Lecture: Muscle Physiology

I. Anatomy of Skeletal Muscle CELL (Muscle Fiber)

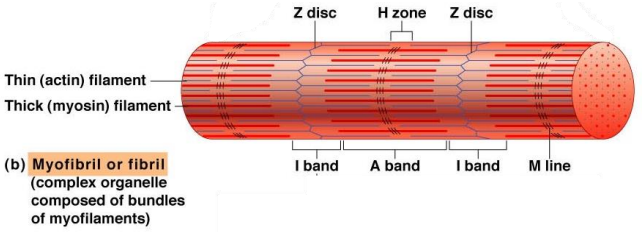
A. General Features

1. multinucleated cells (syncytium: from fusion)
2. sarcolemma - special name for plasma membrane
3. very long compared to other cells (1 - 300 mm)
4. not unusually wide diameter (10 - 100 microns)
5. sarcoplasm - rich in glycogen and myoglobin
6. myoglobin - stores oxygen; similar to hemoglobin
7. special structures: myofibrils and sarcoplasmic reticulum

B. Ultrastructure of Myofibrils

1. muscle cell contains many parallel myofibrils
2. myofibrils have DARK bands (A bands) and LIGHT bands (I bands) that cause "striated" appearance of muscle
3. A band and I band result from the arrangement of overlapping and non-overlapping regions of two types of myofilaments
   a. thick filaments (myosin)
   b. thin filaments (actin)
4. sarcomere - smallest contractile unit of muscle cell
   a. Z-line - connection of actin filaments; dividing line between two adjacent sarcomeres
   b. M-line - connection of myosin filaments
   c. H-zone - non-overlapping region of the myosin filaments around the M-line
   d. A-band - length of myosin filaments
   e. I-band - length of non-overlapping actin filaments

Each muscle cell (fiber) is composed of many myofibrils. Each myofibril contains hundred of accordion-like sarcomeres laid end-to-end. Muscle contraction occurs when the sarcomeres contract by the sliding motion of actin and myosin filaments.



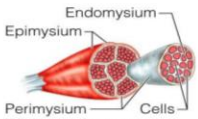
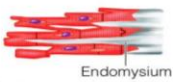
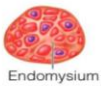
C. Molecular Structure of Actin & Myosin Filaments

1. thick filaments (myosin filaments) 12-16 nm
a. composed of about 200 myosin proteins
i. myosin has a golf club like shape
ii. 2 heads (cross bridges) - can bind to the actin filaments and use ATP
iii. tail - shaft of the thick filament
2. thin filaments (actin filaments) 5-7 nm
a. 2 helical chains of F actin (G actin subunits)
I. G actin can bind with myosin heads
ii. tropomyosin - rod-like protein that helps to stiffen F actin structure
iii. troponin - globular protein that can bind Ca^{++} to regulate actin/myosin binding

D. Sarcoplasmic Reticulum and T Tubules

1. sarcoplasmic reticulum - smooth ER that houses Ca^{++}
a. surrounds each myofibril
b. fused to each other at H zones and A/I bands
c. terminal cisternae - around A/I bands
2. T (transverse) Tubules - passageways from extracellular space to the terminal cisternae of SR
a. passage of nerve message directly to SR
b. passage of glucose, oxygen, salts to fiber

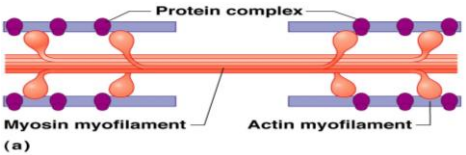
TABLE 6.1 Comparison of Skeletal, Cardiac, and Smooth Muscles *(continued)*

Characteristic	Skeletal	Cardiac	Smooth
Connective tissue components	Epimysium, perimysium, and endomysium 	Endomysium attached to the fibrous skeleton of the heart 	Endomysium 
Regulation of contraction	Voluntary; via nervous system controls	Involuntary; the heart has a pacemaker; also nervous system controls; hormones	Involuntary; nervous system controls; hormones, chemicals, stretch
Speed of contraction	Slow to fast	Slow	Very slow
Rhythmic contraction	No 	Yes 	Yes, in some 

II. Contraction of Skeletal Muscle Cell

A. Sliding Filament Model (Actin/Myosin Sliding Mechanism)

1. Ca^{++} released from sarcoplasmic reticulum
2. Ca^{++} binds to TnC region of Troponin
3. Troponin changes shape, moving Tropomyosin, exposing binding site on actin filament
4. Attachment - myosin head with ADP + P_i binds actin
5. Power Stroke - myosin head bends, pulling along the actin filament, ADP + P_i are released
6. Detachment - ATP binds to the myosin head, causing detachment from Actin
7. Re-cocking the Head - hydrolysis of ATP → ADP + P releases energy to re-cock the myosin
8. some myosin heads are in contact with actin at all times, allowing "walking motion" to occur
9. 1 cycle = 1 % muscle contraction
10. motion continues until no more ATP is present or Ca^{++} levels drop by re-uptake into SR
11. rigor mortis - muscles stiffen because Myosin heads remain attached to the Actin filaments



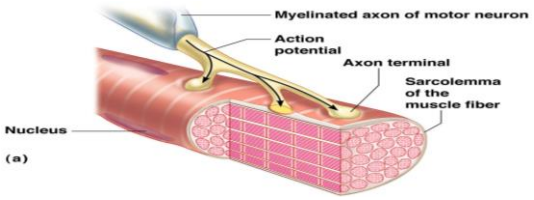
In a relaxed muscle cell, the regulatory proteins forming part of the actin myofilaments prevent myosin binding (see a). When an action potential sweeps along its sarcolemma and a muscle cell is excited, calcium ions (Ca^{2+}) are released from intracellular storage areas (the sacs of the sarcoplasmic reticulum).

III. Regulation of Contraction of a Single Skeletal Muscle Cell

A. Neuromuscular Junction (nmj)

1. neuromuscular junction - nerve/muscle intersection
   a. 1 motor neuron/axon supplies several fibers
   b. 1 centrally located junction per fiber
   c. synaptic vesicles - sacs that contain acetylcholine (ACh-neurotransmitter)
   d. synaptic cleft - space between the axon terminal and the sarcolemma of the muscle cell

e. motor end plate - highly folded part of sarcolemma beneath the synaptic cleft; rich in ACh receptors



B. Signal Transmission and Electrical Excitation of Muscle

1. Nerve Signal Causes Release of ACh from Axon End
   a. action potential along axon causes depolarization of axon terminal
   b. decreased membrane potential causes Voltage-Dependent Ca^{++} Channels on axon terminal to open
   c. Ca^{++} influx into axon terminal causes exocytosis of ACh containing synaptic vesicles
   d. ACh diffuses across the synaptic cleft to bind to ACh receptors of the motor end plate

2. Electrical Excitation of the Sarcolemma
   I. Like most cell membranes, the sarcolemma of muscle cells is polarized: it has more negative charge inside than outside.
   II. ACh triggers an Electrical Excitation of the sarcolemma by opening chemically gated Na^+ Channels, allowing positive charge to rush into the cell. The muscle cell becomes less negative or becomes depolarized.
      a. ACh binds to ACh Receptors which open ACh-Dependent Na+ Channels
      b. these Na^+ Channels allow Na^+ to flow into the muscle cell, causing depolarization
      c. depolarization at the neuromuscular junctions spreads to adjacent sites
      d. Vo1tage-Dependent Na^+ Channels at the adjacent sites open, allowing more Na^+ in
      e. A wave of depolarization therefore spreads across the entire cell
      f. this cannot be stopped and is called an all-or-none response
      g. entire process occurs in about 1 millisecond (1/1000 second)

      h. A refractory period occurs in which the muscle cell must

repolarize to its resting state.

This happens when the Voltage-Dependent Na^+ Channels close, Voltage-Dependent
K^+ Channels open, and the Na^+-K^+ ATPase pump rebalances the ion concentrations.
Repolarization generally takes very little time (3 milliseconds), while contraction can last
up to 100 milliseconds (1/10 sec). Limits how fast the cell can "re-fire" and contract!

3. Importance of Acetylcholine and Neuromuscular Junction
   a. After binding to ACh Receptors on sarcolemma, ACh is quickly broken down by an enzyme known as Acetylcholinesterase (AChE)
   b. myasthenia gravis - autoimmune disease where immune system attacks ACh Receptors
   c. ACh Antagonists - chemicals that block an ACh receptor
      i. snake venoms - curare and other venoms
4. Coupling of Excitation and Contraction
   a. latent period - time between excitation & contraction
      i. action potential passes down the T Tubules from the sarcolemma surface
      ii. T Tubule depolarization causes the release of Ca^{++} from the sarcoplasmic reticulum
      iii. Ca^{++} increase causes uncoupling of Troponin and sliding of filaments described above
      iv. ATP-Dependent Ca^{++} Pumps pump the Ca^{++} back into the sarcoplasmic reticulum
      v. Low Ca^{++} levels allows Troponin/Tropomyosin blockade of actin and muscle relaxes
   b. Calcium Sequesters - bind Ca^{++} in the cell so it will not form Calcium Phosphate crystals
      i. calmodulin and calsequestrin

REMEMBER: A Skeletal Muscle CELL (Fiber) will contract in an All-or-None fashion when ITS motor neuron stimulates it to fire by releasing ACh!!!!!!!!!!

IV. Contraction of a Skeletal MUSCLE

A. Motor Unit - a single motor neuron and all of the muscle cells stimulated by it

1. # muscle cells per motor neuron = 4 - 400
   i. muscles of fine control (fingers, eyes and face): fewer muscle cells per neuron
   ii. muscles of posture and gross movement (gluteus maximus): more muscle cells per neuron
2. axon terminals are distributed on muscle fibers throughout the muscle (not one region)

i. stimulation of one motor unit causes weak contraction throughout the whole muscle

B. Muscle Twitch - the response of a muscle to a single short electrical stimulus

1. strong twitch - many motor units activated; weak twitch - few motor units are activated
2. latent period (3 ms) - time after stimulation for coupling to occur and contraction to start
3. contraction period (10 - 100 ms) - from beginning of contraction to maximum force (tension)
4. relaxation period (10 - 100 ms) - time from maximum force to original relaxed state

C. Graded Muscle Responses (smooth, not All-or-None)

1. Frequency of Stimulation (Wave Summation) - a motor unit may be stimulated over and over again so no relaxation period is possible
   i. frequency of stimulation cannot be greater than 1 every 3 ms (REFRACTORY PERIOD)
   ii. motor neurons generally deliver action potentials in volleys with varying frequency
   iii. tetanus - smooth muscle contraction that occurs when summation is so great that the relaxation period disappears
2. Summation of Multiple Motor Units - as strength of stimulus is increased, more and more motor units are activated in the muscle itself
   i. threshold stimulus - level of stimulus at which first motor units are activated
   ii. maximal stimulus - level of stimulus at which all motor units of a

muscle are activated

Muscles of the hand show summation of motor units well. When weak force and delicate motion is needed, few motor units are activated (those with the least # muscle fibers per motor unit). However, when great force is needed, the strength of the stimulus is increased to recruit more motor units (with many muscle fibers per motor unit).

3. Asynchronous Motor Unit Summation - motor units activated in different cycles "average out to produce a smooth muscle contraction

D. Treppe: The Staircase Effect - When a muscle is first used, it will show a gradual increase in force with a maximal stimulus until it is 'warmed up".

E. Muscle Tone - slightly contracted state of muscle that is maintained by reflexes originating in the spinal cord. Maintains posture and readiness for active contraction.

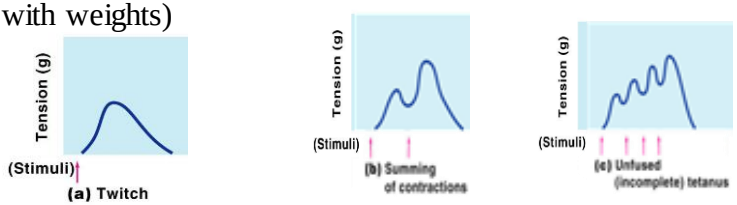
F. Isometric and Isotonic Contractions

a. muscle tension - force generated by a muscle

b. load - force resisting movement of a muscle.
Muscle tension must be greater than load to move it.

c. isometric contraction - muscle doesn't change length (trying to lift a box that is too heavy)

d. isotonic contraction - muscle moves the load (doing bicep curls with weights)



V Force, Velocity, and Duration of Skeletal Muscle Contraction

A. Force of Contraction - determined by several factors

1. number of motor units activated
2. size of muscle (in cross section)
   a. size increased by increasing the SIZE of individual muscle cells (not increasing cell #)
3. Series-Elastic Elements
   a. sheath around the muscle and the connective tissue tendons that attach muscle to bone
   b. "stretching" of non-contractile parts allows time for muscle to produce a tetanic contraction

4. Degree of Muscle Stretch (Actin-Myosin Overlap)
   a. optimal force can be generated when muscle is between 80 - 120% of resting length

B. Velocity and Duration of Contraction
   1. Effect of the Load on a Muscle
      a. smaller the load, faster the contraction
      b. larger load: slower contraction/less duration
   2. Type of Muscle Fiber

      a. Red Slow-Twitch Fibers (small, red)
         i. slow twitch; slow acting myosin ATPases
         ii lots of myoglobin (red) to store oxygen
         iii. many mitochondria, active enzymes
         iv. use fat as primary fuel source
         v. very aerobic, long duration contraction
      b. White Fast-Twitch Fibers (large, pale)
         i. fast twitch; fast acting myosin ATPases
         ii. few mitochondria, primarily anaerobic
         iii. glycogen stores used for anaerobic resp.
         iv. lactic acid produced, fatigues quickly
         V. rapid, intense, short duration contraction
      c. Intermediate Fast-Twitch Fibers (medium, pink)
         i. fast twitch; fast acting myosin ATPases
         ii. aerobic with myoglobin present
         iii. somewhat resistant to fatigue
   3. Muscle Composition by Fiber Type
      a. most muscles have combinations of all 3 types
      b. people differences are genetically determined

VI. Effect of Exercise (and no exercise) on Skeletal Muscle

A. Physiological Adaptations from Exercise
1. aerobic exercise - that requiring steady oxygen

   a. capillaries, myoglobin, mitochondria increase
   b. better endurance and strength

2. resistance exercise - short duration, high load

a. actin, myosin, myofibers all increase
b. hypertrophy - increase in muscle size
b. glycogen stores and connective tissue increase

B Disuse Atrophy

1. lack of use can result in loss of size (atrophy) and strength of a muscle
2. denervation - lack of nervous stimulation can also cause severe atrophy

VII. Muscle Metabolism

A. Pathways for Synthesis of ATP for Contraction

1. ADP - Creatine Phosphate (Immediate Reserve)

Creatine-phosphate + ADP → Creatine + ATP
(Creatine Kinase)

a. used for first 3 - 5 seconds of activity while respiration processes are warming up

2. Anaerobic Respiration (Lactic Acid Fermentation) (Insufficent Oxygen Supply)

glycolyis glucose → pyruvic acid (INSUFFICIENT oxygen)
pyruvic acid → lactic acid

** used for short-term, intense activity (10 - 15 sec)
** used when oxygen demand CANNOT be met by resp/circ
** yields only 2 ATP per glucose
** lactic acid is reconverted to pyruvic acid when oxygen becomes available
** pyruvic acid then broken down all the way to $C0_2$ to release 34 more ATP

3. Aerobic Respiration (Sufficient Oxygen Supply)

glycolyis glucose → pyruvic acid (SUFFICIENT oxygen)
pyruvic acid → $H_20 + C0_2$

** used for more prolonged, steady activity (walking)
** used when oxygen demand CAN be met by resp/circ
** yields 36-38 ATP per glucose (18-19 X anaerobic!!!)
** glycolysis occurs in the sarcoplasm
** oxidative reactions, using pyruvic acid to make more ATP, occurs in the mitochondria

B. Muscle Fatigue, Oxygen Debt, and Heat Production

1 muscle fatigue - inability of a muscle to contract on a physiological basis

a. when there is less ATP than the muscle requires
b. lactic acid decreases pH, affects enzymes
c. salt loss (Na^+, K^+, Ca^{++}); ionic imbalance
d. ATP required to drive Na^+-K^+ ATPase Pump

2. contractures - continuous contracted state of the muscle ("heads" are not released)

3. oxygen debt - oxygen must be "paid back" in order to restore muscle to original rested state:

a. restore reserves of ATP and Creatine Phosphate
b. lactic acid converted back to pyruvic acid
c. restore reserves of glucose and glycogen
d. restore oxygen reserves (stored in myoglobin)
e. athletic conditioning increases the efficiency of oxygen use, thereby reducing oxygen debt

4. heat production - muscle contraction produces heat which can be dangerous (extreme body temperature) or can be useful (generate heat by shivering)