Physiology of muscle

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Muscles are classified according to morphological and functional bases into:

1- Skeletal muscles:

- attached to bones and moves skeleton
- Also called striated muscle (because of its appearance under the microscope, as shown in the photo to the left)
- Voluntary muscle

2- Smooth muscles:

- Involuntary muscle
- Muscle of the viscera (e.g., in walls of blood vessels, intestine, & other 'hollow' structures and organs in the body)

3- Cardiacmuscles:

- Muscle of the heart
- Involuntary

Approximately 40% of the body is skeletal m. and almost another 10% is smooth and cardiac ms.

Skeletal muscles (attached to skeleton)

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Morphology:

The skeletal muscle is made up of individual muscle fibers that bundled together by connective tissue.

Muscle fibers:

They are cylindrical, elongated multinucleated cells. Each muscle fiber is a single cell that is enveloped by glycoprotien sheath “Sarcolemma” which present outside the plasma membrane of the cell. The sarcolemma has holes that lead into transverse tubules known as "T-tubules".

Myofibril:

Each muscle fiber is made up of many parallel myofibrils that are embeded in its cytoplasm “sarcoplasm”. They are threadlike structures that contain the contractile protien filaments including; thick filaments “myosin protien” and thin filament

“primarily actin protien”. In additiion, there are two additional protiens located on the actin molecule “troponin and tropomyosin”. They regulate muscular contraction by controlling the interaction of actin and myosin.

They are classified into functional units known as “sarcomeres” or myofilaments by means of transverse protien sheath known as “Z lines”. Thick filaments are arrenged in the middle of each sarcomere while, the thin filaments are attached from one end to Z line and the other end overlaps a part of the thick filament.
N.B: There are projections that arrise from the thick filament and extend toward the thin filament.

Myofibrils are striated, due to the presence of alternating

a- Dark band (A band A): they are dark areas in the center of the sarcomeres that contain thick filaments. The thick and thin filaments overlap to some extent in the A band. In the center of A band there is a less refractile region called H-zone “it is the area of A band without any thin filament”.

b- Light band (I band): they are on either sides of Z lines.

N.B. The region between two successive Z- disks is called **Sarcomer (one A band + 2 halves of I band on either side of the Z disk).**

Tubular system:

Two tubular networks are present in:

(I) Transverse (T) tubule:

- Very small tubules, run transverse to the myofibril.
- Invagination of the surface muscle membrane at the junction of the A and I band.
- contains extracellular fluid.
- Functions:1- conduct AP to sarcoplasmic reticulum.
  2- contains voltage-sensitive dihydropyridine **(DHP)** receptors that opens the ryanodine Ca^{++} release channel.

(II) Sarcoplasmic reticulum (SR) = endoplasmic reticulum of mf

- Long, longitudinal tubules that run parallel to the myofibrils
- Ends of SR expands to form **terminal cisrenae (TC)** thatmake contact with T tubules on either sides of sarcomer (at the junction `between A and I bands).

- **Foot process:** small projection separate the two tubular membranes (TC and T tubules).

- Functions: 1- has a high conc of Ca^{++} initiate muscle contraction.

2- Foot processes contain ryanodine receptors (ryanodine ca^{++} release channels).

N.B: Fine (thin) myofilaments:

Extends from Z disk (in both direction) toward the middle of dark band

- Where it interdigitate with the coarse filament.
- Not meet at the middle

Muscle proteins:

(A) Thick filament Myosin:

- About 300 myosin molecules coalesce to form the myosin thick filament.
- The myosin molecule consists of 2 heavy chains and 4 light chains.
- The two heavy chains coil around each other forming helix. The terminal portions of heavy chains together with the 4 light chains combine to form 2 globular heads.
- The heads contain an actin binding site, ATP-binding site and catalytic site that hydrolyses ATP. The protruding arms with their heads are called **cross bridges**

(B) Thin filament potein:

1- Actin protein: (300-400 actin molecules/ filament)

- shape:

two chains (of globular-shaped actin molecules) twisted to form a helix.

- function:

each actin molecule has a specific site (active site) with which the cross bridge combine during muscular contraction.

2- Tropomyosin: (40- 60 molecules/ filament)

- shape:

long filamentous protein.

- lies in the grooves between the two chains of actin.
- function:

cover the active sites on the actin during rest.

3- Troponin:

- located at intervals along tropomyosin molecule.

- Each molecule is formed of 3 globular protein molecules:

1- Troponin I:

- has strong affinity for actin--- inhibit its interaction with myocin.

2- Troponin T:

- has strong affinity for tropomyocin.

3- Troponin C:

- has strong affinity to bind Ca^{++} $\rightarrow$ initiate contraction.

(C) ∝- Actinin:

This is a muscle protein that binds actin to Z lines.

Neuromuscular junction
(motor End-Plate)

Skeletal muscle fibers contract only under the control of the nervous system. Communication between the nervous system and a skeletal muscle fiber occurs at a specialized intercellular connection known as a neuromuscular junction (NMJ), or myoneural junction.

Each skeletal muscle fiber is controlled by a neuron at a single neuromuscular junction. A single axon branches within the perimysium to form a number of fine branches. Each branch ends at an expanded **synaptic terminal.** The cytoplasm of the synaptic terminal contains mitochondria and vesicles filled with molecules of **acetylcholine** "**ACh**" which is a neurotransmitter "a chemical released by a neuron to change the membrane properties of another cell".

The synaptic cleft: a narrow space separates the synaptic terminal of the neuron from the opposing sarcolemmal surface. It is occupied by connective tissue (basal lamina) to which acetylcholinesterase (ACHEase) is bound and extracellular fluid.

Motor end plate (MEP): sarcolemma opposite to the end feet is thickened and exhibits numerous invagination (junctional folds) that contain receptors for acetyl choline (Ach).

Sequence of events during neuro muscular transmission:

1- Release of AcH (presynaptic response):

When AP is propagated in the nerve ending that increases the membrane permeability to Ca2+ through opening of voltage-gated Ca channels. Ca^{++} moves from ECF into end feet and triggers marked increase in exocytosis of acetylcholine – containing vesicles that is followed by rupture and release of their content into synaptic cleft.

2- Postsynaptic response:

The released Ach binds to Ach receptors on the junctional folds (MEP) of sarcolemma which undergo confirmatory changes that by opening the channel gates (present in the receptors) to increase permeability to Na^+ and K^+. However, Na^+ entery (influx) exceds K^+ leaving (outflux) = depolarization (End-plate potential = EPP).

N.B: later in time, new vesicles are formed from invagination of presynaptic membrane and then refilled with Ach.

3- EPP depolarizes the m membrane to threshold:

Epp is graded, non propagated and act as a stimulus that depolarizes the adjacent muscle membrane to its firing level. EPP generated are conducted away (from the end-plate) in both direction along the muscle fiber and initiate muscle contraction

4- Rapid degradation of Ach:

Even before the action potential has spread across the entire membrane, the ACh has been broken down by Ach estrase. The sodium channels close, and the field is cleared for the arrival of another nerve impulse. Degradation of Ach is important to prevent multiple m contraction. The resting potential of the fiber is restored by an outflow of potassium ions. The brief (1–2 msec) period needed to restore the resting potential is called the **refractory period**.

This sequence of events can now be repeated if another action potential arrives at the synaptic terminal

Miniature EPP:

During rest: few Ach vesicles rupture spontaneously and release their Ach content that leads to production of a minute depolarization at the motor end-plate.

Properties of neuromuscular transmission:

1- Unidirectional:

occurs only in one direction; from nerve to muscle.

2- There is a delay of about 0.5msec:

It is the time needed for release of Ach, change in permeability of muscle fiber membrane, Na+ influx and building up of depolarization to firing level.

3- Easily fatigued:

repeated stimulation leads to exhaustion of Ach.

4- Effect of ions:

- **$Ca^{++}\rightarrow\uparrow$** rupture of Ach vesicles
- **$Mg^{++}\rightarrow\downarrow$** rupture of Ach vesicles
- **$K^{+}\rightarrow$** anti-curare action on MEP

5- Effect of drugs:

-**Agonistic drugs:**

a- Ach like action: Small dose of nicotine, Methacholine and Carbachol.

b- Anticholine esterase: Neostigmine and Physostigmine.

-Antagonistic drugs:

Compete with Ach for its receptors on end plate and so inhibit Ach action such as curare and flaxedil.

Changes occur following skeletal muscle stimulation

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1- Electrical changes
2- Excitability changes.
3- Mechanical changes.
4- Metabolic changes.
5- Heat changes.

I) Electrical changes:

	Large nerve fiber	Skeletal m
RMP (polarised):	-90 mV	-90mV
Duration of AP:	2 msec	2-4 msec
Velocity of conduction of AP:	20 m/ sec	5 m/sec
AP preceeds contraction by about:	--------	2 msec

N.B: Electrical events in sk m. are similar to those in nerves.

II) Exitability changes:

(A) ARP:	(B) RRP:
(C) Supernormal phase:	(D) Subnormal phase:

III) Mechanical changes:

= Contractile process = Molecular mechanism of muscle contraction

= Excitation-contraction (EC) coupling

= Process by which AP initiates process of contraction. It involves 4 steps:

1- Release of Ca^{++}:

During rest Ca^{++} is present in high concentration in SR. The impulse travels along the sarcolemma and down the T-Tubules. From the T- Tubules, the impulse passes to the sarcoplasmic reticulum into the terminal cisternae to open Ca^{++} channels and flow of Ca^{++} out of TC into cytoplasm.

2- Activation of muscle protein:

Calcium fills the binding sites in the troponin molecules. This alters the shape and position of the troponin which in turn causes movement of the attached tropomyosin molecule. Movement of tropomyosin permits the myosin head to contact with actin.

3- Generation of tension.

Tension is the force developed when a muscle contract.

First step: Binding of cross bridge with active site (receptor) on actin. This occurs spontaneously after binding of calcium with troponin and movement of tropomyosin away from actin active sites.

Second step: Bending of the cross bridge that will pull the actin thin filament over the thick filament.

N.B: Energy used in this step is derived from ATP. Both ATP and its hydrolyzing enzyme A TPase are attached to the cross- bridges

Third step (detachement):

detachment of cross bridge from thin filament. ATP fits into the binding site on the cross-bridge and this breaks the bond between the cross-bridge (myosin) and actin. The myosin head then swivels back. As it swivels back, the ATP breaks down to ADP & P and the cross-bridge again binds to an actin molecule.

Fourth step: cross bridge returns to its original upright position. Then, another cycle starts and so on.

This process is accompanied by shortening of sarcomer:

- Z lines close to each other.
- narrowing of H zone and light band.
- Dark band length does not change

4- Relaxation: (active process)

Ca^{++} is removed from cytoplasm by Ca^{++} pump at SR that decreases intracellular Ca^{++} conc and troponin returns to its original state. Tropomyocin moves back to cover the actin binding site.

Once the contraction has ended, the sarcomere does not automatically return to its original length. Sarcomeres shorten actively, but there is no active mechanism for reversing the process. External forces must act on the contracted muscle fiber to stretch the myofibrils and sarcomeres to their original dimensions.

All or Non law:

Skeletal muscle fiber contracts maximally or does not contract at all.

- This law is applied to single skeletal muscle fiber (motor unit).
- Threshold or over threshold $\rightarrow$ AP of maximal magnitude.

Muscle Twitch:

The response of a skeletal muscle to a single stimulation (or action potential):

- latent period - no change in length; time during which impulse is traveling along sarcolemma and down T-tubules to sarcoplasmic reticulum, calcium is being released, and so on (in other words, muscle cannot contract instantaneously!)
- contraction period - tension increases (cross-bridges are swivelling)
- relaxation period - muscle relaxes (tension decreases) and tends to return to its original length

Types of skeletal muscle contraction:

1 - isotonic - tension or force generated by the muscle is greater than the load the muscle shortens.

2 - isometric - load is greater than the tension or force generated by the muscle and the muscle does not shorten.

N.B.:

- **Motor unit is** a motor neuron plus all of the muscle fibers it innervates**.**

- The degree of contraction of a skeletal muscle is influenced by the number of motor units being stimulated.

- Skeletal muscles consist of numerous motor units and, therefore, stimulating more motor units creates a stronger contraction.

Factors affecting skeletal m. contraction:

(1) Type of muscle:

Slow (red) fibers = Type I fibers	**Fast (pale) ms**
(1) Slow: - Contraction is slow and prolonged (100 msec). (2) not easily fatigued.	(1) Rapid: - contraction is rapid and short (7.5 msec). (2) Easily fatigue.
(3) Red: - Rich in red pigment myoglobin to store O2 - More blood supply	(3) Pale: - Lack pigment. - Poor blood supply.
(4) Histology: a- Sarcoplasm: - Abundant and granular - Large number of mitochondria: to supprrt high oxidative metabolism. - Rich fat content. b- Nuclei: - Numerous and sometimes central. c- Myofibril: - Thick and irregular - Irregular striation d- SR:	 - Less abundant. - Few number of mitochondria. - Poor fat content - Always peripheral. - Thin and regular - Regular striation. - Extensive for rapid release of Ca^{++}
(5) Adapted for: - Long, slow activity (posture maintaining)	- fine, skilled movement.

e.g.: Soleus m.	eg.: External occular ms.
(6) Excitability: - Low	 - High

Most muscles contains both types of MF e.g. gastrocnemius m.

(2) Stimulus factors:

A- Strength of stimulus

Stimulation of the muscle fiber with subminimal (subthreshold) stimulus) willonly induce local excitatory changes in the motor end plate (no contraction). Increasing the strength of stimulus will increase the number of activated motor units and so increase the force of muscle contraction untill all motor units become activated (by maximal stimulus). Supramaximal stimulus would not give further response as each fiber responds maximally according to all or none law.

B- Frequency of muscle stimulation (effect of repeated stimulation)**:**

Repeated stimulation increases the frequency of alpha motor neuron firings and as a result more Ca^{++} is released from the SR. Levels of Ca^{++} remains continuously high even between action potentials. That will lead to continuous cycling of the cross-bridges and the individual responses fuse into one continuous contraction (**Tetanus = summation of contraction**)

a) moderate frequency → clonic contraction (incomplete tetanus ie periods of incomplete relaxation).

b) high frequency→ motor units contract a synchronously → individual responses of various motor units fuse into a smooth contraction of greater force (complete tetanus) ie no relaxation.

c) Repetitive stimulation after a period of rest→ Stair Case phenomenon (**Treppe**): progressive increase in the magnitude of separate twich contraction of skeletal m till uniform tension/ contraction is reached). This phenomenon occur as more Ca^{++} is released from the SR (with each muscle AP) with failure to recapture Ca^{++} immediately.

(3) Length-tension relationship:

Starling's law: When the muscle is stimulated to contract isometrically, increasing or decreasing the initial length of muscle fiber decrease the active tension develops.

Muscles can generate greater forces when they are partially stretched just before contraction occurs i.e. the actin and myosin molecules are just overlapping. If the muscle is stretched too far, no contraction can occur i.e. the actin and myosin are not overlapping at all, so they cannot form cross bridges. If the myofilaments overlap too much, no further contraction can occur i.e. the thin filaments interfere with each other and the thick filaments run into the Z disc sarcomeres cannot shorten any further.

Total tension = tension develops by the muscle when stimulated to contract isometrically.

Passive tension = tension develop by the unstimulated m.

Active tension = tension develops by the contractile process
= difference between total tension and passive tension at any length

(4) Velocity of Muscle Contraction

Each step involved in the contraction of a muscle fiber takes time (from the propagation of the AP to the cycling of the cross bridges) anything affecting the speed of these steps affects the speed of contraction including:

- speed of impulse propagation down the axon
- Amount of slack in the elastic components (tension must be developed before contraction can occur.

(5) Muscle fatigue:

Prolonged and strong contraction of a muscle leads to depletion of ATP (which is needed for separation between actin and myosin filaments during relaxation), depletion of muscle glycogen and creatine phosphate, accumulation of metabolites as lactic acid, interruption of blood flow through the muscle that leads to decrease O_2 and nutrient and decrease in transmission at neuromuscular junction.

- Decrease in strength of contraction
- Prolonged duration of contraction

- Incomplete relaxation

Rigor mortis:

= several hours after death, all muscles of the body go in a state of contracture (ie. muscle contract and becomes rigid even without action potential)

Cause:

Depletion of ATP therefore, the muscle remains in a state of partial contraction till the muscle proteins are destroyed (usually by bacterial putrifaction, 15-25 hours later).

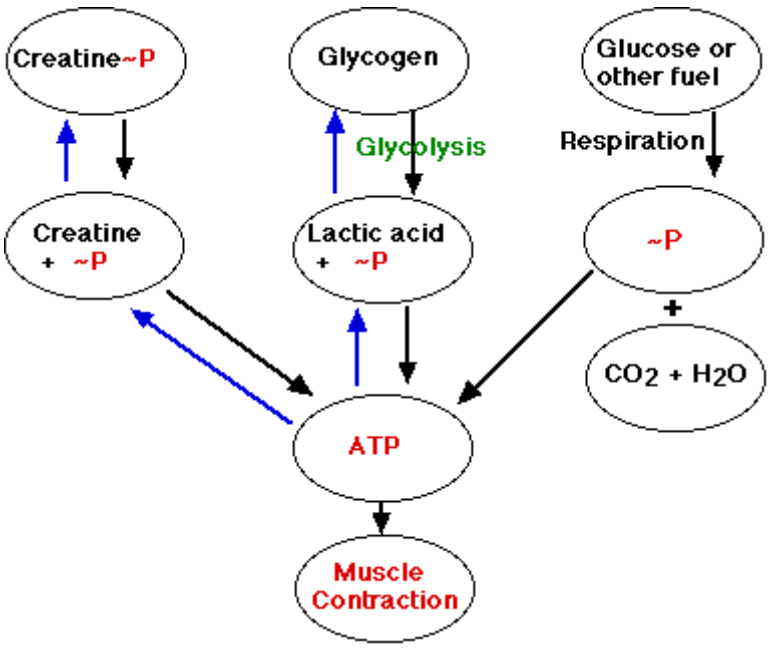
Significance:

Helps in the determination of time of death

IV) Metabolic changes:

During rest energy is required for maintenance of RMP, synthesis of chemical substances as glycogen s well as production of muscle tone.

ATP is the immediate source of energy for muscle contraction. Although a muscle fiber contains only enough ATP to power a few twitches, its ATP "pool" is replenished as needed. There are three sources of high-energy phosphate to keep the ATP pool filled. These include; creatine phosphate, glycogen and cellular respiration in the mitochondria of the fibers.



Creatine phosphate:

The phosphate group in creatine phosphate is attached by a "high-energy" bond like that in ATP. Creatine phosphate derives its high-energy phosphate from ATP and can donate it back to ADP to form ATP.

Creatine phosphate + ADP ↔ creatine + ATP

The pool of creatine phosphate in the fiber is about 10 times larger than that of ATP and thus serves as a modest reservoir of ATP.

Glycogen:

Skeletal muscle fibers contain about 1% glycogen. The muscle fiber can degrade this glycogen by glycogenolysis producing glucose-1-phosphate. This enters the glycolytic pathway to yield two molecules of ATP for each pair of lactic acid molecules produced. Not much, but enough to keep the muscle functioning if it fails to receive sufficient oxygen to meet its ATP needs by respiration. However, this source is limited and eventually the muscle must depend on cellular respiration.

Cellular respiration:

Cellular respiration (oxidation of food stuffs in the mitochondria to liberate E) not only is required to meet the ATP needs of a muscle engaged in prolonged activity (thus causing more rapid and deeper breathing), but is also required to enable the body to resynthesize glycogen from the lactic acid produced earlier

$$(\text{Glucose} + 2\ \text{ATP}) \text{ or } (\text{Glycogen} + 1\ \text{ATP}) \xrightarrow{O_2} 6\ CO_2 + 6\ H_2O + 40\ \text{ATP}$$

Oxygen Debt

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(1) During muscular exercise:

muscular BVs dilate→ ↑blood flow and consequently O_2 supply to m.

up to a point:

↑O_2 consumption α Energy expended (all E is derived from aerocbic system).

(2) Very great muscular exercise:

Some ATP is derived from **anaerobic system,** where

- ATP from creatine~PO_3 ⟶ are depleted

- O_2 of myoglobin⟶

(3) During recovery (after cessation of muscular exercise)**:**

Extra O_2 is consumed (for some time) to:

1- remove excess lactate

2- replenish →ATP

&

→ creatine~PO_3 stores.

3- replace O_2 of myoglobin.

N.B:

The Extra O_2 (O_2 debt) consumption continues for some time till basal consumption is reached.

O_2 debt = Total O_2 consumption (after muscular exercise)- Basal O_2 consumption.