Skeletal Muscle Physiology
Part 2

The material contained in these slides corresponds to your assigned readings found in Chapter 10 of our text.
1. Explain the events that lead to release of the neurotransmitter Ach from a motor neuron.

2. Describe the steps in excitation-contraction coupling.

3. Summarize the changes that occur within a sarcomere during contraction.

4. Discuss what happens to each of the following to allow for skeletal muscle relaxation: ACh, action potential, Ca$^{2+}$ concentration in sarcoplasm, and troponin-tropomyosin complex.

5. Explain the relationship of skeletal muscle elasticity and muscle relaxation.

• Learning Objectives:
Overview of Events in Skeletal Muscle Contraction

- From start to finish, muscle contraction is a process that involves a series of sequential steps beginning with stimulation by a motor neuron and culminating in cross-bridge cycling.
- It involves a series of proteins and regulatory elements which work together through three major sets of events:
  1. Events at the NMJ
  2. Excitation-Contraction (EC) coupling
  3. Cross-bridge cycling
Neuromuscular Junction: Excitation of a Skeletal Muscle Fiber

- Step 1: Neuron excites muscle fiber
  - Calcium enters synaptic knob
    - Nerve signal travels down axon, opens voltage-gated Ca\(^{2+}\) channels
    - Ca\(^{2+}\) diffuses into synaptic knob
    - Ca\(^{2+}\) binds to proteins on surface of synaptic vesicles
  - Synaptic knob releases ACh
    - Vesicles merge with cell membrane at synaptic knob: exocytosis
    - Thousands of ACh molecules released from about 300 vesicles
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B. Synaptic knob releases ACh
- Vesicles merge with cell membrane at synaptic knob: exocytosis
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C. ACh binds to its receptors at motor end plate

- ACh diffuses across cleft, binds to receptors, excites fiber
Sarcolemma, T-tubules, and SR: Excitation-Contraction Coupling

- Stimulation of the fiber is coupled with the sliding of filaments
- Coupling includes the end-plate potential (EPP), muscle action potential, and release of Ca\(^{2+}\) from the sarcoplasmic reticulum
Sarcolemma, T-tubules, and SR: Excitation-Contraction Coupling

A. End-plate potential (EPP)

- ACh receptors are chemically gated channels that open when ACh binds to them
- $\text{Na}^+$ diffuses into the cell through the channels (while a little $\text{K}^+$ diffuses out)
- Cell membrane briefly becomes less negative at the end plate region
- EPP is local but it does lead to the opening of voltage-gated ion channels in the adjacent region of the sarcolemma
B. Initiation and propagation of action potential along the sarcolemma and T-tubules

- An **action potential** is propagated along the sarcolemma if the membrane at EPP reaches threshold
- Na\(^+\) diffuses into the cell through voltage-gated channels
  - Cell **depolarizes**
  - This results in the opening of adjacent voltage-gated Na\(^+\) channels and more Na\(^+\) entry
Sarcolemma, T-tubules, and SR: Excitation-Contraction Coupling

A chain reaction occurs as depolarization-repolarizations in an action potential (as indicated by the red arrow) are propagated down the membrane and T-tubules.
Sarcolemma, T-tubules, and SR: Excitation-Contraction Coupling

- Release of Ca\(^{2+}\) from the sarcoplasmic reticulum caused by
  - Action potential opening voltage-gated Ca\(^{2+}\) channels of SR
  - Ca\(^{2+}\) diffuses out of cisternae into sarcoplasm
  - Ca\(^{2+}\) interacts with myofilaments triggering contraction

Fig 10.12
3. When Ca\(^{2+}\) (released from the SR AND from the ECF) binds to troponin, it triggers crossbridge cycling

- Troponin and tropomyosin expose myosin binding sites on actin filaments
Sarcomere: Crossbridge Cycling/Sliding Filament Theory

• Crossbridge cycling: four repeating steps
  1) Crossbridge formation
  2) Power stroke
  3) Release of myosin head
  4) Reset myosin head

Figure 10.13
Sarcomere: Crossbridge Cycling/Sliding Filament Theory

- Crossbridge cycling: four repeating steps
  1) Crossbridge formation
     - Myosin head attaches to exposed binding site on actin

Figure 10.13

Crossbridge formation ("attach")
Myosin heads, which are in the "cocked" position, bind to the exposed myosin binding site on actin forming a crossbridge between myosin and actin.
• Crossbridge cycling: four repeating steps
  2) Power stroke (due to release of P\textsubscript{i})
  • Myosin head pulls thin filament toward center of sarcomere
    • ADP and P\textsubscript{i} released

3c Power stroke (“pull”) The myosin head swivels toward the center of the sarcomere, pulling along the attached thin filament. This motion is called a power stroke. ADP and P\textsubscript{i} are released during this process.
Sarcomere: Crossbridge Cycling/Sliding Filament Theory

- Crossbridge cycling: four repeating steps
  3) Release of myosin head
     - ATP binds to myosin head causing its release from actin
Crossbridge cycling: four repeating steps

4) Reset myosin head
   - ATP is hydrolyzed to ADP and $P_i$ by myosin ATPase
   - Provides energy to "cock" the myosin head

![Figure 10.13](image)
Sarcomere: Crossbridge Cycling/Sliding Filament Theory

- Sarcomere shortening occurs when
  - Cycling continues as long as \( \text{Ca}^{2+} \) and ATP are present
  - \( Z \) discs move closer together
  - Narrowing (or disappearance) of \( H \) zone and \( I \) band
  - Thick and thin filaments remain the same length but slide past each other
Clinical View: Myasthenia Gravis

- Autoimmune disease, primarily in women
- Antibodies bind to ACh receptors in neuromuscular junctions
- Receptors removed from muscle fiber by endocytosis
- Results in decreased muscle stimulation
- Rapid fatigue and muscle weakness
- Eye (ptosis/’lazy eye’) and facial muscles often involved first
- May be followed by swallowing problems, limb weakness
Clinical Implications: Muscular Paralysis and Neurotoxins

- **Tetanus**
  - Spastic paralysis caused by toxin from *Clostridium tetani*
  - Blocks release of inhibitory neurotransmitter in spinal cord, resulting in overstimulation of muscles
  - Vaccination prevents this life-threatening condition

- **Botulism**
  - Muscular paralysis caused by toxin from *Clostridium botulinum*
  - Prevents release of ACh at synaptic knobs
  - Although toxin ingestion can be life-threatening, careful injections of it can treat spasticity (e.g., due to cerebral palsy) or can be used for cosmetic purposes (diminishing wrinkles)
Skeletal Muscle Relaxation

• Muscle relaxation is an “active” process

• Any event that disrupts the reverses the sequence of events at any of the steps (NMJ events, EC coupling, cross-bridge cycling) will result in muscle relaxation

• Events in muscle relaxation include:
  • Termination of nerve signal and ACh release from motor neuron
  • Hydrolysis of ACh by acetylcholinesterase
  • Closure of ACh receptor causes cessation of end plate potential
  • Closure of calcium channels in sarcoplasmic reticulum
  • Return of Ca\(^{2+}\) to sarcoplasmic reticulum by pumps
  • Return of troponin to original shape
  • Return of tropomyosin blockade of actin’s myosin binding sites
  • Return of muscle to original position due to its elasticity
Measurement of Skeletal Muscle Tension

• Learning Objectives:

1. Describe what occurs in a muscle during a single twitch, and relate each event to a graph of a twitch.
2. Explain the events that occur in motor unit recruitment as the intensity of stimulation is increased.
3. Distinguish between treppe, wave summation, incomplete tetany, and tetany that occur with an increase in frequency of stimulation.
Measurement of Skeletal Muscle Tension

- **Muscle tension**
  - Tension is the force generated when a muscle is stimulated to contract
  
- Lab experiments measure tension and graph it (myogram)

Fig 10.21
Analysis of a Muscle Twitch

- A twitch is a brief contraction to a *single* stimulus
  - For a twitch to occur a minimum *(threshold)* voltage has to be applied

- Periods of the twitch
  - **Latent period**
    - Time after stimulus but before contraction begins
    - No change in tension
  - **Contraction period**
    - Time when tension is increasing
    - Begins as power strokes pull thin filaments
  - **Relaxation period**
    - Time when tension is decreasing to baseline
    - Begins with release of crossbridges
    - Generally lasts a little longer than contraction period
What’s the difference?
Motor Unit Recruitment

• Muscle (not just single muscle fiber) is stimulated **repeatedly**

• As voltage increases, more units are recruited to contract

Recruitment (**multiple motor unit summation**) is the basis for how muscles exhibit varying degrees of force

• Recruit just a few motor units to lift a pencil
• Recruit many motor units to lift a suitcase

• Above a certain voltage, all units are recruited, and so maximum contraction occurs (regardless of how much higher voltage is)
Treppe, Wave Summation, Tetany: incomplete vs complete

- **Treppe**
  - An increase in twitch tension when stimuli occur 10–20 times per second
  - Voltage is the same for each stimulus and relaxation is complete for each twitch
  - Twitches get stronger because there’s insufficient time to remove all Ca^{2+} between twitches

![Figure 10.23b](image-url)
Wave summation (temporal summation) occurs if stimulus frequency set at about 20 per second
- Relaxation is not completed between twitches
- Contractile forces add up to produce higher tensions

Incomplete tetany and tetany
- If frequency is increased further, myogram exhibits incomplete tetany
  - Tension increases and twitches partially fuse
- If frequency is increased to 40–50 per second, tetanus occurs (smooth line without any relaxation) – can only be induced experimentally
- High frequency stimuli lead to fatigue (decreased tension production)

(c) Wave summation, incomplete tetany, and tetany

Figure 10.23c
Factors Affecting Skeletal Muscle Tension Within the Body

Learning Objectives:

1. Describe muscle tone, and explain its significance.
2. Distinguish between isometric and isotonic contractions, and give examples of both.
3. Explain the length-tension relationship in skeletal muscle contraction.
4. Define muscle fatigue, and explain some of its causes.
Muscle Tone

- **Muscle tone**
  - Resting tension in a muscle
  - Generated by involuntary nervous stimulation of muscle
  - Some motor units stimulated randomly at any time
  - Change continuously so motor units (whole muscle) are not fatigued
  - No movement (sarcomere shortening) generated
  - Decreases during deep sleep
Contractions: Isometric vs Isotonic

• **Isometric contraction**
  - Although tension is increased, it is insufficient to overcome resistance
  - *Muscle length stays the same*
  - E.g., holding a weight while arm doesn’t move

• **Isotonic contraction**
  - Muscle tension overcomes resistance resulting in movement
  - *Tone stays constant, but length changes*
  - **Concentric contraction** (muscle shortens)
  - **Eccentric contraction**, (muscle lengths)
Length-Tension Relationship in Muscle Contraction

The tension a muscle produces depends on its length at the time of stimulation:

- Fiber at resting length generates maximum contractile force due to optimal overlap between actin and myosin.

Fiber at a shortened length generates weaker force:
- Filament movement is limited (already close to Z disc).

Fiber at an extended length generates weaker force:
- Minimal thick and thin filament overlap for crossbridge formation.

[Graph showing muscle tension in relation to sarcomere length]
Muscle Fatigue

- **Fatigue:** reduced ability to produce muscle tension
  - Primarily caused by a decrease in glycogen stores during prolonged exercise
- Other *possible* causes of fatigue
  - Neural fatigue
    - Insufficient Ca\(^{2+}\) to enter synaptic knob
    - Decreased number of synaptic vesicles
  - Problems with EC coupling
    - Altered ion concentrations impair action potential conduction and Ca\(^{2+}\) release from sarcoplasmic reticulum
  - Problems with crossbridge cycling
    - Excessive P\(_i\) slows release of P\(_i\) from myosin head
    - Less Ca\(^{2+}\) available for troponin (some Ca\(^{2+}\) is bound to P\(_i\))