Chapter 10.3

The Nerve Muscle Relationship

Neural Muscular Junction

Contraction and Relaxation

Motor Units
The Nerve-Muscle Relationship

• skeletal muscles require nerve stimulation to contract

  – if nerve connections are severed or poisoned a muscle is paralyzed

  – **denervation atrophy** // shrinkage of paralyzed muscle when nerve connections are not restored

• loss of muscle fiber’s cytoplasm = the sacroplasm / mostly the contractile proteins
The Nerve-Muscle Relationship

- somatic motor neurons or cranial nerves
  - nerve cells whose cell bodies are in the brainstem and/or spinal cord
  - Nerve axons “connect to” skeletal muscles
  - somatic motor fibers (axons)
    - axons of somatic motor neurons that lead to the skeletal muscle
    - each nerve fiber branches out to a number of muscle fibers (terminal knobs)
    - each muscle fiber is supplied by only one motor neuron
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The Neuromuscular Junction

• **synapse** = point where a nerve fiber meets target tissue
  
  – pre-synaptic membrane / synaptic cleft / post-synaptic membrane

• **neuromuscular junction (NMJ)** = special type of synapse // when target cell is a muscle fiber
  
  – each terminal branch of the nerve fiber within the NMJ forms separate synapse with the muscle fiber
Components of Neuromuscular Junction

• **synaptic knob** - swollen end of nerve fiber
  - contains synaptic vesicles filled with acetylcholine (ACh)
  - synaptic vesicles undergo exocytosis releasing ACh into synaptic cleft

• **synaptic cleft** - tiny gap between synaptic knob and muscle sarcolemma

• **Schwann cell** - envelops & isolates all of the NMJ from surrounding tissue fluid
Components of Neuromuscular Junction

- ACh receptors – 50 million protein receptors incorporated into muscle cell plasma membrane
  - junctional folds of sarcolemma beneath synaptic knob // increases surface area holding ACh receptors
  - lack of receptors leads to paralysis in disease myasthenia gravis

- basal lamina - thin layer of collagen and glycoprotein separates Schwann cell and entire muscle cell from surrounding tissues
  - contains acetylcholinesterase (AChE) that breaks down ACh after contraction causing relaxation
The Neuromuscular Junction

- Motor nerve fiber
- Myelin
- Schwann cell
- Basal lamina
- Synaptic knob
- Synaptic vesicles (containing ACh)
- Synaptic cleft
- Sarcolemma
- ACh receptor
- Junctional folds
- Nucleus
- Sarcoplasm
- Mitochondria
- Myofilaments
Neuromuscular Junction - LM

Motor nerve fibers

Neuromuscular junction

Muscle fibers

100 μm
Electrically Excitable Cells

- muscle fibers and neurons are electrically excitable cells
  - their plasma membrane open voltage regulated channels in response to stimulation

- electrophysiology - the study of the electrical activity of cells

- voltage = an electrical potential
  - a difference in electrical charge between two points
  - a difference in “ions” can cause an electrical potential
  - in cells it occurs across the plasma membrane

- resting membrane potential // about -90mV // maintained by sodium-potassium pump
Electrically Excitable Cells

- In an unstimulated (resting) cell
  - there are more anions (negative ions) on the inside of the plasma membrane than on the outside
  - the plasma membrane is electrically polarized (charged)
  - there are excess sodium ions (Na⁺) in the extracellular fluid (ECF)
  - there are excess potassium ions (K⁺) in the intracellular fluid (ICF)
  - also in the ICF, there are anions such as proteins, nucleic acids, and phosphates that cannot penetrate the plasma membrane
  - these anions make the inside of the plasma membrane negatively charged by comparison to its outer surface
Stimulated (active) muscle fiber or nerve cell

1. **ion gates open** in the plasma membrane
2. **Na**⁺ instantly diffuses down its concentration gradient into the cell
3. these cations override the negative charges in the ICF
4. **depolarization** - inside of the plasma membrane becomes briefly positive
5. immediately, **Na**⁺ **gates close** and **K**⁺ **gates open**
6. **K**⁺ **rushing out** of cell
7. repelled by the positive sodium charge and partly because of its concentration gradient
8. loss of positive potassium ions turns the membrane negative again (**repolarization**)
Electrically Excitable Cells

- **action potential**
  
  - quick up-and-down voltage shift from the negative RMP to a positive value, and back to the negative value again.
  
  - seen in an *active stimulated cell*
  
  - an action potential at one point on a plasma membrane causes another one to happen immediately in front of it
  
  - which triggers another one a little farther along and so forth (appropriates a wave of negativity moving across the plasma membrane)

- **RMP (resting membrane potential)** is a stable voltage seen in an non-stimulated or waiting muscle or nerve cell
In the early 1950s the hypothesis to explain skeletal muscle function was thought to be proteins which folded like an accordion.

With the introduction of the electron microscope, we were able to “see” the thin and thick proteins in skeletal muscles.

These proteins did not shorten during contraction (no accordion-like action).

Original hypothesis proved wrong and new hypothesis formulated suggesting that as the muscle fiber shortened the proteins would slide across each other. This hypothesis was proven to be correct which became known as the sliding filament theory.
The Contraction Cycle

• Contraction cycle = repeating sequence of events

• Results in myosin and actin sliding across each other – bringing Z-disc closer together (muscle shortening)

• Four Steps:
  – ATP hydrolysis
  – Attachment of myosin to actin to form cross-bridge
  – Power stroke
  – Detachment of myosin from actin
1. Myosin heads hydrolyze ATP and become reoriented and energized.

2. Myosin heads bind to actin, forming cross-bridges.

3. Myosin cross-bridges rotate toward the center of the sarcomere (power stroke).

4. As myosin heads bind ATP, the cross-bridges detach from actin.

Contraction cycle continues if ATP is available and Ca²⁺ level in sarcoplasm is high.

Key:

- dot = Ca²⁺
Muscle Contraction & Relaxation

• Four major phases of contraction and relaxation

  – **excitation**
    • the process in which nerve action potentials lead to muscle action potentials

  – **excitation-contraction coupling**
    • events that link the action potentials on the sarcolemma to activation of the myofilaments, thereby preparing them to contract

  – **contraction (the contraction cycle)**
    • step in which the muscle fiber develops tension and may shorten

  – **relaxation**
    • when its work is done, a muscle fiber relaxes and returns to its resting length
Excitation (steps 1 and 2)

- nerve signal opens voltage-gated calcium channels in synaptic knob
- calcium stimulates exocytosis of ACh from synaptic vesicles
- ACh released into synaptic cleft
Excitation (steps 3 and 4)

- two ACh molecules bind to each receptor protein, opening Na⁺ and K⁺ channels.

- Na⁺ enters shifting RMP goes from -90mV to +75mV then K⁺ exits and RMP returns to -90mV quick voltage shift is called an end-plate potential (EPP).
Excitation (step 5)

Voltage change (EPP) in end-plate region opens nearby voltage-gated channels producing an action potential that spreads over muscle surface.
Excitation-Contraction Coupling
(steps 6 and 7)

- action potential spreads down into T tubules
- opens voltage-gated ion channels in T tubules and Ca\(^{+2}\) channels in SR
- Ca\(^{+2}\) enters the cytosol
• calcium binds to troponin in thin filaments

• troponin-tropomyosin complex changes shape and exposes active sites on actin
**Contraction**
(Steps 10 and 11)

- **Myosin ATPase enzyme in myosin head hydrolyzes an ATP molecule**

- **This reaction occurs independent of the actin – troponin – tropomyosin event**

- **Myosin head is activated = the head “cocking” that extends head**
  - ADP + P<sub>i</sub> remain attached

- **Head binds to actin active site forming a myosin - actin cross-bridge**

- **Now ADP + P released**
• **The Power Stroke**
  
  – Myosin head flexes
  
  – Myosin head releases ADP and P_i
  
  – Pulling thin filament past thick
  
  – Myosin head can not release actin until ATP binds to myosin and “breaks bridge”
  
• Only upon binding more **ATP** to the myosin head
  
  – Myosin releases actin and process is repeated
  
  – each head performs 5 power strokes per second
  
  – each stroke utilizes one molecule of ATP
Relaxation (steps 14 and 15)

- Stopping nerve stimulation stops ACh release
- AChE breaks down Ach // fragments reabsorbed into synaptic knob
- Stimulation by ACh stops
Relaxation (step 16)

- $\text{Ca}^{+2}$ pumped back into SR by active transport.

- $\text{Ca}^{+2}$ binds to calsequestrin while in storage in SR.

- ATP is needed for
  - muscle relaxation
  - as well as muscle contraction.

Reabsorption of calcium ions by sarcoplasmic reticulum.
Relaxation (steps 17 and 18)

- Ca\(^{2+}\) removed from troponin is pumped back into SR
- Tropomyosin reblocks the active sites
- Muscle fiber ceases to produce or maintain tension
- Muscle fiber returns to its resting length
  - due to recoil of elastic components & contraction of antagonistic muscles

\[ \text{ADP} \rightarrow \text{ATP} \]

\[ \text{Pi} \]

\[ \text{Ca}^{2+} \]

\[ \text{Tropomyosin} \]

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Motor unit = one nerve fiber and all the muscle fibers innervated by the single nerve fiber
Motor Units

- **small motor units** - fine degree of control // 3-6 muscle fibers per neuron // eg eye and hand muscles

- **large motor units** – more strength than control // many muscle fibers per motor unit
Motor Units

How do we use motor units?
Motor Units

- dispersed throughout the muscle
- contract in unison
- produce weak contraction over wide area
- Activate more motor units to increase strength of contraction
- provides ability to sustain long-term contraction as motor units take turns contracting (postural control)
- effective contraction usually requires the contraction of several motor units at once
Rigor Mortis

• Hardening of muscles and stiffening of body after death

  – begins 3 to 4 hours after death // peaks after twelve hours

  – deteriorating sarcoplasmic reticulum releases Ca\(^{+2}\)

  – deteriorating sarcolemma allows Ca\(^{+2}\) to enter cytosol

  – Ca\(^{+2}\) activates myosin-actin cross-bridge

  – muscle contracts

  – but muscle can not relax // new ATP required to “break” myosin-actin cross bridge
Rigor Mortis

- True muscle relaxation requires ATP
  - “free” ATP only last a few seconds in the cytoplasm
  - ATP production not produced after death

- After rigor mortis muscle organ “starts to relax” as myofilaments proteins start to be hydrolyzed by lysosomal activity
  - then diminishes over the next 48 to 60 hours
Neuromuscular Toxins

Some toxins interfere with synaptic function and can result in either spastic paralysis or flaccid paralysis of the muscles

- Spastic paralysis – over stimulated and muscle can not relax
  - some pesticides contain cholinesterase inhibitors
- bind to acetylcholinesterase and prevent it from degrading ACh
- spastic paralysis - a state of continual contraction of the muscles
- possible suffocation
  - tetanus (lockjaw) is a form of spastic paralysis caused by toxin of Clostridium tetani
- glycine in the spinal cord normally stops motor neurons from producing unwanted muscle contractions
  - tetanus toxin blocks glycine release in the spinal cord and causes over stimulation and spastic paralysis of the muscles
Neuromuscular Toxins

Some toxins interfere with synaptic function and can result in either spastic paralysis or flaccid paralysis of the muscles.

- Flaccid paralysis – a state in which the muscles are limp and cannot contract
  - curare – compete with ACh for receptor sites, without stimulating the muscles
    - plant poison used by South American natives to poison blowgun darts
  - botulism – type of food poisoning caused by a neuromuscular toxin secreted by the bacterium *Clostridium botulinum*
    - blocks release of ACh causing flaccid paralysis
    - *Botox Cosmetic* injections for wrinkle removal