SLIDING FILAMENT THEORY

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What are Cross-bridges?

- With an electron microscope, fine cross bridges can be seen extending from each thick filament to the thin filament. These are formed by the arm and head of the myosin molecules projecting outward from the tail, and pointing towards the thin filaments.
SLIDING FILAMENT THEORY

Definition:
When a muscle cell contracts, the thin filaments slide past the thick filaments, and the sarcomere shortens. This process comprised of several steps is called the Sliding Filament Theory. It is also called the Walk Along Theory or the Ratchet Theory.
After the ATP has bound to the myosin head, the binding of Myosin to Actin molecule takes place:
Once the actin active sites are uncovered, the myosin binds to it:
Power Stroke

Movement

Active sites

Actin filament

Hinges

Power stroke

Myosin filament
POWER STROKE

1. Binding: Myosin cross bridge binds to actin molecule.

2. Power stroke: Cross bridge bends, pulling thin myofilament inward.

3. Detachment: Cross bridge detaches at end of power stroke and returns to original conformation.

4. Binding: Cross bridge binds to more distal actin molecule; cycle repeats.
SLIDING FILAMENT THEORY

It has the following steps:
1. Before contraction begins, an ATP molecule binds to the myosin head of the cross-bridges.
2. The ATPase activity of the myosin head immediately cleaves the ATP molecule but the products (ADP+P) remains bound to the head. Now the myosin head is in a high energy state and ready to bind to the actin molecule.
3. When the troponin-tropomyosin complex binds with calcium ions that come from the sarcoplasmic reticulum, it pulls the tropomyosin so that the active sites on the actin filaments for the attachment of the myosin molecule are uncovered.
4. Myosin head binds to the active site on the actin molecule.
5. The bond b/w the head of the cross bridges (myosin) & the actin filaments causes the bridge to change shape bending 45° inwards as if it was on a hinge, stroking towards the centre of the sarcomere, like the stroking of a boat oar. This is called a **POWER STROKE**.

6. This power stroke pulls the thin filament inward only a small distance.

7. Once the head tilts, this allows release of ADP & phosphate ions.

8. At the site of release of ADP, a new ATP binds. This binding causes the detachment of the myosin head from the actin.


10. Repeated cycles of cross-bridge binding, bending and detachment complete the shortening and contraction of the muscle.
Shortening of the Muscle:

- The thick and thin filaments DO NOT shorten.
- Contraction is accomplished by the thin filaments from opposite sides of each sarcomere sliding closer together or overlapping the thick filaments further.
- The H-zone becomes smaller as the thin filaments approach each other.
- The I band becomes smaller as the thin filaments further overlap the thick filaments.
- The width of the A band remains unchanged as it depends on the thick filaments and the thick filaments do not change length.
When muscle contracts, the sarcomere shortens. The I band and H Zone also shorten. But the length of the A band remains the same.
NEUROMUSCULAR JUNCTION
**NEUROMUSCULAR JUNCTION**

A NEUROMUSCULAR JUNCTION is an area of contact between a muscle fibre and a neuron.

Fig. An electron micrographic sketch of the junction between a single axon terminal and the muscle fiber membrane.
**MOTOR END-PLATE**

**Definition:**

It is the specialized portion of a muscle fibre immediately under a terminal nerve fibre. The nerve fibre invaginates a muscle fibre but lies outside the muscle fibre plasma membrane. The entire structure is called the motor end-plate.
A neuromuscular junction thus consists of:

- **Presynaptic terminal** (Nerve fibre) with vesicles containing the NT.
- A **synaptic cleft** (20-30 nm wide): which is a synaptic trough or gutter.
- **Motor End Plate**: which has numerous folds that are called **subneural clefts**.
- **Neuroreceptors** for the NT.

The NT at an NMJ is **ACETYLCHOLINE** (Ach). The synaptic cleft contains the enzyme which helps break down Ach and is called **Acetylcholinesterase**.
The Steps in Neuromuscular Junction

1. An AP reaches the presynaptic terminal of the NMJ.
2. The change in voltage causes the opening of the voltage-gated calcium channels which cause exocytosis of the Ach containing secretory vesicles.
3. The NT Ach is secreted into the synaptic cleft.
4. Ach crosses the synaptic cleft to reach the subneural clefts which contains the Ligand-gated Ach channel.
5. The channels are activated and open allowing the Na+ to move to the inside of the muscle fiber. As long as the Ach is present in the synaptic cleft, it keeps activating the Ach channels which remain open.
6. The influx of Na+ into the muscle lead to the initiation of the END PLATE POTENTIAL (EPP).
Degradation of Ach:

• The Ach present in the synaptic cleft is broken down by the enzyme Acetylcholinesterase, into Acetyl coA+ choline.
• Both the products are reuptaken by the presynaptic terminal.
• The Ach is again synthesized by the nerve cell body and then send by anterograde flow to the presynaptic terminal for packaging into secretory vesicles.
Remember:

- The Neurotransmitter at the NMJ is Acetylcholine.
- Acetylcholine is degraded by the Acetylcholinesterase.
- End-plate potential is the name given to the potential generated at the motor end-plate.
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.
- 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
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.

- 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.

**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.
- Fatigue is usually more pronounced in the proximal muscles as tongue, oculomotor (eye movements), pharyngeal (swallowing), laryngeal muscles (talking),
- Ptosis (drooping of the eyelids)
- Diplopia (double vision)
- Symptoms get better with rest & administration of anti-cholinesterase 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 studies
• Edrophonium test

TREATMENT:
• Anti-cholinesterase drugs. E.g: Neostigmine
• Immunosuppressant drugs. E.g: glucocorticoids
• Thymectomy: removal of thymus helps rebalances the immune system.
EXCITATION-CONTRACTION COUPLING
The process by which depolarization of the muscle fiber initiates muscle contraction is called **EXCITATION-CONTRACTION COUPLING**.
1. Somatic motor neuron releases ACh at neuromuscular junction.

2. Net entry of Na+ through ACh receptor-channel initiates a muscle action potential.
3. Action potential in t-tubule alters conformation of DHP receptor.
4. DHP receptor opens Ca\(^{2+}\) release channels in sarcoplasmic reticulum and Ca\(^{2+}\) enters cytoplasm.
5. Ca\(^{2+}\) binds to troponin, allowing strong actin-myosin binding.
6. Myosin heads execute power stroke.
7. Actin filament slides toward center of sarcomere.
**Excitation – Contraction Coupling**

**Steps in contraction:**

1. Discharge of motor neuron.
2. Release of NT (Ach) at motor end-plate.
3. Binding of Ach to Ach receptors on the motor end plate.
5. Generation of end-plate potential EPP).
6. EPP leading to generation of Action Potential (AP).
7. Inward spread of depolarization (as AP) along T tubules.
8. Release of Ca$^{2+}$ from terminal cisterns of SR.
9. Binding of Ca$^{2+}$ to Troponin C.
10. Troponin C pulls the tropomyosin off the actin uncovering binding sites on actin.
11. Formation of cross-linkages between actin & myosin.
12. Sliding of thin on thick filaments, producing contraction.
EXCITATION-CONTRACTION COUPLING

Steps in relaxation:

- $\text{Ca}^{2+}$ pumped back into Sarcoplasmic Reticulum (SR) by the ATP-dependant $\text{Ca}^{2+}$ pump in SR membrane.
- Release of $\text{Ca}^{2+}$ from troponin C.
- A new ATP binds to the myosin head

\[ \text{Interaction between actin and myosin STOPS and RELAXATION of the muscle fiber takes place.} \]
IMPORTANT TERMS

• **Calsequestrin**: the protein present in the SR to which is attached the Calcium.

• **ATPase dependant Calcium Pump**: the pump which helps pump the Calcium back into the SR once the contraction is over.
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).

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.