General Education Program

Physiology 1

Skeletal Muscle Physiology (part 2)

Presented by:

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Objectives

• Muscle energetics
• Abnormalities in muscle contraction
• Changes Following Skeletal Muscle Stimulation
MUSCLE ENERGETICS
• 1 muscle fiber = 15 billion filaments
• 1 filament uses 2500 ATPs/second
• Can’t store all necessary ATP
• Resting fiber contains enough ATP to sustain contraction until more can be generated
• ATP used at same rate as created
• ATP & CP reserves
• ATP Generation (Cellular Respiration)
• Muscle Activity
• Muscle Fatigue
• Muscle Recovery
• Hormones & Muscle Metabolism
ATP & CP Reserves

- ATP + creatine $\rightarrow$ ADP + CP
- Reverse reaction for use during contraction
- Creatine Phosphokinase (CPK) facilitator
- Resting fibers contains 6 times as much CP as ATP
- 17 second reserves
- Table 10-2 Sources of Energy in Fiber
ATP Generation

- Glycolysis breaks down glucose to pyruvate in the_________
- Aerobic Metabolism occurs in __________
**Muscle Activity**

- Resting Skeletal Muscle
  - CP + build Glycogen reserves from fatty acids & glucose
- Moderate Levels of Activity
  - All ATP is needed
- Peak Levels of Activity (anaerobic)
  - Lactic Acid fermentation and Glycolysis
  - Drop pH, exhaustion CP + ATP
Muscle Fatigue

- Normal Functioning Requirements
- Causes of Muscle Fatigue
  - ATP & CP
  - Lactic Acid (anaerobic conditions)
- Types of Fatigue
  - ATP & CP
  - Lactic acid
  - Glycogen, aa, lipid reserves
- Disorders
A New Explanation of Muscle Fatigue

Muscle contraction and relaxation are controlled by the release and storage of calcium ions within muscle fibers. Scientists at Columbia University say that muscle fatigue, largely misunderstood for decades, is caused by calcium leaking into muscle cells.

**MUSCLE CONTRACTION**
Calcium ions are released into the cell, causing filaments in the muscle fiber to contract.

**MUSCLE RELAXATION**
Calcium ions are pumped into storage, allowing the muscle filaments to relax.

Sources: Andy Marks; PNAS

THE NEW YORK TIMES
Muscle Recovery Period

- Lactic Acid Removal and Recycling (Liver & Muscles- Cori cycle)
- Oxygen Debt (resp., circ., liver, muscles, secretory)
- Heat Loss
a. To start contracting, muscles break down creatine phosphate.

b. To continue contracting, muscles either carry on cellular respiration (preferred) or carry on fermentation, which can lead to fatigue.

Creatine phosphate breakdown

In resting muscle, creatine phosphate is built up.

In a contracting muscle, ATP is broken down to ADP + P.
Hormones & Muscle Metabolism

- **Growth Hormone**- pituitary
- **Testosterone**
  - Stimulate synthesis contractile proteins & enlarge muscles
- **Thyroid Hormones**
  - Elevate rate of energy consumption of muscles
- **Adrenal Hormones**- Epinephrine/Adrenaline
  - Stimulate muscle metabolism, increase duration of stimulation & force contraction
CHANGES FOLLOWING SKELETAL MUSCLE STIMULATION
Changes Following Skeletal Muscle Stimulation

- Stimulation of the skeletal muscle through its nerve supply is followed by many changes:

1. Electrical changes.
2. Excitability changes
3. Mechanical changes.
4. Metabolic changes.
Electrical Changes Following Skeletal Muscle Stimulation

- The electrical events in skeletal muscle and the ionic fluxes underlying them are similar to those in nerve, although there are quantitative differences in timing and magnitude. The resting membrane potential of skeletal muscle is about -90 mV.
- The action potential lasts 2-4 ms and is conducted along the muscle fibre at about 5 m/sec. The action potential precedes the contraction by about 2 msec.
The electrical and mechanical responses of a mammalian skeletal muscle fiber to a single maximal stimulus.
Excitability Changes Following Skeletal Muscle Stimulation

• Skeletal muscle fibre, like nerve fibre, is refractory to re-stimulation during the action potential. It will be noted that as the muscle begins to contract, it has regained its excitability.
Excitability Changes Following Skeletal Muscle Stimulation

• The latent period of the mechanical response coincides with the ascending limb and part of the descending limb of spike potential, which corresponds to the absolute refractory period.
Mechanical Changes Following Skeletal Muscle Stimulation

• The contractile Response
• "Excitation-Contraction (EC) Coupling"
• It is the process by which an action potential initiates the contractile process.
Calcium Release: Excitation/Contraction Coupling

1. Acetylcholine released by axon of motor neuron across cleft and binds to receptors/channels on motor end plate.

2. Action potential generated in response to binding of acetylcholine and subsequent end plate potential is propagated across surface membrane and down T tubules of muscle cell.

3. Action potential triggers Ca$^{2+}$ release from sarcoplasmic reticulum.

4. Calcium ions released from lateral sacs bind to troponin on actin filaments; troponin physically moves aside to uncover cross-bridge binding sites on actin.

5. Ca$^{2+}$ actively taken up by sarcoplasmic reticulum when there is no longer local action potential.

6. Calcium ions no longer bound to troponin, troponymosin slips back to its binding position over binding sites on actin; contraction ends; actin slides back to original resting position.

7. Myosin cross bridges attach to actin and bend, pulling actin filaments toward center of sarcomere; powered by energy provided by ATP.
Types of Contraction of Skeletal Muscle:

There are 2 types of muscle contraction:

1- Isotonic contraction:

This occurs when the muscle shortens but the muscle tension remains constant.

2- Isometric contraction:

Refers to a contraction in which the external length of the muscle does not change through the tension is highly increased.
The skeletal muscles contain, in addition to the contractile element (CE), they have elastic and viscous elements in series with the contractile element and present mainly in the tendons, the series elastic component (SEC).
• During muscle contraction a load (weight) is moved.
• In isotonic contraction, the “CE” shortens and the “SEC” is not markedly stretched “because the load is moved " because the load is moved " So, the whole muscle is shortened & its tension remains constant.
• In isometric Contraction, the " CE" shortens & the " SEC" is greatly stretched " because the load is not moved " So, the whole muscle is not shortened & its tension is markedly increased.
The work done by the muscle is:
Weight in Kg X the distance the weight is moved in motor = Kgm.
Muscle contracts (isotonic contraction)

Muscle contracts (isometric contraction)

Amount of resistance

Peak tension production

Contraction begins

Muscle relaxes

Muscle tension (kg)

Contraction begins

Resting length

Muscle length (percent of resting length)

Time

Amount of resistance

Peak tension production

Muscle relaxes

Contraction begins

Length unchanged

Muscle tension (kg)

Muscle length (percent of resting length)

Time
There are several basic differences between isometric and isotonic contractions.

1- Tension changes. Mentioned above

2- Length changes. Mentioned above

3- In isometric contraction, there is no much sliding of myofibrils along each others, in contrast to isotonic contraction.
There are several basic differences between isometric and isotonic contractions.

4- In isotonic contraction a load is moved a distance, which involves the phenomenon of inertia [that is the weight being moved must first be accelerated] and momentum that interfere greatly with the record of the twitch.

Therefore, isotonic contraction lasts longer and needs a greater amount of energy than isometric contraction.
There are several basic differences between isometric and isotonic contractions.

5- Isotonic contraction does **external work** since the load is moved a distance. The **mechanical efficiency** (the percentage of energy input that is converted into work instead of heat) is about 20-25%.

In isometric contraction since load $X$ distance is zero, no external work is done by the muscle and the mechanical efficiency is zero.
There are several basic differences between isometric and isotonic contractions.

6- Isotonic contraction evokes movement of part of the body or the body as a whole. Isometric contraction tenses a part of the body and maintains the posture against gravity.
• **N.B.:** Muscles can contract both isometrically and isotonically in the body, but most contractions are actually a mixture of the two.

• a. When standing, person tenses the quadriceps muscles to tighten the knee joints and to keep the leg stiff (isometric contraction).

• During running, contractions of leg muscles are a mixture of isometric [when the legs hit the ground] and isotonic contractions [to move the limbs].

• When a person lifts a heavy weight using the biceps, the contraction starts isometrically and completed isotonically.

• With heavier loads:
  • The duration of isometric contraction phase is longer.
  • The rate and extent of muscle shortening during isotonic contraction is less.
Factors Affecting Skeletal Muscle Contraction

• The contractile properties of the skeletal muscle by recording isometric and isotonic contractions reveal that muscle contraction is affected by many factors.

• 1- Type of muscle fibers;

• Human skeletal muscles contain mainly 2 types of muscle fibers:
a. **Slow (Red) Fibers**:

These are also called: **type I fibers**, which are characterized by the following:

- They are small muscle fibres innervated by small slowly conducting motor neurons.
- They contain large numbers of oxidative enzymes (i.e. high mitochondrial volume).
- They have *low* ATPase activity.
- They are surrounded by more extensive capillaries to supply extra amounts of oxygen.
- They contain a higher concentration of myoglobin, which stores oxygen until need.

*The above data provides fibre with:*

- Large capacity for aerobic metabolism and a high resistance to fatigue.
- Slow contractile mechanism.
b. Fast (pale) Fibers:

These are also called: type II b fibers, which are characterized by the following:

- They are larger fibers innervated by large rapidly-conducting motor neurons.
- They contain extensive sarcoplasmic reticulum for rapid release of calcium ions.
- They have large amounts of glycolytic enzymes for rapid release of energy by the glycolytic process.
- They have high AT Pase activity.
- They contain less blood supply, less myoglobin content, and fewer mitochondria.

The above data provide type II b fibers with:

a. Rapid contractile mechanisms
b. Less resistance to fatigue
% of Maximal Tension

Time in milliseconds (msec)

Peak Tension/fiber area

0 30 75

Type II (fast)
Type I (slow)
Factors Affecting Skeletal Muscle Contraction

(2) **Stimulus Factors:**

- **a- Strength of the stimulus:**

  Increasing the strength of stimulus will increase the number of activated fibers [recruitment] with gradual increase in whole muscle response. Maximal stimulus activates all muscle fibers. Supra maximal stimulus would not give further response as each fiber responds maximally according to all or none law.
Factors Affecting Skeletal Muscle Contraction

(2) **Stimulus Factors:**

- **b- The frequency of muscle stimulation:**
  - The force of contraction can be increased by increasing the frequency of muscle stimulation because more Ca\(^{2+}\) is released from the SR each time the muscle is stimulated.
  - With rapidly repeated stimulation, activation of the contractile mechanism occurs repeatedly before any relaxation has occurred, and the individual responses fuse into one continuous contraction called a **tetanus**.
Factors Affecting Skeletal Muscle Contraction

• (2) **Stimulus Factors:**
  
• **b- The frequency of muscle stimulation:**
  
It is **complete tetanus** when there is no relaxation between stimuli and an **incomplete tetanus** when there are periods of incomplete relaxation between the gathered stimuli. This phenomenon is known as **summation of contractions.**
Factors Affecting Skeletal Muscle Contraction

- (2) **Stimulus Factors:**
  - **b- The frequency of muscle stimulation:**
  - During a complete tetanus, the tension developed is about 4 times that developed by the individual twitch contractions. This phenomenon may be described as follows: By repeatedly stimulating the muscle, the level of free calcium ions in the myofibrils remains continuously above the level required for full activation of the contractile process i.e. continuous cycling of the cross-bridges.
• **Treppe "The Stair Case Phenomenon":**
  - It refers to the progressive increase in the magnitude of separate twitch contraction of skeletal muscle to a plateau value during repetitive stimulation after a period of rest. This phenomenon is explained by the persistent elevated levels of free Ca$^{2+}$ in the cytoplasm.
Fig. [12]: Effects of Repeated Stimulation.
(a) Treppe is an increase in peak tension with each successive stimulus delivered shortly after the completion of the relaxation phase of the preceding twitch. (b) Wave summation occurs when successive stimuli arrive before the relaxation phase has been completed. (c) Incomplete tetanus occurs if the stimulus frequency increases further. Tension production rises to a peak, and the periods of relaxation are very brief. (d) During complete tetanus, the stimulus frequency is so high that the relaxation phase is eliminated; tension plateaus at maximal level.
Factors Affecting Skeletal Muscle Contraction

- (3) **Length-tension relationship**
  - Measures tension developed during isometric contractions when the muscle is set to fixed lengths (preload).
  - a. Passive, tension is the tension developed by stretching the muscle to different lengths.
  - b. Total tension is the tension developed when the muscle is stimulated to contract at different lengths.
  - c. Active., tension is the difference between total tension and passive tension.
• There is a relationship between the initial muscle fibre length [preload] and the active tension developed during its isometric contraction.
a- Maximal force is obtained when the muscle fibre length is set at a sarcomere length of 2.2 u. This is the resting length of the muscle inside the body. At this length, the overlap between thick and thin filaments is optimal, since every cross-bridges from the thick filament is opposite an actin molecule.
b- Increasing the length of the muscle fibre causes a decrease in the force development. At sarcomere length greater than 2.2 u, the overlap between thick and thin filaments is decreased. Thus, some cross-bridges do not have actin filaments to combine with.
• c- Decreasing the sarcomere length below 2.2um causes a decrease in force development. At this condition, the ends of the two action filaments overlap each other, in addition to overlapping the myosin filaments, making it more difficult for the muscle to develop force.
Factors Affecting Skeletal Muscle Contraction

• (4) **Load-Velocity Relationship:**

• In isotonic contraction, for the muscle to shorten, it must lift a weight, called **afterload**, which is applied after the muscle begins to contract. Increasing the afterload has the following effects:

  • a. The velocity of shortening decreases as the afterload increases because each cross-bridge cycle takes longer.

  • b. The amount of shortening decreases as the afterload increases. As the muscle shortens below a sarcomere length of 2.2 um, its ability to generate force decreases.

  • c. The maximal velocity of shortening (\( V_{\text{max}} \)) occurs when there is no external load (zero load).
N.B. 1. $V_{\text{max}}$ is theoretical, because load can not be zero.
2. Muscles with predominant fast fibres have a greater $V_{\text{max}}$. 
N.B. a) **Preload** is the load that a muscle experiences before the onset of contraction.

b) **After load** is a load that is encountered by the muscle only after it starts to contract.
Factors Affecting Skeletal Muscle Contraction

5) **Muscle Fatigue:**

Prolonged and strong contraction of a muscle leads to a state of muscle fatigue, which decreases the strength of contraction, prolongs its duration, and relaxation becomes incomplete [**contracture**]. This effect is due to:

a- Accumulation of metabolites, such as lactic acid which increases intracellular acidity.

b- Depletion of muscle ATP, glycogen and creatine phosphate.

c- Interruption of blood flow through a contracting muscle and loss of nutrient supply, especially loss of oxygen.

d- Diminished transmission at neuromuscular junction.
Metabolic Changes Following Skeletal Muscle Stimulation

**Diagram:**
- **Blood:**
  1. Phosphorylcreatine → Creatine
  2. Glucose → Glycolysis → Lactic Acid
  3. Oxygen → Oxidative Phosphorylation

- **Muscle Fiber:**
  - Contraction
  - ADP + Pi → ATP
  - Ca²⁺ ATPase → Relaxation
  - Myosine ATPase
Grading muscular activity: Increase force of contraction inside the body

- It has been shown by electromyography that there is little activity in the muscle at rest.

a- With minimal voluntary activity, a few motor units discharge, and with increasing voluntary effort more units contract, this process is called recruitment of motor units.

b- The force of a voluntary movement is also increased by increasing the frequency of discharge of impulses to the motor unit leading to tetanic contractions
Grading muscular activity: Increase force of contraction inside the body

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Grading muscular activity: Increase force of contraction inside the body

It was observed by electromyography that during voluntary movements of moderate intensity the rate of discharge of impulses to the motor units would produce clonic contractions. The motor units contract a synchronously, the responses of the various motor units merge into a smooth contraction of the whole muscle.
Two motor unit A and B show subtetanic (clone) contractions. Asynchronous discharge of both units will lead to smooth contraction of greater force (C).
Muscular hypertrophy

• It is the increase in size of muscle as a result of forceful muscular activity.
• The number of the muscle fibers in the muscle does not change.
• The muscle fibers increase in thickness.
• They gain in total number of myofibrils as well as in their content of ATP, creatine phosphate and glycogen
ABNORMALITIES IN MUSCLE CONTRACTION
Reaction of muscle to denervation

- If the nerve supply to the muscle is injured, the muscle is paralyzed. This is known as lower motor neurone lesion:
Reaction of muscle to denervation

- a) **The muscle atrophies** i.e. it decreases in size and muscle fibers are replaced gradually by fibrous tissue.
Reaction of muscle to denervation

b) **Muscle fasciculation**: as the nerve fibers degenerate, spontaneous impulses are discharged during the first few days. This produces contraction of the motor units sufficient to be seen in the skin over the muscle. Electromyographic records of such fasiculatory muscle contractions can be picked by metal disc electrodes placed on the skin overlying the paralyzed muscles.
Reaction of muscle to denervation

- **c) Muscle fibrillation**: After all nerves to the muscle are destroyed and the nerve fibers stop to function, spontaneous impulses begin to appear in the denervated muscle fibers. The contractions of the muscle fibers as a result of these spontaneous impulses are very weak and cannot be seen. Electromyographic records of these spontaneous contractions can be picked only by needle electrodes inserted in the muscle.

- These spontaneous impulses from the denervated muscle fibers are due to **increased sensitivity** of the denervated muscle fibers to circulating acetylcholine i.e. **denervation hypersensitivity**.
Reaction of muscle to denervation

d) Reaction of degeneration:
- It is the changes, which occur in the response of the denervated muscle to electrical stimulation
Drugs that increase or block transmission at the Neuromuscular Junction:
1. Drugs that block release of Ach.

• E.g: Botulinum toxin, lack of Ca, excess of Mg.
• Botulinum prevents the release of Ach by blocking the fusion of Ach containing vesicles with the postsynaptic membrane & thus prevents the exocytosis of these vesicles. It has some therapeutic use to relieve pain of pathological contraction.
• Lack of Calcium also leads to blocking of exocytosis of the secretory vesicles.
2. Drugs that stimulate the muscle fibre by Ach-like Action

- Example: *methacholine, carbachol, and nicotine*

- They have the same effect on the muscle fiber as does Ach. The difference b/w these drugs and Ach is that the drugs are **NOT** destroyed by cholinesterase or are destroyed so slowly that their action often persists for many minutes to several hours.
2. Drugs that stimulate the muscle fibre by Ach-like Action

• The drugs work by causing localized areas of depolarization of the muscle fiber membrane at the motor end plate where the acetylcholine receptors are located. Then, every time the muscle fiber recovers from a previous contraction, these depolarized areas, by virtue of leaking ions, initiate a new action potential. Thus, there is a **constant state of muscle spasm**.
3. Drugs That Stimulate the Neuromuscular Junction by Inactivating Acetylcholinesterase.

- Neostigmine, physostigmine, and diisopropyl fluorophosphate

- They inactivate the acetylcholinesterase by combining with it in the synaptic cleft so that it no longer hydrolyzes acetylcholine. Therefore, with each successive nerve impulse, additional acetylcholine accumulates and stimulates the muscle fiber repetitively.
3. Drugs That Stimulate the Neuromuscular Junction by Inactivating Acetylcholinesterase.

- This causes *muscle spasm* when even a few nerve impulses reach the muscle. Unfortunately, it can also cause death due to laryngeal spasm, which smothers the person.
- Neostigmine and physostigmine work for a few hours.
- Diisopropyl fluorophosphate is effective for weeks. This makes it a particularly lethal poison with great military potential. It is thus used as a powerful “nerve gas poison”.

Nerve Gas
4. NON-DEPOLARIZING DRUGS: Drugs That Block Transmission at the Neuromuscular Junction.

- A group of drugs known as *curariform drugs e.g. D-tubocurarine* can prevent passage of impulses from the nerve ending into the muscle. This is done by competing with the Ach for the receptor sites on the postsynaptic membrane. When this drug is bound to these receptor sites, then Ach cannot act on them, thus preventing sufficient increase in permeability of the muscle membrane channels to initiate an action potential.
4. NON-DEPOLARIZING DRUGS: Drugs That Block Transmission at the Neuromuscular Junction.

- It can have some therapeutic uses:
  - used with artificial respiration to control convulsions in tetanus.
  - used during surgery when complete muscle relaxation is required.
Myasthenia Gravis

Regional distribution of muscle weakness:
- 95%
- 60%
- 30%
- 10%

Ptosis and weakness of smile are common early signs.

Improvement after edrophonium chloride.

In early stages, patient may feel fine in the morning but develops diplopia and speech slurs later in the day.

Patient with chin on chest cannot resist when physician pushes head back.

Mulroney & Myers: Netter's Essential Physiology.
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MYASTHENIA GRAVIS
It is an autoimmune neuromuscular disorder in which the Neuromuscular junction is blocked.
MYASTHENIA GRAVIS

**Cause:** Auto-antibodies are formed against the Ach receptors on the Motor End Plate. These antibodies completely destroy the receptors. As the receptors are destroyed, the Ach present cannot act upon them and cause an AP. Some patients have other auto-immune disorders as well such as RA, poliomyelitis.
SYMPTOMS:

- Fatigue is the hallmark of Myasthenia gravis. Fatigue is especially seen with prolonged use of the skeletal muscles. Muscles become progressively weaker during periods of activity and improve after periods of rest.
SYMPTOMS:

- Fatigue is usually more pronounced in the proximal muscles as tongue, occulomotor (eye movements), phryngeal (swallowing), laryngeal muscles (talking),
SYMPTOMS:

- Ptosis (drooping of the eyelids)
- Diplopia (double vision)
- Symptoms get better with rest & administration of anticholinesterase drugs (drugs that prevent the Acetylcholinesterase from breaking down the Ach). E.g. edrophonium & neostigmine.
- Patients are usually women in their 30’s.
DIAGNOSIS:
- Presence of autoantibodies in the plasma
- Nerve conduction study
- Edrophonium test

TREATMENT:
- Anti-cholinesterase drugs. E.g: Neostigmine
- Immunosuppressant drugs. E.g: glucocorticoids
- Thymectomy: removal of thymus helps rebalances the immune system.
MYASTHENIC CRISIS:
This occurs when the muscles that control breathing weaken to the point that ventilation is inadequate, creating a medical emergency and requiring a respirator for assisted ventilation. In patients whose respiratory muscles are weak, crises - which generally call for immediate medical attention - may be triggered by infection, fever, or an adverse reaction to medication.
RIGOR MORTIS

Definition:
It is one of the recognizable signs of death in which several hours after death, all the muscles of the body go into a state of irreversible rigidity and contracture called *Rigor Mortis*. The body then becomes difficult to move or manipulate.

On Microscopy:
Continuous Actin-Myosin interaction.

Cause:
After death, cellular respiration in organisms ceases to occur, depleting the corpse (dead body) of oxygen used in the making of *adenosine triphosphate* (ATP).
RIGOR MORTIS

Unlike in normal muscle contraction, after death as ATP is **NOT** available, the body is unable to complete the contraction cycle and release the coupling b/w actin and myosin. We know that a new molecule of ATP is required to interact with the myosin molecule to cause relaxation at the end of a power stroke. When it is not available, relaxation cannot take place and thus, there is a state of continuous muscular contraction.
RIGOR MORTIS (cont)

Mechanism:

1. Absence of ATP → No reuptake of Ca\(^{2+}\) into the SR as Ca\(^{2+}\) uptake also requires ATP-dependant Ca\(^{2+}\) pump → Ca\(^{2+}\) level of sarcoplasm ↑ → continued binding of Ca\(^{2+}\) to Troponin C → Abnormal, rigid and uninterrupted contraction.

2. No ATP → No relaxation a new molecule of ATP must attach to the myosin head for detachment of actin-myosin interaction → thus, when NO ATP is present, then myosin heads cannot detach themselves from actin.
Time Taken:
In humans, it commences after about three to four hours after death,
reaches maximum stiffness after 12 hours, and gradually dissipates until approximately 48 to 60 hours (three days) after death.

Warm conditions can speed up the process of rigor mortis.

When does Rigor Mortis end:
when contractile proteins of the muscle like other body tissues undergo autolysis caused by enzymes released by lysosomes.
Botulism

- *C. Botulinum*
  - Gram-positive obligate anaerobic bacillus
  - Spore-forming
  - Produces botulinum toxin
  - Heat sensitive as bacillus
  - Prefers low acid environment
Microbiology

- *C. Botulinum* spores
  - Ubiquitous
    - Soil
    - Airborne dust
    - Surfaces of raw fruits and vegetables
    - Seafood
  - Heat resistant, hardy
Microbiology

- Botulinum toxins
  - Consist of light and heavy chains
    - Light chain – zinc endopeptidase
      - The bioactive component
  - Colorless, odorless
  - Environmental survival
    - Inactivated by heat >85°C for 5 min
    - pH <4.5
Microbiology

• Toxin Classification
  • All have same clinical effect
  • Types A-G, antigenically distinct
    • Type A- 54%, Type B- 15%, Type E- 27%
    • Type A- Western U.S., Type B- Eastern
    • Types C, D reported in animals only
    • Type G in soil samples only
    • Humans likely susceptible to all types
Pathogenesis

• Possible routes of exposure
  • Inhalation of toxin (in a biological attack)
  • Food or water toxin contamination
  • Wound infected with *C. Botulinum*
  • Ingestion of *C. botulinum*
Pathogenesis

• Toxin must enter body
  • Direct toxin absorption from mucosal surface
    • Gut – foodborne
    • Lungs – inhalational
  • Via toxin produced by infection with \textit{C.botulinum}
    • Skin breaks – wound botulism after trauma, IV drugs
    • Gut – intestinal botulism
    • Would not be seen in BT event, as toxin would be used
• Does not penetrate intact skin
Pathogenesis

- All forms of disease lead to same process
  - Toxin absorbed into bloodstream
  - Irreversibly binds peripheral cholinergic synapses
  - Cleaves fusion proteins used by neuronal vesicles to release acetylcholine into neuromuscular junction
  - Blocks Acetylcholine release permanently
    - Results in paralysis of that muscle
  - Reinnervation via regeneration of axon twigs
    - Takes weeks to months
Normal Neurotransmitter Release

SNARE Proteins Form Complex

Vesicle and Terminal Membranes Fuse

Neurotransmitter Released

Acetylcholine

Muscle Fiber Contracts
B Exposure to Botulinum Toxin

Botulinum Toxin Endocytosed

Light Chain Cleaves Specific SNARE Proteins

Types B, D, F, G

Light Chain

Types A, C, E

Heavy Chain

Type C

SNARE Complex Does Not Form

Membranes Do Not Fuse

Botulinum Toxin

Neurotransmitter Not Released

Muscle Fiber Paralyzed

MUSCLE CELL

C. Lynn
Clinical Features

- Symptoms
- All forms same neuro symptoms
  - Diplopia / blurred vision
  - Ptosis
  - Slurred speech
  - Dysphagia / dry mouth
  - Muscle weakness
Clinical Features

- Infant botulism specifically
  - Appears lethargic
  - Feeds poorly
  - Constipated
  - Weak cry
  - Poor muscle tone
Clinical Features

• **Classic Triad**
  - Symmetric, descending flaccid paralysis with prominent bulbar palsies
  - Afebrile
  - Clear sensorium

• **Bulbar palsies summarized as "4 Ds"**
  - Diplopia, dysarthria, dysphonia, dysphagia
Clinical Features

Ptosis, disconjugate gaze, mild asymmetric smile.

Patient at rest, bilateral mild ptosis, disconjugate gaze, symmetric facial muscles.
Clinical Features

• Symptom progression
  • Descending paralysis
    • Lose head control
    • Lose gag – require intubation
    • Lose diaphragm – mechanical ventilation
  • Loss of deep tendon reflexes
<table>
<thead>
<tr>
<th>Gastrointestinal/Urinary</th>
<th>Neurologic</th>
<th>Muscular</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>Dry Mouth</td>
<td>Symmetrical skeletal muscle weakness</td>
</tr>
<tr>
<td>Vomiting</td>
<td>Blurry vision</td>
<td>Respiratory muscle paralysis</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Diplopia</td>
<td>Fatigue</td>
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<tr>
<td>Abdominal Pain</td>
<td>Dilated or unreactive pupils</td>
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<td>Intestinal ileus</td>
<td>Dysphagia</td>
<td></td>
</tr>
<tr>
<td>Urinary retention</td>
<td>Decreased gag reflex</td>
<td></td>
</tr>
</tbody>
</table>
Clinical Features

• 4 clinical forms of botulism
  • Food-borne (first described in 1897)
  • Wound (1943)
  • Infant (1976)
  • Indeterminate (1977)
Clinical Features

• Infant
  • Occurs in children < one year old
  • Ingests spores, grows in bowel & release toxin
  • Intestinal colonization of organisms
  • Normal intestinal flora not developed
Clinical Features

• Indeterminate
  • No specific food or wound source identified
  • Similar to infant but occurs only in adults
  • Risk factor: surgical alterations of the GI tract and/or antibiotic therapy
  • Leads to colonization
Botulism
Thank You!