Skeletal Muscle and the Molecular Basis of Contraction

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• Like neurons, all muscle cells can be excited chemically, electrically, and mechanically to produce an action potential.

• Contractile proteins: actin and myosin (also troponin and tropomyosin)

• Actin-binding protein myosin is a molecular motor that converts energy from ATP hydrolysis into movement
Three Types:

- Smooth
  lacks cross striations
  found in hollow viscera
  functionally syncytial

- Cardiac
  has cross striations
  functionally syncytial
  contracts rhythmically in the absence of external innervation due to the presence of pacemaker cells

- Skeletal
Skeletal Muscle

• Movement of bones and joints
• Cross-striations
• Neural control
• Voluntary control
• Twitch responses
Morphology

- Each muscle fiber is a single cell that is multi-nucleated.
- Fibers surrounded by a cell membrane or plasma membrane called a sarcolemma.
- Fibers are made up of individual myofibrils divided into individual filaments.
- Filaments made up of the contractile proteins, myosin II, actin, troponin and tropomyosin.
• Action potentials are propagated along the sarcolemma.
• There are tiny openings in the sarcolemma that lead into the transverse tubular network.
• The T tubules encircle each myofibril.
• The action potential travels down the sarcolemma and the depolarization spreads into the cells via the T tubule system.
• The depolarization spreads to the myofibrils through the sarcoplasmic reticulum.
More Morphology

- Z line to Z line represents one sarcomere.
- A Band represents myosin filaments overlapping actin filaments.
- H Band represents portion of the myosin filaments without crossbridge (heads).
- M Line is in the middle of the H Band: formed where crossbridges change their polarity.
- I Band is the light band on either side of the Z line; actin filaments only.
- When muscle contracts, myosin and actin filaments slide over one another bringing the Z lines closer together.
Dystrophin-Glycoprotein Complex

- Actin is attached to the sarcolemma by the protein dystrophin
- dystrophin is attached to a transmembrane protein in the sarcolemma called beta-dystroglycan
- beta-dystroglycan is connected to alpha-dystroglycan which is connected to laminin in the extracellular matrix
- complex provides structural support and strength to the muscle fibrils
- Defects cause Muscular Dystrophy
Motor Unit

- Terminal branch of motor nerve: Called terminal button or end-foot; contains the neurotransmitter acetylcholine
- Depression in muscle membrane: called motor end plate
- End-foot and motor end plate make up neuromuscular junction or myoneural junction
- Motor Unit: grouping of nerve and associated muscle cells
- Motor Unit size: # muscle fibers / motor neuron
Muscle Twitch

- Single AP causes contraction followed by relaxation
- Twitch starts after start of depolarization and before repolarization is complete
- Duration of twitch varies with muscle type
  - Fast: ~ 7.5 ms
  - Slow: ~ 100 ms
Muscle Contraction
Overview

• AP releases acetylcholine at motor end plate
• Depolarization of sarcolemma
• Depolarization travels down T tubule system to sarcoplasmic reticulum
• Sarcoplasmic reticulum releases Ca\(^{2+}\) from cisternae
• Results in muscle contraction
Calcium Mobilization Regulates Skeletal Muscle Contraction

1. Neuromuscular transmission and depolarization of the motor endplate, sarcolemma, and T tubules
2. The mobilization of calcium
3. The action of calcium on the contractile proteins that control cross-bridge cycling
Calcium Channels

• Signal transduction occurs when an action potential triggers calcium release from the terminal cisternae of the sarcoplasmic reticulum.
• Depolarization of the T tubules opens calcium channels in the terminal cisterns
• $\text{Ca}^{2+}$ diffuses into myofibrils
• $\text{Ca}^{2+}$, $\text{Mg}^{2+}$-ATPase pump $\text{Ca}^{2+}$ back into sarcoplasmic reticulum
Contractile Proteins

- Single contractile unit is called a sarcomere
- Z disks link sarcomeres end to end
- Thin filaments: actin, troponin, and tropomyosin
- Thick filaments: myosin
- Myosin: Composed of head and tail region; tails form the thick filaments; heads project toward thin filaments
- Head is called a cross-bridge; contains two actin binding sites and two enzymatic sites
- Sliding Filament Theory: interactions between the cross-bridges and the thin filaments cause the sarcomeres to shorten
Thin Filaments

- Tropomyosin binds to and wraps around the actin molecules
- Troponin is a regulatory protein that binds to the tropomyosin molecule
  - 3 subunits
  - Troponin C contain the Ca\(^{2+}\) binding sites
  - Troponin I binds to actin
  - Troponin T binds to tropomyosin
Initiation of Muscle Contraction by Ca$^{2+}$

• In resting muscle, troponin-tropomyosin complex inhibits interaction between actin and myosin

• When Ca$^{2+}$ is released, it binds to troponin C

• This allows tropomyosin to move laterally, uncovering the sites for the crossbridges

• ATP is hydrolyzed and contraction occurs
Steps Involved in Relaxation

• 1. Calcium is released from troponin.
• 2. Sarcoplasmic reticulum reaccumulates $\text{Ca}^{2+}$ by active transport via Ca-Mg-ATPase. $\text{Ca}^{2+}$ diffuses into the terminal cisterns and stored.
• 3. Interaction between actin and myosin stops and the muscle relaxes.
Cross-Bridge Cycle

1. The exposure of the active site following binding of Ca$^{2+}$ ions to troponin
2. The attachment of myosin cross-bridge to the exposed active site on the thin filaments.
3. The pivoting of the attached myosin head toward the center of the sarcomere and the release of ADP + P$_i$. This step uses energy that was stored in the molecule at rest.
4. The detachment of the cross-bridges when myosin heads bind another ATP molecule.
5. The reactivation of detached myosin head as it splits the ATP and captures the released energy. The cycle is repeated beginning with step 2.
Contractile Properties of Skeletal Muscle

- Two mechanisms control the amount of force generated by a muscle:
  1. Recruitment of more motor units
  2. Increase firing frequency
Summation of Contraction

• The fiber is electrically refractory during the rising and part of the falling phase of the spike potential.

• The contraction initiated by the first potential is only starting by the time the fiber can electrically respond again.

• Contractile mechanism does not have a refractory period ∴ repeated stimulation produces additional activation of contractile elements.
Tetanus

- Rapidly repeated stimulation results in repeated activation of the contractile mechanism before any relaxation can occur.
- Individual responses fuse into one continuous contraction.
- During complete tetanus, tension developed is ~ 4x individual twitch
Metabolic Pathways

• ATP regeneration for muscle contraction is available through different metabolic pathways:

1. Direct phosphorylation
   - No net increase in ATP
   - Creatine phosphate serves as a pool of immediately available phosphate

2. Glycolysis
   - Supplies ATP at high rates
   - Low yield per mole of glucose: 2-3 moles of ATP
   - Pathway fails when glycogen stores are depleted

3. Oxidative phosphorylation
   - Used for moderate levels of activity
   - High yield per mole of glucose: 36 moles of ATP
   - Cannot meet demands of rapid cross-bridge cycling
   - Slower pathway than glycolysis
Fiber Types

1. Slow (Red) fibers:
   - Moderate power output
   - Moderate ATP consumption
   - Fatigue resistant

2. Fast (White) fibers:
   - Maximum power output
   - Maximum ATP consumption
   - Fatigable
Extrinsic Muscles of the Eye

- Extrinsic muscles: extraocular muscles
  - Striated and voluntary muscles
  - Superior rectus, inferior rectus, medial rectus, lateral rectus, inferior oblique, superior oblique

- Intrinsic muscles: Sphincter pupillae and dilator of the iris
  - Smooth muscles
Extraocular Muscles Are Different From Other Striated Muscles

1. Smaller diameter: 5-40\(\mu\)m
2. Smaller motor unit: 10 fibers / motor neuron
3. Higher discharge rates than spinal motor neurons
4. Innervation pattern is different in oculomotor muscles
5. Extraocular muscles have twitch and non-twitch fibers
6. Fatigue resistance in extraocular muscles is the highest of any skeletal muscle
7. Extraocular muscles differ in fiber type
Rectus and Oblique Muscles

- Exhibit two distinct regions, each with a different fiber type content:
  - An outer orbital layer adjacent to the periorbita and orbital bone
  - An inner global layer adjacent to the optic nerve and the eye
- Classification of 6 fiber types based on innervation patterns, ATPase characteristics, myosin isoforms, size
Orbital Layer of Rectus and Oblique Muscles

1. Orbital Singly Innervated Fibers
   - Predominant fiber type
   - Single site neuromuscular contacts
   - Fast twitch, highly fatigue resistant
   - Many large mitochondria, associated oil droplets, and glycogen granules

2. Orbital Multiply Innervated Fibers
   - Fast twitch near it’s center; tonic at it’s proximal and distal ends
   - Multiple neuromuscular contacts
   - Few mitochondria
Global Layer of Rectus and Oblique Muscles

- 3 global singly innervated fibers differ in mitochondrial content so they represent varying degrees of fatigue resistance

1. Global Red Singly Innervated Fibers
   - Fast twitch, highly fatigue resistant
   - Not as many mitochondria as orbital SIF but still has a lot

2. Global Intermediate Singly Innervated Fibers
   - Fast twitch; intermediate level of fatigue

3. Global Pale (white) Singly Innervated Fibers
   - Fast twitch; fatigable

4. Global Multiply Innervated Fibers
   - En Grappe motor endings
   - Contain a few mitochondria
   - Exhibit slow, graded, non-propagated response
   - No counterpart in human skeletal muscle
En Plaque and En Grappe Motor Nerve Endings

• **En Plaque Endings**
  – Motor end plates
  – Found on singly innervated fibers
  – Found in the middle third of the belly of the muscle

• **En Grappe Endings**
  – Smaller than en plaque endings
  – Grape-like in appearance
  – Found on multiply innervated fibers
  – Unique to EOM
Striated Muscles of the Eyelid

• Orbicularis Oculi
  – Striated fibers
  – Function: close the eyelid
  – Innervation: Facial N. (VII) (temporal & zygomatic branches)
  – Dysfunction:
    • Bell’s Palsy
    • Parotid Gland surgery
    • Essential blepharospasm
• **Levator Palpebrae Superioris**
  – Striated, voluntary fibers in upper eyelid
  – Function: Eyelid retractor
  – Innervation: superior branch of the Oculomotor N. (III)
  – Adherent superiorly to the underlying smooth muscle of Müller (Tarsal muscle)
  – Dysfunction:
    • Ptosis caused by:
      – Lesion of the third cranial nerve
      – Myasthenia gravis
      – Senile dihiscence
Myasthenia Gravis

- Autoimmune disease; causes weakness in voluntary muscles
- Antibodies bind to ACh receptor at neuromuscular junction rendering them unavailable
- Anti-ACh receptor antibodies are the immediate cause of MG
Clinical Characteristics

1. Droopy eyelids: initial symptom in 50% of patients
2. Ptosis is absent or less upon awakening: progresses as the day goes on
3. Double vision: diplopia of MG also worsens as the day goes on
Non-Ophthalmalmic Complaints

1. Weakness in one or more muscle groups: Ex: proximal limb muscles resulting in difficulty walking or getting up from a chair
2. Pharyngeal muscles: change in voice
3. Difficulty swallowing or breathing: medical emergency for any patient with MG
Tests for MG

1. Tensilon test: intravenous injection of edrophonium chloride causes reversal of lid and ocular motility signs. Patient will revert to baseline in 2 minutes.

2. Ice test: ice is placed over the ptotic lid for 2 minutes. MG ptosis will improve.

3. Rest test: the patient keeps his or her eyes closed for 20 minutes and ptosis improves.
Treatment for MG

- Include cholinesterase inhibitors,
- Corticosteroids or other immunosuppressive therapy,
- Thymectomy
- Plasmapheresis
Graves Disease

- Most common variety of hyperthyroidism
- Autoimmune basis
- Antibodies attack the muscles associated with the eye and eyelid movement
- Antibodies cause inflammation and swelling of the muscles
- Causes protrusion of the eyes, double vision, and retraction of eyelids
- Eye signs may precede, come at the same time, or follow the onset of hyperthyroidism
- Management begins with the underlying thyroid disease; Ocular involvement is managed by local measures