energy conformation

- cocked head vs. uncocked head.

- each thick filament made up of several hundred myosin molecules, the tails forming the core of the filament and the globular heads (cross bridges) facing outward.

b. Thin filaments
- composed of actin, tropomyosin, troponin complex.

(i) actin: individual actin molecule is a globular protein, G-actin; has ATP binding site; binding of ATP by G-actin leads to polymerization -- the ATP is hydrolyzed, but ADP

held in the actin filaments; G-actin monomers polymerize to form a two stranded helix, F-actin; a molecule of F-actin forms the core of the thin filament, and the F-actin filament has sites on each subunit that can bind myosin (high affinity for myosin heavy chain).

(ii) actin binding proteins -- tropomyosin and troponins; each F-actin strand associated with two molecules of tropomyosin and several molecules of troponin.

- tropomyosin: a fibrous protein (long polypeptide chain), building blocks are dimers; tropomyosin chains cover the myosin binding sites on the F-actin strand.

- troponins: a complex of globular proteins attached to both the actin and tropomyosin molecules; TnI is inhibitory troponin and binds actin; TnT binds tropomyosin; TnC binds calcium ions if they are around.

- thus in resting state, TnC has no Ca++ bound to it; the tropomyosin molecules cover the myosin binding sites on the F-actin strand; when cell is stimulated, intracellular Ca++ increases dramatically, binds TnC; this changes conformation of Tn complex, which in turn causes the tropomyosin chains to slide into the groove between F-actin strands, uncovering the myosin binding sites on the F-actin strands.

3. Sarcotubular system: myofibers have two sets of intracellular tubules that participate in the regulation of muscle cell contraction.

a. transverse or T-tubules: invaginations of the sarcolemma, "winding holes through the cell", bring outside of the cell to the proximity of the contractile machinery of cell, lumen continuous with extracellular space; transverse cell at A-I band junction.

b. longitudinal tubules or L-tubules: the cell's sarcoplasmic reticulum; portions of L-tubule system of special interest are the terminal cisternae; these are expanded areas of the sarcoplasmic reticulum located at the junction of A-I bands, have ability to sequester Ca++.

- triad: complex of two terminal cisternae and a T-tubule

C. Contraction of a skeletal muscle fiber.

1. The sliding filament theory of muscle contraction (Huxley and Huxley, 1954).

- when a muscle contracts the individual sarcomeres shorten; hence myofibrils also shorten; however, none of the myofilaments change length, thin filaments simply slide past the thick filaments so that they overlap to a greater degree.
- H-zone disappears, I bands shorten, A-bands do not change length, move closer together.
- sliding of filaments caused by a series of attachment/detachment cycles of myosin heads on actin binding sites, myosin heads crawl along actin filament.
- recall that in the resting state, TnC has no Ca++ bound to it; the tropomyosin molecules cover the myosin binding sites on the F-actin strand; when cell is stimulated, intracellular Ca++ increases dramatically, binds TnC; this changes conformation of Tn complex, which in turn causes the tropomyosin chains to slide into the groove between F-actin strands, uncovering the myosin binding sites on the F-actin strands.
- myosin head (in high energy conformation, ADP and Pi bound to it) is strongly attracted to exposed binding sites on actin and crossbridge binding quickly occurs; this results in a conformational change in the myosin head, the head swivels, pulling on the actin filament, sliding past it -- the power stroke.
- as myosin head swivels, ADP/Pi released, exposing ATP binding site on the myosin head; ATP binding to head causes a conformational change in the head, and the crossbridge detaches from the actin binding site; this is quickly followed by ATP hydrolysis which generates ADP and Pi and provides energy required to restore myosin head to original high energy conformation, its cocked position.
- each myosin head attaches/detaches several times during a single contraction; only half of myosin heads of a thick filament exerting a pulling force at any given moment, the rest randomly seeking their next binding site.

2. Excitation-contraction coupling.
- a somatic motor neuron branches profusely into axon terminals, each axon terminal innervates a single muscle fiber; the junction between an axon terminal and a muscle fiber is the neuromuscular junction; really a modified synapse.
- the postsynaptic cell in this case is a muscle fiber, and the area of the muscle cell sarcolemma associated with the neuromuscular junction is called the motor end plate (MEP); the sarcolemma in the MEP area is highly folded which increases the surface area available for ACH receptors (these are linked to chemically-gated channels).
- action potential traveling down motor axon ultimately causes release of ACH as previously discussed; ACH binds receptors in motor end plate causing chemically-gated Na^+/K^+ channels to open (more Na^+ enters than K^+ leaves); Na+ enters cell causing a local, graded depolarization, a motor end plate potential (MEPP); if the MEPP is above threshold it causes opening of voltage-gated Na+ channels in area of the sarcolemma adjacent to the MEP, an action potential (AP) is generated - APs initiated on either side of the MEP.
- the AP is propagated along the sarcolemma in the same manner that it is propagated in an unmyelinated axon (a wave of depolarization followed by a wave of repolarization).

- AP moves into core of cell via T-tubules (invaginations of sarcolemma); voltage-gated Ca++ channels in the T-tubules serve as voltage sensor that detect AP and the trigger that unlocks release of Ca++ from the underlying terminal cisternae; Ca++ efflux from terminal cisternae occurs.
- the increase in intracellular Ca++ leads to events of muscle contraction (see above).
- immediately following its release there is quick reuptake of Ca++ by active transport into the SR -- tropomyosin blockage is restored -- contraction ends; muscle fiber relaxes.

KEY CONCEPTS:
- the sequence of events is repeated as long as there is stimulation at the neuromuscular junction and APs are generated; ACH is quickly destroyed, however, by acetylcholinesterase associated with sarcolemma -- thus the only way to produce impulses of long duration is through continued activity of motor neurons.

- also keep in mind that as in nerve cells, the sarcolemma must be repolarized before another AP is generated and conducted; that is, there is an absolute refractory period that must be honored, a time during which the cell is insensitive to stimulation; the duration of such a period ultimately determines the maximum frequency that a muscle cell can be stimulated at.

- furthermore, the all-or none law applies to electrical activity and contraction in a muscle fiber; that is, an AP is always generated in response to adequate stimulation, and that always results in maximal contraction of the muscle fiber for the physiological conditions existing at the time.

D. Contraction of a skeletal muscle.

1. Motor unit.
- in order to understand contraction of a skeletal muscle, you must first be introduced to the pattern of innervation of a skeletal muscle.
- muscles are innervated by motor neurons; the axon of each motor neuron branches profusely, each axon terminal innervating a single muscle fiber (conversely, each muscle fiber is only innervated by a single axon terminal).
- a motor axon and all the muscle fibers that it innervates is called a motor unit; all fibers within a motor unit have the same threshold, when one fiber contracts, all contract and do so maximally; that is, the all-or-none law applies to motor units.
- small motor units have few muscle fibers (5-10) innervated by a motor axon; they are found in muscles for fine control; these motor units tend to have low thresholds.
- large motor units have many (hundreds) muscle fibers innervated by a motor axon; they are found in postural and weight-bearing muscles; these motor units tend to have relatively high thresholds of activation.
- thus, at this point you should realize that different motor units have different thresholds (even those within the same muscle), but that all fibers within a motor unit have the same threshold.

2. The muscle twitch: response of a muscle to a single, brief, threshold stimulus - a recording of contractile activity of muscle.
- has three phases:

a. Latent period: time between stimulus application and onset of contraction; reflects events of excitation-contraction coupling.

b. Period of contraction: time from the onset of shortening to peak of tension development (10-100 ms); cross bridges are active, tension rising to a peak.

c. Period of relaxation: muscle tension gradually decreases to baseline; initiated by Ca++ reentry into the SR; crossbridges no longer active.

3. Graded muscle responses.

a. Graded contractions can occur in skeletal muscles by changing the number of motor units activated.

- subthreshold stimulates -- no twitch.

- threshold stimulus -- only motor unit(s) with the lowest threshold respond.

- as stimulus intensity is increased, the force of the contraction also increases: that is, as the stimulus intensity is increased, motor units with higher thresholds are activated -- recruitment of motor units of higher threshold, strength of contraction increases.

- eventually get a maximal contraction regardless of how strong the stimulus is --all motor units in the muscle are contracting.

- this may at first hand appear to violate the all-or-none law; however, each motor unit is contracting maximally for physiological conditions existing at the time; by recruiting motor units more fibers are contracting at a given time, and the contraction is stronger.

- in the body muscle contraction is achieved by asynchronous activation of motor units -- as some motor units within a muscle are contracting, some are relaxing, but the overall tension generated by the whole muscle remains fairly constant; this system allows for smooth, sustained contractions.

b. Graded contractions can occur in skeletal muscles by changing the speed of stimulation of the muscle.

- to illustrate this phenomenon we will assume a maximal strength stimulus = all motor units are recruited.

- single stimulus application results in one twitch.

- with increased frequency of stimulus application a second contraction is induced before the muscle has completely relaxed after the first contraction.

- the muscle is already partially contracted; more calcium ions are released as a result of the second excitation, more tension produced during the second contraction, therefore more shortening of the muscle, and the contractions sum together -- twitch fusion or wave summation; in other words a second contraction is superimposed on the first, adding to the tension already generated by the first one.

- again this may at first hand appear to violate the all-or-none law; however the physiological conditions have changed, i.e., more calcium is available, hence physiological conditions changed -- the response is still maximal for the physiological conditions now existing.

- if the stimulus is held constant and the frequency of stimulation is increased, relaxation time between twitches is shorter, calcium ion concentration increases, the degree of summation is greater, evidence of relaxation disappears and the individual contractions fuse into a smooth sustained contraction, tetanus.

- note that tetanus reflects the usual manner of muscle contraction in vivo: motor neurons deliver volley of impulses to motor units and one single tetanizing contraction develops rather than a barrage of individual twitches.

4. Treppe: stair case effect.
- stimulate a muscle with one submaximal stimulus a few times (allow full twitch); repeat the process and note that the later contractions have a greater amplitude than earlier ones (stair case).
- this reflects the increased availability of calcium ions, a warming up of the whole muscle contractile machinery.

5. Muscle tone.
- muscle tone is produced by tonic (basal) firing of the gamma-efferent motor neurons innervating the contractile portions of intrafusal fibers in the muscle spindles; this causes basal stimulation of the muscle spindles which in turn leads to basal reflex contraction of surrounding extrafusal muscle fibers -- muscle tone.

6. Isotonic/isometric contractions.
- contraction: the active process of generating a force within a muscle by crossbridge activity.
- the force exerted by muscle on an object is called muscle tension.
- the weight or force exerted by an object on a muscle is called load.

a. Isotonic contraction: muscle changes length and tension remains constant throughout most of the contractile process.

(i) concentric: muscle shortens and does work - lift a book.

(ii) eccentric - muscle contracts as it lengthens - action in calf as one walks up steep hill.

b. Isometric contraction: tension continues to increase but the muscle doesn't shorten or lengthen.
- occurs in muscles that act to maintain posture, stabilize joints, etc., or when load > tension.
-note that most movements involve coordinated activity of many muscles undergoing both isometric and isotonic contractions.

7. Muscle metabolism.

a. resting muscle:

- predominant fuel source are fatty acids and ketone bodies; these are oxidized aerobically (Krebs, ETC) to produce large amounts of ATP.

- ATP destiny: to energize non-contractile needs of muscle cell; excess ATP used to produce creatine phosphate (CP), a high energy storage molecule.

b. contracting muscle:

NOTE: ATP is the only energy source that can be directly used to power contraction.

- at first stored ATP can be used to power contraction (4-6 seconds); then cell digs into CP stores -- CP and ADP combine to transfer a phosphate group and produce ATP (creatine also regenerated); this ATP then used to power further contractile activity for an additional 10 - 15 seconds; so, after this point muscle has exhausted all direct and indirect ATP stores and must begin producing ATP from scratch.

- the fuel source shifts to glucose, either that delivered by circulation or glucose derived from glycogen breakdown.

- if exercise is light and oxygen supply is adequate, glucose is channeled into glycolysis, to Krebs, and to the electron transport chain, the aerobic pathway (very efficient, 36-38 ATP generated per glucose molecule; fueled in this manner, contractile activity can be sustained for many hours.

- if exercise is heavy, however, oxygen cannot be delivered to muscles at fast enough a rate to sustain the level of activity; furthermore the aerobic pathway is slow (despite its high efficiency) and cannot provide the muscle with ATP at the rate it needs to sustain that level of contraction; thus glucose is channeled into the anaerobic pathway, glycolysis, lactic acid formation; since ATP yield per molecule of glucose is much lower, the strenuous activity level can only be maintained for a couple of minutes on average; however, this pathways is much faster and ATP is supplied at a rate that can sustain the high level of activity for its limited duration.

- aerobic endurance: the length of time a muscle can continue to contract using aerobic pathways for ATP production.

- anaerobic threshold: the point at which muscle metabolism converts over to anaerobic glycolysis.

8. Muscle fatigue.
- state of physiological inability to contract; results from relative ATP deficit; do not confuse with psychological fatigue.

9. Heat production.
- only 20-25% of energy released during muscle contraction (ATP hydrolysis) is actually converted to work; the rest is dissipated as heat.

F. Force, velocity, duration of muscle contraction.

1. Factors affecting force of contraction.

a. Number of muscle fibers contracting: the more motor units are recruited, more fibers contract, the greater the strength of contraction.

b. Relative size of muscle: the bulkier the muscle (has more contractile proteins), the more tension it can develop; regular isometric exercise increases muscle strength and causes muscle cells to hypertrophy.

c. The series-elastic elements: in order to do work the muscle must be attached to other movable structures and its connective tissue coverings must be pulled taut; the tension generated by cross bridges transmitted to surface of muscle cell, and then through connective tissue coverings to the load -- then movement occurs.

- all non-contractile structures of a muscle are known as the series-elastic elements (SEE) which are able to stretch and recoil.

- the force, internal tension, generated by the contractile elements (myofibrils) stretches the SEE; these transfer their tension, external tension, to the load.

- during a single muscle twitch, it takes time to take up slack of SEE, by the time this happens internal tension already begins to decline; therefore, in twitch contractions, external tension exerted on load always less than internal tension.

- in tetanic contractions there is more time available to stretch SEE, external tension approaches that generated by cross bridges (internal tension).

d. The degree of muscle stretch: the optimum length for muscle fibers is the length at which they can generate maximum force.

- in an ideal length-tension relationship the muscle is slightly stretched allowing the actin/myosin filaments to barely overlap which permits sliding along the entire length of thin filaments

- if sarcomere is too compressed there is not much more room for shortening to occur, not mush tension can be generated.

- if sarcomere is too stretched, thick and thin filaments do not overlap, no sliding and thus no tension can be generated.

2. Factors influencing velocity of muscle contraction.

a. Load.

- muscle contracts fastest when no load is applied.

- the greater the load, the longer the latent period, the slower the contraction, and the shorter the duration of the contraction.

b. Muscle fiber type: there are three types of skeletal muscle fibers, based on differences in size, speed and endurance.

(i) red slow twitch fibers:

- myoglobin binds oxygen which helps increase the rate of oxygen diffusion throughout the muscle cell; thus are oxygen dependant (oxidative fibers); have high endurance, however are thin fibers that do not generate much power.

(ii) White fast twitch fibers:

- glycolytic fibers depend on anaerobic pathway to generate ATP during a contraction; since glycogen reserves are limited quick exhaustion results, fatigue rapidly; yet they are large fibers, can generate extensive power.

(iii) Intermediate fibers:

- characteristics intermediate to the previous two classes.

- most muscles have a mixture of these three fiber types which gives them a good range of contractile speed and fatigue resistance