Human Physiology PCB 4701

Muscle
Fox Chapter 12

T. Houpt, Ph.D.

Three Types of Muscle

Skeletal Muscle
Muscles attached to bones by tendons, that contract when stimulated by somatic efferent nerves (e.g. from spinal cord); allow for conscious movement of limbs, etc.

Smooth Muscle
Muscles in circular layers around blood vessels, air passages, digestive tract, and other visceral organs. Able to stretch more, capable of long slow pulsatile contractions.
(to be covered in Autonomic & GI lectures)

Cardiac Muscle
(to be covered in heart lectures)

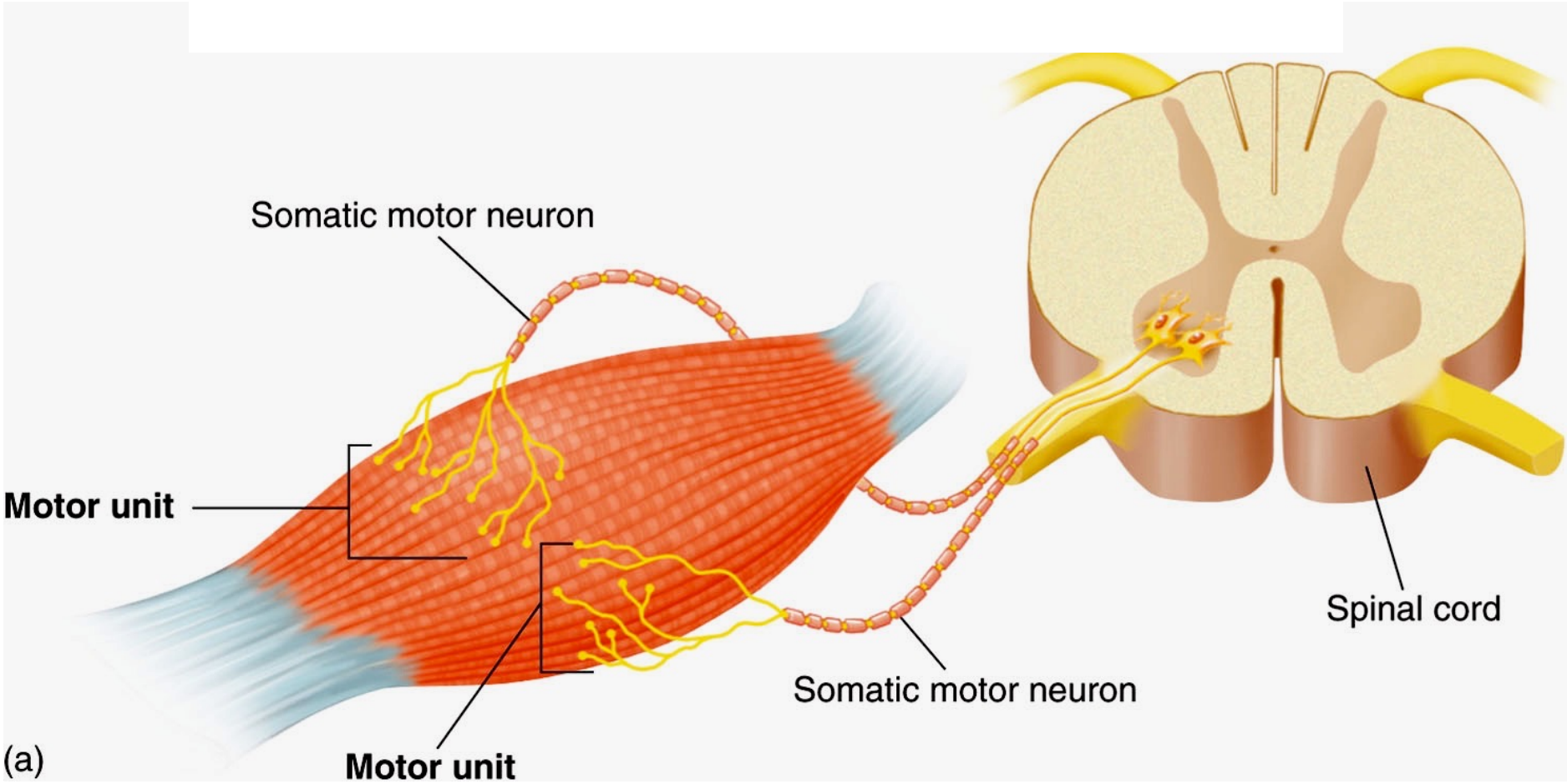
Skeletal Muscle

1. Anatomy of skeletal muscle

2. How myofibrils contract by sliding actin-myosin filaments

3. How nerves control muscles: the release of acetylcholine at neuromuscular junctions

4. Neuromuscular toxins



Fox Figure 12.4a


HHMI

Skeletal Muscle Anatomy

Fibrous connective tissue (epimysium) from tendons covers and divides **fascicles** of muscle.

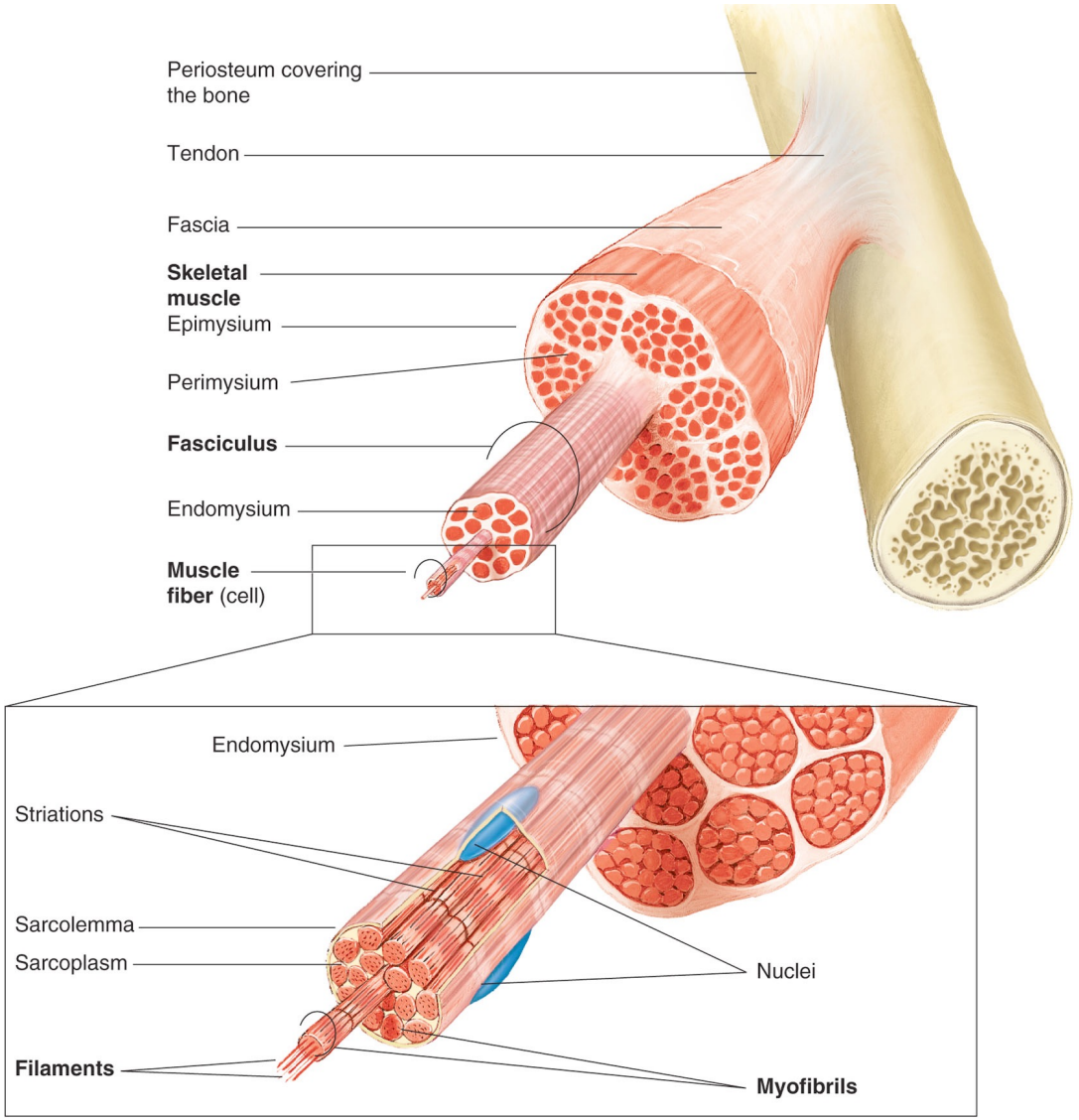
Fascicles made up of striated **myofibrils** (fused muscle cells).

Myofibrils divided into **sarcomeres** with dark A band and light I band

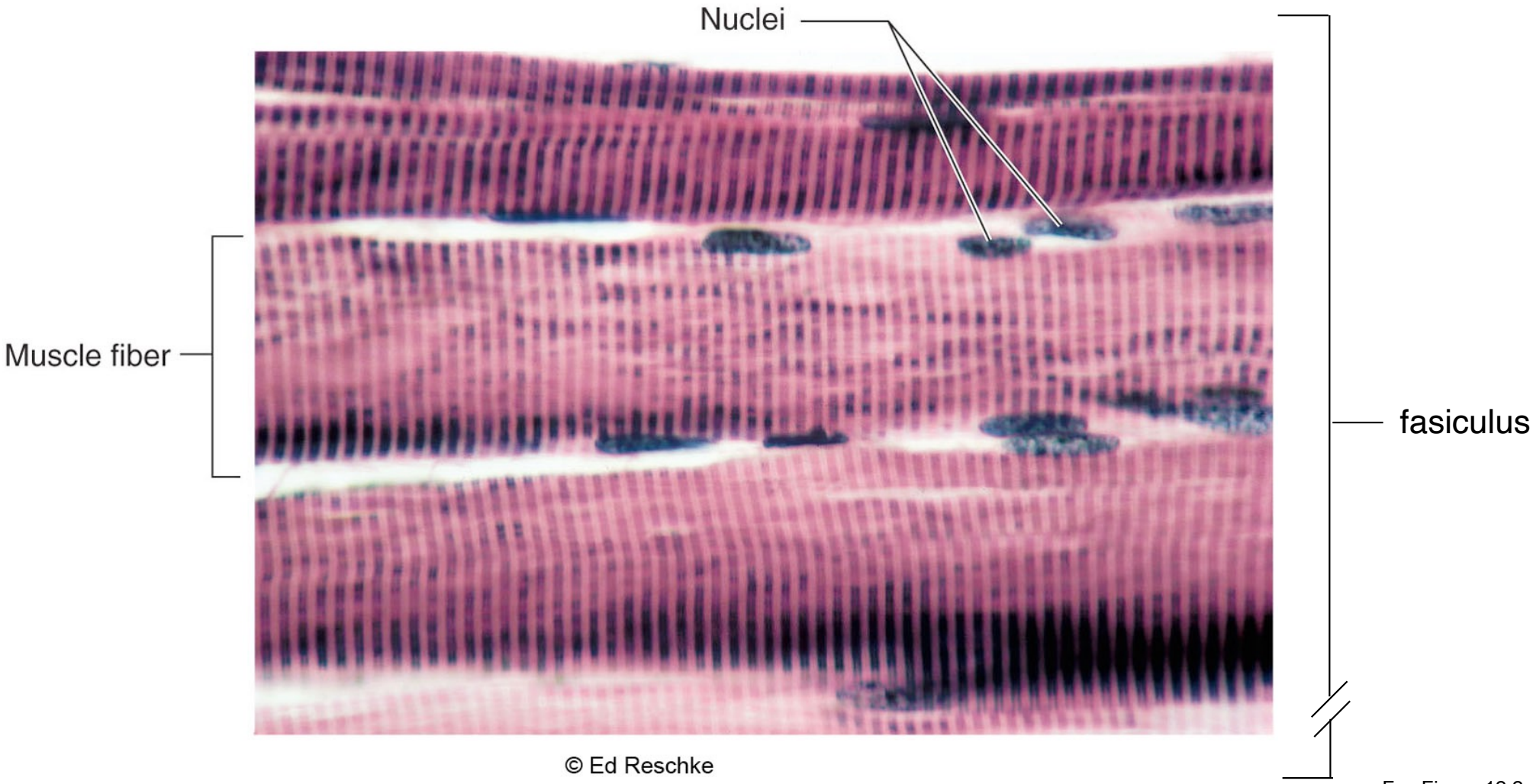
Sarcomere components:
Z-discs: at either end of sarcomere
I band: area of thin filaments
A band: overlap of thin filament and thick filaments
H zone: center of thick filaments
M line: center of sarcomere, joining thick filaments
titin: elastic filament running through center of thick filaments

Sarcoplasmic Reticulum: internal storage of Ca++ ions

myo-, mysi- muscle
epi-, peri-, endo- outside, middle, inside
fasci- bundle, *fasciculus-* little bundle
sarco- flesh (e.g. sarcophagus, the coffin that eats (decomposes) flesh)
-lemma - membrane
-mere - subunit

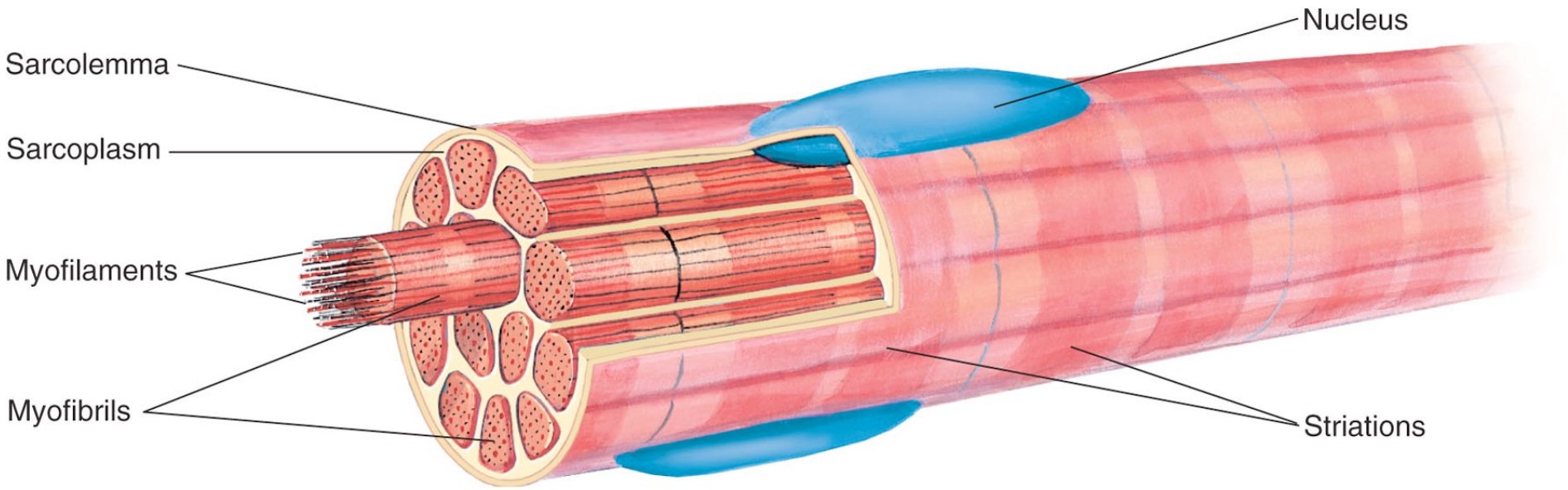


Fox Figure 12.1



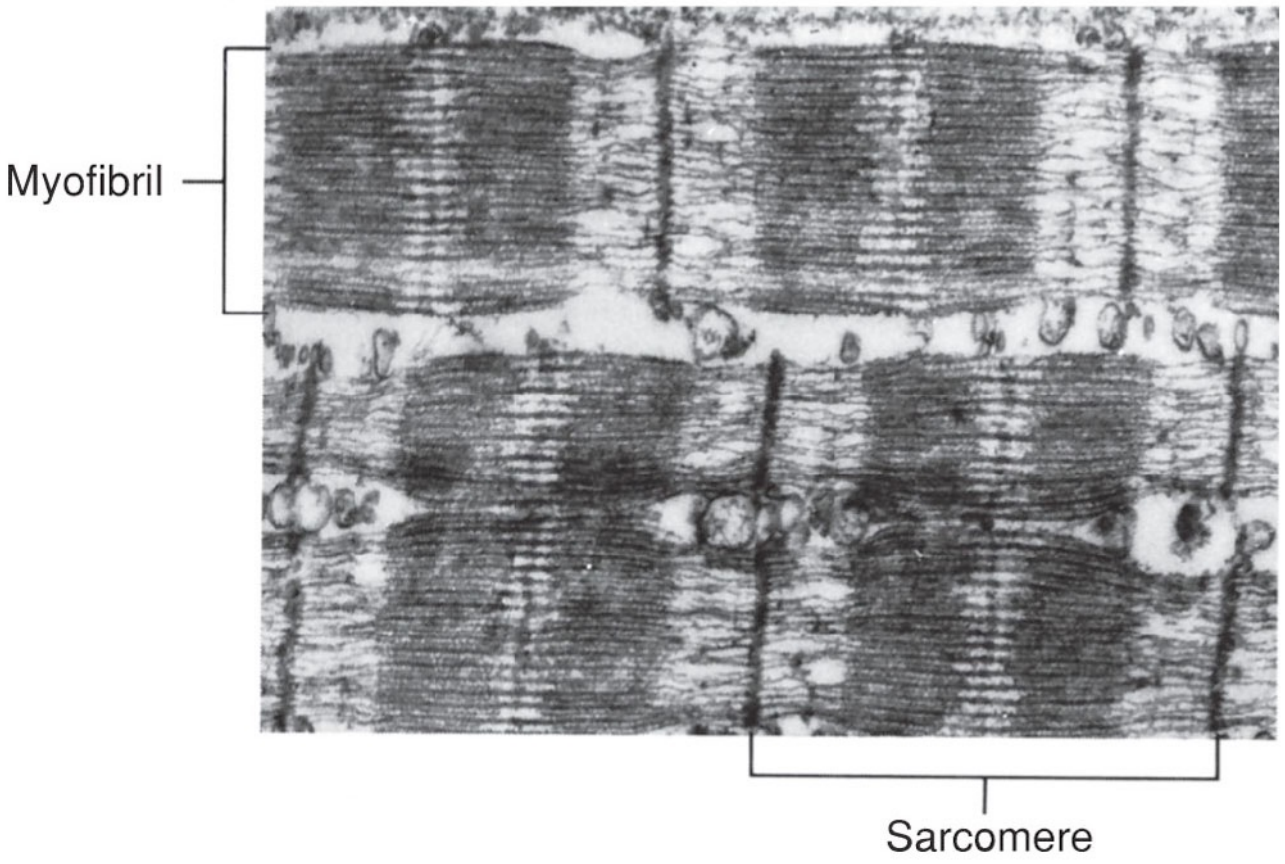
Fox Figure 12.2

muscle fiber (a fused cell) -> myofibrils -> myofilaments

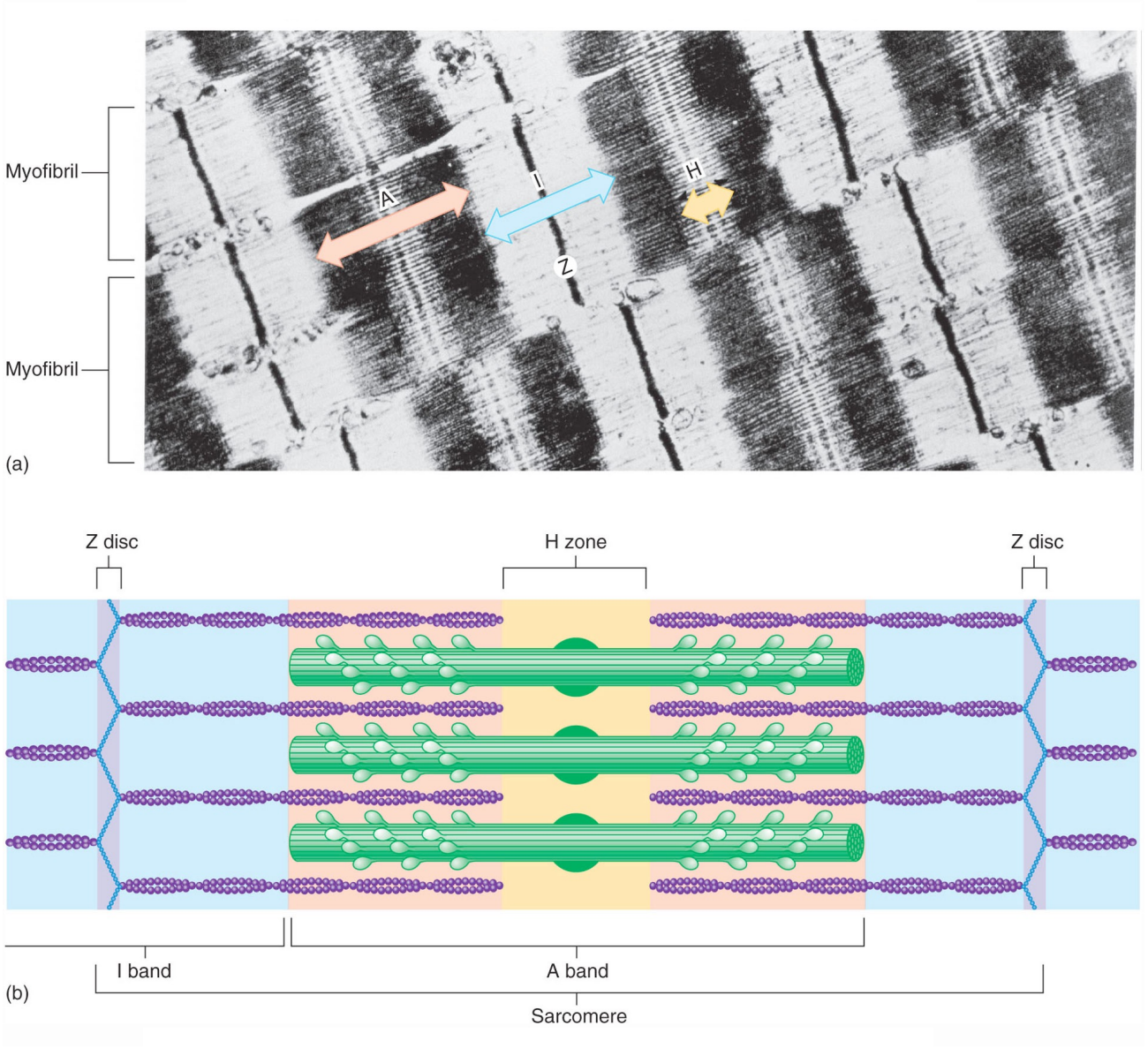


Fox Figure 12.5

Biceps: 250,000 myofibrils; 100,000 sarcomeres/myofibril (end-to-end, so 200 mm long)

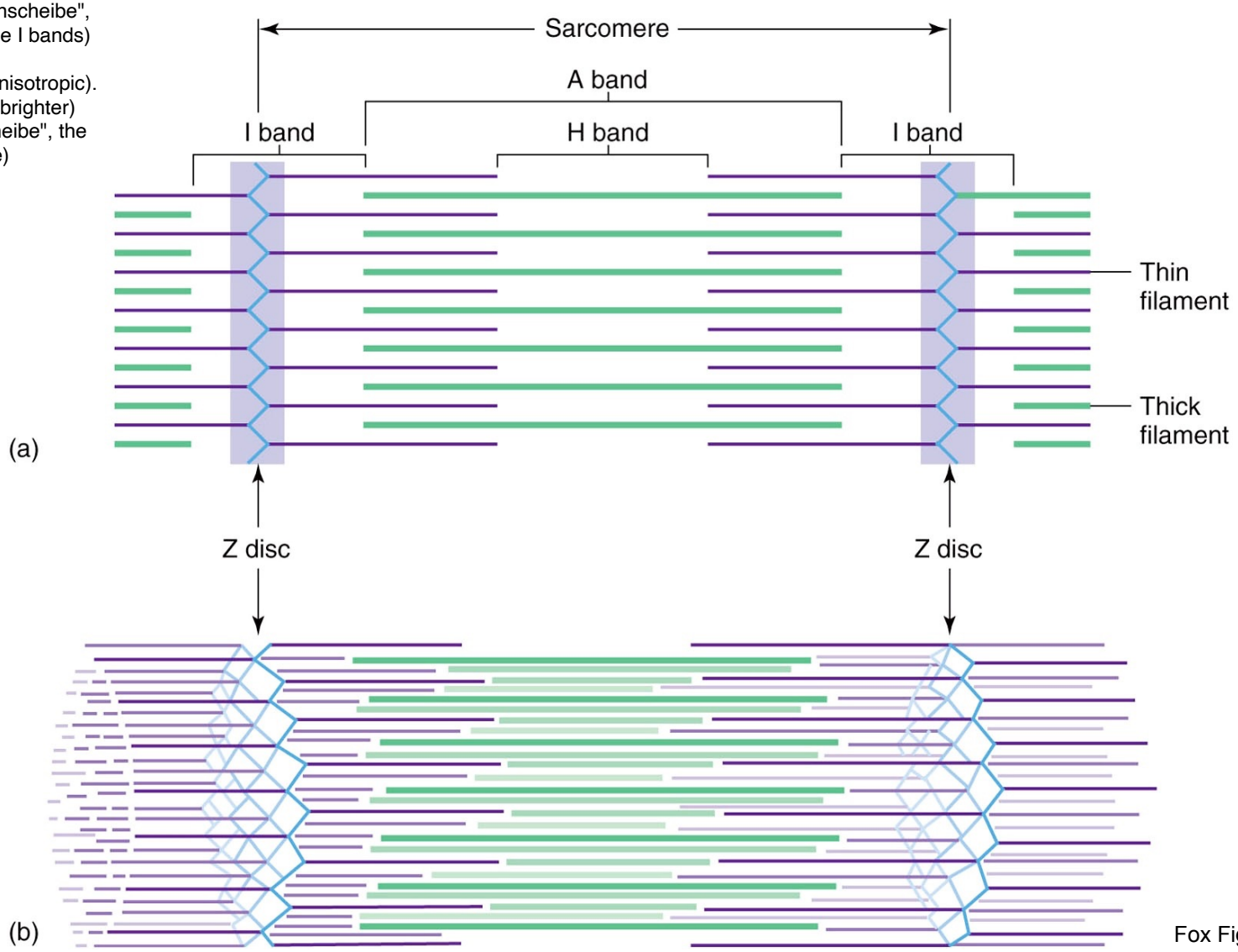


Fox Figure 12.7a



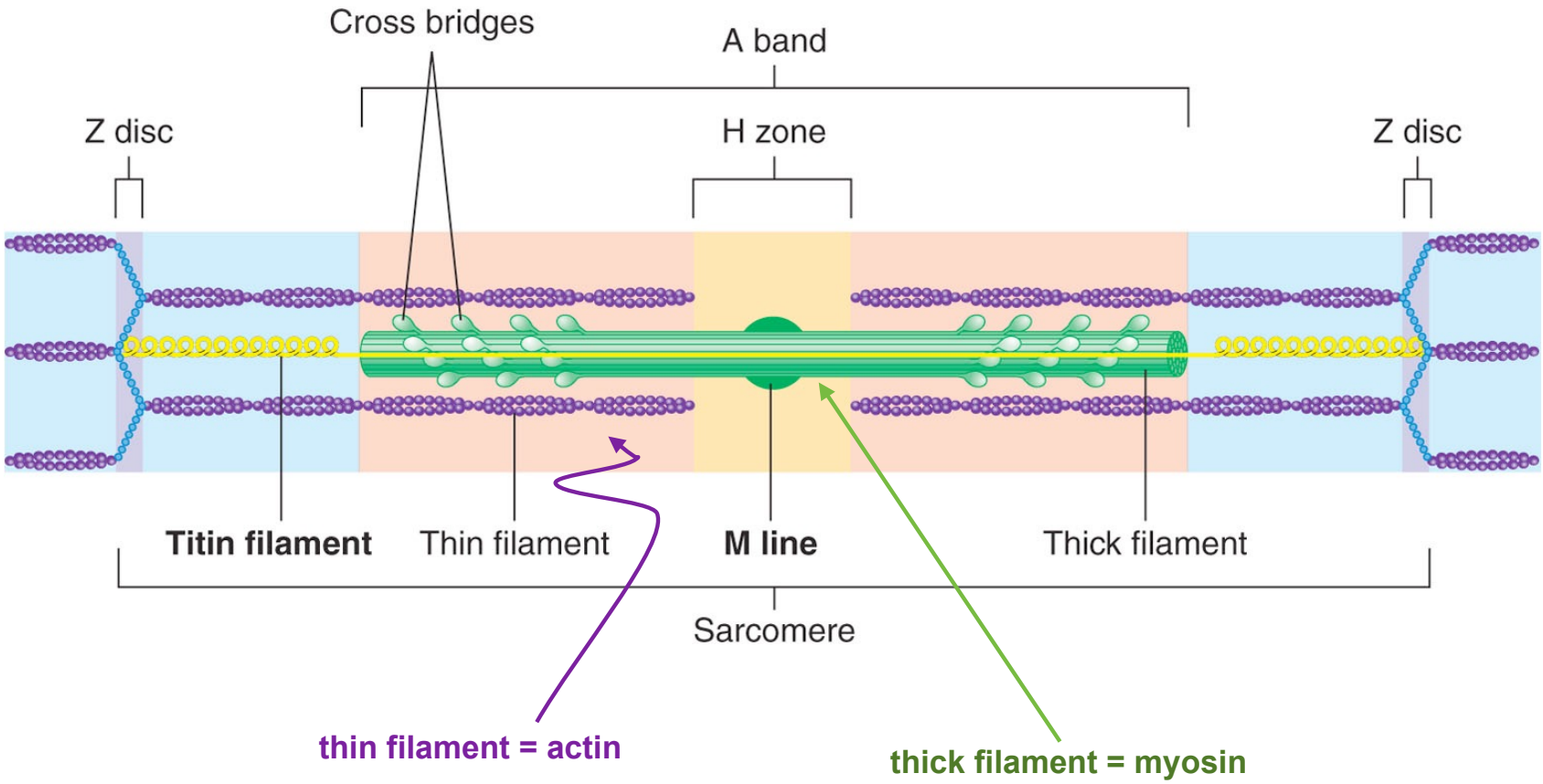
Fox Figure 12.6

Z-disc (from the German "Zwischenscheibe", the intermediiae disc in between the I bands) appears as a series of dark lines.
I-band (for isotropic), A-band (for anisotropic).
H-zone (from the German "heller", brighter)
M-line (from the German "Mittelscheibe", the disc in the middle of the sarcomere)

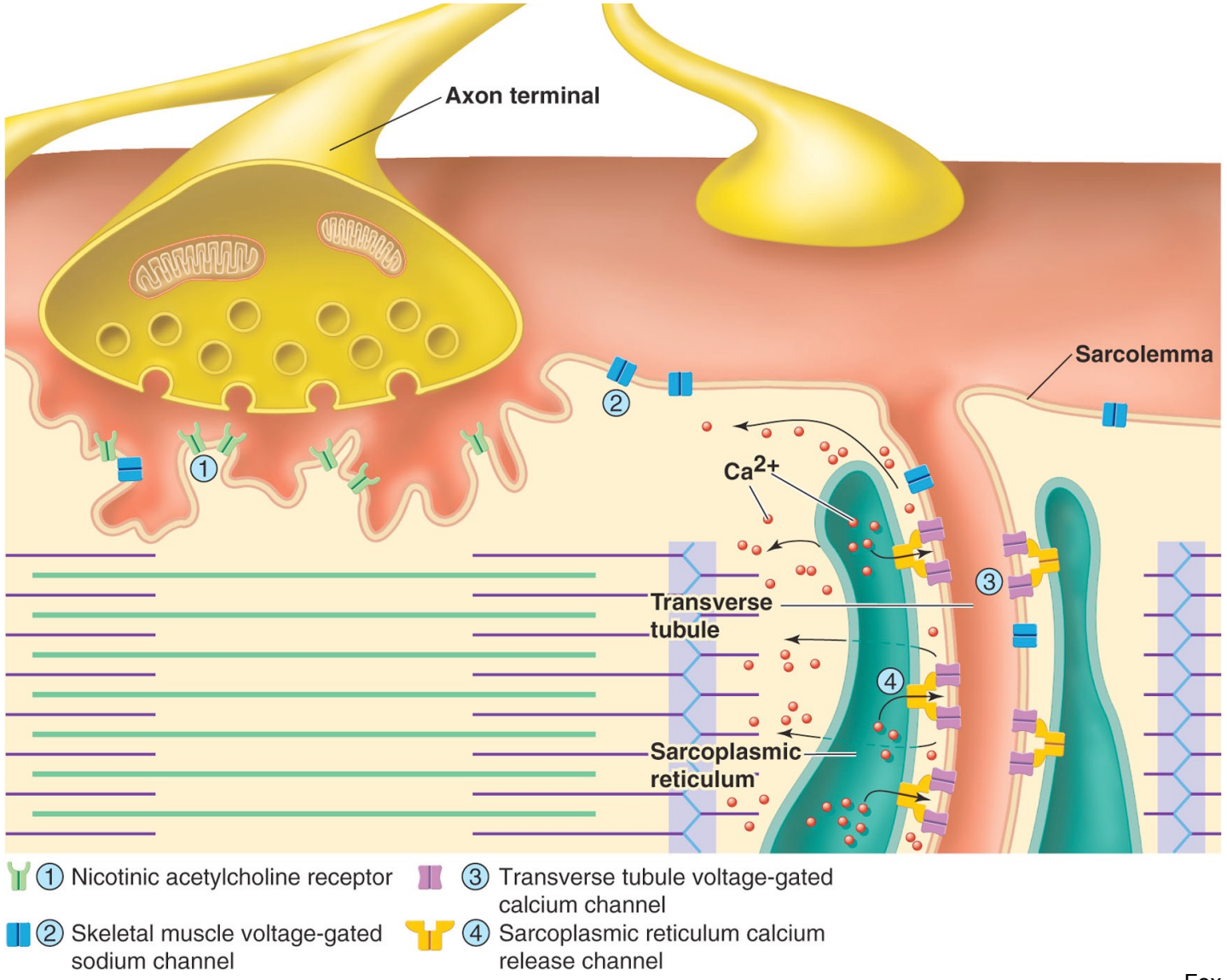


Fox Figure 12.7ab

I band = just thin filament
H zone = just thick filament
A band = overlap of thick & thin filaments



Fox Figure 12.8



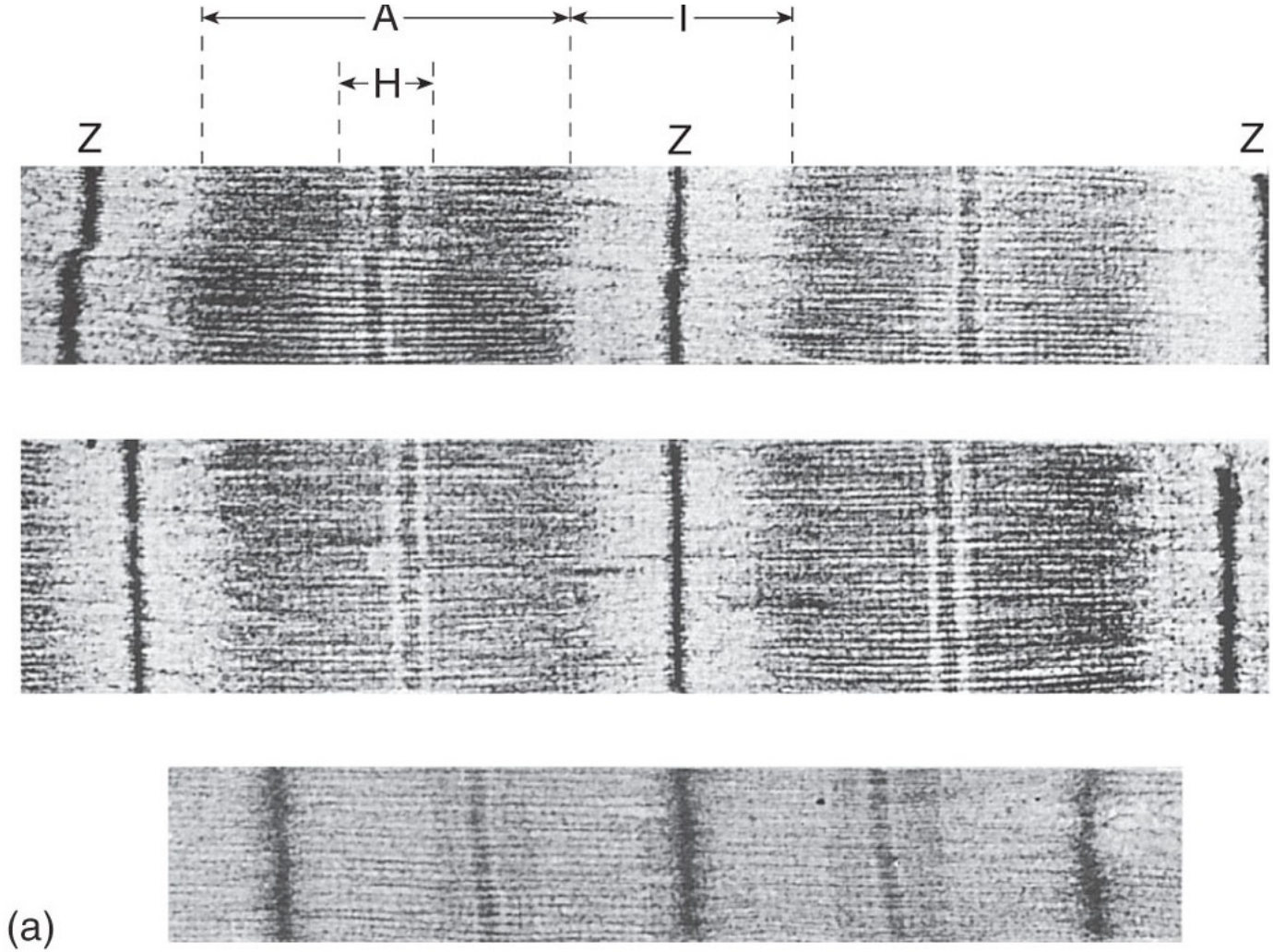
Fox Figure 12.16

Myofibril Contraction

Table 12.2 | Summary of the Sliding Filament Theory of Contraction

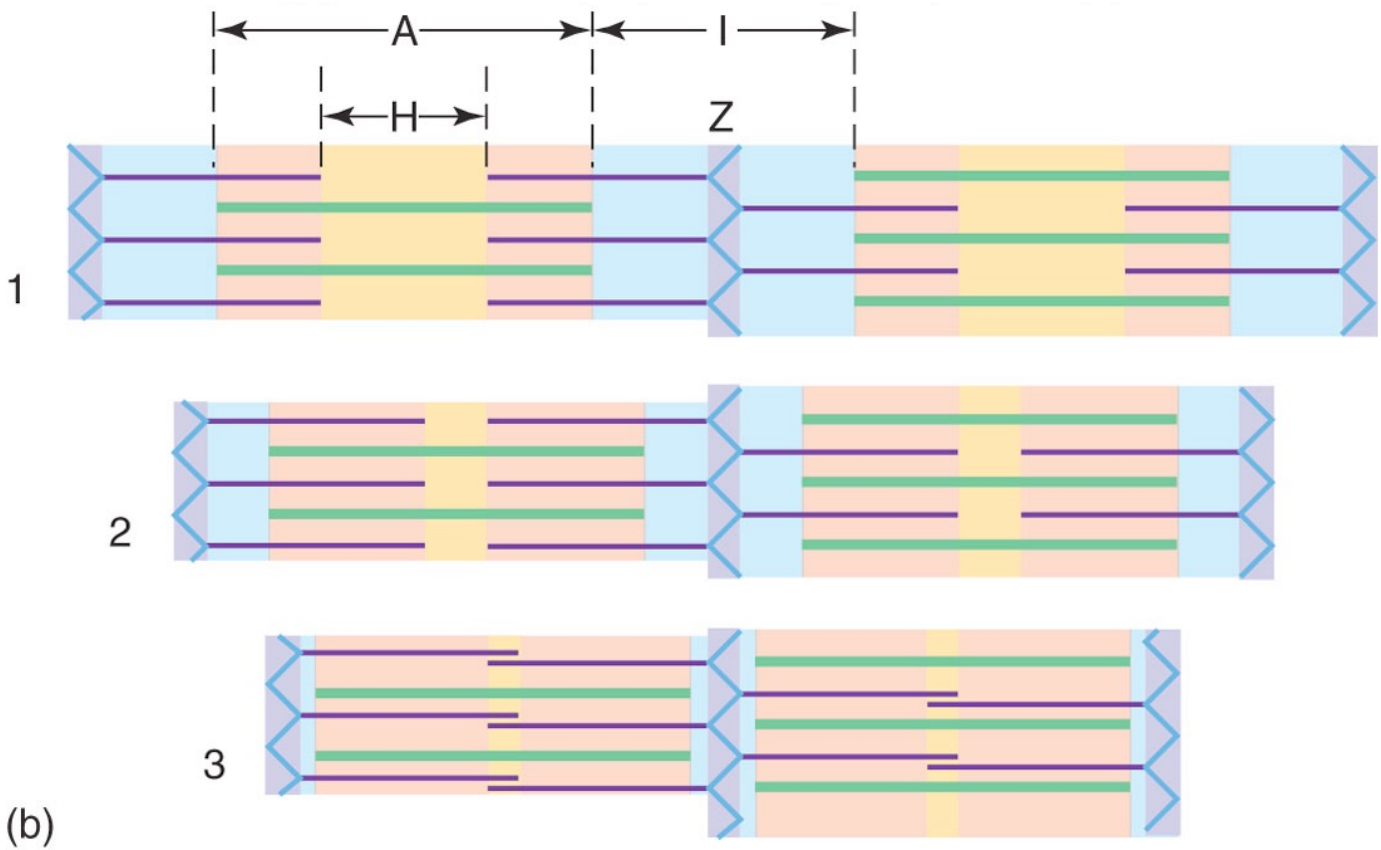
1. A myofiber, together with all its myofibrils, shortens by movement of the insertion toward the origin of the muscle.
2. Shortening of the myofibrils is caused by shortening of the sarcomeres—the distance between Z lines (or discs) is reduced.
3. Shortening of the sarcomeres is accomplished by sliding of the myofilaments—the length of each filament remains the same during contraction.
4. Sliding of the filaments is produced by asynchronous power strokes of myosin cross bridges, which pull the thin filaments (actin) over the thick filaments (myosin).
5. The A bands remain the same length during contraction, but are pulled toward the origin of the muscle.
6. Adjacent A bands are pulled closer together as the I bands between them shorten.
7. The H bands shorten during contraction as the thin filaments on the sides of the sarcomeres are pulled toward the middle.

Contraction of sarcomere = overlap of thick & thin filaments

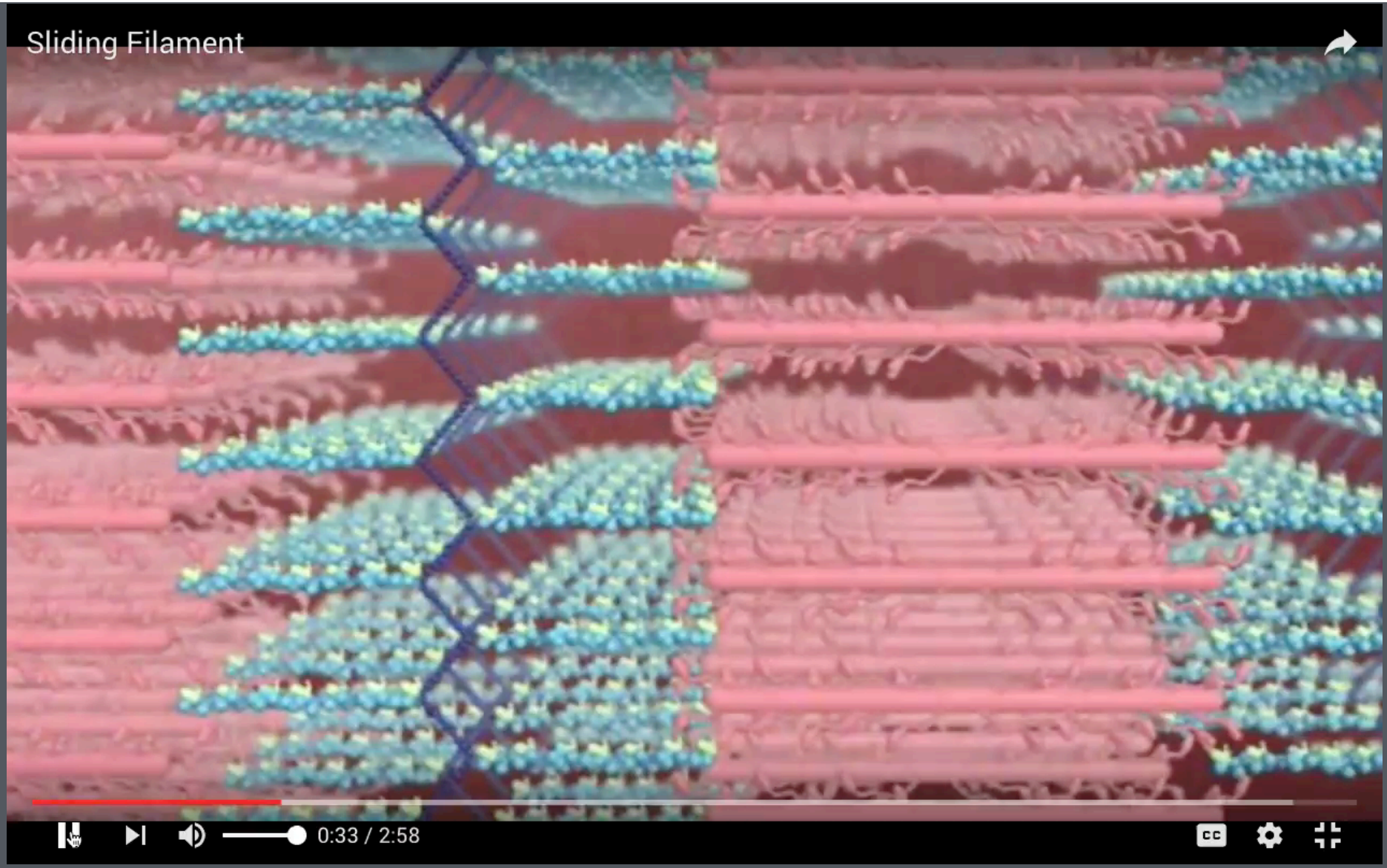


Fox Figure 12.9a

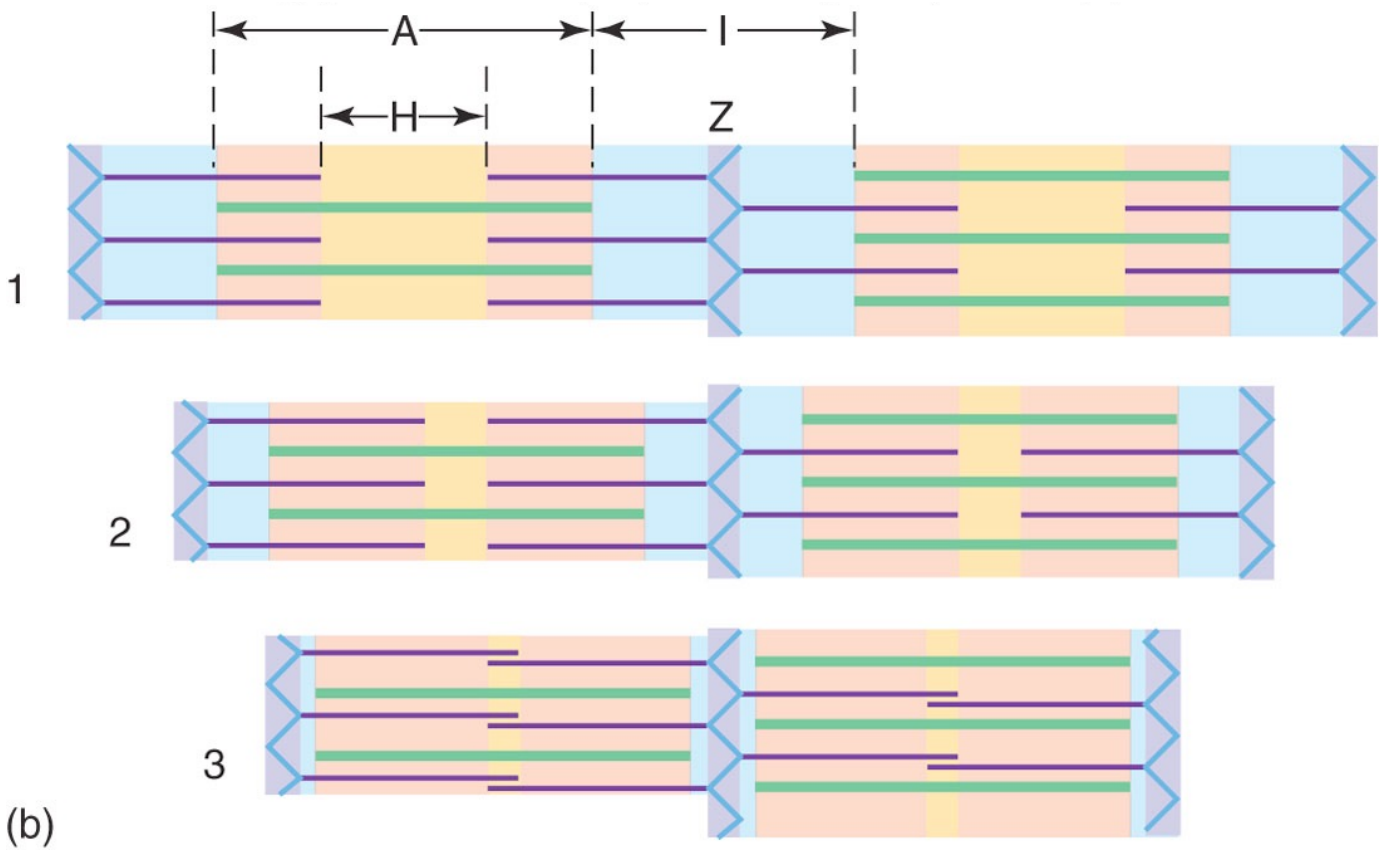
Contraction of sarcomere = overlap of thick & thin filaments



Fox Figure 12.9b

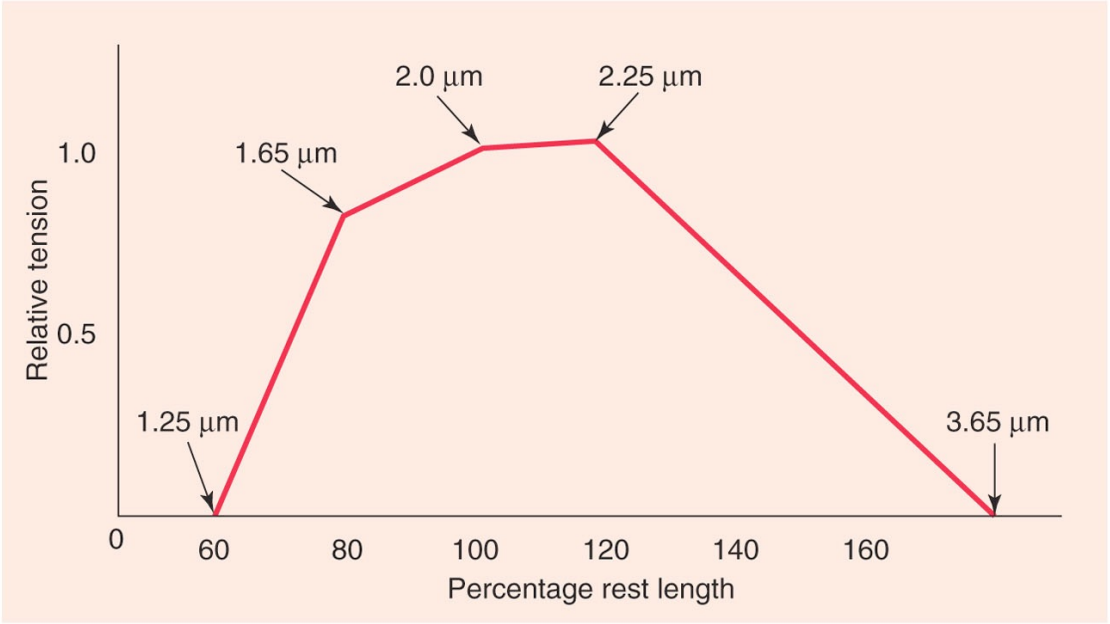

Sliding Filament
0:33 / 2:58

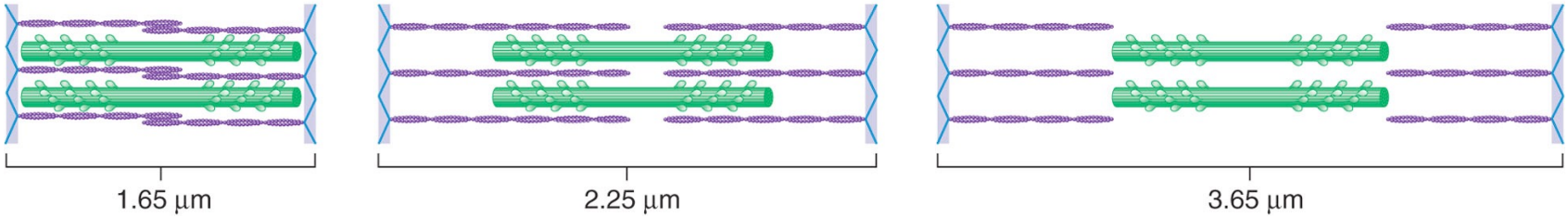
Contraction of sarcomere = overlap of thick & thin filaments



Fox Figure 12.9b

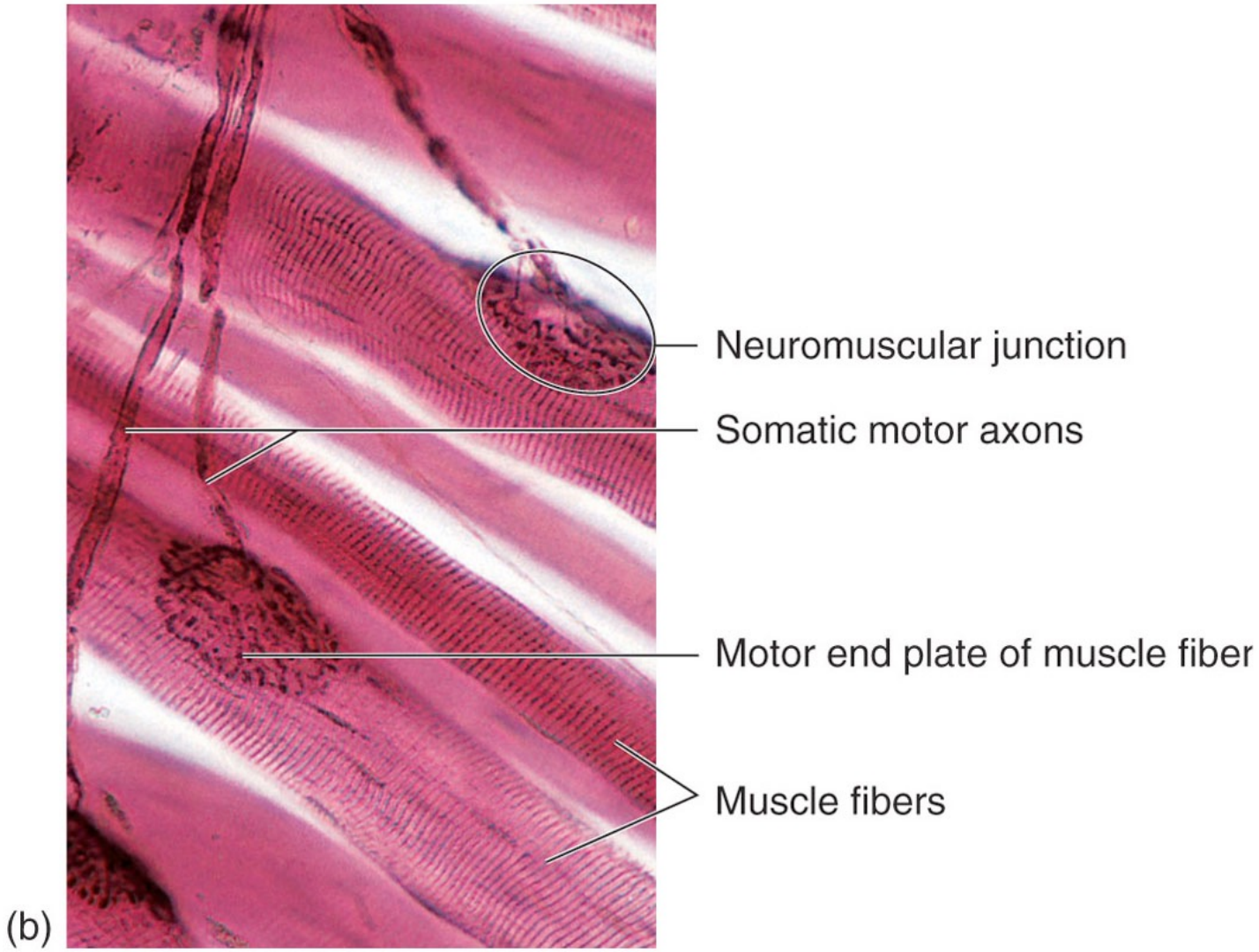
Length-Tension Relationship



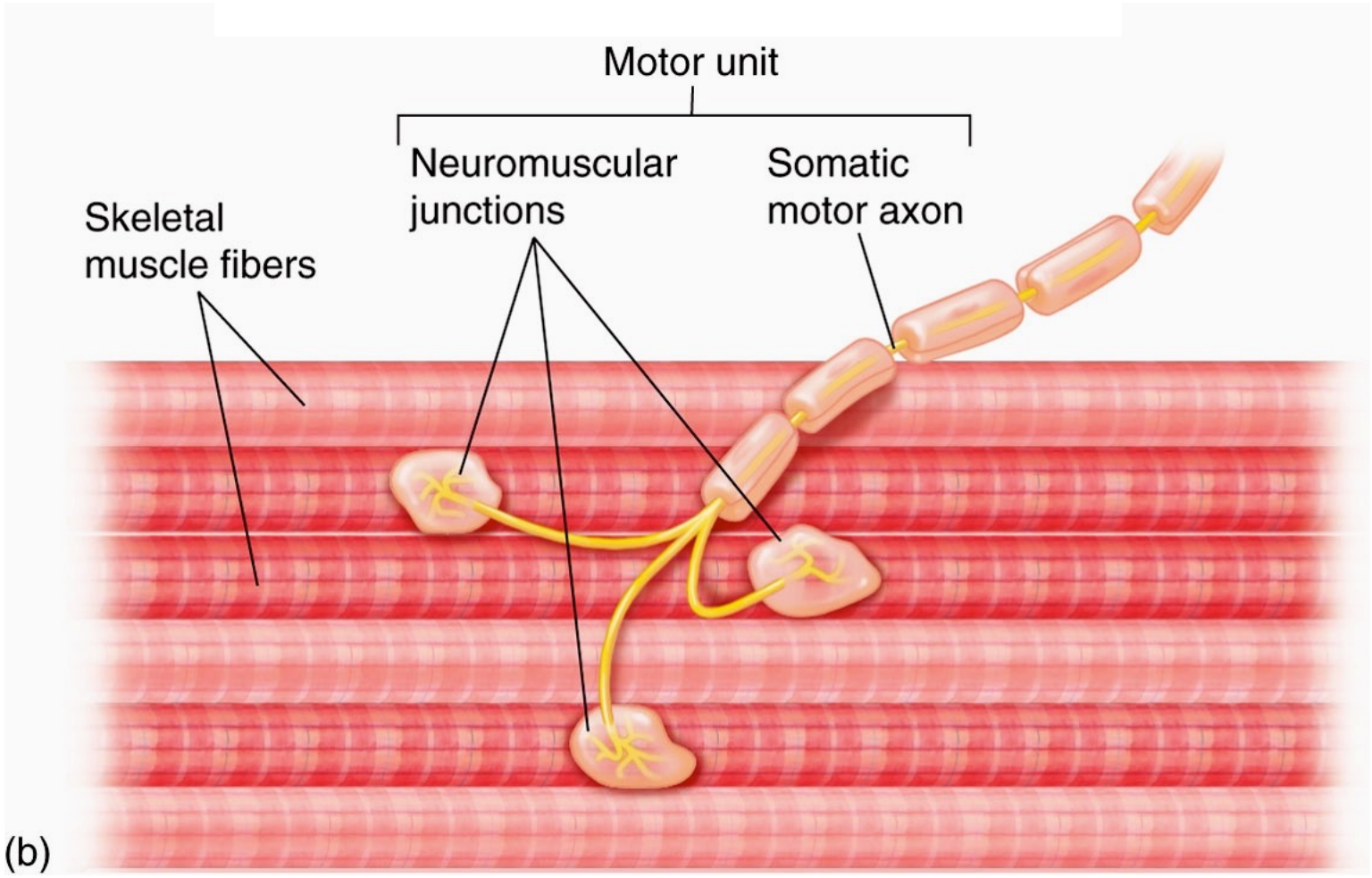


Fox Figure 12.21

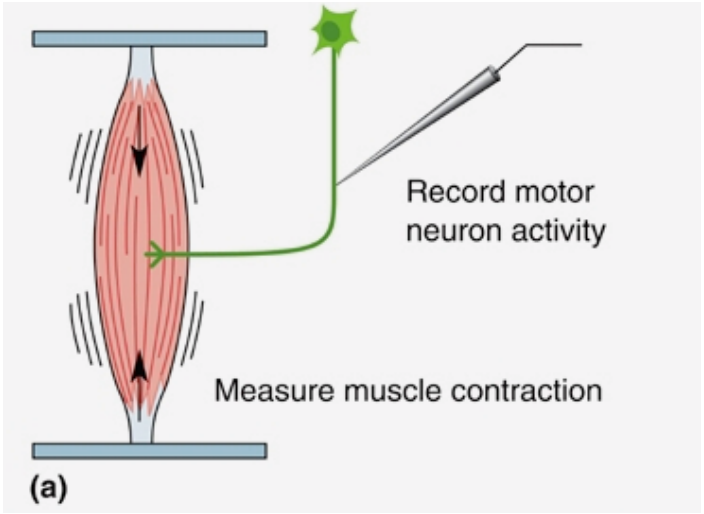

HHMI

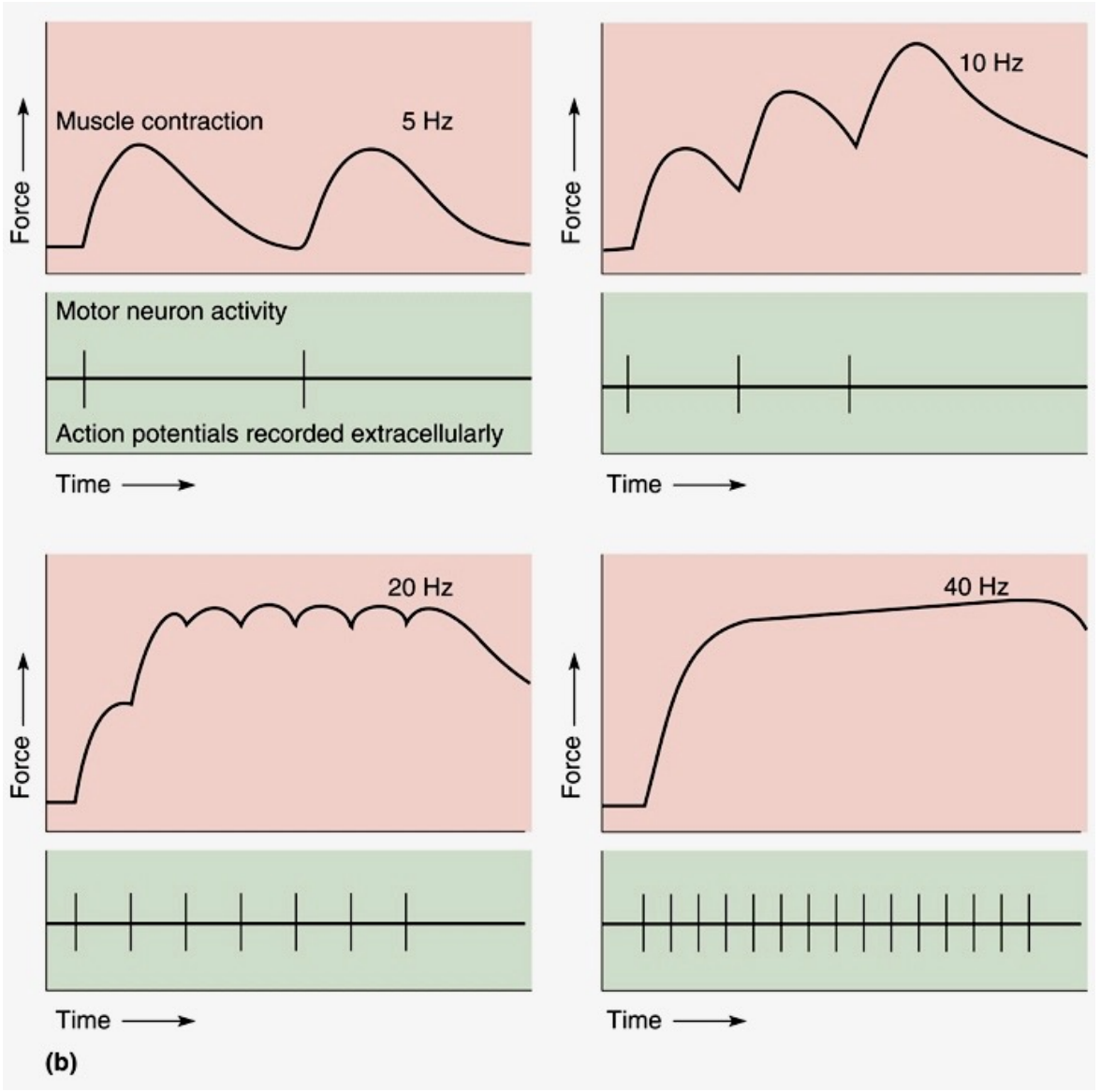


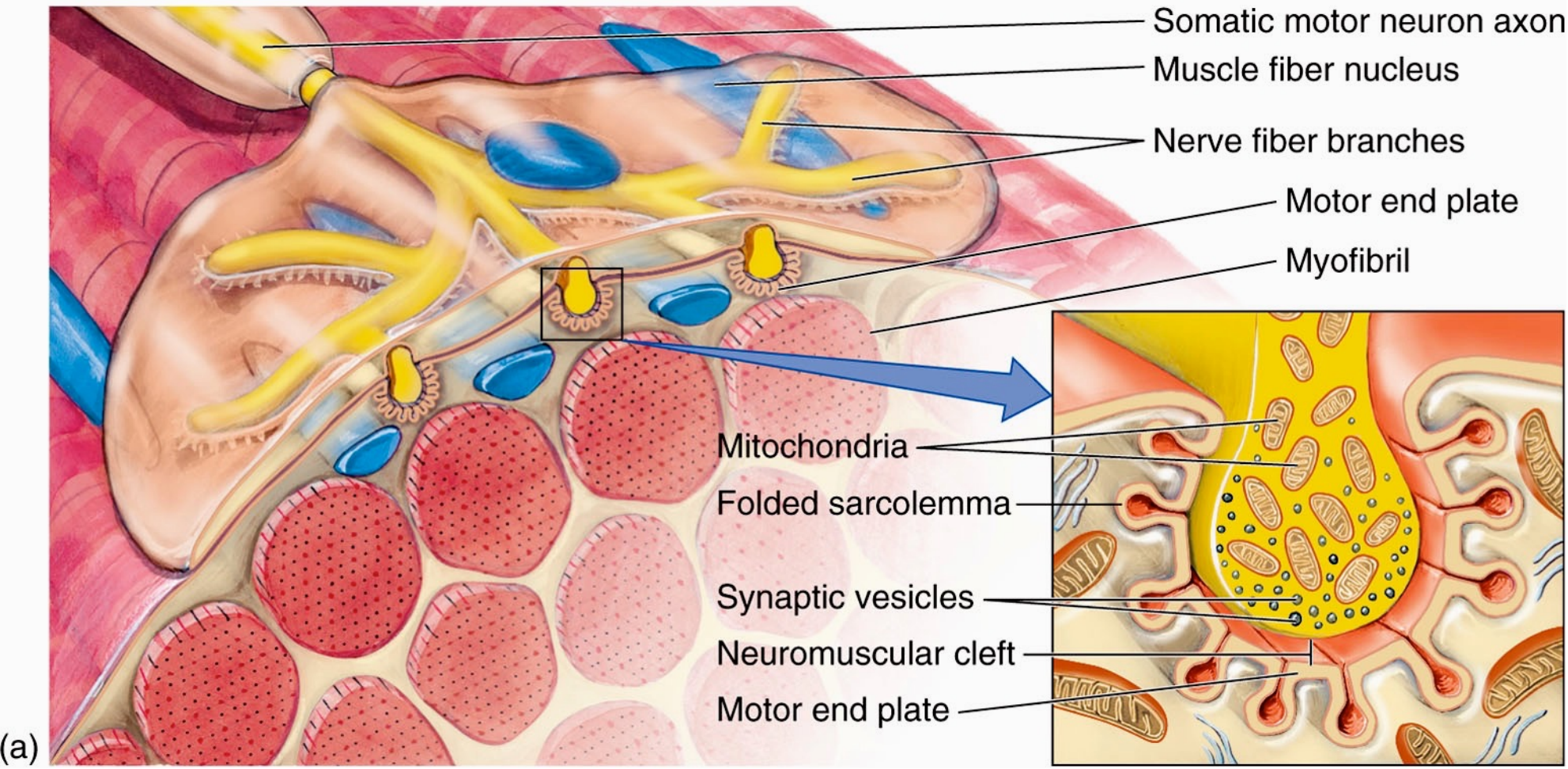
Fox Figure 12.3b



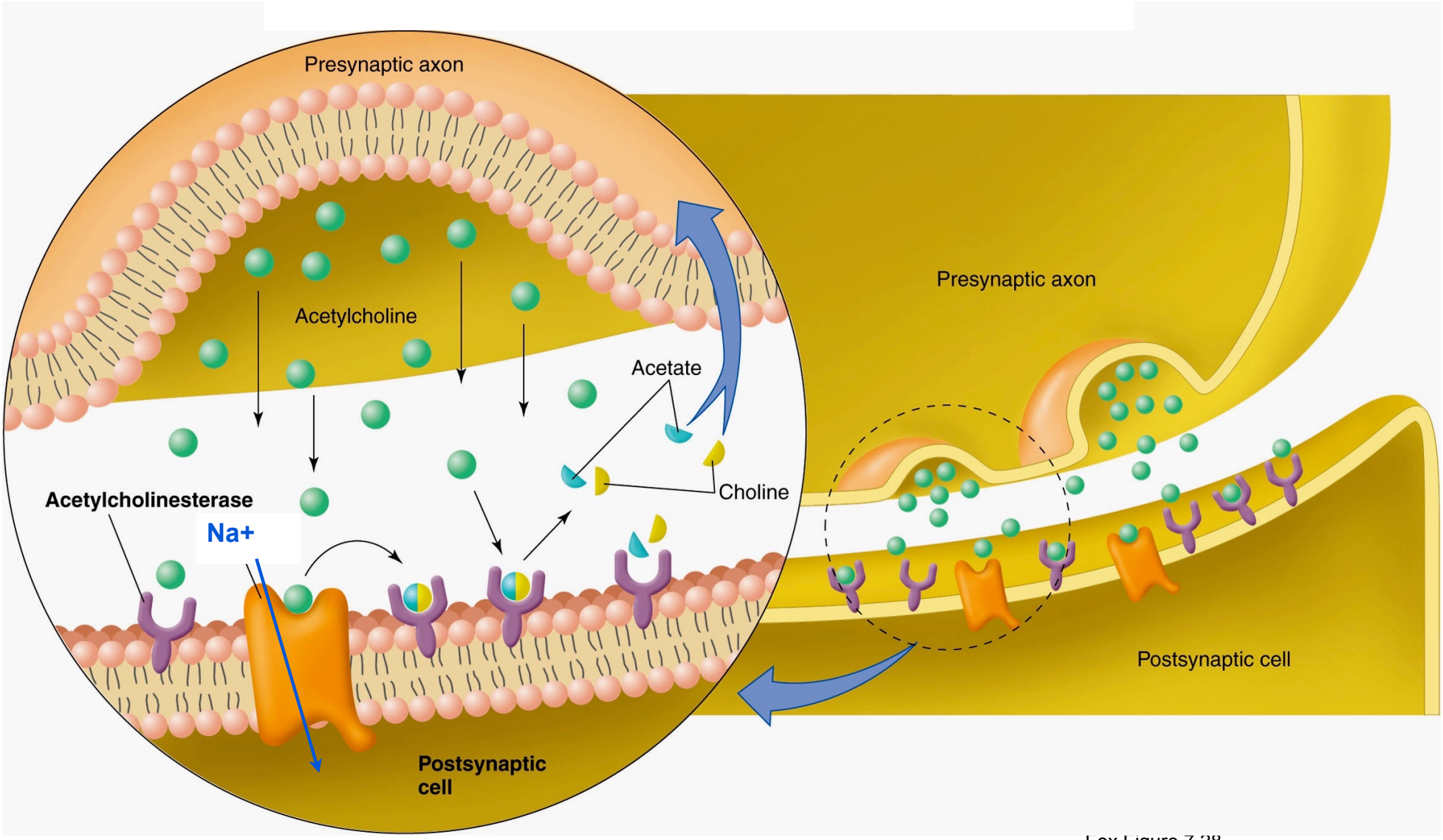
Fox Figure 12.4b


Record motor
neuron activity
Measure muscle contraction
(a)

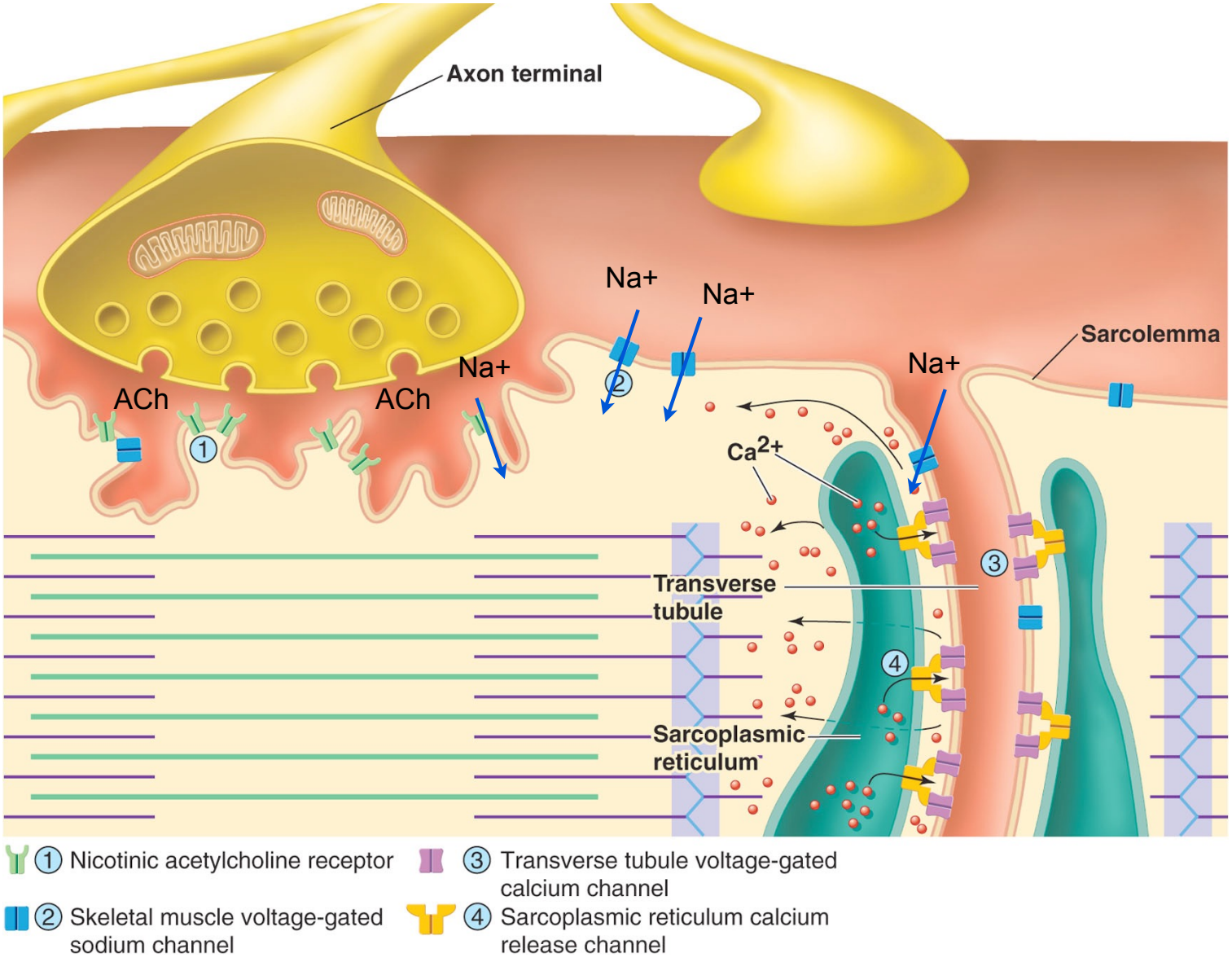

Muscle contraction
5 Hz
Force
Motor neuron activity
Action potentials recorded extracellularly
Time
10 Hz
20 Hz
40 Hz
(b)



Fox Figure 12.3a



Fox Figure 7.28



Fox Figure 12.16

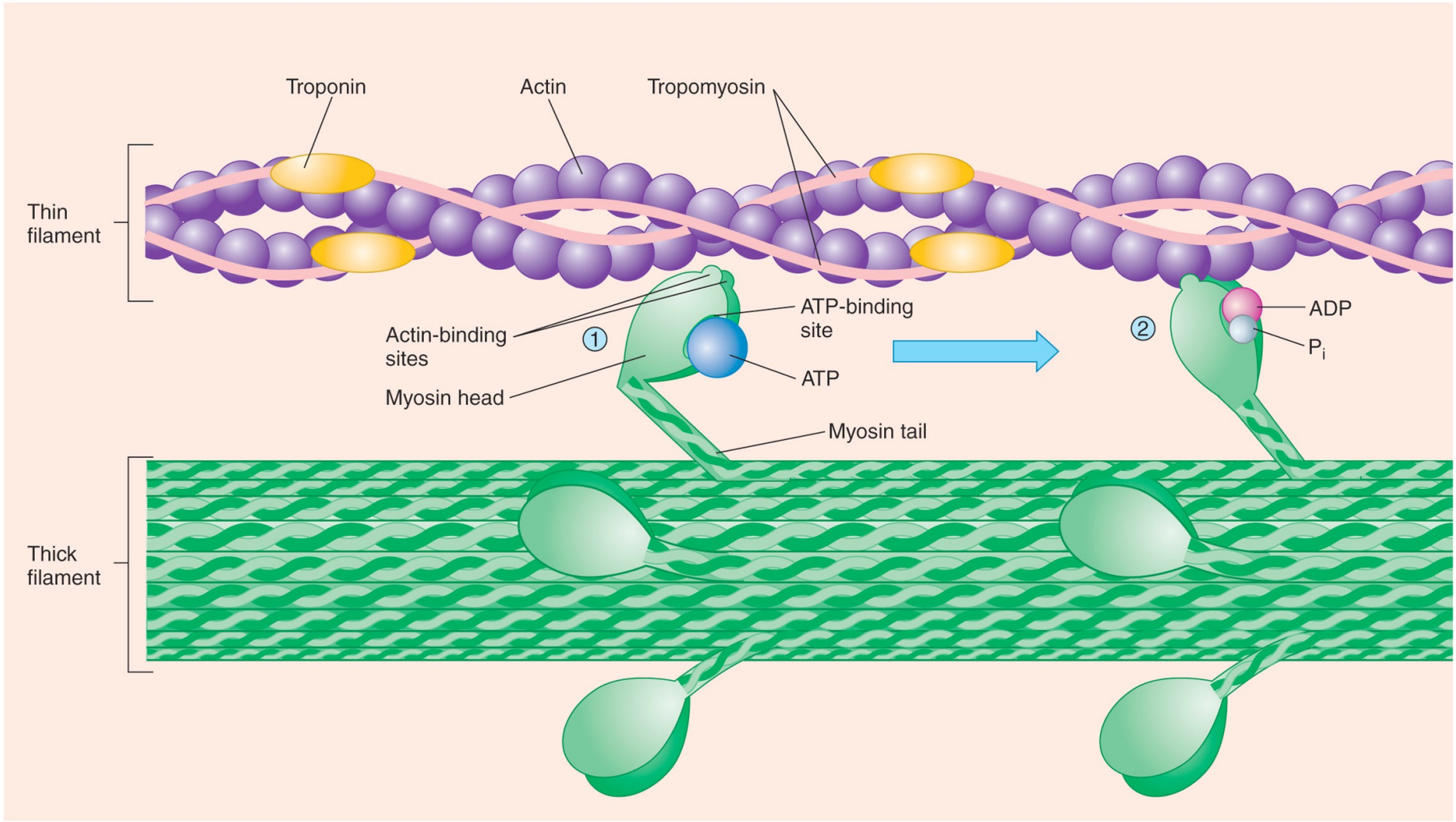
Actin/Myosin Sliding Filament Model

When high intracellular [Ca^{++}], **myosin** grabs **actin** and pulls itself along actin fiber, causing contraction.

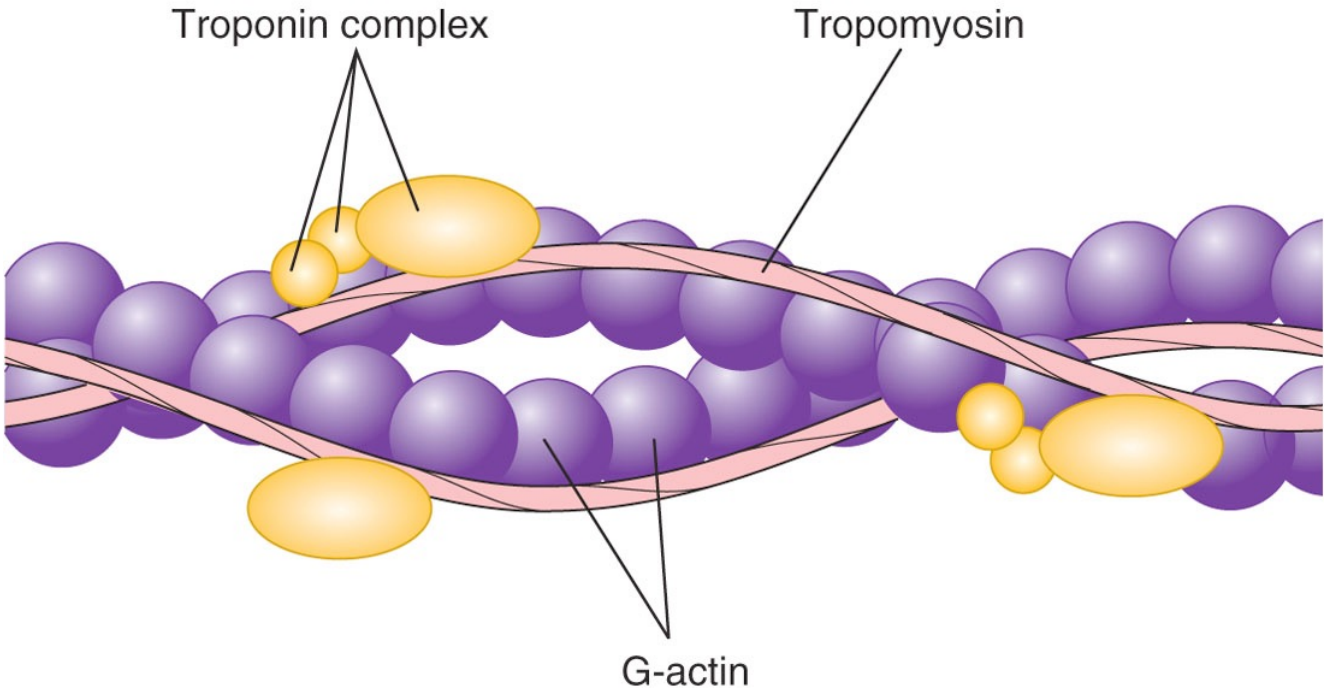
1. Ca++ binds to **troponin** on actin and exposes **myosin-binding sites**.
2. **ATP binds to myosin** head and gets hydrolyzed to ADP; myosin head now in high-energy state.
3. Myosin head **binds to actin**.
4. During the power stroke, **myosin drops ADP and pulls** on the thin filament.
5. **ATP binds to myosin** to cause myosin to **release actin** and restart cycle.

tropo - to move

Cycle continues until Ca^{++} is pumped back into sacroplasmic reticulum or ATP runs out.



Fox Figure 12.10



Fox Figure 12.13

Figure 49.34 Hypothetical mechanism for the control of muscle contraction

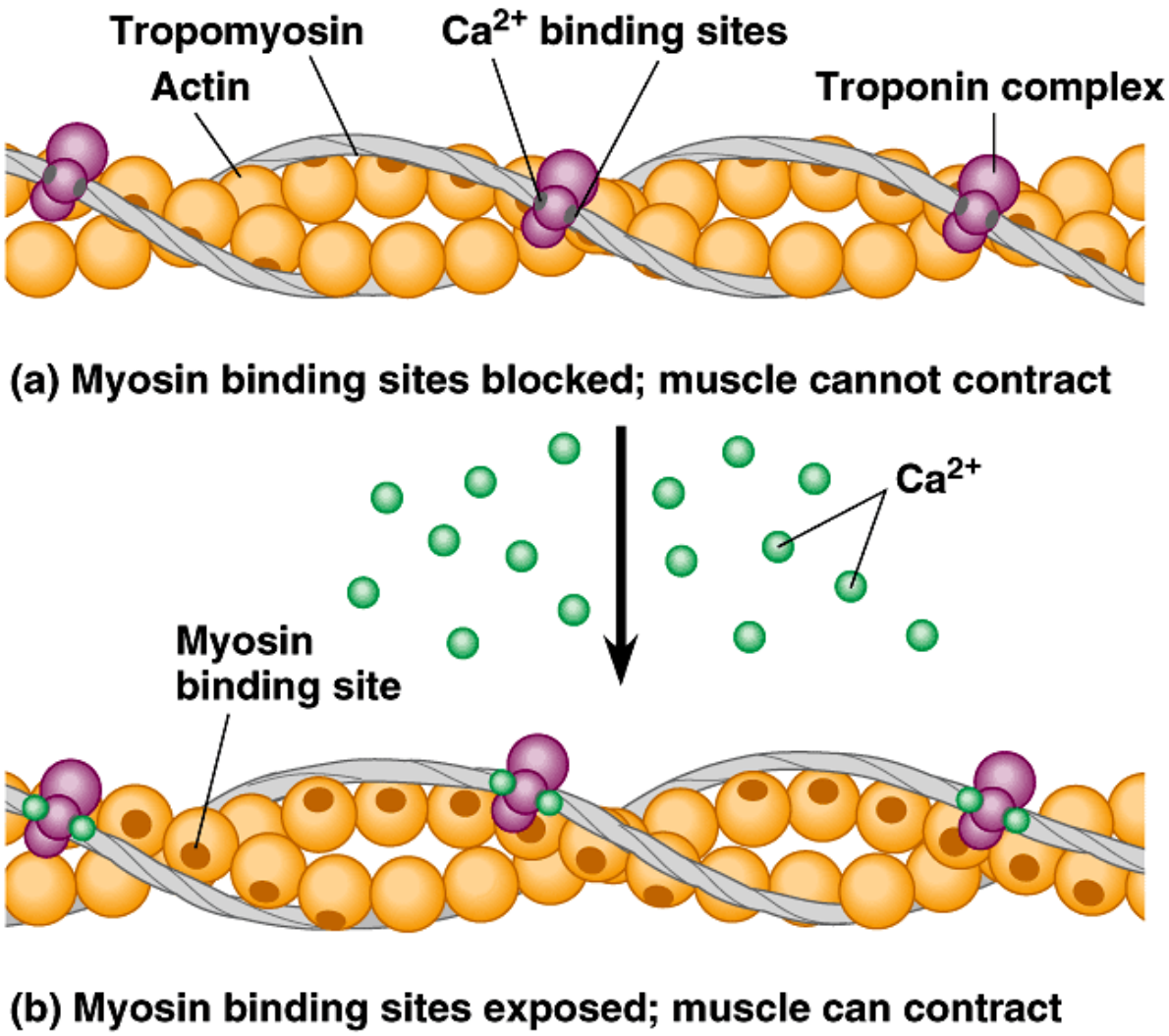


Figure 49.33 One hypothesis for how myosin-actin interactions generate the force for muscle contraction (Layer 1)

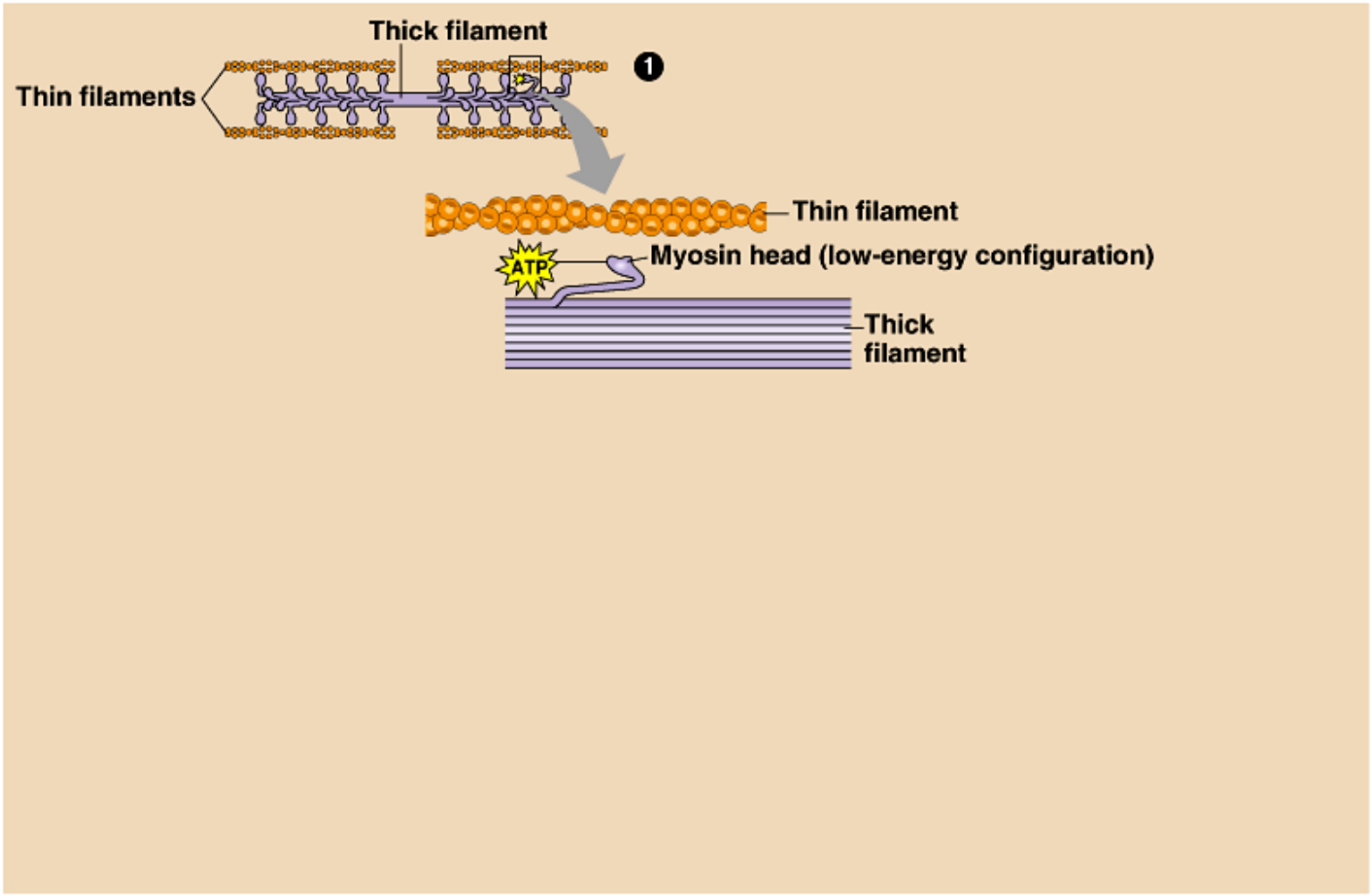


Figure 49.33 One hypothesis for how myosin-actin interactions generate the force for muscle contraction (Layer 2)

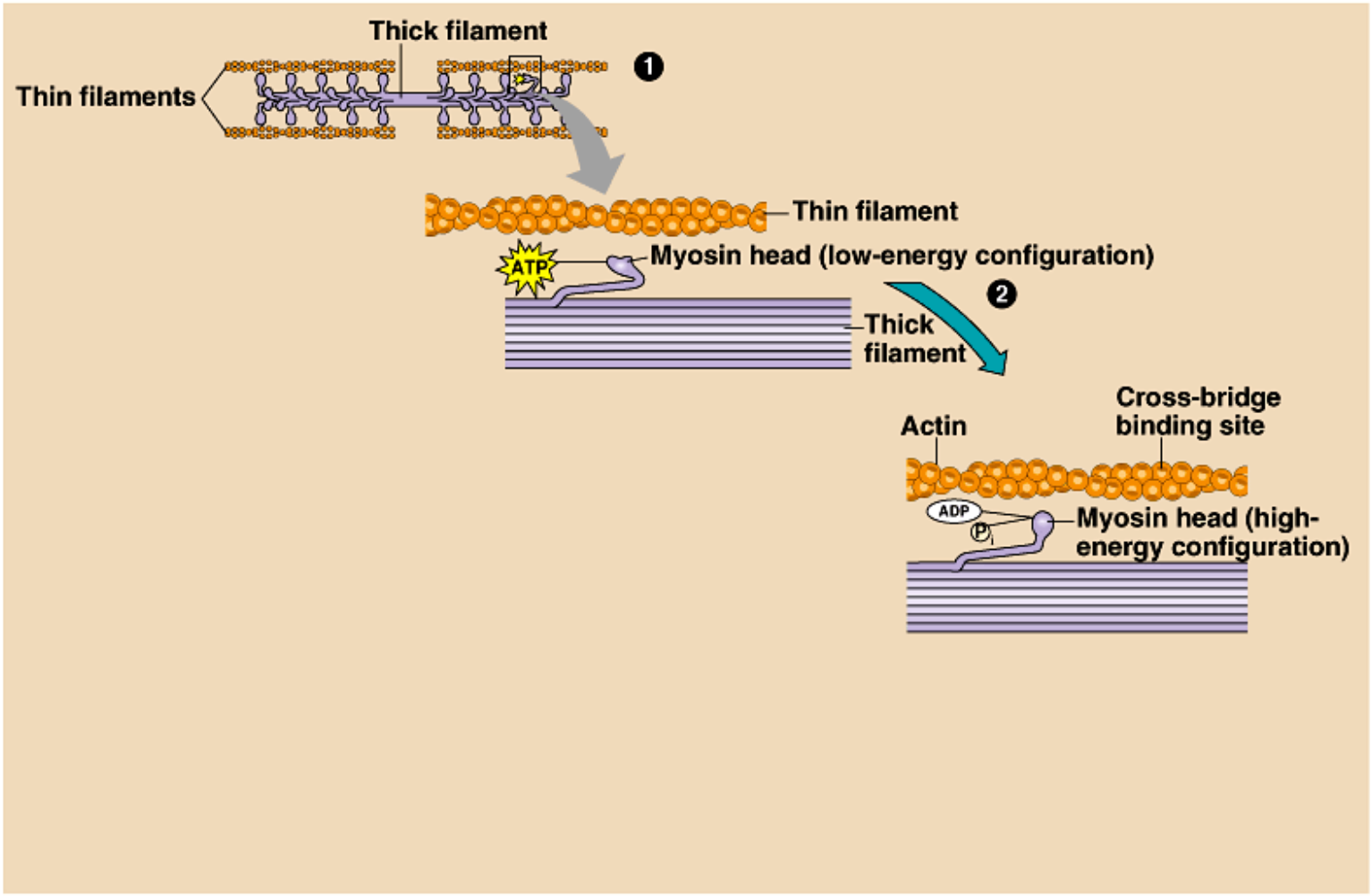


Figure 49.33 One hypothesis for how myosin-actin interactions generate the force for muscle contraction (Layer 3)

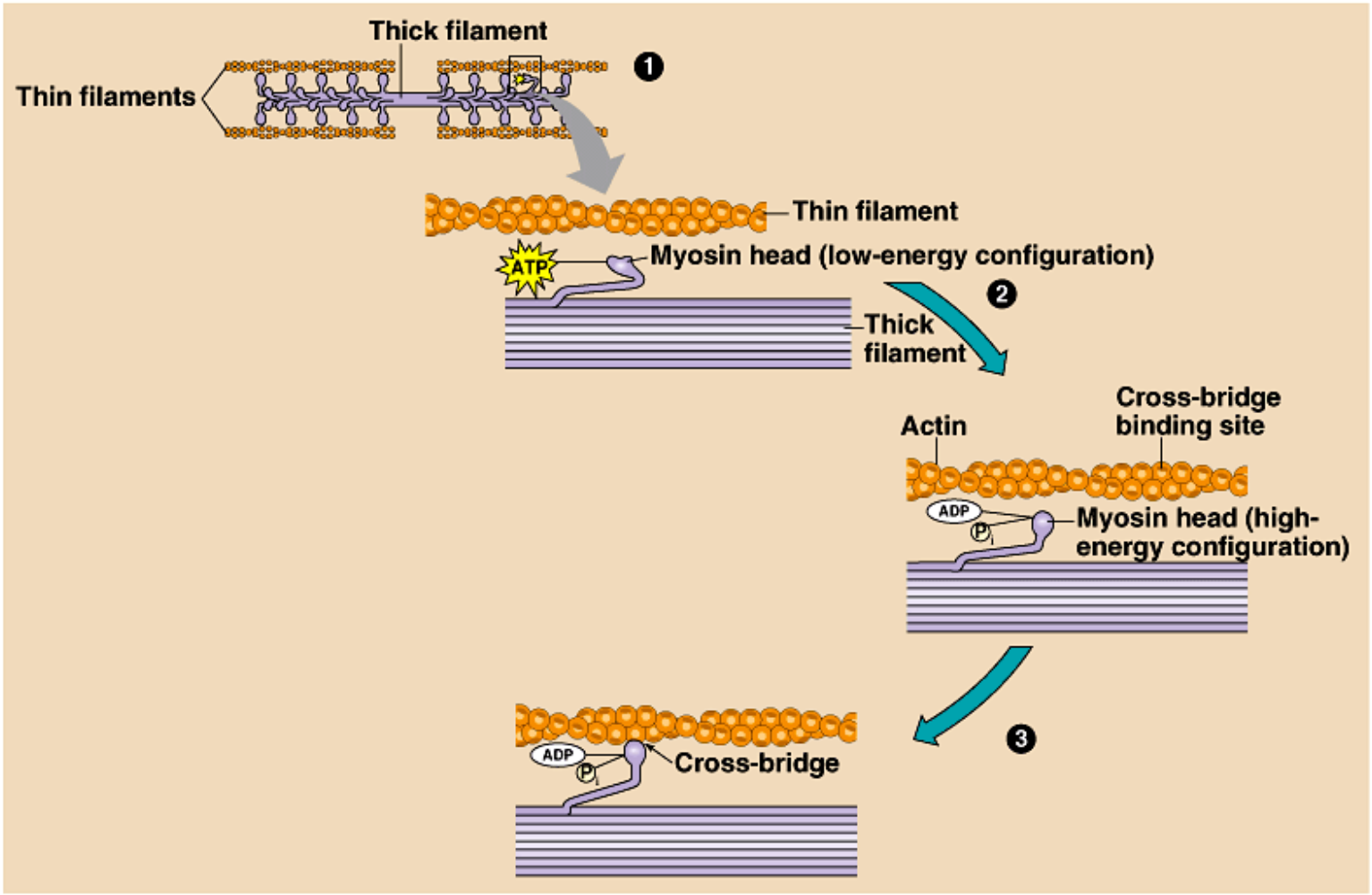
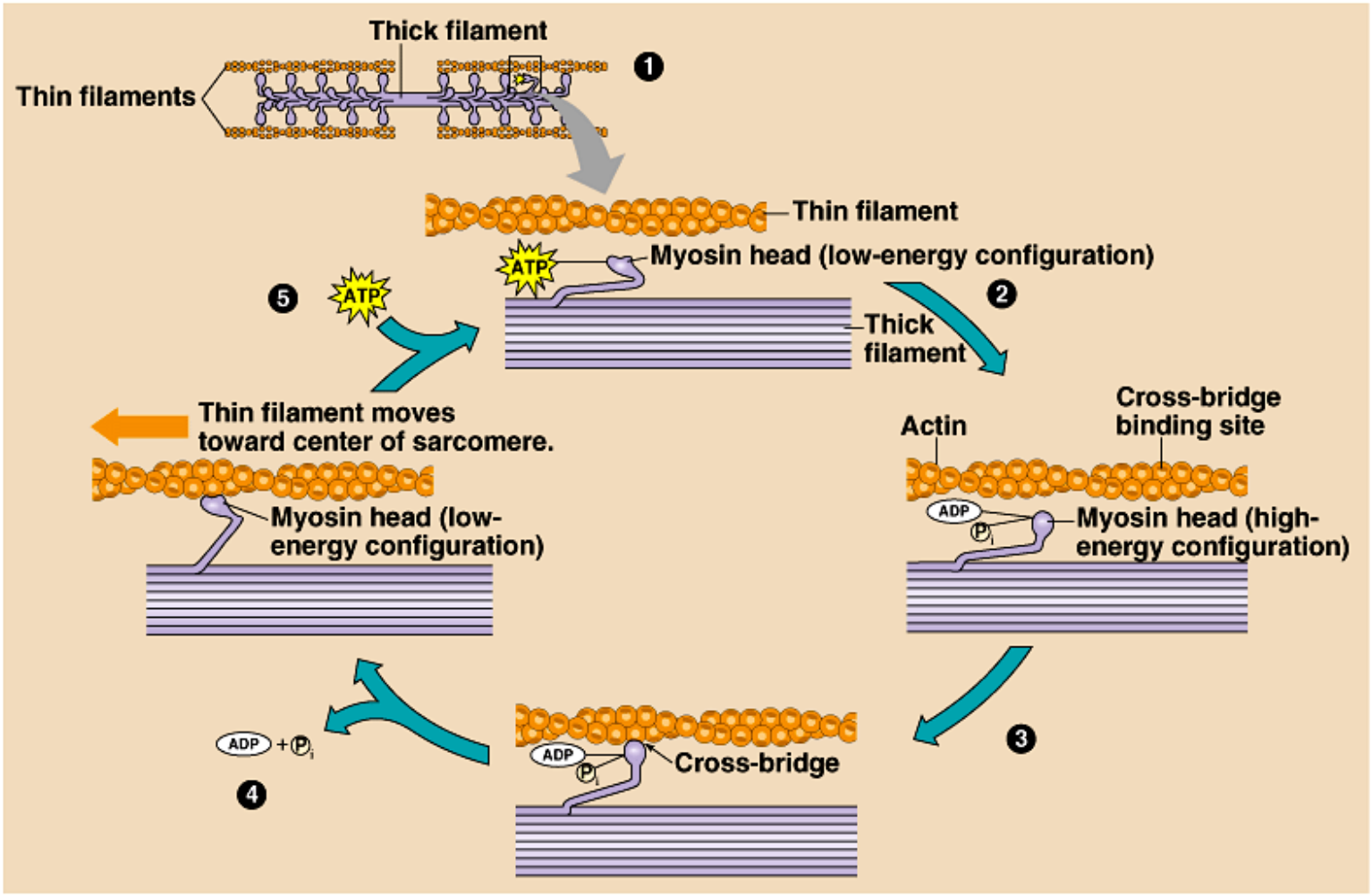
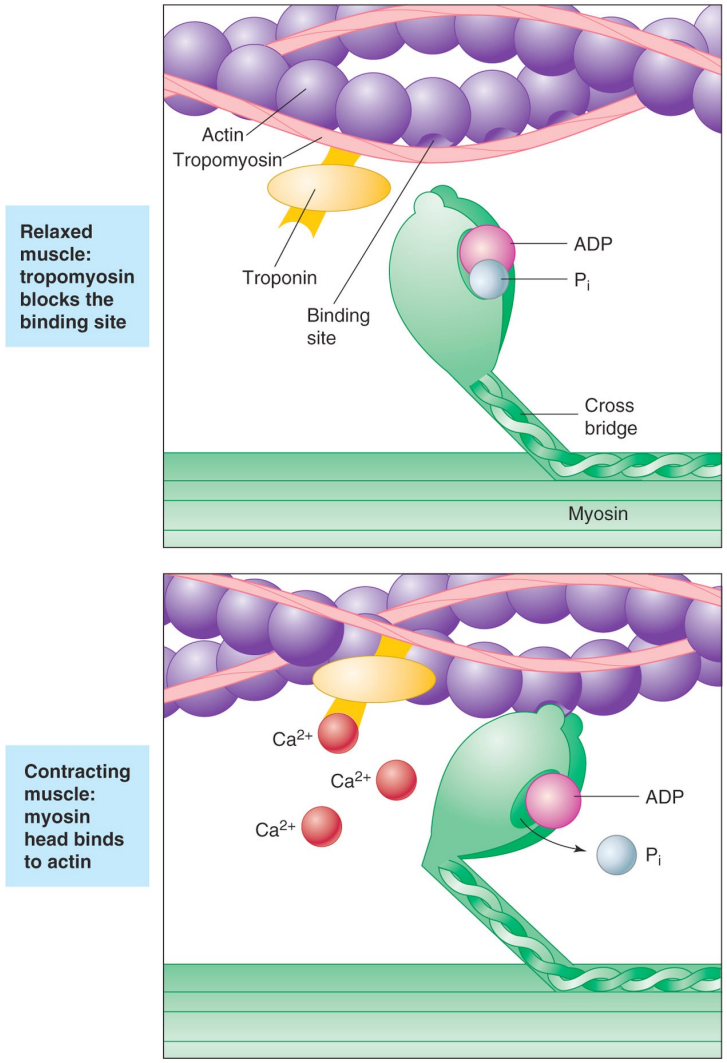
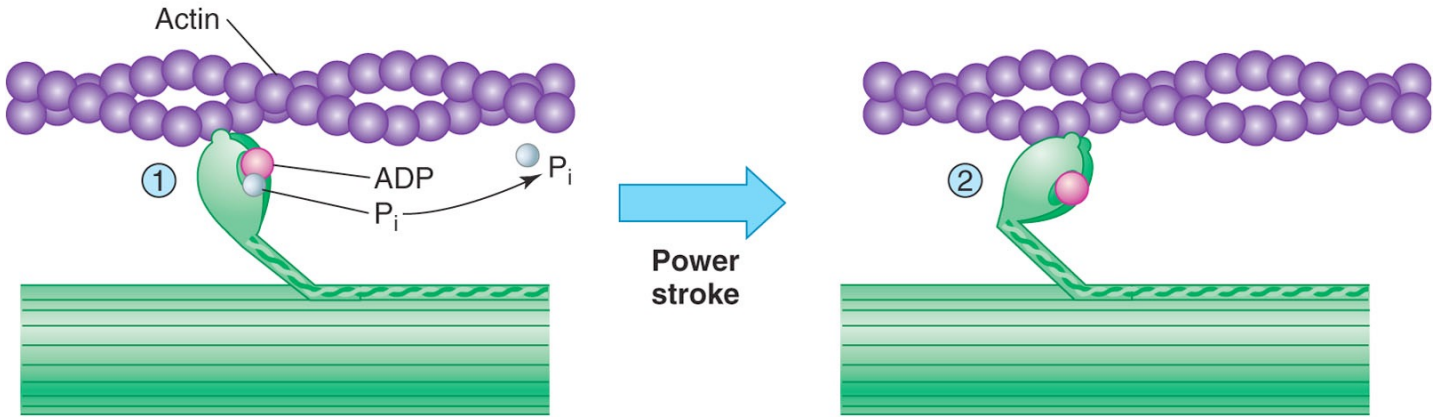


Figure 49.33 One hypothesis for how myosin-actin interactions generate the force for muscle contraction (Layer 4)

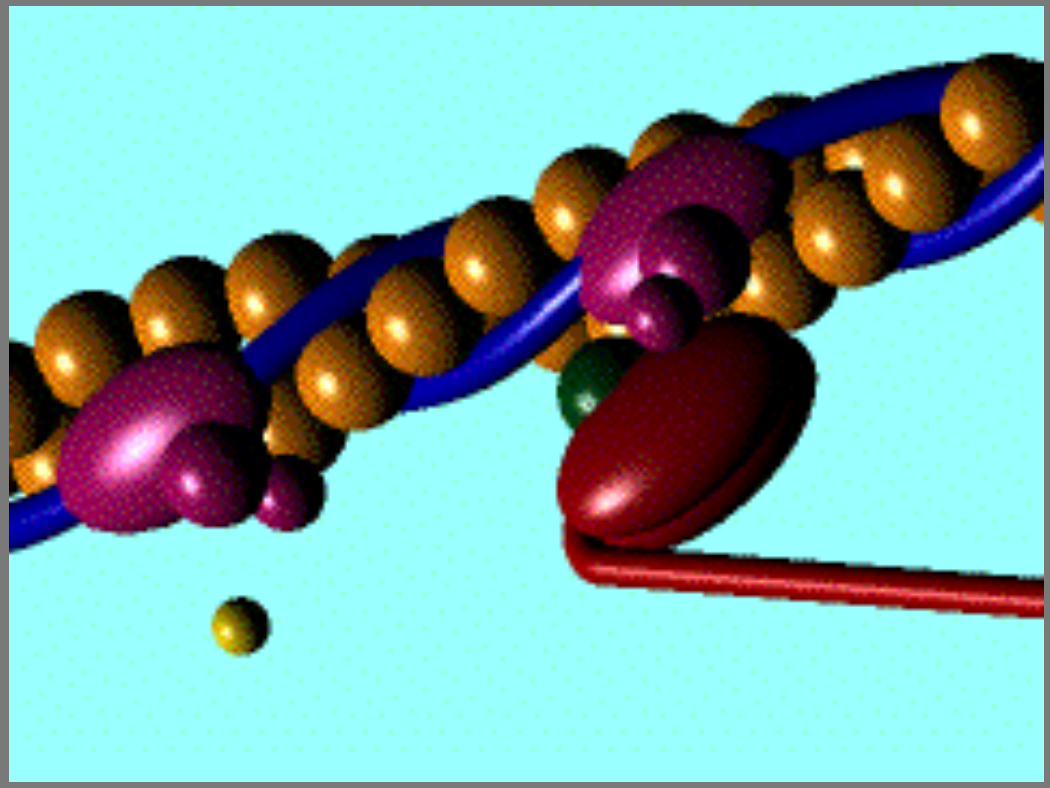




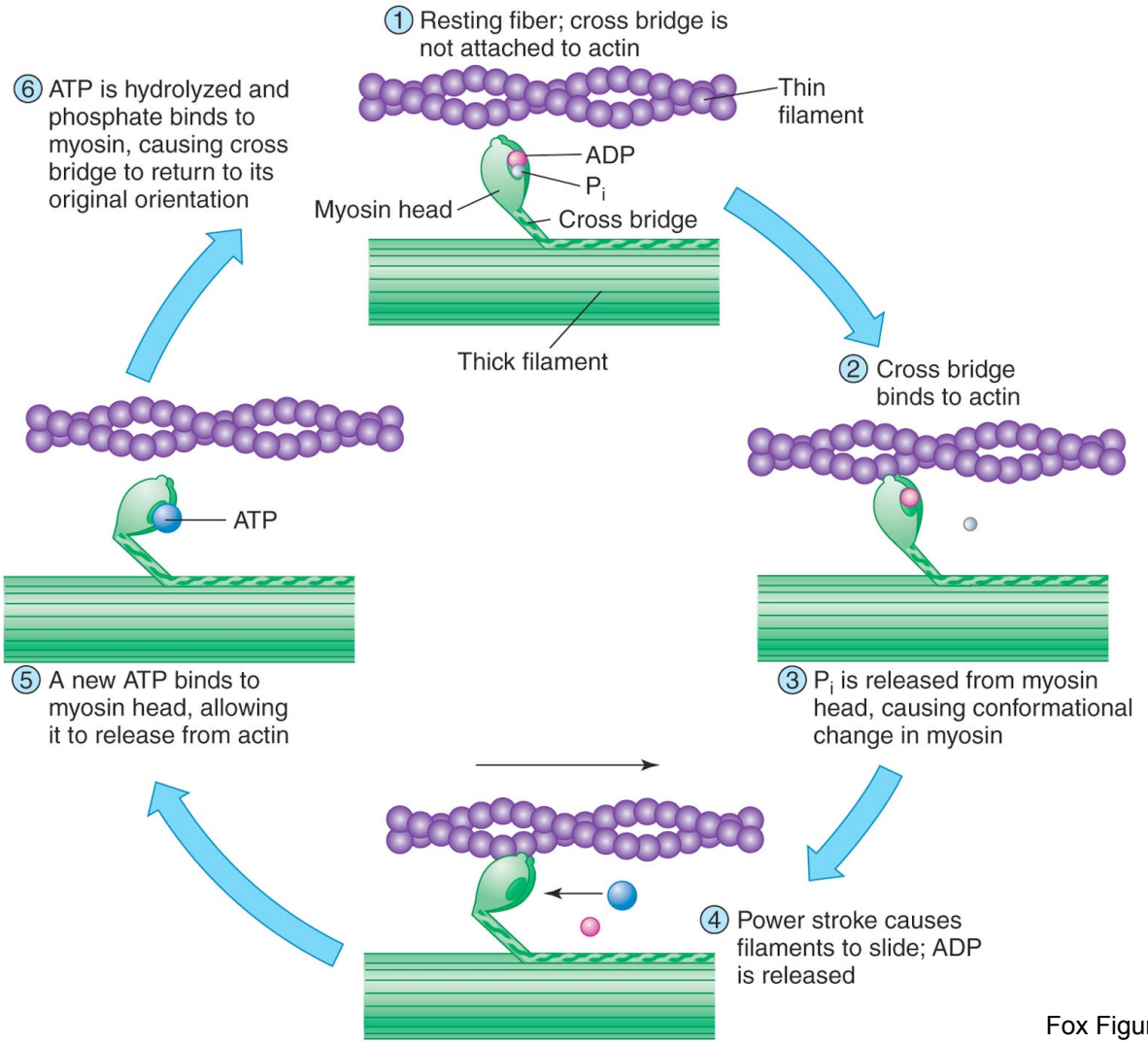
Fox Figure 12.14



Fox Figure 12.11



http://www.sci.sdsu.edu/movies/actin_myosin_gif.html



Fox Figure 12.12

Muscle contraction:

1. requires Myosin in hi-energy configuration (ADP bound to Myosin)

2. requires Ca++ bound to troponin/actin to reveal myosin-binding sites

Note:

i. no energy required for ADP to stay on Myosin & Myosin to attach to Actin

ii. Ca++ can leak from sarcoplasmic reticulum for thin filament binding

Muscle Relaxation:

1. replace ADP on myosin with ATP to cause myosin to release actin (requires ATP synthesis)

2. remove Ca++ by pumping back into sarcoplasmic reticulum (requires ATP-fueled pump)

Note:

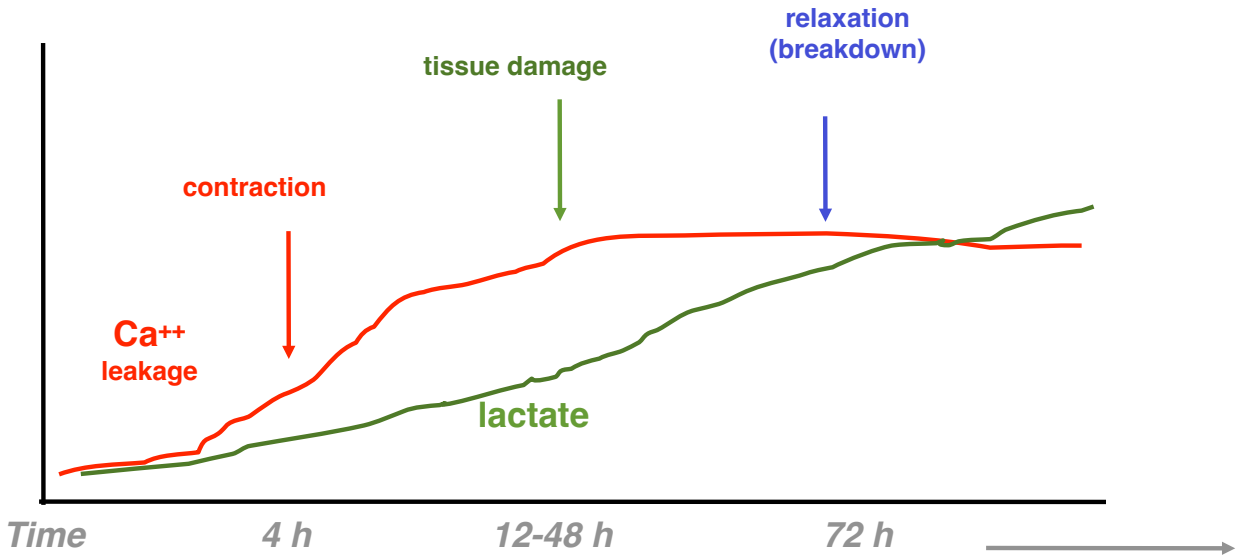
muscle **relaxation** ***requires energy from ATP***

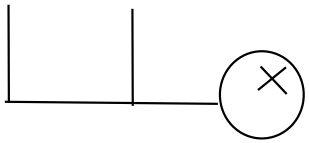
Rigor Mortis “stiffness of death”

After death:
- no circulation/breathing
- so no cellular respiration
- so little ATP production.

4- 12 h:
- Sarcoplasmic Reticulum allows Ca++ leak
- Muscles contract.
- No energy for relaxation.

48-72 h:
- Lactic Acid builds up in muscle cells during anaerobic respiration
- Drop in pH causes tissue damage
- Muscle fibers relax as the filaments degrade.


relaxation
(breakdown)
tissue damage
contraction
Ca++
leakage
lactate
Time
4 h
12-48 h
72 h



Neuromuscular Junction

Motor Neuron innervates one group of muscle fibers = motor unit.

Muscle cell, like nerve cell, has membrane potential.

Motor neurons release acetylcholine onto neuromuscular junction.

Acetylcholine binds to nicotinic receptors (ligand-gated Na+ channels)

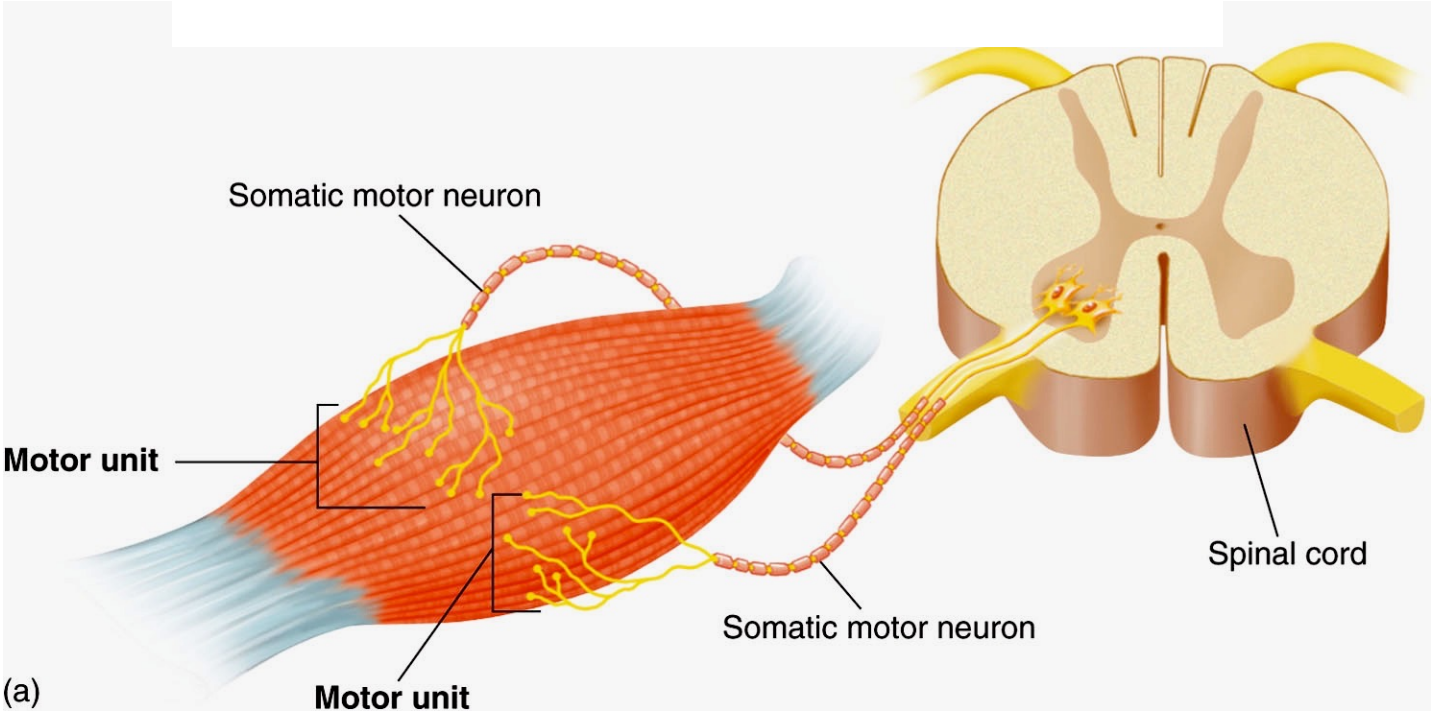
Nicotinic Receptors let Na+ into cell, causing muscle action potentials across entire muscle fiber and down through transverse tubules (T-tubules).

Action potential causes opening of voltage-gated Ca++ channels, causing Ca^{++} release from sarcoplasmic reticulum.

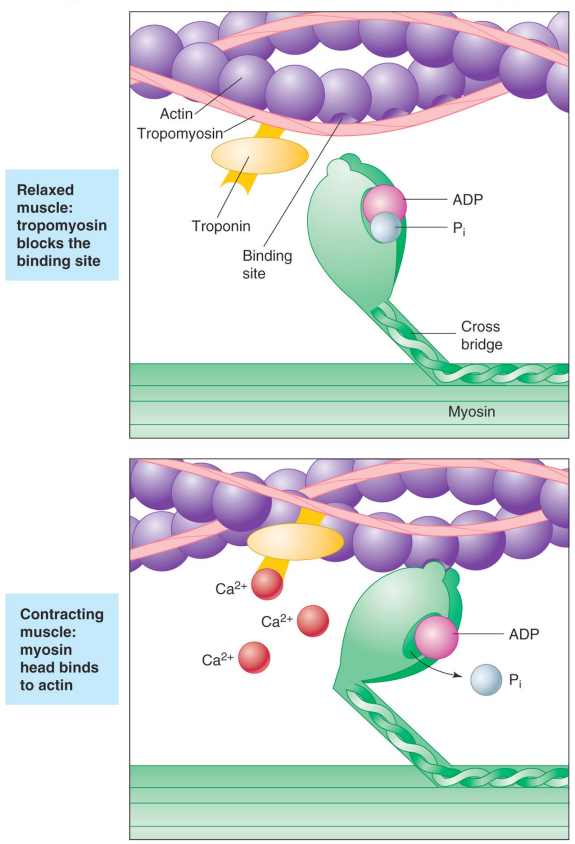
[Ca^{++}] rise in cytoplasm causes muscle contraction.

Ca^{++} ATPase pumps transport Ca++ from cytoplasm back into sarcoplasmic reticulum

cholinesterase degrades ACh; terminates chemical transmission

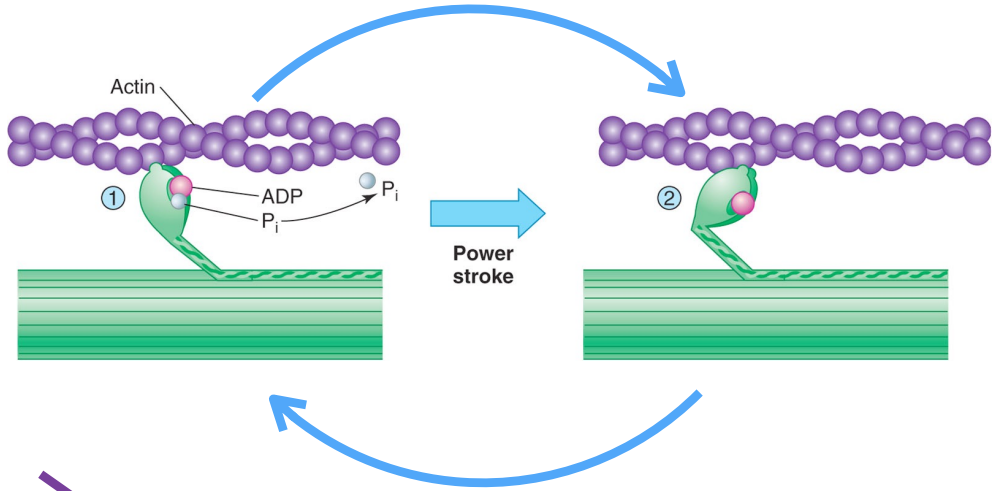


Fox Figure 12.4a



Fox Figure 12.14

Action Potentials -> Ca++ release from Sarcoplasmic Reticulum



End of Action Potentials -> end of Ca++ release
Ca++ ATPase pumps Ca++ back into Sarcoplasmic Reticulum

Fox Figure 12.11

Toxins & Diseases of Neuromuscular Junction

Tetrodotoxin (pufferfish):
blocks voltage-gated Na+ channels, so no action potentials down nerves

Batrachotoxin (golden poison frog)
opens voltage-gated Na+ channels, causing persistent depolarization

Botox (Clostridium botulinum)
blocks release of acetylcholine from the motor neurons

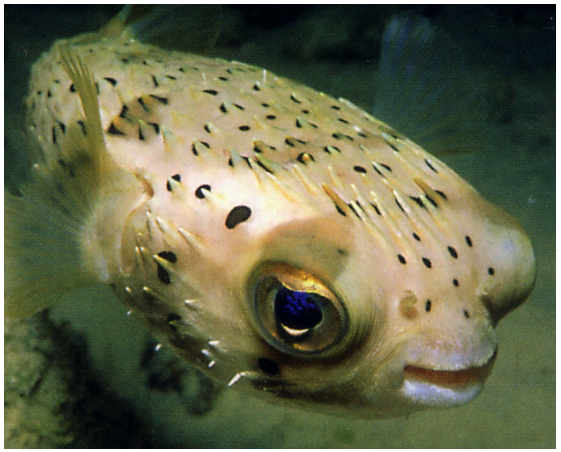
curare (plant toxin)
binds weakly to ACh receptor

a-bungarotoxin (krait & cobra snake venom)
binds tightly to ACh receptor

mysathenia gravis (autoimmune disease)
immune system attacks ACh receptors, causes weakness of muscles

Sarin Nerve Gas
cholinesterase inhibitor, so peristent neuromuscular activation

Tetrodotoxin -- blocks voltage-gated Na+ channels



Weight-for-weight, tetrodotoxin is ten times as deadly as the venom of the many-banded krait of Southeast Asia. It is 10 to 100 times as lethal as black widow spider venom (depending upon the species) when administered to mice, and more than 10,000 times deadlier than cyanide. It has the same toxicity as saxitoxin which causes paralytic shellfish poisoning ([both TTX and saxitoxin block the Na+ channel - and both are found in the tissues of pufferfish])

1 pufferfish/30 humans

The first recorded cases of tetrodotoxin poisoning were from the logs of Captain James Cook. He recorded his crew eating some local tropic fish (pufferfish), then feeding the remains to the pigs kept on board. The crew experienced numbness and shortness of breath, while the pigs were all found dead the next morning. In hindsight, it is clear that the crew received a mild dose of tetrodotoxin, while the pigs ate the pufferfish body parts that contain most of the toxin, thus killing them.

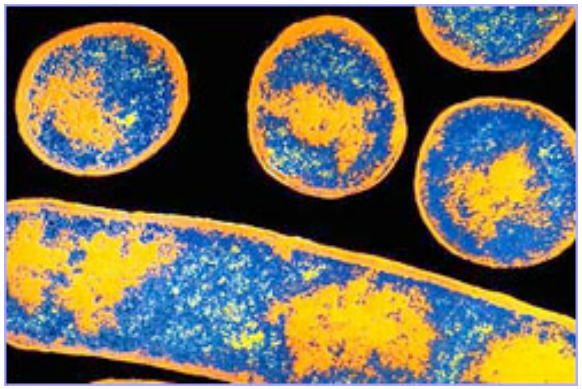
The toxin was first isolated and named in 1909 by Japanese scientist Dr. Yoshizumi Tahara.

Batrachotoxin -- opens Na+ channels, causing persistent depolarization

1 frog / 50 humans

Phyllobates terribilis, or the **Golden Poison Frog**

Botox -- Clostridium botulinum



http://www.dbtechno.com/health/2008/01/19/canned-beans-recalled-due-to-botulism-contamination/

http://nabc.ksu.edu/content/factsheets/category/Botulism

Blocks release of Acetylcholine from motor neuron.

Symptoms include double vision, blurred vision, drooping eyelids, slurred speech, difficulty swallowing, dry mouth and muscle weakness. Treatment may include antitoxins, intensive medical care or surgery of infected wounds. if left untreated, botulism can temporarily paralyze your arms, legs, trunk, and the muscles that help you breathe. The paralysis usually improves slowly over several weeks. People who develop severe botulism experience breathing failure and paralysis and need to be put on ventilators (breathing machines) (NIH website)

30 yr old cans

"botulus" = home-fermented sausage

Botulism, a serious but relatively rare disease, is caused by an extremely potent toxin produced by the bacterium Clostridium botulinum. C. botulinum is an anaerobic, gram-positive, spore-forming bacterium that most commonly affects wild fowl and poultry, cattle, horses, and some species of fish.

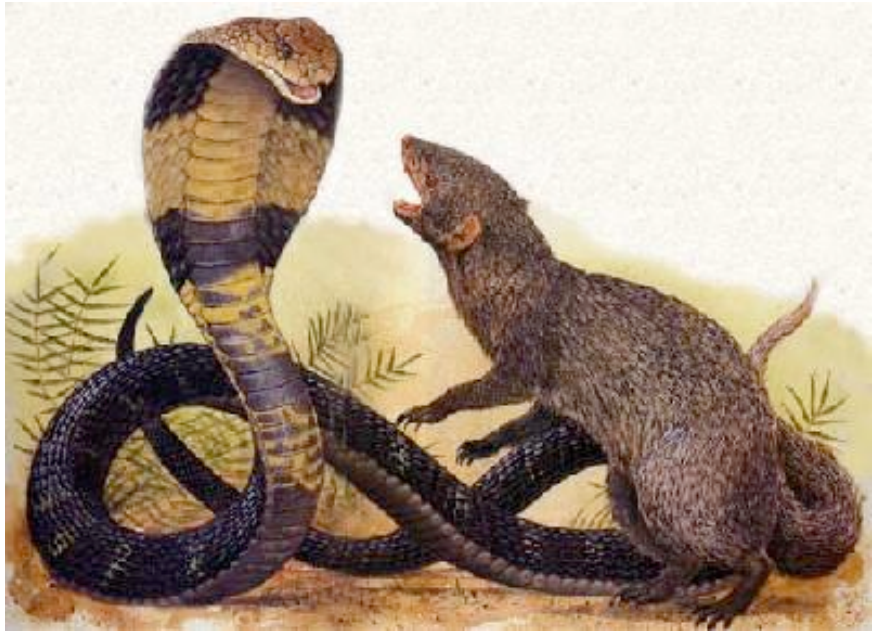
Although the incidence of botulism is relatively low in humans (~ 9 outbreaks of foodborne botulism per year with and average of 2.4 cases per outbreak), the disease is of considerable concern because of its high infectivity and high mortality rate (untreated). Only a few nanograms of toxin can cause human illness. And, in the 962 recorded botulism outbreaks in humans (2,320 cases) in the U.S. from 1899 to 1990, there have been 1,036 deaths.

Curare -- Acetylcholine Receptor Blocker

Strychnos Toxifera by Koehler 1887

During 1811-1812 Sir Benjamin Collins Brody (1783-1862) experimented with curare. He was the first to show that curare does not kill the animal and the recovery is complete if the animal's respiration is maintained artificially. In 1825 Charles Waterton (1783-1865) (who gained fame by riding a captured alligator) described a classical experiment in which he kept a curarized she-ass alive by artificial ventilation with a bellows through a tracheostomy. Waterton is also credited with bringing curare to Europe. Robert Hermann Schomburgk, who was a trained botanist, identified the vine as one of the Strychnos species and gave it the now accepted name Strychnos toxifera.

a-bungarotoxin (krait & cobra snake venom)
binds tightly to ACh receptor



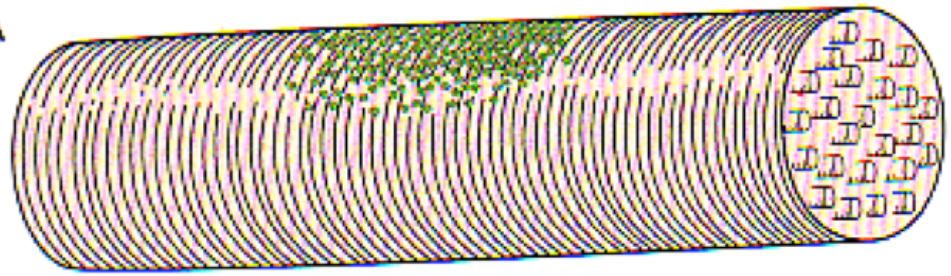
mongoose acetylcholine receptors are resistant to bungarotoxin in cobra venom

Disease of Neuromuscular Junction: Myasthenia Gravis

Ach R

A

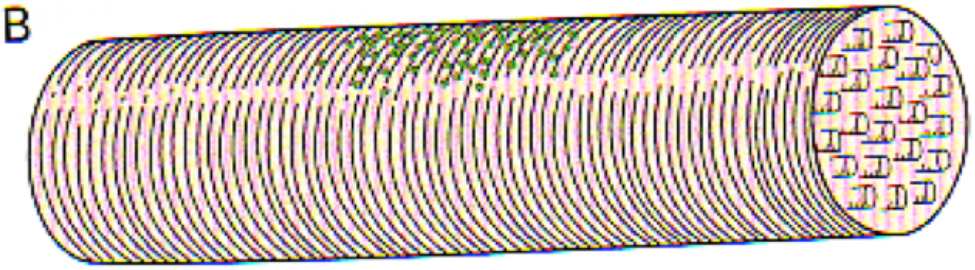
Normal



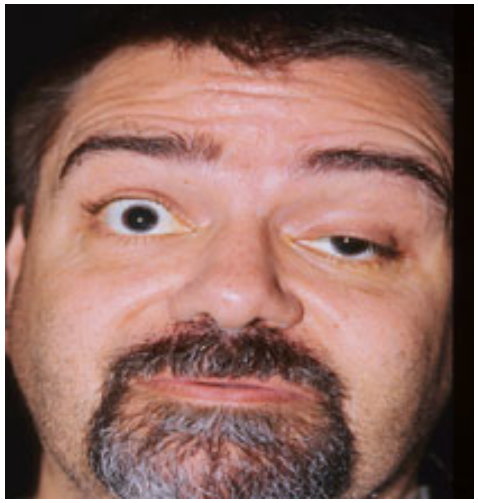
Myasthenia Gravis

reduced Ach R

B



Myasthenia Gravis



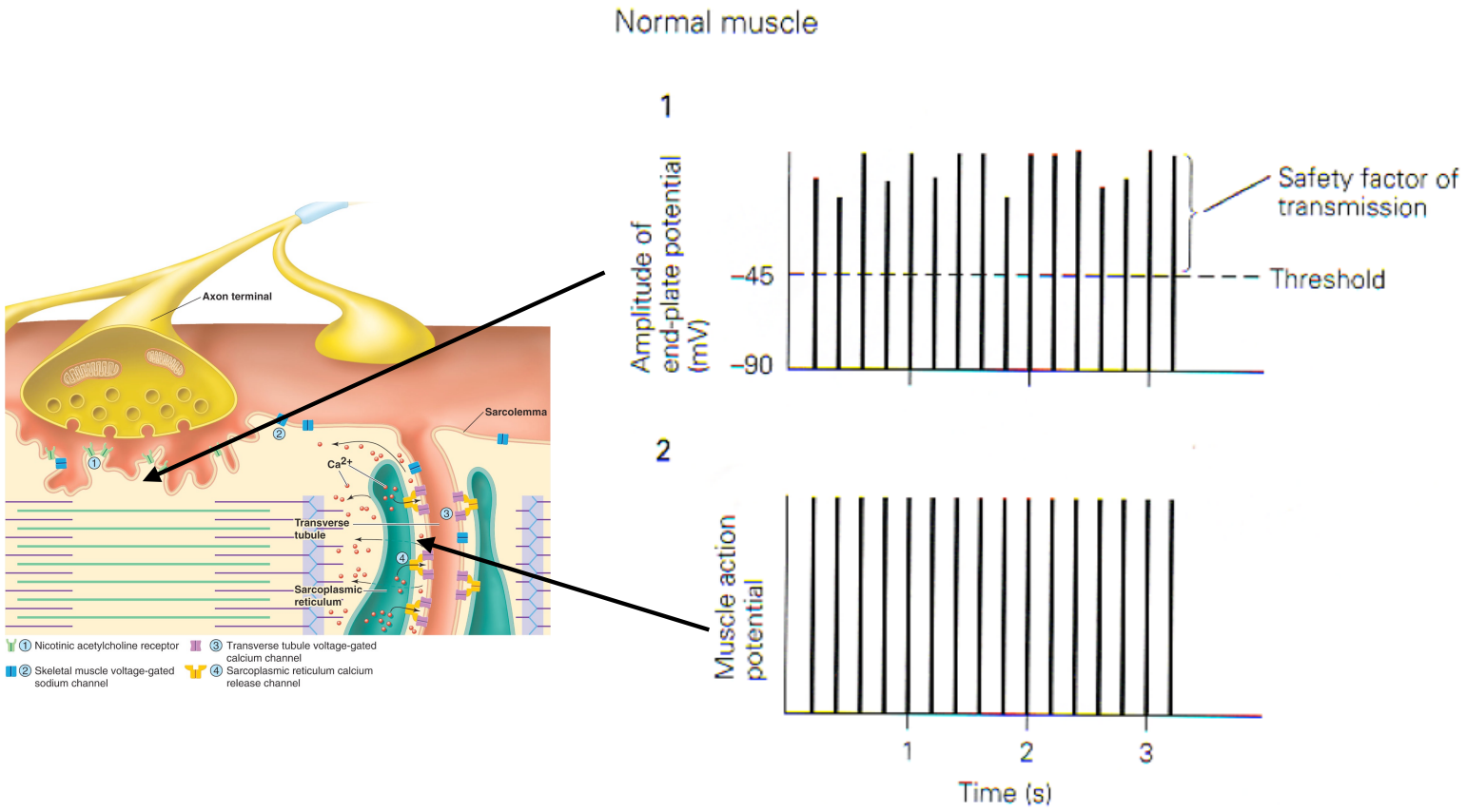
Symptoms

The most common symptoms of MG relate to weakness of the muscles that lift up the lid (ptosis) or move the eyes (double vision). MG can affect muscles anywhere in the body including those of swallowing or even breathing. Shortness of breath or difficulty swallowing may be very serious symptoms of MG and must be brought to your doctor's attention immediately. MG does not produce pain or numbness. If pain is present there must be something else going on and you need to tell your doctor.

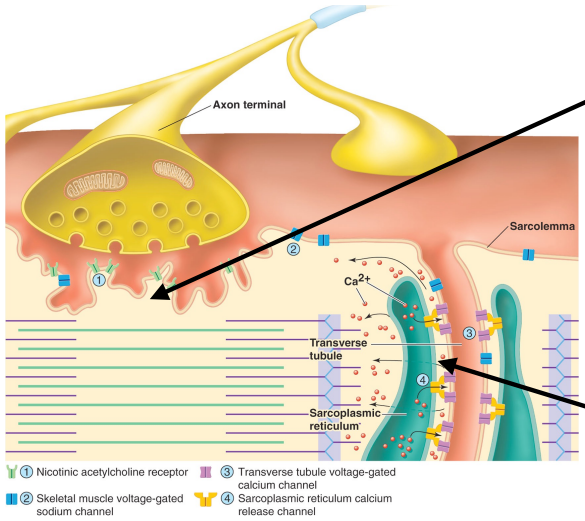
www.beverlyhillsneurology.com

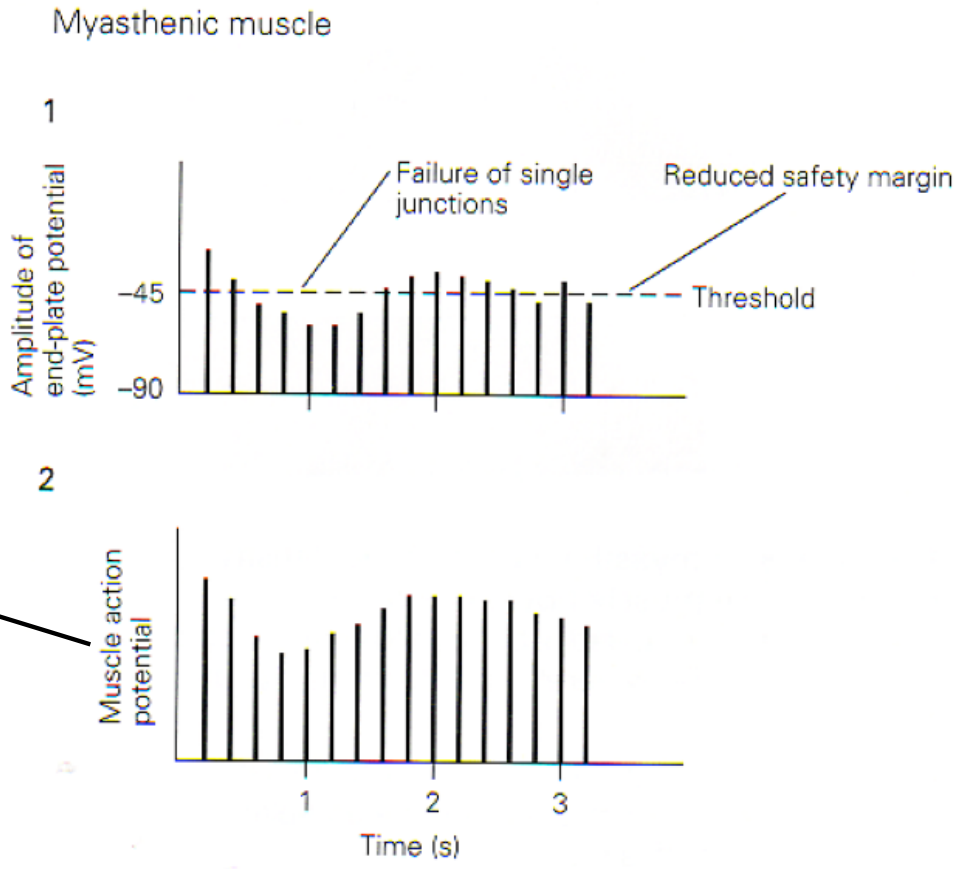
http://meds.queensu.ca/medicine/oph/patients/myastheniagravis.shtml

Postsynaptic Potentials in Normal Muscle fiber



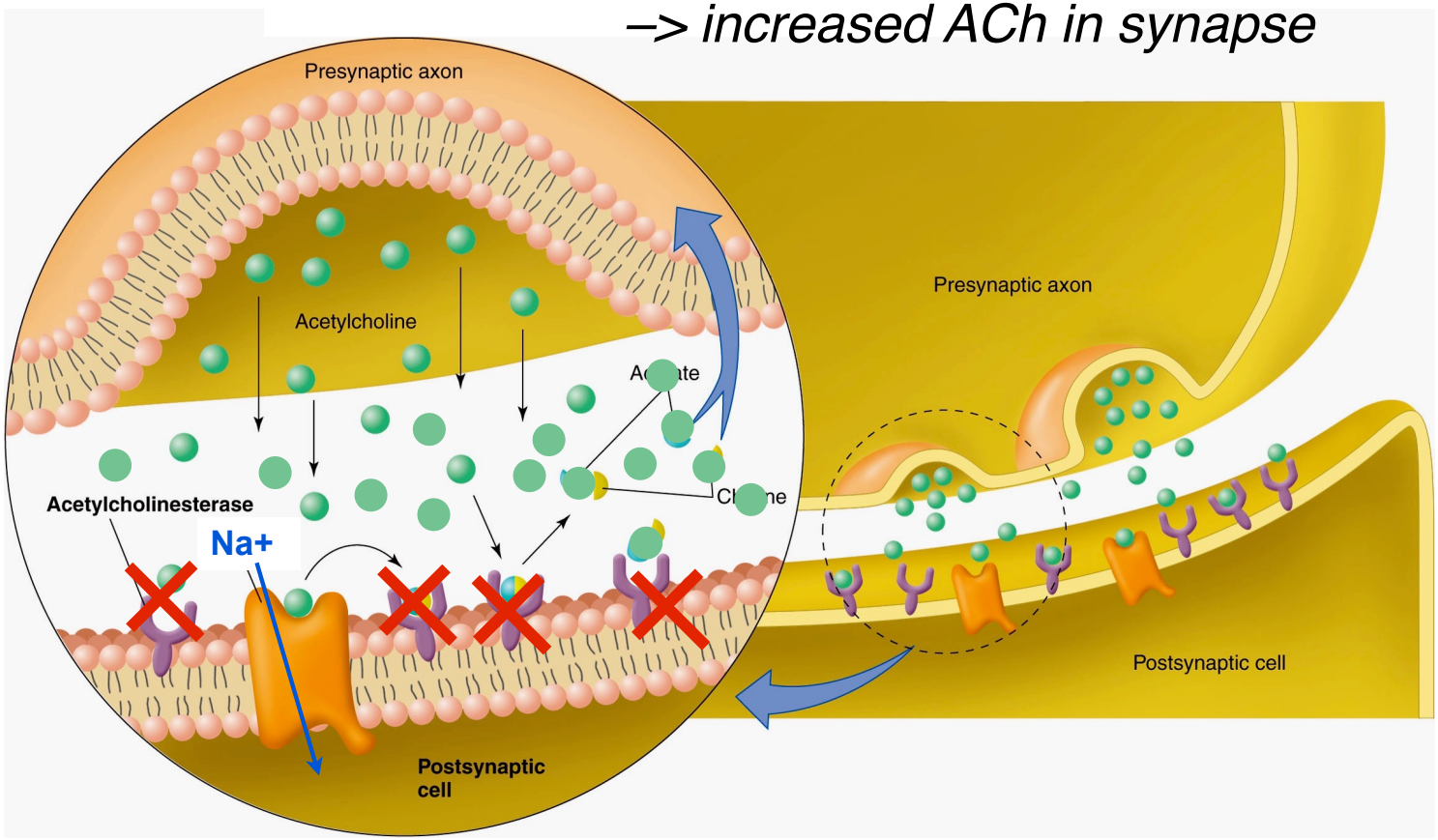
Postsynaptic Potentials in Muscle fiber with Myasthenia Gravis





Sarin Nerve Gas -- cholinesterase inhibitor

–> increased ACh in synapse



Fox Figure 7.28

Sarin Nerve Gas -- cholinesterase inhibitor

Tokyo Subway Attack 1995 by Aum Shinrikyo

news.bbc.co.uk/ 1/hi/uk/413827.stm

Initial symptoms usually include intense sweating, runny nose and twitching of muscles. The pupils of the eyes constrict, dimming sight and causing other visual difficulties. If enough sarin is inhaled or absorbed, a victim quickly develops tightness of the chest and begins gasping for breath. The heart rate slows and the blood pressure can drop to dangerous levels. Sarin also can cause nausea and vomiting, abdominal cramps, diarrhea, headache, drowsiness, convulsions and coma.

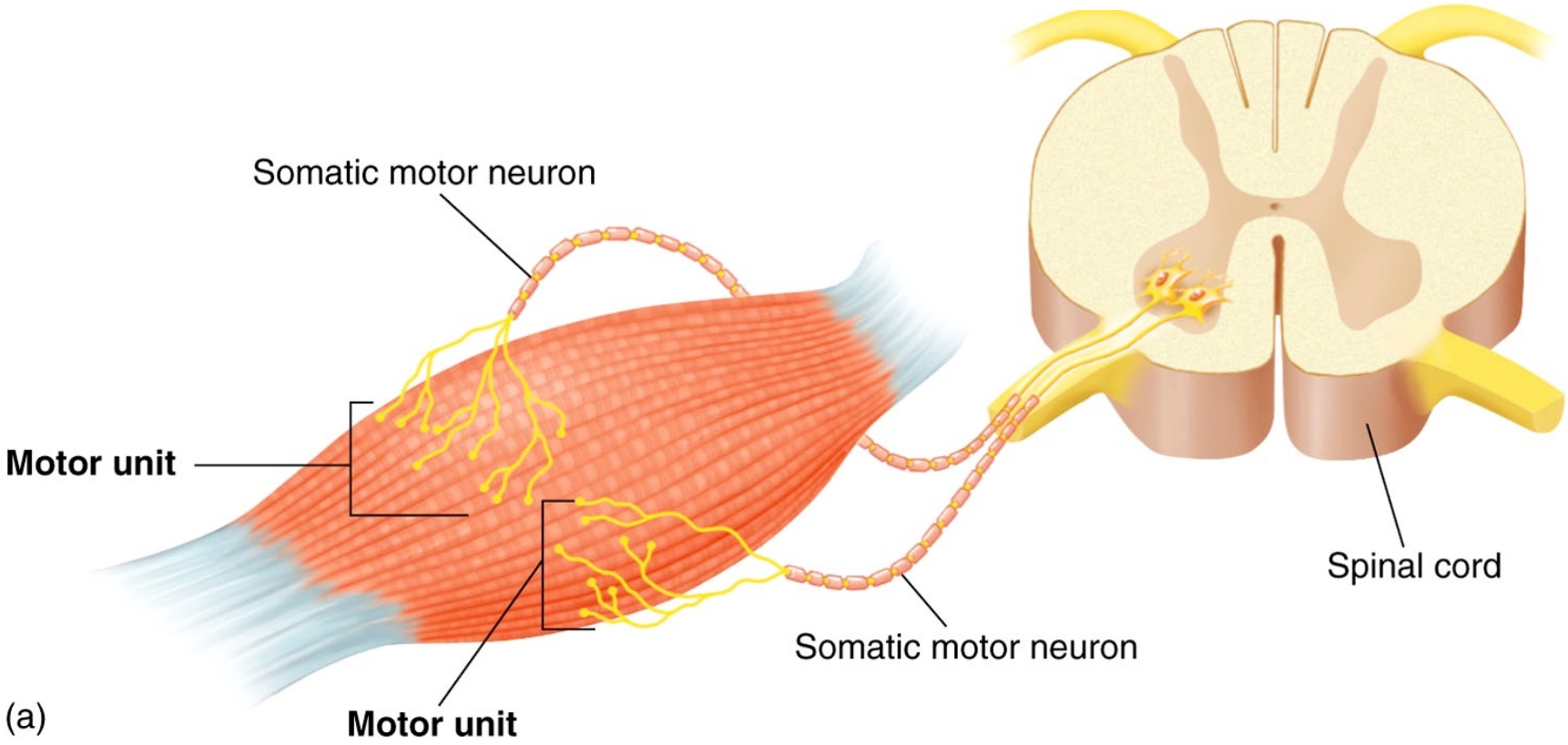
What would muscular contraction look like in presence of:

botulism?

curare?

sarin?

tetanus?



Fox Figure 12.4a

Electric Fish & Electrogenesis

The electric eel is able to generate a current of up to 5000 volts by synchronized activation in sequence of some 5000 electrocytes (electric cells) located in the animal's electric organ in the tail.

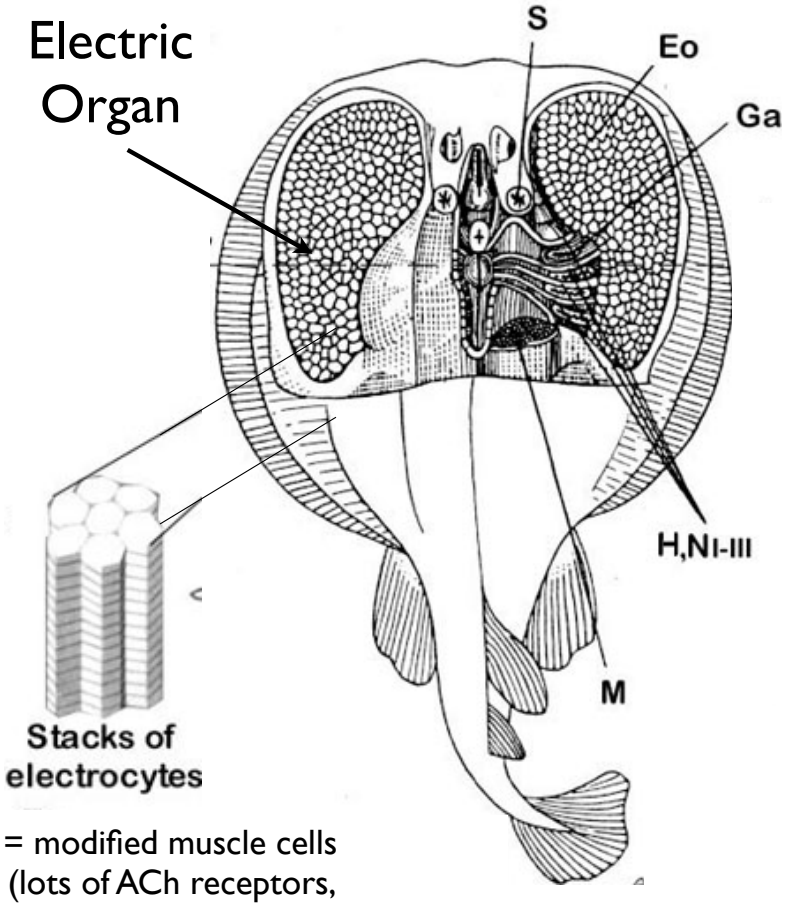
At rest, Na+/K+ channels pump positive ions out of the cell, creating a resting potential. Upon stimulation by acetylcholine from nerve cells, the ions are allowed to flow back into the cell freely, creating unequal potentials at the ends of the cell and generating current flow.

http://archive.org/details/electric_eel

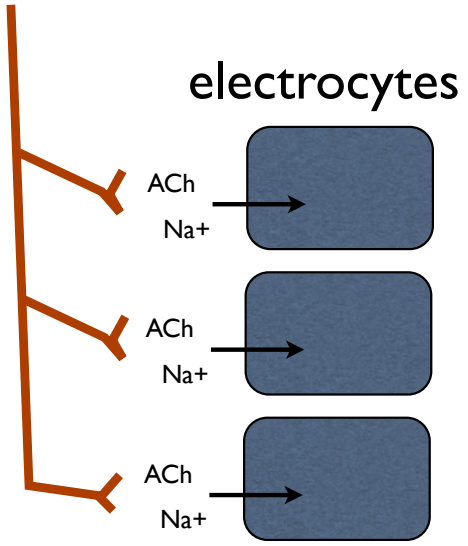
Electric Eel

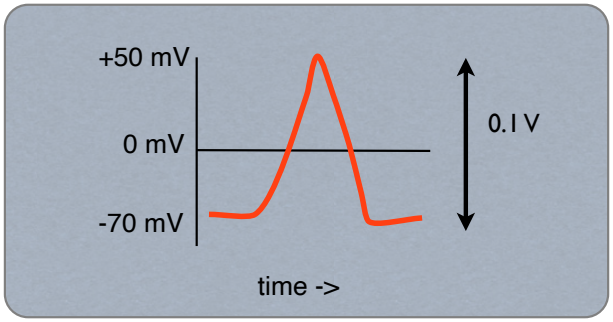
Torpedo Ray

used by ancient Greeks for anesthetic effect, called “narke” (root of narcotics)

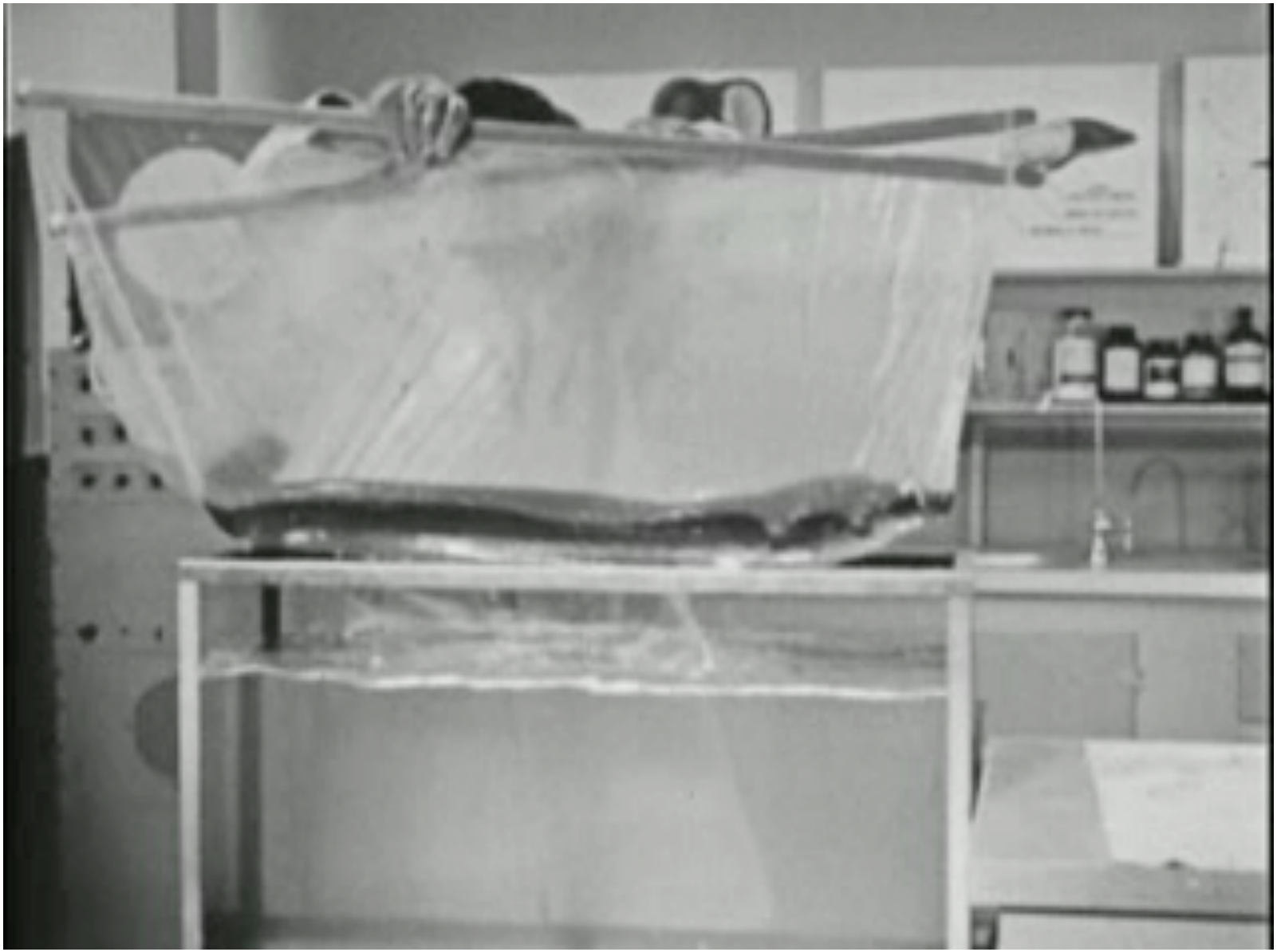


= modified muscle cells (lots of ACh receptors, no contraction)





E_{K+} to E_{Na+} = ~100 mV/cell
5000 cells x 100 mV = 500 V



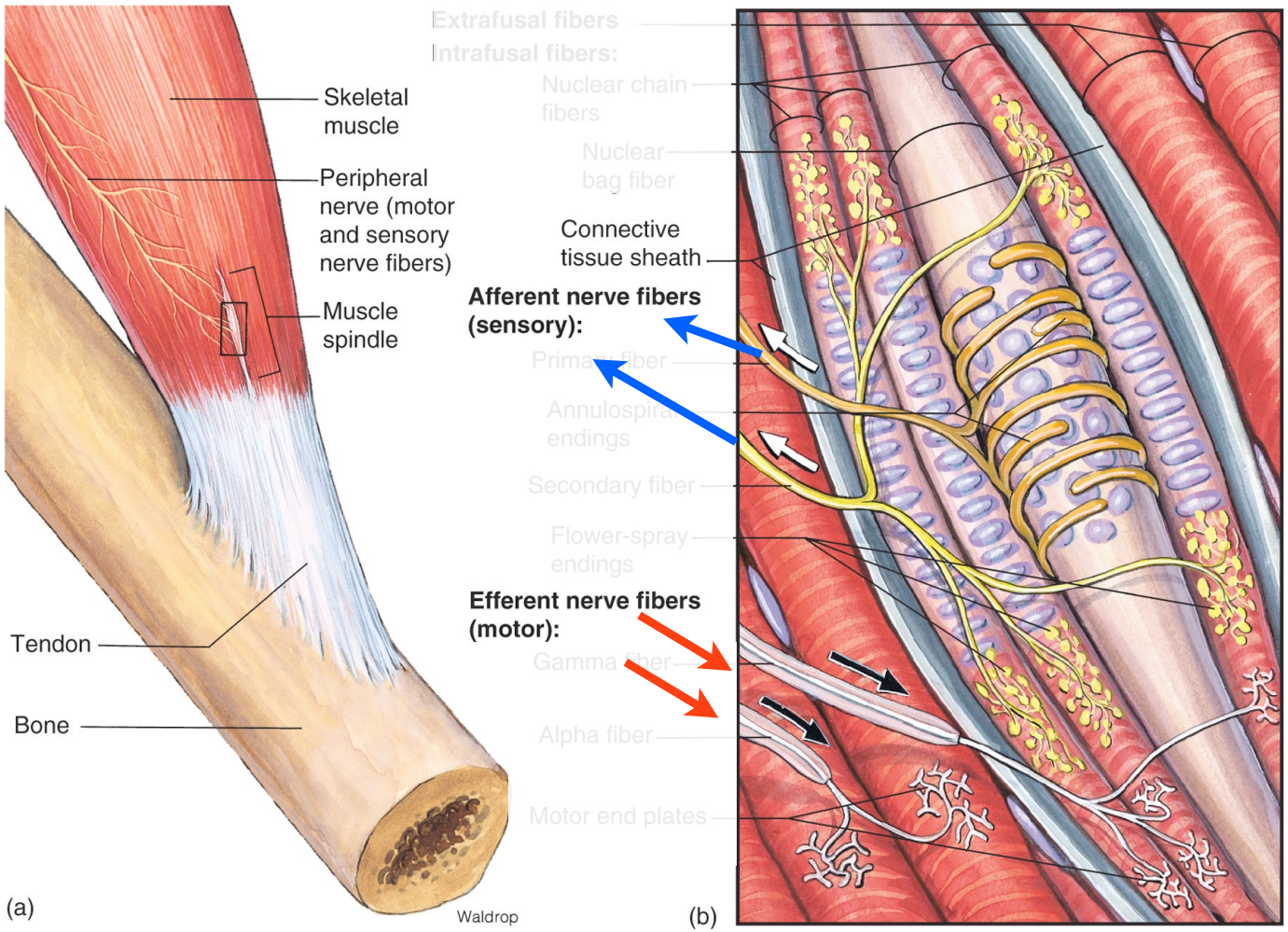
Monosynaptic Stretch Reflex (Knee-jerk reflex)

stretch of patellar tendon ->
spindle stretch in quadriceps ->
firing of dynamic Ia afferent sensory nerves ->

monosynaptic connection (via glutamate) to
causes spinal motor neurons to fire.

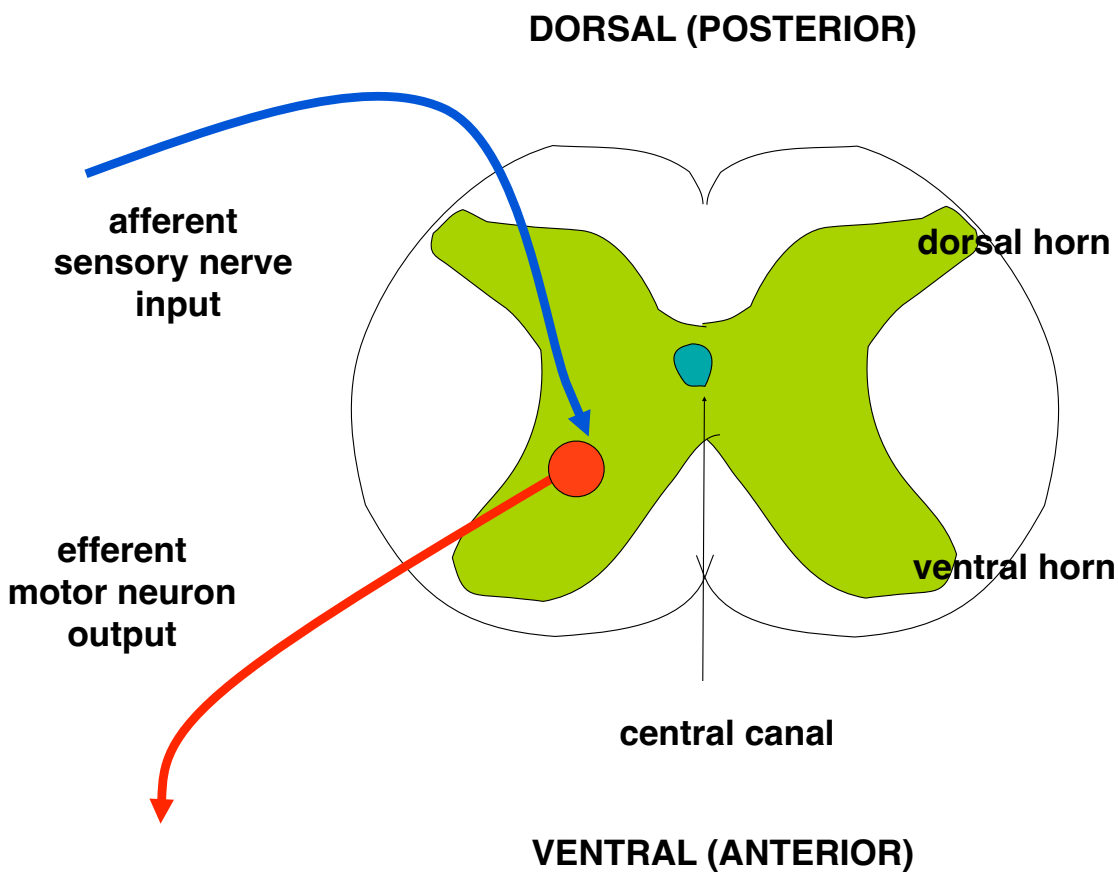
-> quadriceps contraction
-> decreased stretch of spindle
-> silent Ia afferents.
-> decreased motor neuron activity/contraction

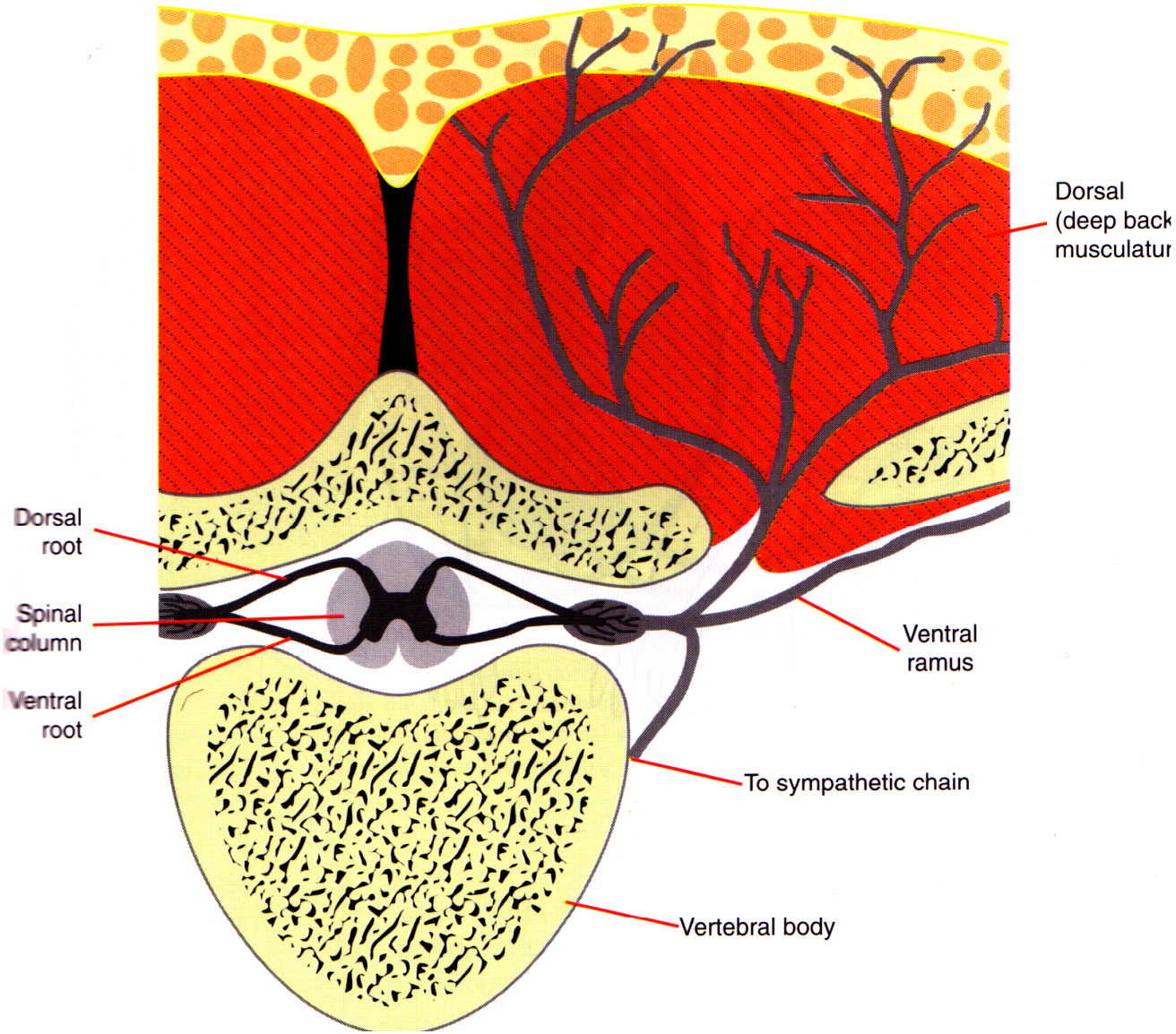
Descending corticospinal input from cerebral cortex normally inhibits the reflex by activating inhibitory interneurons in spinal cord.

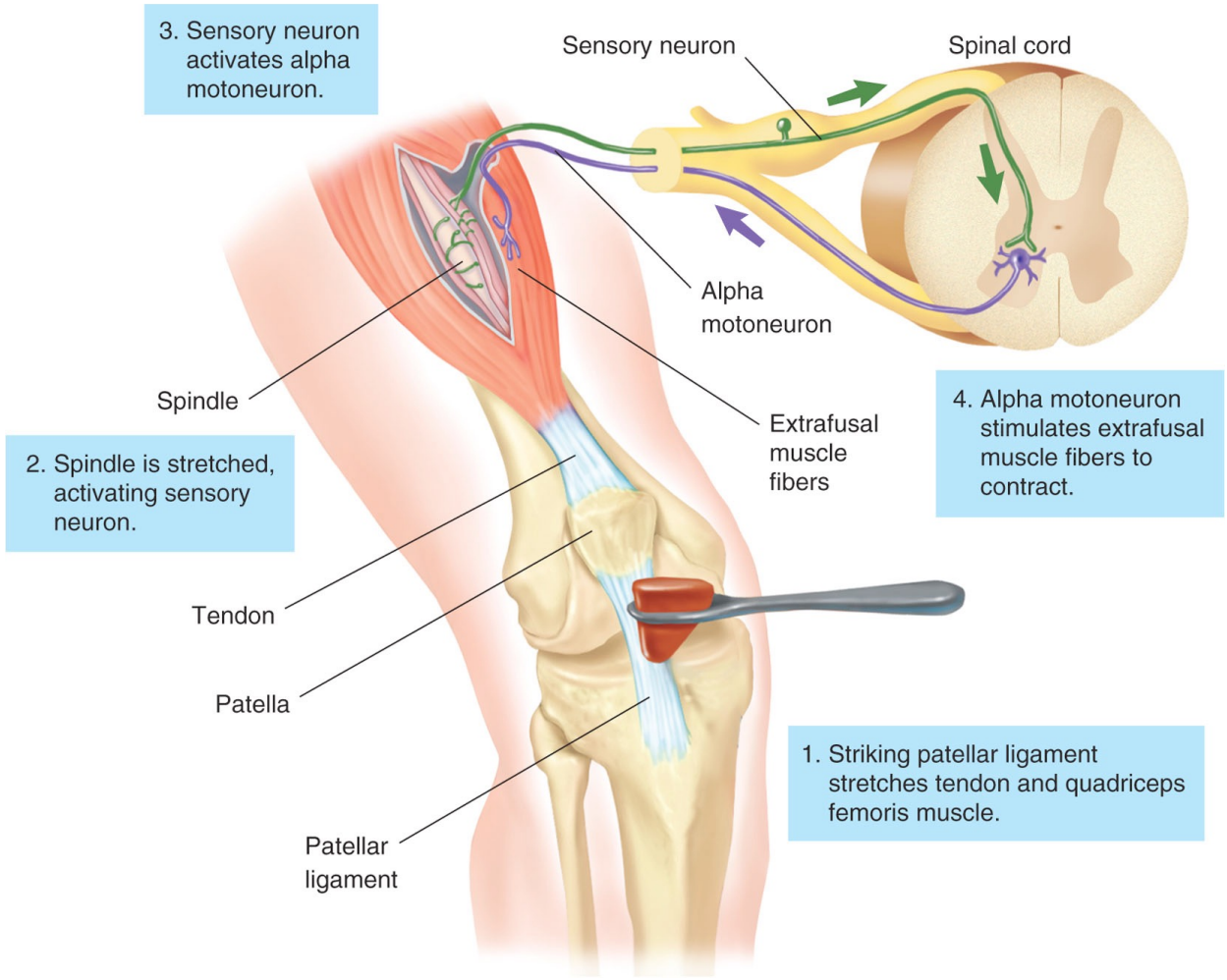


Fox Figure 12.27

Spinal Cord: reflex processing of sensory input

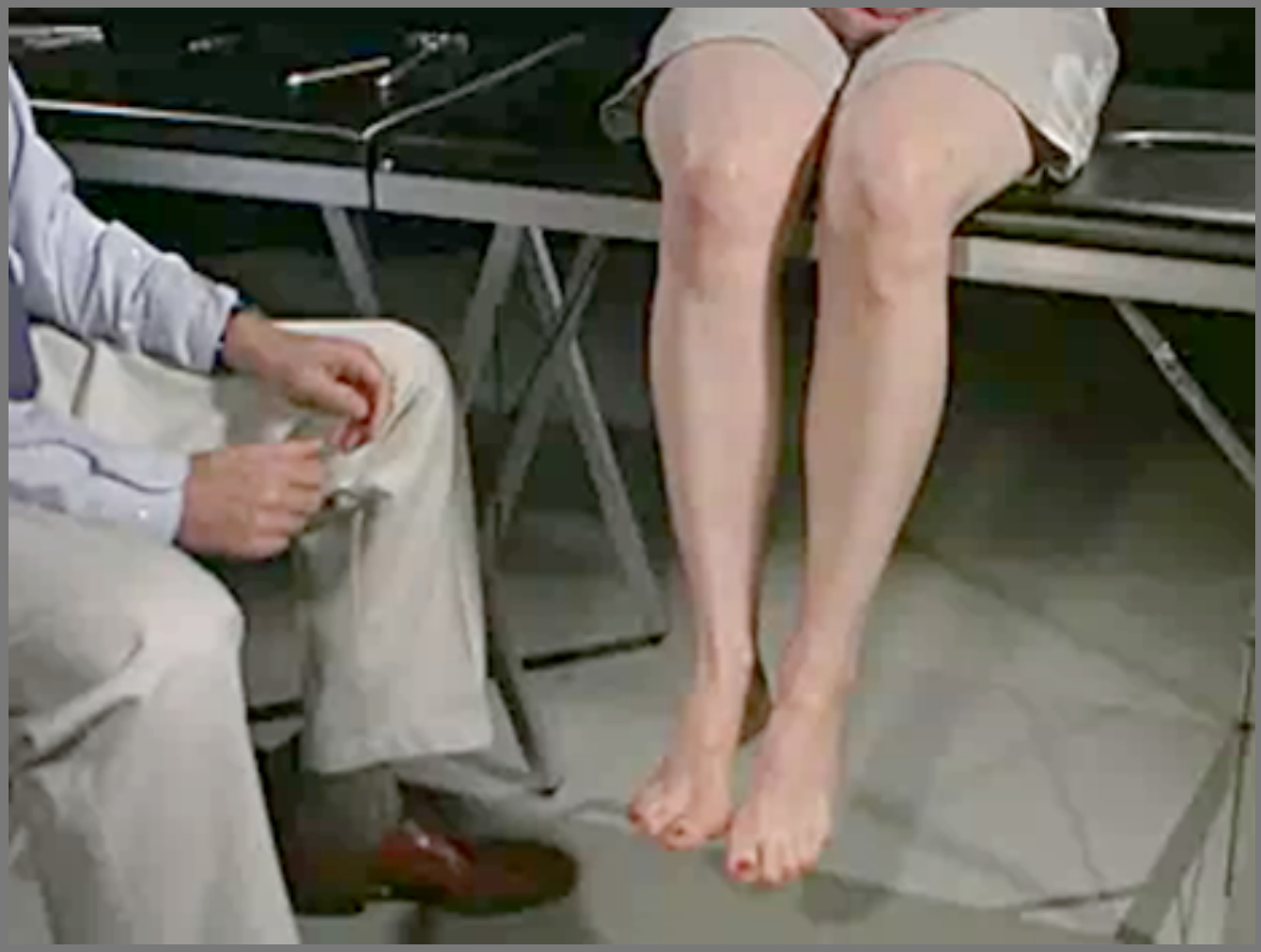



Dorsal
(deep back
musculatur
Dorsal
root
Spinal
column
Ventral
root
Ventral
ramus
To sympathetic chain
Vertebral body

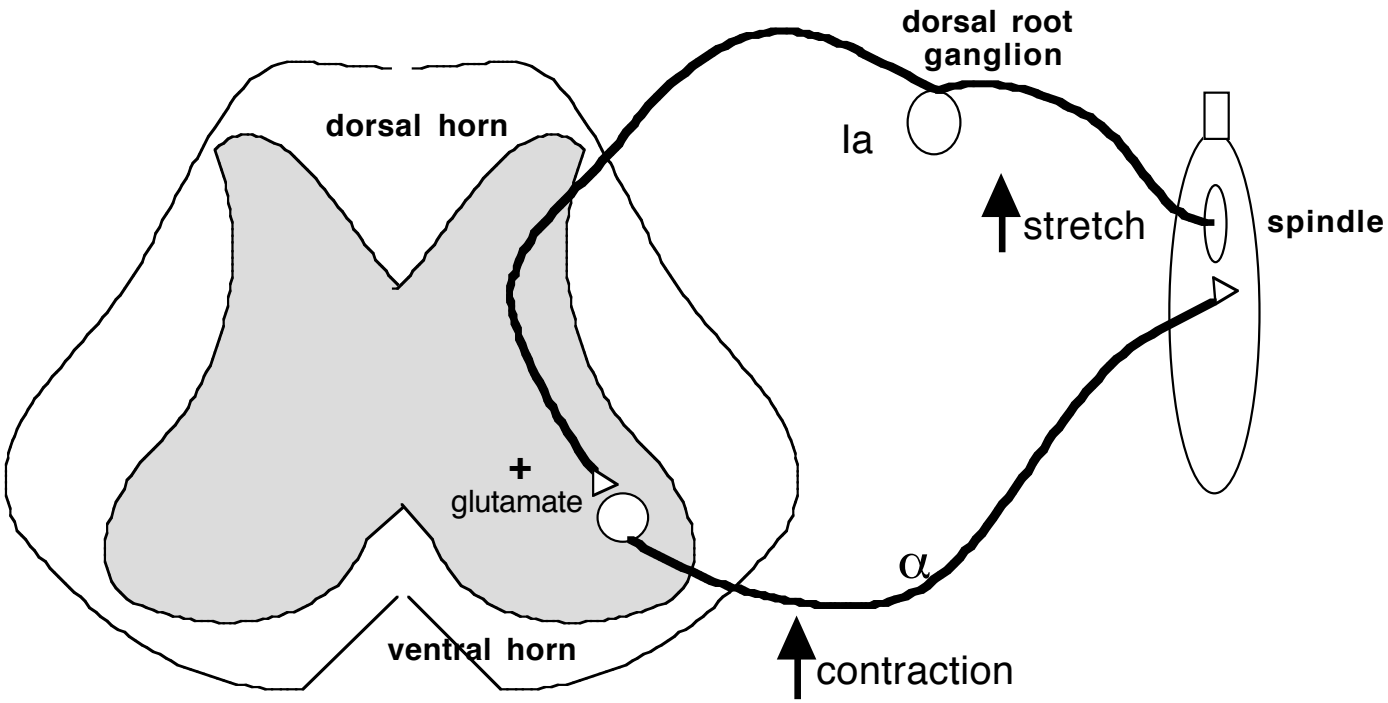


Fox Figure 12.28

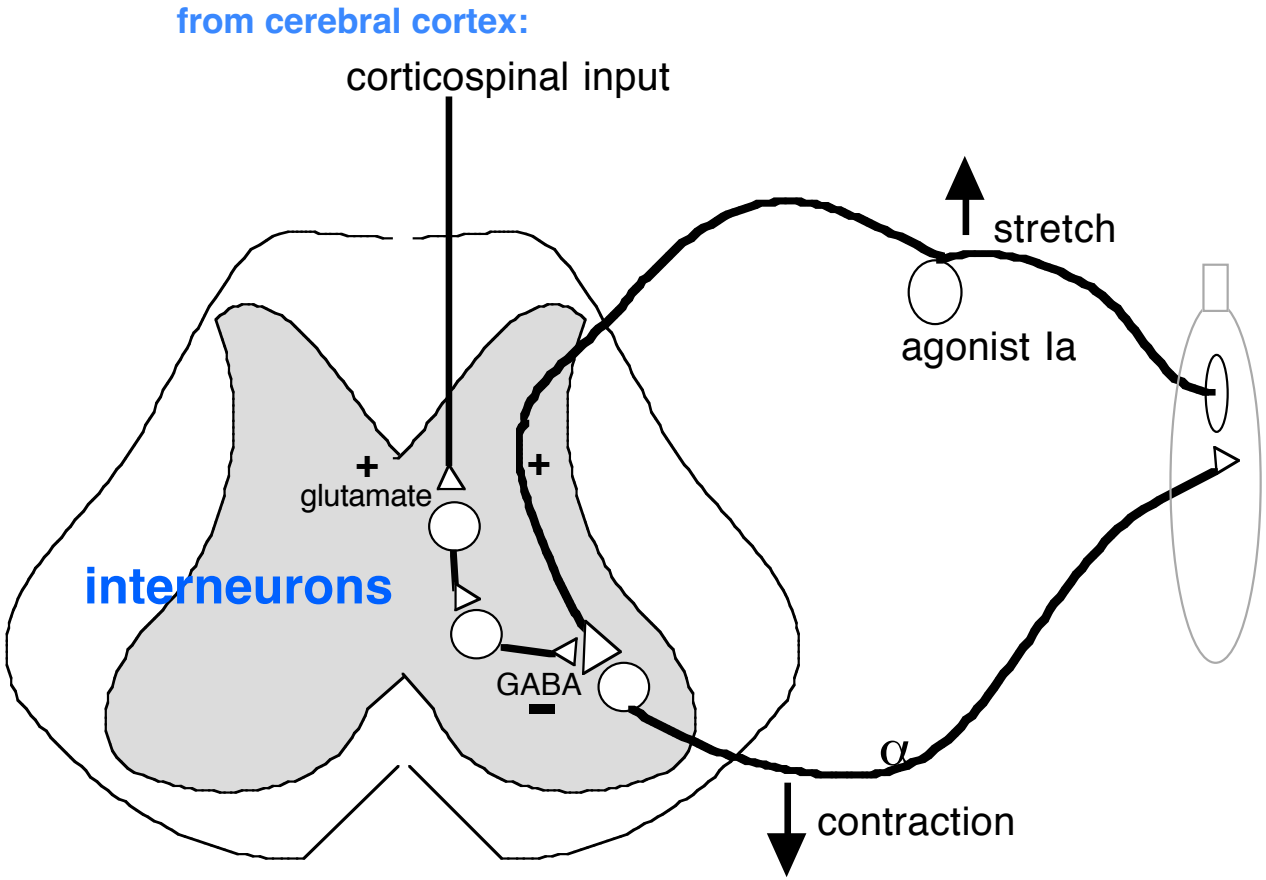
Stretch Reflex



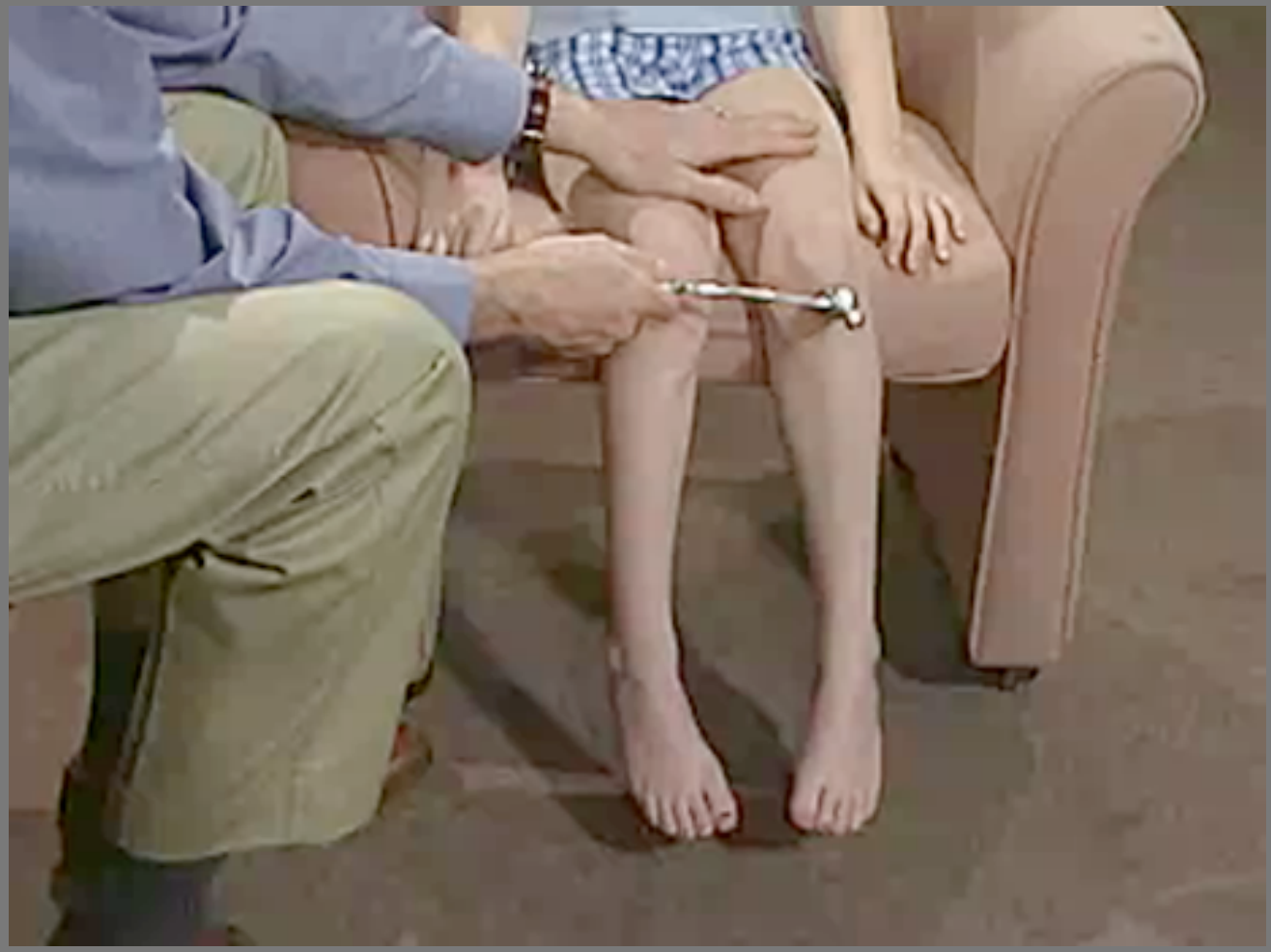
Stretch Reflex: monosynaptic



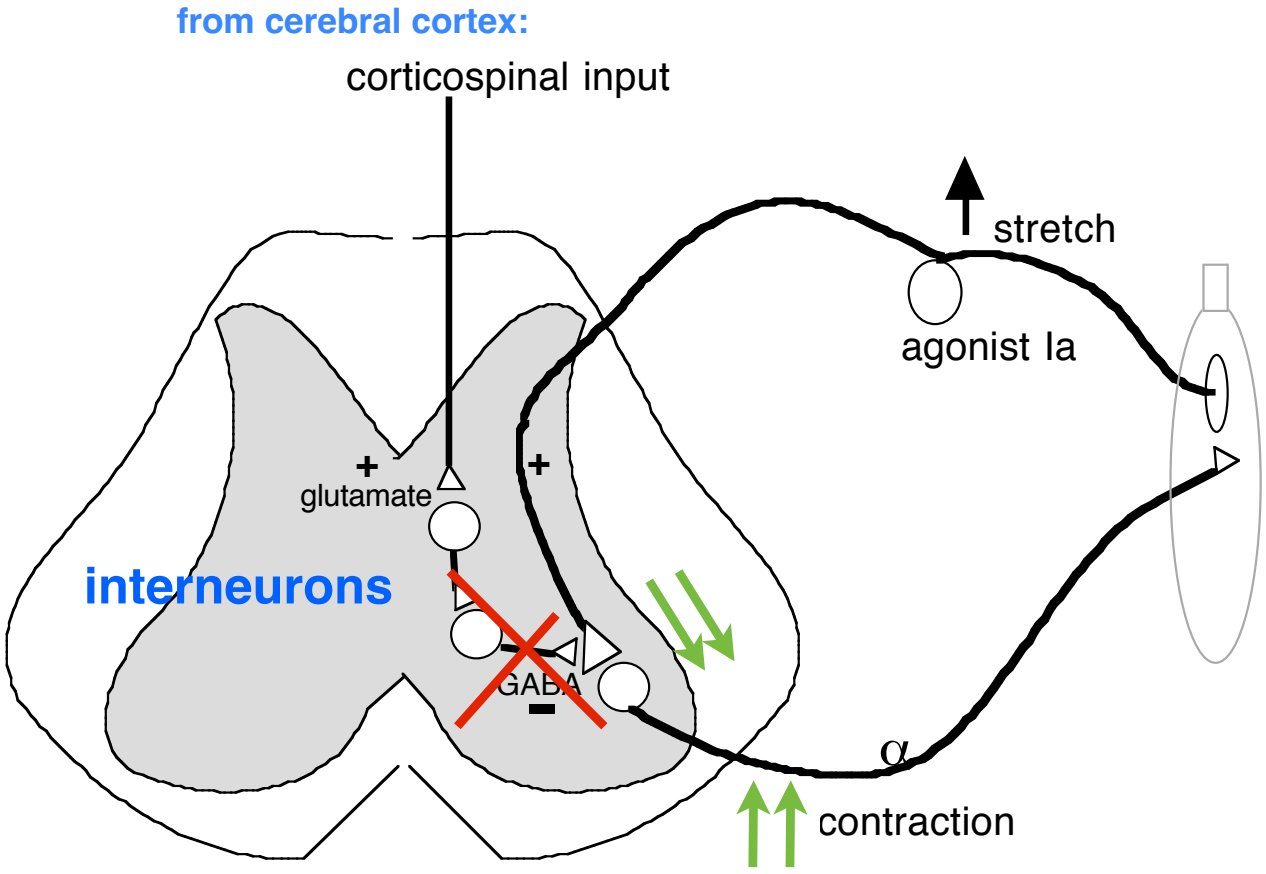
Descending Corticospinal Inhibition



Hyper-Stretch Reflex (abnormal)



Tetanus Toxin:
Blocks Descending Corticospinal Inhibition



Tetanus (Lockjaw) - *Clostridium tetani* bacteria, whose spores are ubiquitous

Tetanospasmin -- prevents neurotransmiter release, especially of inhibitory neurotransmitters in the spinal cord that inhibit motor neuron reflexes.

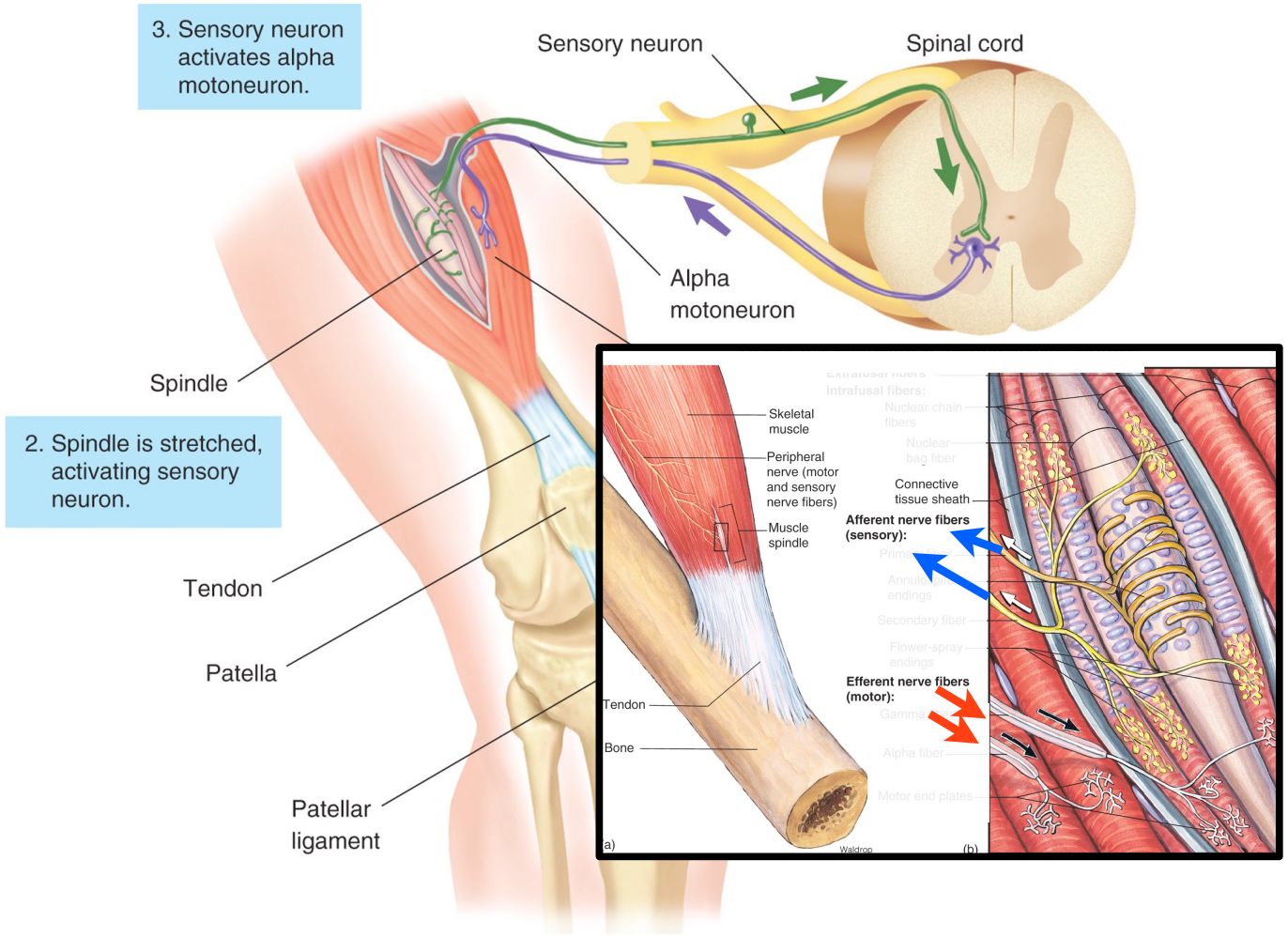
Generalized tetanus is the most common type of tetanus, representing about 80% of cases. The generalized form usually presents with a descending pattern. The first sign is trismus or lockjaw, followed by stiffness of the neck, difficulty in swallowing, and rigidity of pectoral and calf muscles. Other symptoms include elevated temperature, sweating, elevated blood pressure, and episodic rapid heart rate. Spasms may occur frequently and last for several minutes. Spasms continue for 3–4 weeks and complete recovery may take months.

Monosynaptic Stretch Reflex

Table 12.6 | Summary of Events in a Monosynaptic Stretch Reflex

1. Passive stretch of a muscle (produced by tapping its tendon) stretches the spindle (intrafusal) fibers.
2. Stretching of a spindle distorts its central (bag or chain) region, which stimulates dendritic endings of sensory nerves.
3. Action potentials are conducted by afferent (sensory) nerve fibers into the spinal cord on the dorsal roots of spinal nerves.
4. Axons of sensory neurons synapse with dendrites and cell bodies of somatic motor neurons located in the ventral horn gray matter of the spinal cord.
5. Efferent nerve impulses in the axons of somatic motor neurons (which form the ventral roots of spinal nerves) are conducted to the ordinary (extrafusal) muscle fibers. These neurons are alpha motoneurons.
6. Release of acetylcholine from the endings of alpha motoneurons stimulates the contraction of the extrafusal fibers, and thus of the whole muscle.
7. Contraction of the muscle relieves the stretch of its spindles, thus decreasing activity in the spindle afferent nerve fibers.

Proprioception: Awareness of position of joints and limbs



Fox Figure 12.28

Proprioception: Awareness of position of joints and limbs