Molecular mechanisms of skeletal muscle contraction, types of contraction and tetanus

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Excitation–Contraction Coupling

- Sequence of events by which an action potential in the plasma membrane activates the force-generating mechanisms

- Action potential – 1-2 msec
- Mechanical activity ≥ 100 msec

- Action potential → internal Ca^{2+} concentration

Ca^{2+} in Cross-Bridge Formation

- Tropomyosin
  - Equal to the length of seven actin monomers
  - Partially cover the myosin binding site on each actin monomer
- Troponin
  - Holds tropomyosin in blocking position
  - I: inhibitory, T: tropomyosin-binding, C: Ca^{2+} binding

Ca^{2+} in Cross-Bridge Formation

- Ca^{2+} binding to troponin
- Change in tertiary structure
- Moving of tropomyosin from cross-bridge binding site
- Initiation of contraction

Mechanism of Cytosolic Increase in Ca^{2+}

- Ca^{2+} concentration in a resting muscle fiber cytosol 10^{-7} mol/L
- Source of internal Ca2+ is sarcoplasmic reticulum
- Junctional feet
  - Dihydropyridine (DHP) receptor
    - Voltage sensor
  - Ryanodine receptor
    - Ca^{2+} channel
- Ca^{2+} release to cytoplasm from terminal cisternae
  - Single AP is enough for all troponin-binding sites

Contraction Termination

- Removal of Ca^{2+} cytosol back to sarcoplasmic reticulum
  - primary active-transport proteins—Ca^{2+}ATPases
  - Active transport takes longer time
    - Cytosolic concentrations remains elevated for a longer time

Sliding-Filament Mechanism

- During shortening of the sarcomeres, there is no change in the lengths of either the thick or thin filaments

- Thick and thin filaments in each sarcomere move past each other by movements of cross-bridges

Sarcomere Shortening

- Z lines move toward the center
- I band reduce
- H band reduce
- A band stable

- One end of the muscle is stable, the other end shortens toward it

Cross-bridge cycle

- The sequence of events that occurs between the time a cross-bridge binds to a thin filament, moves, and then is set to repeat the process

1. Attachment of the cross-bridge to a thin filament
2. Movement of the cross-bridge, producing tension in the thin filament
3. Detachment of the cross-bridge from the thin filament
4. Energizing the cross-bridge so it can again attach to a thin filament

Cross-Bridge Cycle

A single power stroke pulls the thin filament inward only a small percentage of the total shortening distance.

Repeated cycles of cross-bridge binding and bending complete the shortening.

Each cross-bridge has its own cycle (not all the cross-bridges active at the same time)

Mechanics of Single-Fiber Contraction

- Muscle tension: the force exerted on an object by a contracting muscle
- Load: the force exerted on the muscle by an object (usually its weight)

- For muscle fibers to shorten and move a load, muscle tension must be greater than the opposing load

Isometric contraction

- Constant Length
- Muscle develops tension but does not shorten or lengthen
  - Holding a load in a constant position
  - Attempts to move an higher load that is greater than the tension
  - Postural muscles of body

Isotonic Contraction

- Constant Tension
- Muscle changes length while the load on the muscle remains constant
- Concentric Contraction
  - Tension exceeds the load, shortening occurs
- Eccentric Contraction
  - Unsupported load greater than the tension
  - The load pulls the muscle to a longer length in spite of the opposing force produced by the cross-bridges

Contraction

- Only the effect of power stroke changes depending on the load
  - Binding, ATP hydrolyses and release steps are the same

- Concentric isotonic contraction
  - Cross-bridges rotate through actin and shortens sarcomeres

- Isometric contraction
  - the bound cross-bridges do exert a force on the thin filaments but they are unable to move it
  - The rotation during power stroke is absorbed by elastic elements within the sarcomere and muscle
  - If contraction is prolonged, cycling cross-bridges repeatedly rebind to the same actin molecule

- Eccentric isotonic contraction
  - The load pulls the cross-bridges backward towards Z lines while they are still bound to actin and exerting force

Twitch Contractions

- The mechanical response of a muscle fiber to a single action potential
- Latent period: few milliseconds between the action potential and beginning of the tension in the muscle fiber (excitation-contraction coupling)
- Contraction time: time interval from the begining of tension development to the peak tension

Twitch Contractions

- Fast twitch muscles
  - Contraction time around 10 msec
- Slow twitch muscles
  - Contraction time around 100 msec or more

  - Depends on?
- Time that cytosolic Ca 2+ remains elevated
  - Ca 2+ ATPase activity in the sarcoplasmic reticulum (Greater in fast twitch fibers)
- Time that it takes for cross-bridges to complete their cycle
  - Type of myosin

Twitch Contractions

- Latent period is longer in isotonic twitch
  - Time for excitation-contraction coupling and a brief isometric contraction

- The duration of the mechanical event—shortening—is briefer in an isotonic twitch than the duration of force generation in an isometric twitch
  - Another brief period of isometric contraction at the end

Twitch Contractions

- At heavier loads for isotonic contraction:
  - the latent period is longer
  - the velocity of shortening is slower
  - the distance shortened is less

Load-Velocity Relation

- Increased load
  - The distance shortened decrease
  - velocity of shortening decrease
  - duration of shortening decrease
  - the time from stimulation to the beginning of shortening increase

Load-Velocity Relation

- The unloaded shortening velocity is determined by the rate at which individual cross-bridges undergo their cyclical activity, which is a function of the maximum intrinsic rate of the myosin ATPase enzyme
- Increasing the load on a cross-bridge, however, slows its forward movement during the power stroke. This reduces the overall rate of ATP hydrolysis and, thus, decreases the velocity of shortening

Frequency–Tension Relation

- A second action potential can be initiated during the period of mechanical activity
- Summation: increase in muscle tension from successive action potentials occurring during the phase of mechanical activity
  - the effect of additional attached cross-bridges

Tetanus

- Maintained contraction in response to repetitive stimulation (tetanic contraction)
  - Ca2+ availability and cross-bridge binding
- Unfused tetanus: low stimulation frequencies, the tension oscillates - muscle fiber partially relaxes between stimuli
- Fused tetanus: at higher stimulation frequencies, no oscillations – muscle fiber can not relax

Tetanus

- Maximal fused tetanic tension
  - no longer increases in tension even with further increases in stimulation frequency
  - three to five times greater than the isometric twitch tension
  - the stimulus frequency that will produce a maximal tetanic tension differs from fiber to fiber
  - beneficial when maximal, sustained work is required
    - holding a heavy object in place
    - maintaining posture

Length–Tension Relation

- Passive elastic properties of relaxed muscle fibers are maintained by titin

- As the stretch increases, passive tension increases from the elongation of titin (streched rubber band)

- Magnitude of the active tension vary with length

- Optimal length (L_0): The length at which the fiber develops the greatest isometric active tension

Length–Tension Relation

- Overlap between thin and thick filaments
- < 60% L_0, no tension when stimulated
- > 175 % L_0 no tension when stimulated but the passive elastic tension is quite high
- Physiologically ± 30%
  - Always able to develop tension