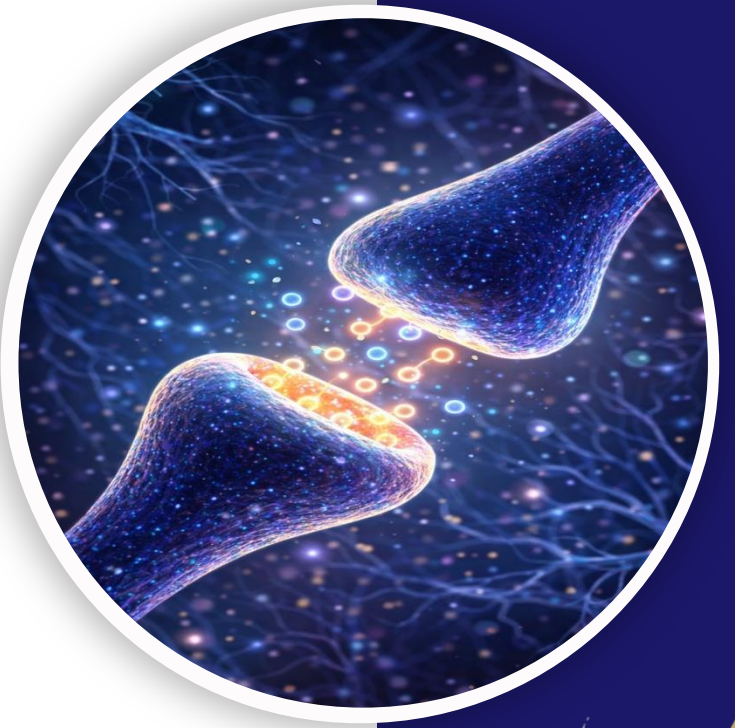
بسم الله الرحمٰن الرحيم

(وَفَوْقَ كُلِّ ذِي عِلْمٍ عَلِيمٌ)

Physiology | MID 3

Muscle Physiology pt.2 (Muscle mechanics)



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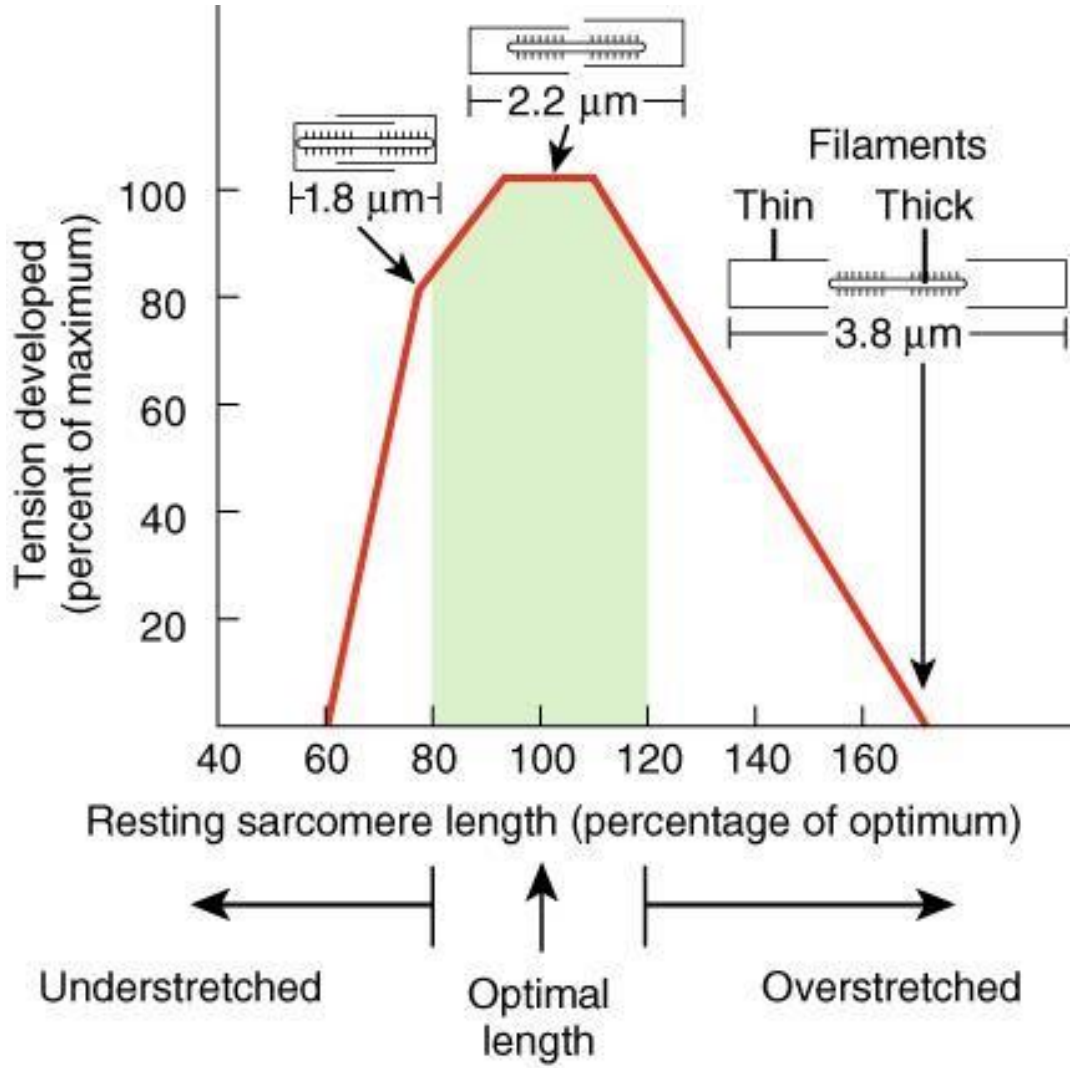
مبارك عليكم الشهر

Muscle Mechanics

Fig. 10.10



10.10

The previous curve explains the relationship between sarcomere length and the tension developed in a myofibril.

1. Excessive Stretching (Sarcomere length ≈ 3.8 µm)

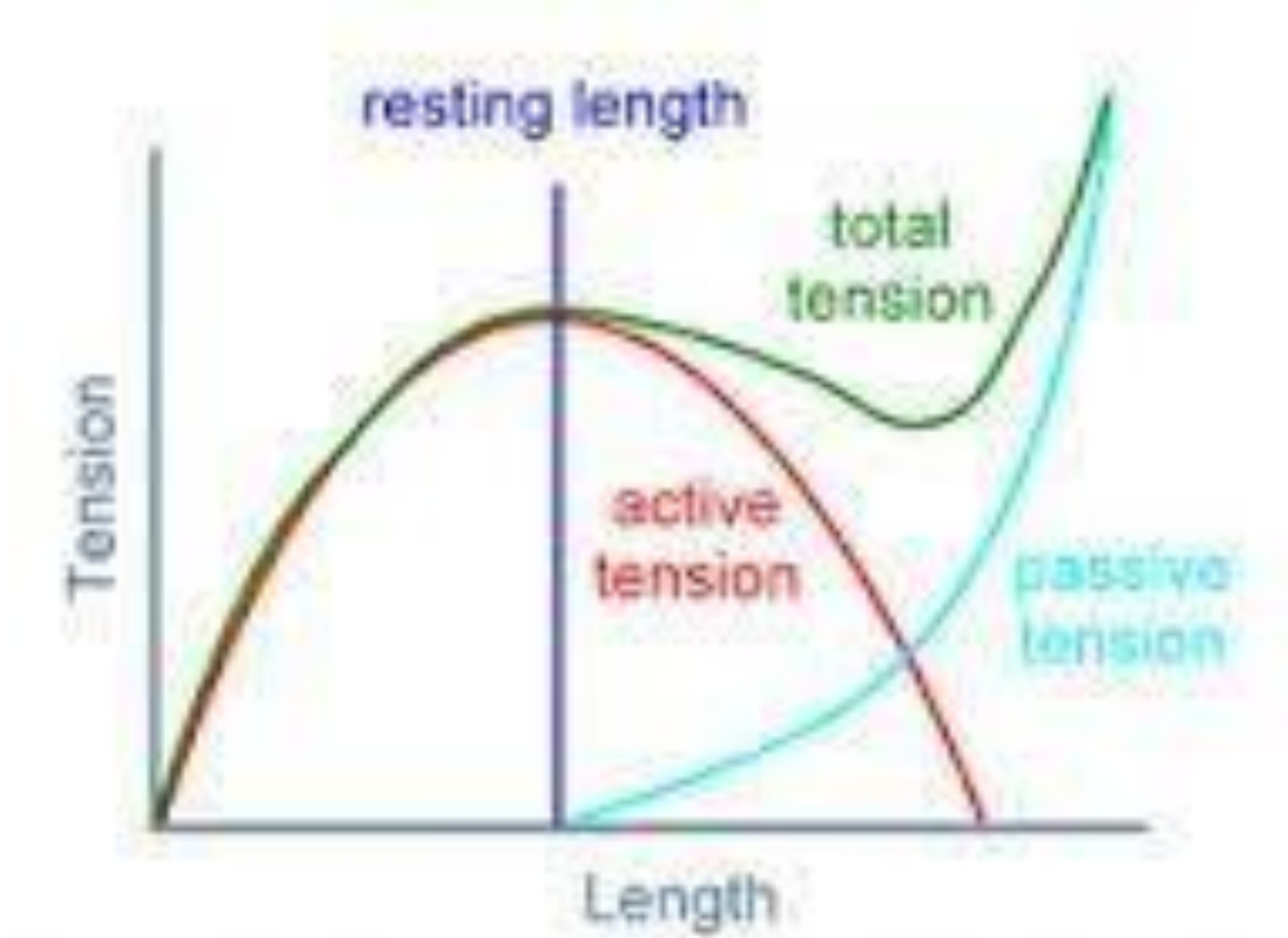
- When a myofibril is stretched to a sarcomere length of about 3.8 µm, There is no overlap between the thick (myosin) and thin (actin) filaments because cross-bridges cannot form, no tension is generated. Therefore, no tension can be recorded.

2. Optimal Shortening (Sarcomere length < 3.8 µm)

- As the sarcomere shortens below 3.8 µm, The overlap between thick and thin filaments increases. Increased overlap allows more cross-bridge formation. As a result, tension starts to be recorded.
- Maximum tension is achieved when there is maximal overlap between thin filaments and one half of the thick filament. This represents the optimal sarcomere length for tension generation.

3. Excessive Shortening (Sarcomere length < 2.2 µm)

- With further shortening below 2.2 µm, There is overlap of thin filaments with the second half of the thick filament. Thin filaments may also begin to interfere with each other. This reduces effective cross-bridge formation. Consequently, tension starts to decrease, even though overlap is increased.



Length-Tension Curve of a Muscle

Notes on the previous curve

1. Passive Tension

- This curve shows that even when the muscle is stretched without stimulation, tension is still recorded.
- This tension is called passive tension.
- Passive tension results from stretching the elastic components of the muscle.

2. Active Tension

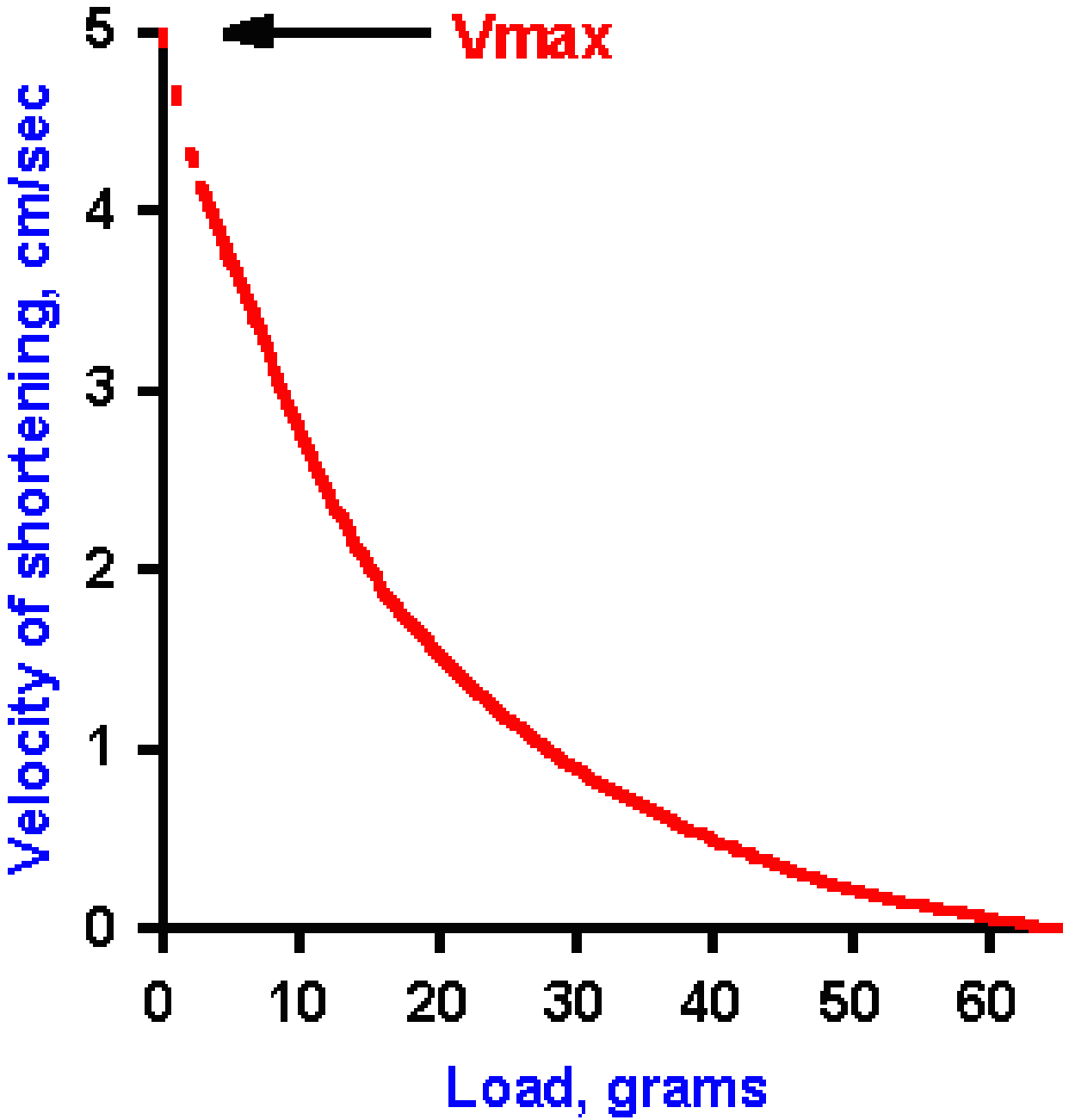
- Active tension is the tension developed after the muscle has been stimulated.
- It is produced by the process of muscle contraction (cross-bridge formation).
- Maximum active tension is at the resting length of the muscle.

3. Total Tension

- Total tension is the sum of active tension and passive tension. Total tension= Active tension+ Passive tension

4. Relationship Between the Tensions

- The difference between total tension and passive tension represents the active tension.
- Maximum active tension occurs at the resting length of the muscle. At this length, the interaction between thick and thin filaments is optimal.


Vmax
Velocity of shortening, cm/sec
5
4
3
2
1
0
0
10
20
30
40
50
60
Load, grams

The previous curve represents the relationship between the velocity of muscle contraction and the load applied to the muscle.

1. No Load (Load = 0)

- When the muscle is not loaded, the muscle shortens at the fastest rate. The velocity of contraction is maximal.
- Under this condition, the muscle performs an isotonic contraction which is a type of contraction where tension remains constant, while the length of the muscle decreases (shortening occurs).

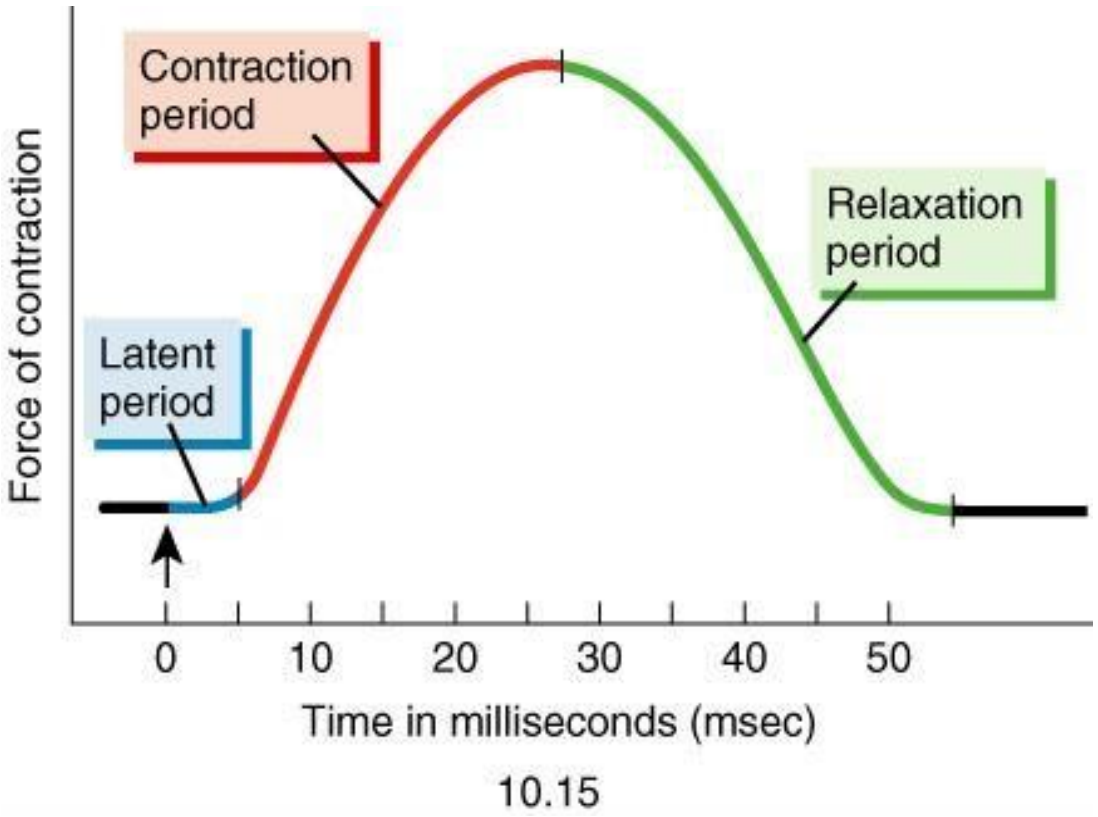
2. Increasing Load

- As the load on the muscle increases, the velocity of muscle shortening decreases. There is an inverse relationship between load and velocity of contraction.

3. Maximum Load (Fully Loaded Muscle)

- When the muscle is fully loaded, no shortening occurs. The velocity of shortening equals zero (V = 0).
- At this point, the muscle develops maximum tension. The contraction is called an isometric contraction. Isometric contraction means muscle contraction that occurs without shortening (muscle length remains constant) but tension increases.

Fig. 10.15



10.15

Simple Muscle Twitch Curve

Definition

- A simple muscle twitch is the mechanical response of a muscle to a single stimulus.

Experimental Setup

- Upon stimulation of the nerve, the muscle shortens.
- One end of the muscle is fixed, and the shortening of the muscle is recorded.
- The curve represents muscle shortening and relaxation over time.
- Recorded at high speed

Axes of the Curve

- X-axis → Time
- Y-axis → Muscle shortening

General Shape of the Curve

- Upon stimulation, the muscle shows shortening (contraction), followed by relaxation
- The curve includes Latent period, Contraction period, Relaxation period

Phases of a Simple Muscle Twitch

1. Latent Period

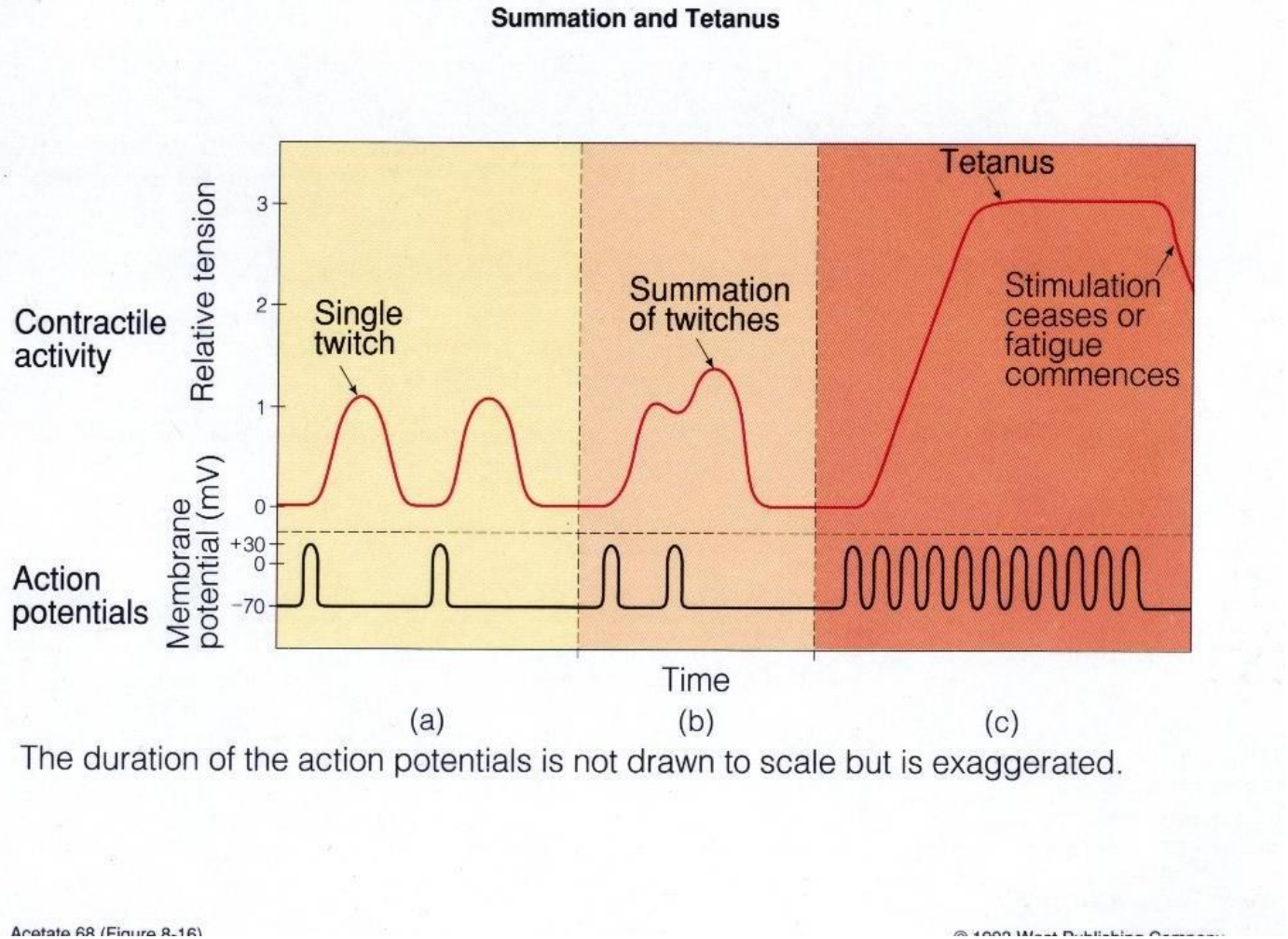
- There is a short time gap between the moment of stimulation and the start of muscle contraction, this time gap is called the latent period.
- Any event that occurs before the rise in Ca^{2+} concentration happens during the latent period.

2. Contraction Period

- The contraction period begins when Ca^{2+} concentration increases in the sarcoplasm.
- During this phase, Ca^{2+} continues to increase and Cross-bridge formation occurs
- Muscle shortening increases until it reaches maximum amplitude of contraction (maximum shortening of the muscle)

3. Relaxation Period

- After maximum shortening the muscle begins to relax
- During the relaxation period, Ca^{2+} is pumped back into the sarcoplasmic reticulum thus calcium concentration in the sarcoplasm decreases and Cross-bridges detach so the muscle returns toward its resting length



Wave Summation

Basic Concept

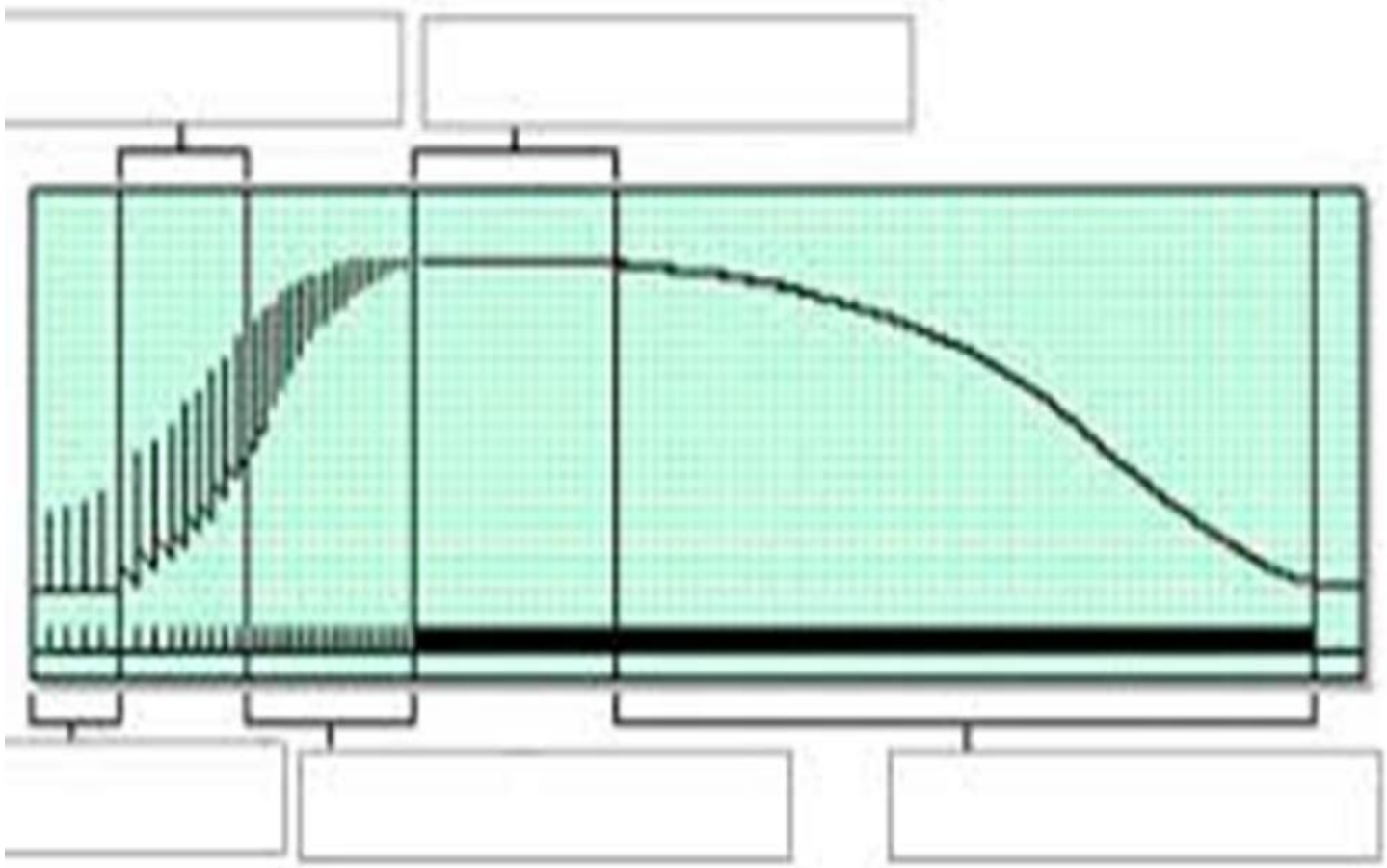
- A single stimulus applied to a muscle produces a simple muscle twitch.

Wave Summation

- If two stimuli are applied to the muscle and the second stimulus occurs during the relaxation period of the first muscle twitch,
- The muscle produces another contraction before it has completely relaxed.
- The two contractions add together, producing a greater force of contraction.

Definition

- This process is called wave summation.
- In wave summation, we obtain the sum of two contraction waves occurring close together in time



Recording at Low Speed

- When recording at a low speed we cannot see the full simple muscle twitch curve. Contraction and relaxation appear to occur at the same time. Multiple twitches are visually merged into a single curve.

Axes of the Curve

- X-axis → Time
- Y-axis → Force of contraction

Effect of Increasing Frequency of Stimulation

- By increasing the frequency of stimuli, the time between two stimuli becomes shorter than the contraction and relaxation period.
- As a result, summation occur and the muscle does not fully relax between stimuli and reach the baseline.

Tetanization

- If the second stimulus arrives during the contraction period, the muscle continues contracting without relaxation. This phenomenon is called tetanization. Therefore, tetanization is a form of wave summation. It occurs when the time between two stimuli is less than the contraction period or the time between two stimuli is more than the latent period.

Electrical vs Mechanical Events

- During the mechanical events (recorded contraction curves) the refractory period occurs during the latent period. A lot of events occur during the latent period:
  - Fast depolarization occurs
  - Fast repolarization of the muscle membrane occurs
  - All electrical events are completed before the mechanical contraction begins.

In cardiac muscle:

- The action potential is very long. Therefore, the refractory period is very long. This means that the cardiac muscle contracts and relaxes almost until the end of the refractory period. The muscle cannot receive a new stimulus before contraction is completed. As a result, tetanization is not possible in cardiac muscle. Tetanization occurs only in skeletal muscle.

Fatigue

- If tetanic stimulation is maintained for a long time, the amplitude of contraction gradually decreases. Eventually, even with continuous stimulation no contraction occurs. This phenomenon is called fatigue.

Cause of Fatigue

- The main problem in fatigue occurs at the neuromuscular junction: Most neurotransmitters are consumed. As a result, if the nerve is stimulated, the muscle does not respond. But if the muscle itself is stimulated, a contraction still occurs. Therefore, fatigue is due to failure of transmission, not failure of the muscle fibers

Fatigue vs Muscle Spasm

- Fatigue:
  - No transmission at the neuromuscular junction
  - No contraction despite nerve stimulation
- Muscle spasm:
  - Painful condition
  - Common in athletes
  - Caused by accumulation of lactic acid
  - Pain is felt during contraction

Staircase Phenomenon

So far, we have discussed summation as a way of increasing muscle contraction. However, pay attention: not every increase in contraction force is summation.If one stimulus is applied to a muscle, it produces a full contraction followed by complete relaxation.If a second stimulus is applied after complete relaxation, it also produces a full contraction.

Now the important question:Is the amplitude of contraction the same each time?If we observe carefully, we notice that the amplitude of contraction gradually increases with repeated stimuli (about 10–15 contractions), and then it stabilizes.This is called the Staircase phenomenon).It is NOT summation because the muscle relaxes completely between each stimulus.

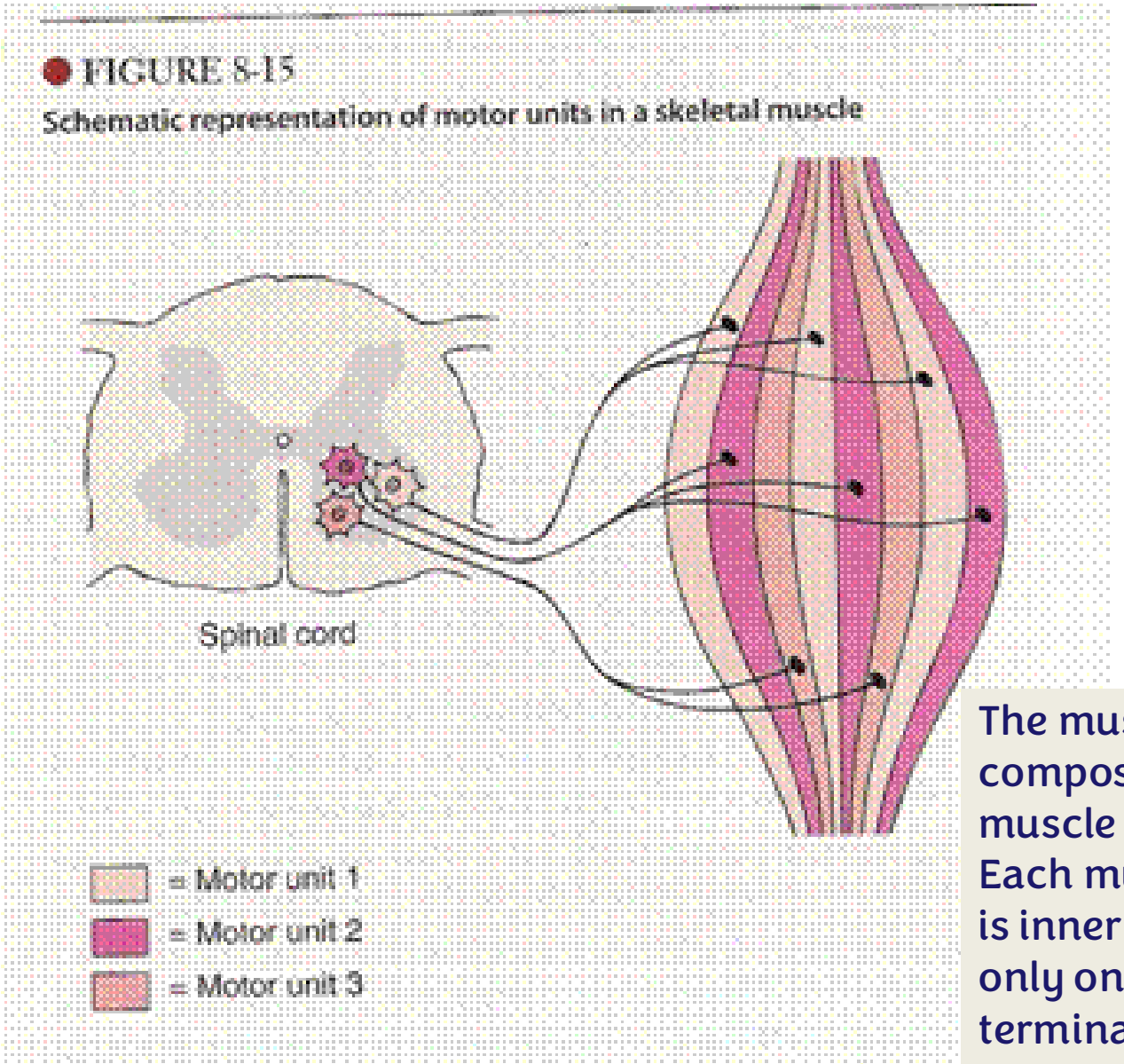
Why does the amplitude increase?

1. Calcium accumulation:With each stimulus, Ca^{2+} is released from the sarcoplasmic reticulum.Not all the calcium is reabsorbed before the next stimulus.As a result, there is a slight accumulation of Ca^{2+} in the cytosol.This increases the probability of **Ca^{2+} binding to Troponin C**, leading to more cross-bridge formation and a stronger contraction to increase the efficiency of muscle activity.
2. Increased muscle temperature:Repeated contractions produce heat.Heat decreases muscle viscosity This improves the efficiency of contraction.

- Important Exam Note:

In Staircase phenomenon → complete relaxation occurs between stimuli.
In summation → no complete relaxation occurs.

Practical Importance:
This explains why warm-up exercises improve muscle performance in athletes, as repeated activity increases contraction efficiency.



The muscle is composed of many muscle fibers. Each muscle fiber is innervated by only one motor terminal .

Figure 4. One motor unit can control multiple muscle cells.

Taken from Sherwook, 2004

Now we have another type of summation called Motor Unit Summation.

One motor neuron can innervate a group of muscle fibers
That group of muscle fibers is called a motor unit, which means they are working together upon stimulation of that motor neuron and that is the Motor unit summation

The question: When you are using your muscle, are you using all muscle fibers in that muscle?

If you are lifting a very light object, there is no need for a large group of muscle fibers to contract.

But if you are lifting a heavier object, you need to recruit more motor units by activating more motor neurons.

This is called motor unit summation.

More motor units → more powerful contraction.

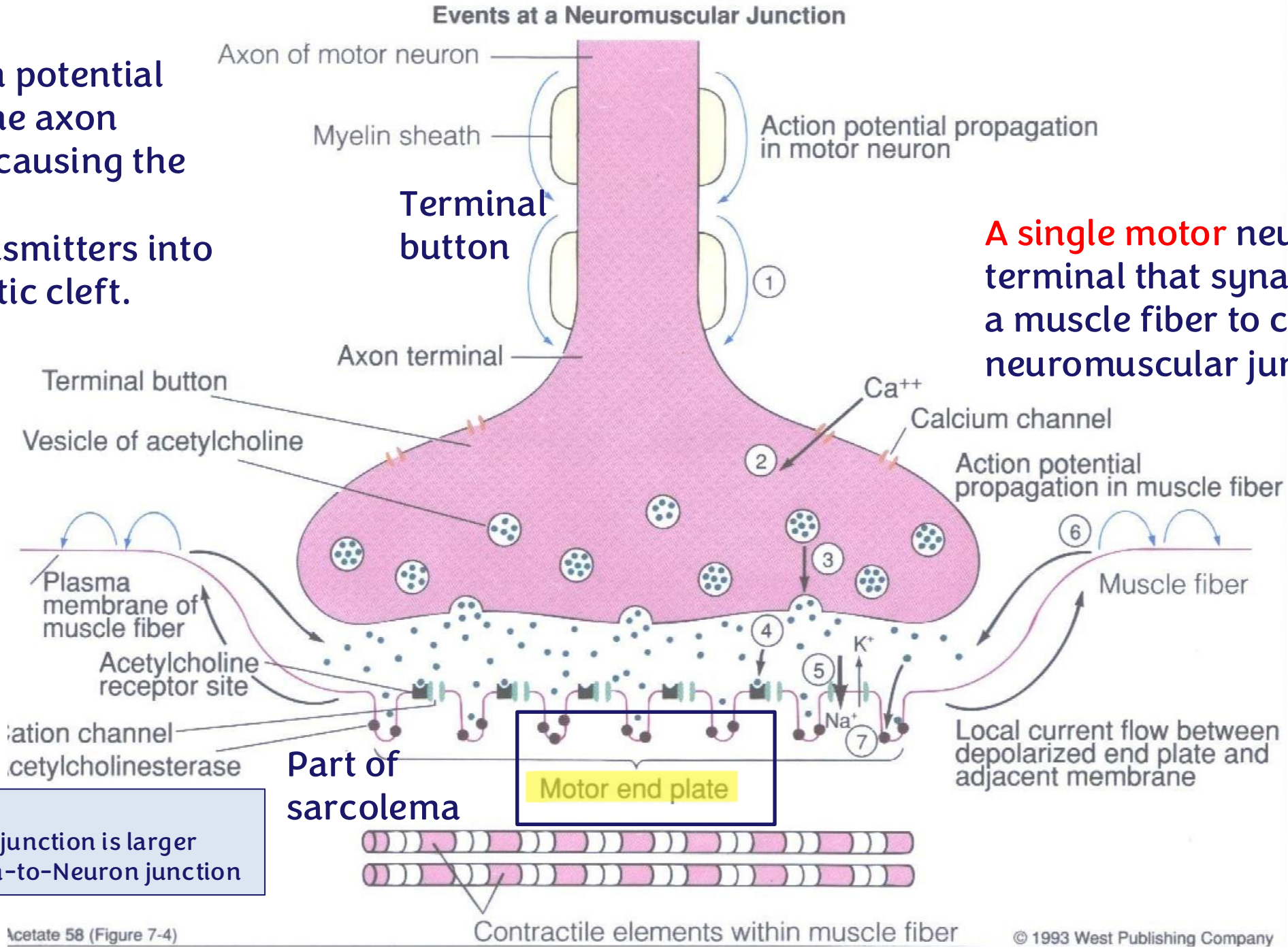
IF you want to lift an object that you think is light and realized that it is heavy you will not be able to lift it until more muscle fibers are activated because a small number of muscle fibers are activated.
IF you want to lift an object that you think is heavy and realized that it is light you will be able to lift it with high speed because a large number of muscle fibers are activated.

Excitation – Contraction Coupling

- https://www.youtube.com/watch?v=Llgazi PCFU0

  It is the process that converts an electrical event (action potential) into a mechanical event (muscle shortening), and this is called excitation-contraction coupling

The action potential reaches the axon terminal, causing the release of neurotransmitters into the synaptic cleft.



A single motor neuron terminal that synapses with a muscle fiber to create a neuromuscular junction

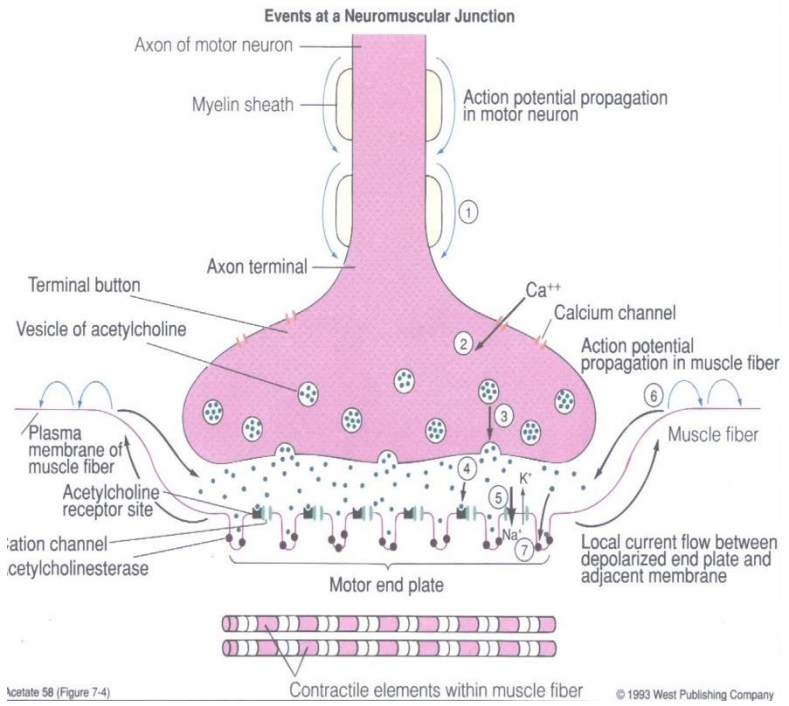
NOTE:
Neuromuscular junction is larger than the Neuron-to-Neuron junction

Steps of the Neuromuscular Junction:

1.An action potential travels down the motor neuron to the axon terminal.
2.Voltage-gated calcium channels open.
3.Calcium ions (Ca^{2+}) enter the presynaptic terminal.
4.Synaptic vesicles fuse with the membrane.
5.Acetylcholine (ACh) is released into the synaptic cleft.
6.ACh binds to receptors on the motor end plate (muscle membrane).
7.Sodium channels open, causing depolarization (chemical channel)
8. Are you immediately getting an action potential? Only a small change in the membrane potential occurs, which is called the motor end-plate potential, and it is similar to an excitatory postsynaptic potential (EPSP).
9.At the periphery, they sum with each other through the process of summation. This leads to the activation of many voltage-gated sodium channels, and once the membrane reaches the threshold, an action potential is generated.

If acetylcholine remains at a high concentration in the synaptic cleft, the muscle will continue to be stimulated. This would cause continuous muscle contraction. Therefore, acetylcholine must be rapidly removed from the synaptic cleft by an enzyme called acetylcholinesterase, which breaks it down and allows the muscle to relax.

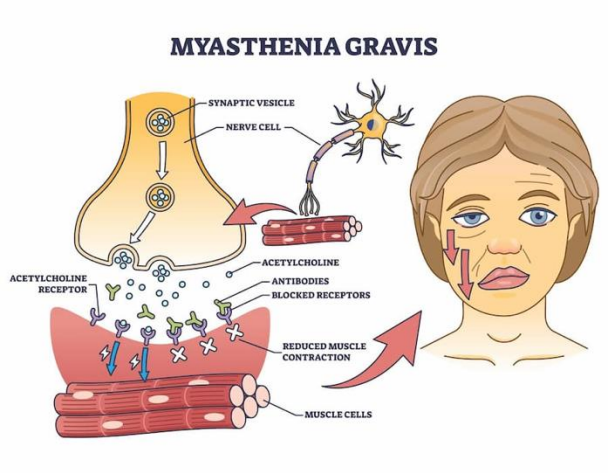
Are we having a zero concentration of acetylcholine?
No, there is a small amount of acetylcholine present. However, this small amount is not sufficient to generate an action potential. Instead, it produces an excitatory potential. This potential must spread (migrate) across the membrane. It differs from an action potential, as these waves decrease in amplitude with distance.

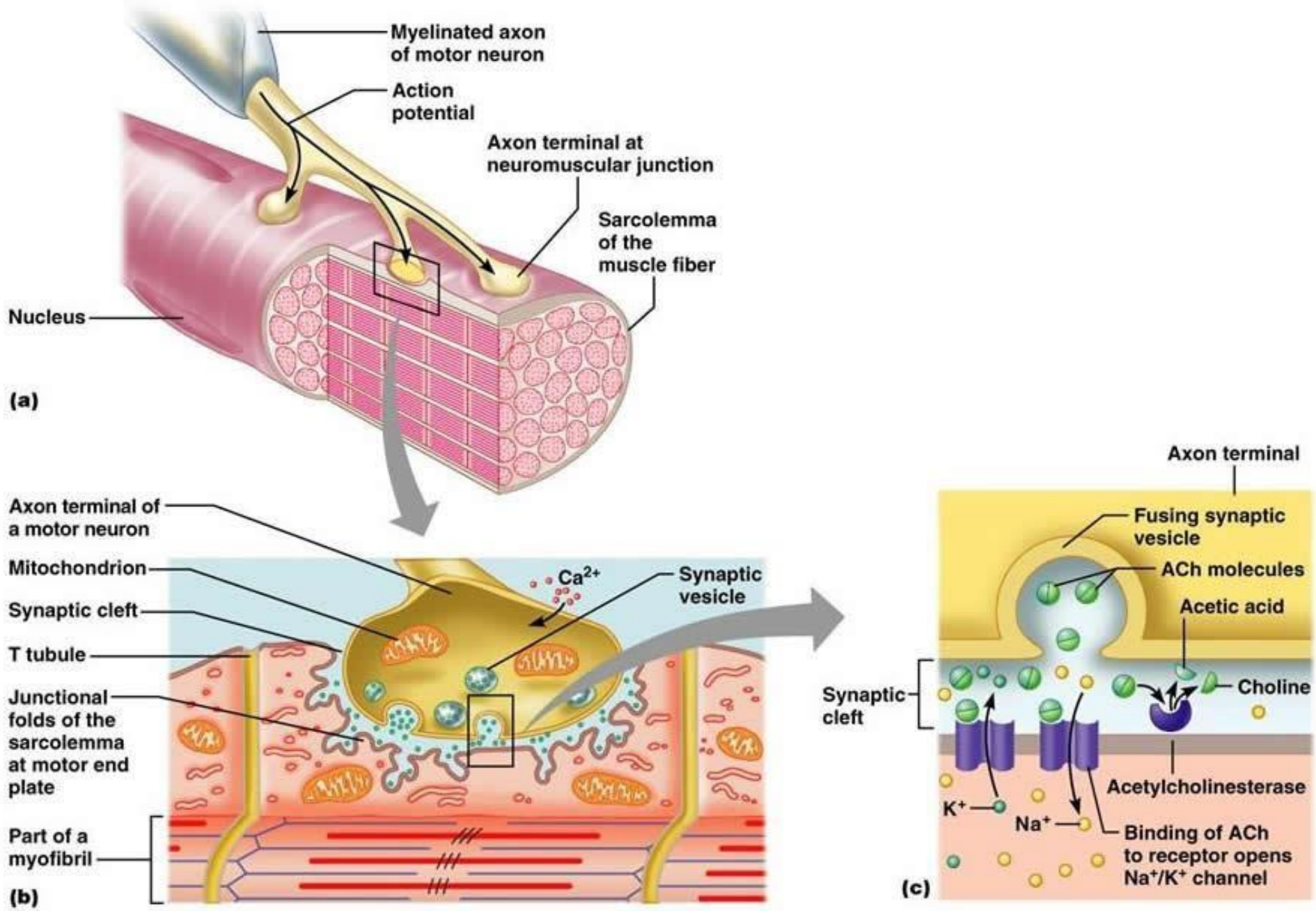


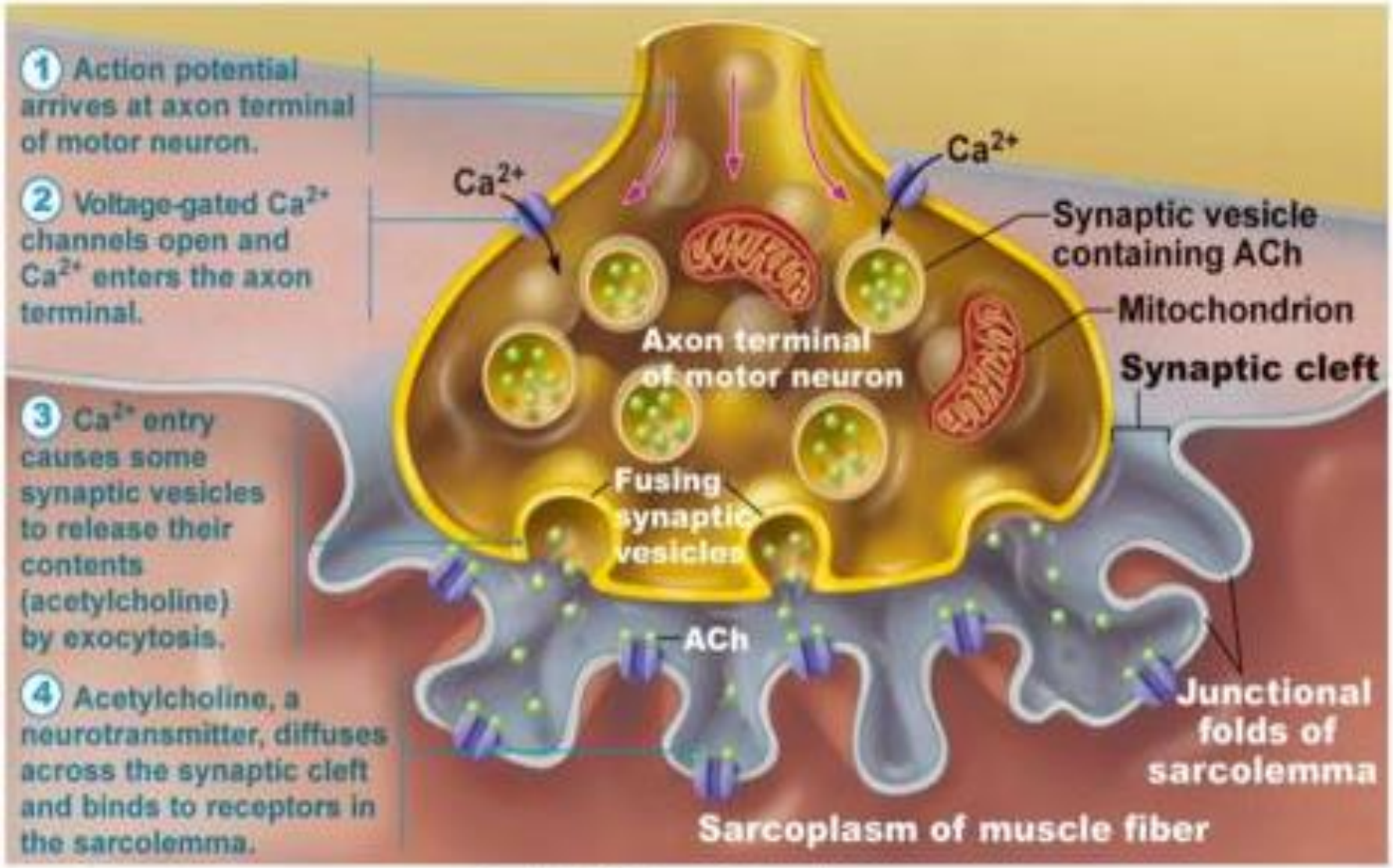
Sometimes the transmission from the nerve terminal to the muscle is reduced. For example, there is a disease called **myasthenia gravis,** (There is damage to the sodium channels, which leads to impaired action potential generation)This leads to reduced effectiveness of acetylcholine.

How can we treat this condition?
How can we increase the acetylcholine concentration?

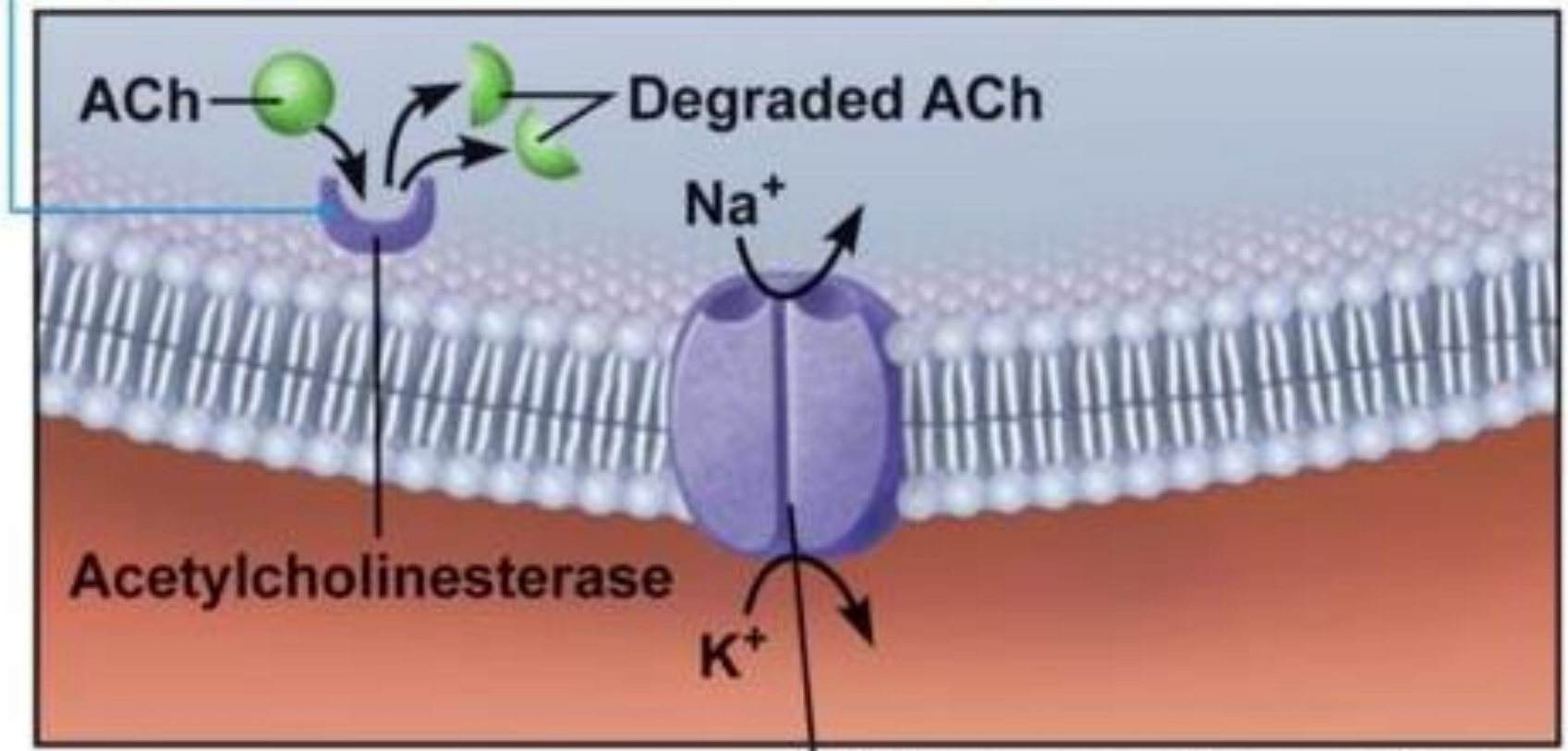
We can treat it by using acetylcholinesterase inhibitors, which prevent the breakdown of acetylcholine and therefore increase its concentration in the synaptic cleft. Additionally, agonist drugs that stimulate nicotinic acetylcholine receptors can also be used to improve neuromuscular transmission.




Myelinated axon of motor neuron
Action potential
Axon terminal at neuromuscular junction
Sarcolemma of the muscle fiber
Nucleus
(a)
Axon terminal of a motor neuron
Mitochondrion
Synaptic cleft
T tubule
Junctional folds of the sarcolemma at motor end plate
Part of a myofibril
(b)
Ca2+
Synaptic vesicle
Axon terminal
Fusing synaptic vesicle
ACh molecules
Acetic acid
Synaptic cleft
Choline
Acetylcholinesterase
K+
Na+
Binding of ACh to receptor opens Na+/K+ channel
(c)



⑥ ACh effects are terminated by its enzymatic breakdown in the synaptic cleft by acetylcholinesterase.



DR.'S HANDOUT

2.0-1.6 μm) an interaction between thin filaments and cross bridges from the other half of the sarcomere is suggested, which may result in a decrease in tension.

From this, we can conclude that more overlap between thin and thick filaments located in the same half of sarcomere will induce more tension. This tension is reduced by decreasing the overlap in the same side, or increase in the interaction of thin filaments with cross bridges from the other side of thick filaments (increasing overlap with the other side).

Tension and whole muscle length relation:

We have seen that maximum tension develops at a sarcomere length of 2.0 –2.2 μm. This corresponds with the resting length of the muscle. At its normal length, the muscle also responded with the maximum *active tension* (tension induced by stimulation). By stretching muscle (increasing its length), before stimulation we increase the inactive (passive) tension (due to elastic property) in the muscle. When the muscle stimulated at this new length will develop less active tension. That corresponds to the increase in sarcomere length beyond 2.2μm.

Velocity of contraction and load:

Skeletal muscle contracts with maximum velocity when it is not loaded. By loading the muscle, the velocity of contraction decreases as the load increases.

Muscle twitches and characteristics:

Once a nerve of a nerve and muscle preparation is electrically stimulated, the muscle will respond by a contraction then followed by relaxation. The whole recordings from the beginning of stimulation until the end of muscle relaxation is known as *simple muscle twitch*. The simple muscle twitch can take less time in muscles composed of fast fibers such as ocular muscle, or longer time in muscles composed of slow fibers such a soleus muscle. These muscles not only differ in their speed of contraction but also in their color and composition. Fast fibers are large fibers, have extensive sarcoplasmic reticulum, contain large amount of glycolytic enzymes, and fewer mitochondria. These fibers also have less extensive blood supply. Slow fibers are smaller, have more extensive blood supply, and contain more mitochondria. These fibers also contain a larger amount of myoglobin (an iron containing molecule similar to

hemoglobin that can combine with O2), which stores O2 until needed by fibers for oxidative phosphorylation. The presence of large amounts of myoglobin gives the slow fibers a reddish appearance. For this reason, slow muscles are known as red muscles while the muscles containing fast fibers are white muscle.

Skeletal muscles are innervated by motor neurons that originate from the central nervous system (CNS). Each neuron innervates a certain number of muscle fibers. Muscle fibers that are innervated by a single nerve fiber are called **motor unit**. The number of muscle fibers in a motor unit depends on the function of the muscle. Some muscle that controls fine movements such as laryngeal muscles have only two or three muscle fibers in a motor unit. Movements that do not need fine control of muscle contraction may contain up to 100 muscle fibers in one unit.

Summation of simple muscle twitches:

Two types of summation are known in the muscle:

1. Frequency summation (wave summation) and tetanization:
   When muscle stimulated by more than one stimulus,
   this will result in successive and complete simple twitches if the time between 2 successive stimuli is more than the duration of a simple muscle twitch. Increasing the frequency of stimulation (shorten the time between stimuli) permits excitation by another stimulus while the muscle is in simple muscle twitch. This may result in summing of the successive contractions. When frequency of stimulation is more increased and the muscle responds by contraction without any relaxation, we can say that the muscle is in **tetanization**.

2. Motor unit summation (multiple fibers' summation): If only few nerve fibers in a nerve that innervates a muscle are stimulated, this will induce shortening in the muscle that corresponds to contraction of motor units that are innervated by stimulated nerve fibers. When the number of nerve fibers stimulated increases, this will recruit more motor units in contraction. The increase in contraction will result in an increase in the

amplitude of simple muscle twitch. In human body, this summation is important for gradation of forces during contraction.

Staircase effect (Treppe):

When a muscle contracts after a period of rest, the simple muscle twitch has a certain amplitude. After several contractions, the amplitude of simple muscle twitches increases. This is known as *Treppe* or *staircase effect*. This effect is probably due to an increase in Ca++ concentration inside the cytosol with each muscle stimulation and inability of sarcoplasmic reticulum to recapture Ca++ immediately.

EXCITATION-CONTRACTION COUPLING:

Skeletal muscle is voluntary. It contracts upon stimulation by motor neurons. A large and myelinated nerve fiber that originates in the anterior horn of the spinal cord after entering the muscle branches in axonal terminals that end about near the midpoint of muscle by forming a **neuromuscular junction** (motor end plate). At that point, the nerve terminal ends into a small invaginated part of the muscle membrane called *synaptic gutter* (*synaptic trough*). At the bottom of synaptic gutter, muscle membrane has small folds called *subneural clefts*, which increase the surface area of synaptic gutter. The small space (20-30nm) between the terminal and muscle membrane, where the neurotransmitter is released to stimulate muscle, is called *synaptic cleft* (*synaptic space*). In this space, large quantity of *acetylcholinesterase* (an enzyme that destroys Ach after its release into synaptic cleft) is found. The enzyme can be inactivated by drugs, such as neostigmine, physostigmine, and diisopropyl fluorophosphates, which result in increased Ach cleft, and prolonged action of thistransmitter.

Secretion of Ach from the terminal:

When the impulse reaches the terminal, this will cause Ach to be released into the synaptic cleft. The mechanism of release includes activation of voltage gated Ca++ channels, which results in Ca++ influx into the axon terminal. The increased Ca++ concentration in the terminal will cause the vesicles containing Ach to dock and fuse with the terminal membrane, and release their content into the synaptic cleft by a process called **exocytosis**. About 125 vesicles release their content after one stimulus. Stimulation of the release of neurotransmitter for long time may

result in depletion of vesicles containing neurotransmitter. This will induce fatigue of neuromuscular junction.

Once released into the synaptic cleft, Ach binds to its receptor (a complex protein of 5 subunits, 2α, β, δ, γ subunits). Two molecules of Ach bind to the α subunits and cause activation of chemical gated ion channel, which induces Na+ influx (diffusion) into the muscle fiber and causes local change in the membrane potential at the end plate known as *end plate potential*. The receptor is a subject of inhibition by curariform drugs such as D-tubocurarine, which can affect transmission of impulse from the nerve terminal to the muscle membrane by blocking the action of Ach on its receptor.

Transmission can also fail by destruction of chemical gated ion channels. This appears in myasthenia gravis (an autoimmune disease that generate antibodies against acetylcholine gated ion channels on the muscle) which results in muscle paralysis. The paralysis can be partially ameliorated by anticholinesterase drugs (neostigmine or physostigmine), which increase Ach in the synaptic cleft.

In addition to its stimulation by Ach, the receptor can also be stimulated by many compounds, including methacholine, nicotine, and carbachol. These compounds produce prolonged activation of the receptor (due to the absence of destroying enzymes that can destroy these compounds), which results in muscle spasm.

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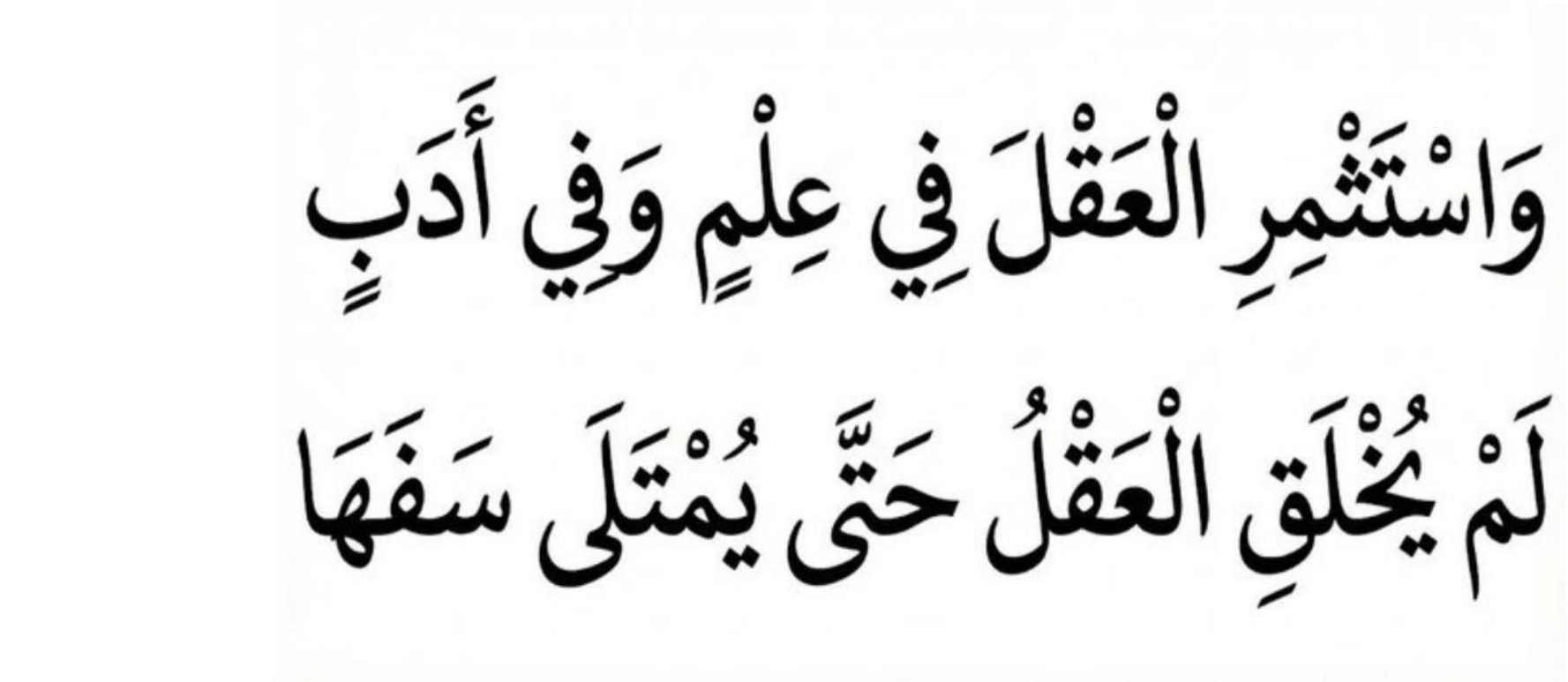

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Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1			
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