


**We only live once,
Snoopy.**

**Wrong! We only
die once. We live
every day!**

اللهم إني أسألك علماً نافعاً
ورزقاً طيباً، وعملاً متقبلاً

@ 7 B Y L L A H





NEUROMUSCULAR JUNCTION & TRANSMISSION

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PHYSIOLOGY DEPT.

LEARNING OBJECTIVES

- ❖ **Explain the mechanism of transmission of impulses from nerve endings to muscle fibers**
- ❖ **Explain Formation and Secretion of acetylcholine at nerve terminals**
- ❖ **Describe Action of acetylcholine at postsynaptic membrane**
- ❖ **Describe Degradation of released acetylcholine**
- ❖ **Describe End plate potential**

LET'S RECALL OUR PREVIOUS KNOWLEDGE...

- Somatic Nerves
- Synapse
- Neurotransmitters
- Action potential in nerves
- Types of muscle fibers



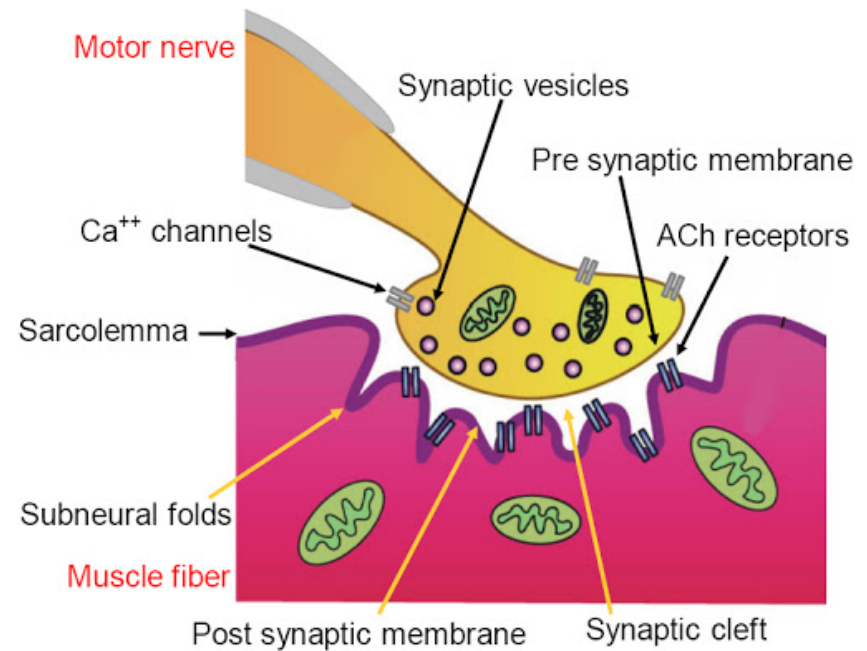


PART 1 - THE NEUROMUSCULAR JUNCTION

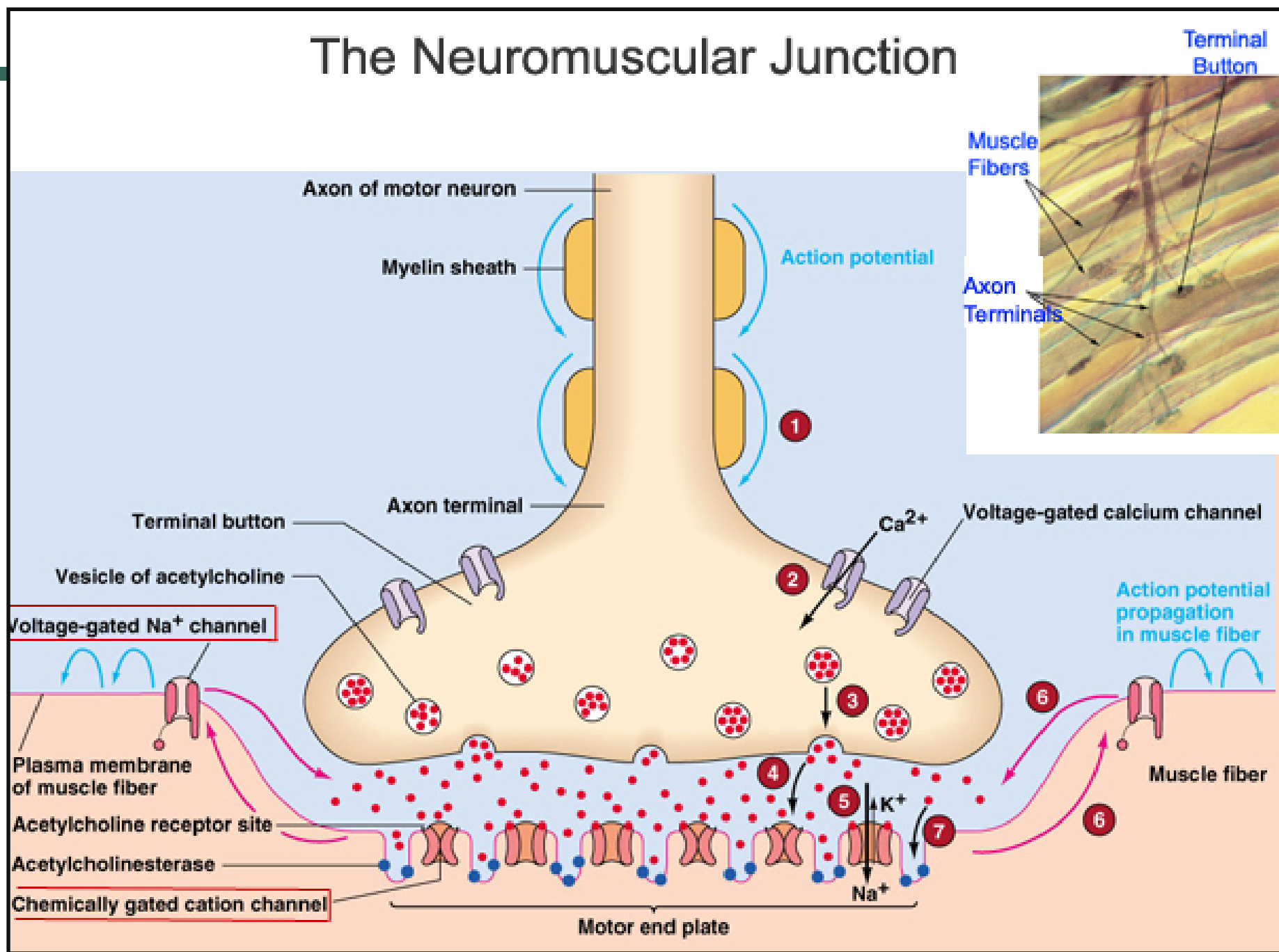


NEUROMUSCULAR JUNCTION

The neuromuscular junction is a specialized form of a chemical synapse comprised of an alpha motor neuron and the muscle fiber it innervates.

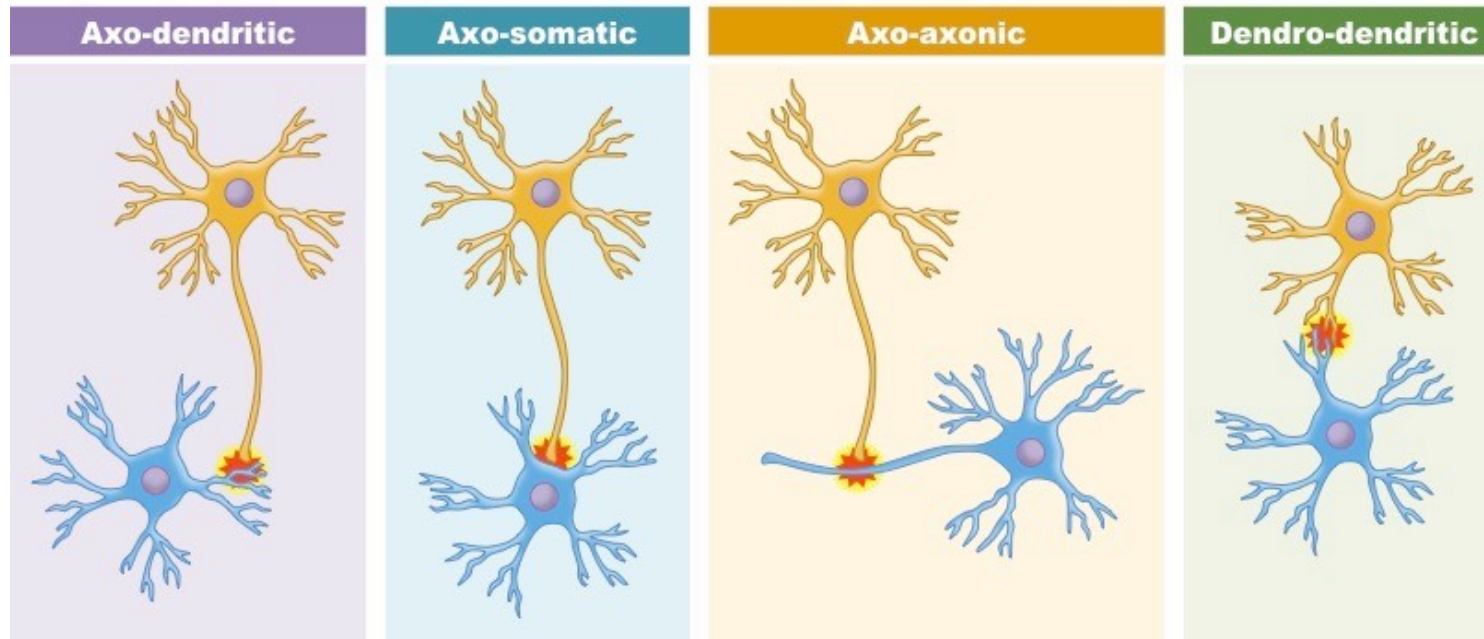


The Neuromuscular Junction



JUNCTIONS VS. SYNAPSES

- ▶ A junction will always respond to an action potential in the presynaptic nerve. Synapses may or may not.



Compare and contrast the features of synapses and neuromuscular junctions

Synapse	Neuromuscular junction
Neurone to neurone	Neurone to skeletal muscle cell
Post synaptic stimulation leads to action potential in post synaptic neurone: muscle/gland	Post synaptic stimulation leads to depolarisation of sarcolemma, muscle contraction
Excitatory/inhibitory	Always excitatory
Synaptic knob is smooth and rounded	End plate has brushed appearance: microvilli and is flattened up to muscle fibre
<i>Neurotransmitter in vesicles in presynaptic cytoplasm</i>	<i>Neurotransmitter in vesicles in presynaptic cytoplasm</i>
Vesicles release neurotransmitter into cleft on stimulation: synaptic cleft	Vesicles release neurotransmitter into cleft on stimulation: neuromuscular cleft

Compare and contrast the features of synapses and neuromuscular junctions

Synapse	Neuromuscular junction
Neurotransmitter diffuses across synaptic cleft and binds to <i>post synaptic receptor</i>	Neurotransmitter diffuses across synaptic cleft and binds to post synaptic receptor: <i>sarcolemma</i>
Binding of neurotransmitter results in opening of sodium channels and depolarisation of the post synaptic membrane	Binding of neurotransmitter results in opening of sodium channels and depolarisation of the post synaptic membrane: <i>T-system tubules</i>
Enzymes present to breakdown neurotransmitter to avoid continual stimulation of postsynaptic membrane.	Enzymes present to breakdown neurotransmitter to avoid continual stimulation of postsynaptic membrane. And muscle contraction

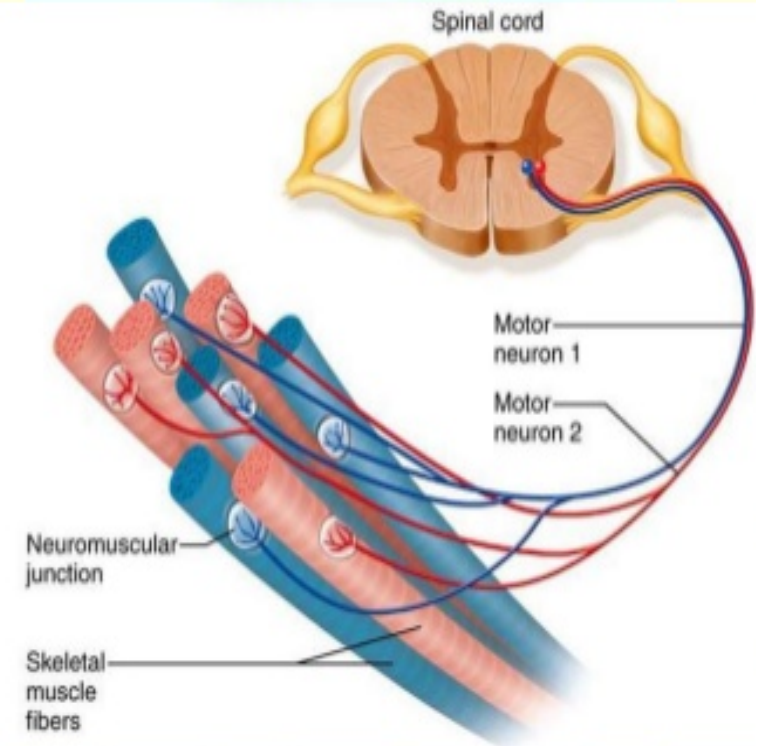
NEUROMUSCULAR JUNCTION INTRODUCTION

Motor neurons

(Alpha motor neurons)

- large myelinated nerve fibers
- cell bodies located in the spinal cord or brain stem

- Motor neurons have their cell bodies in anterior horn of spinal cord or in brain stem.
- Their axons are myelinated and are the largest diameter axons in the body.



NEUROMUSCULAR JUNCTION -INTRODUCTION

- ▶ **each nerve fiber branches many times and stimulates from 3 to several hundred muscle fibers**
- ▶ **usually each muscle fiber has only one NMJ**
- ▶ **terminal nerve endings make a junction at the midpoint of a muscle fiber**
- ▶ **AP on the muscle fiber travels from midpoint toward both ends of the muscle fiber**

Neuromuscular Junction

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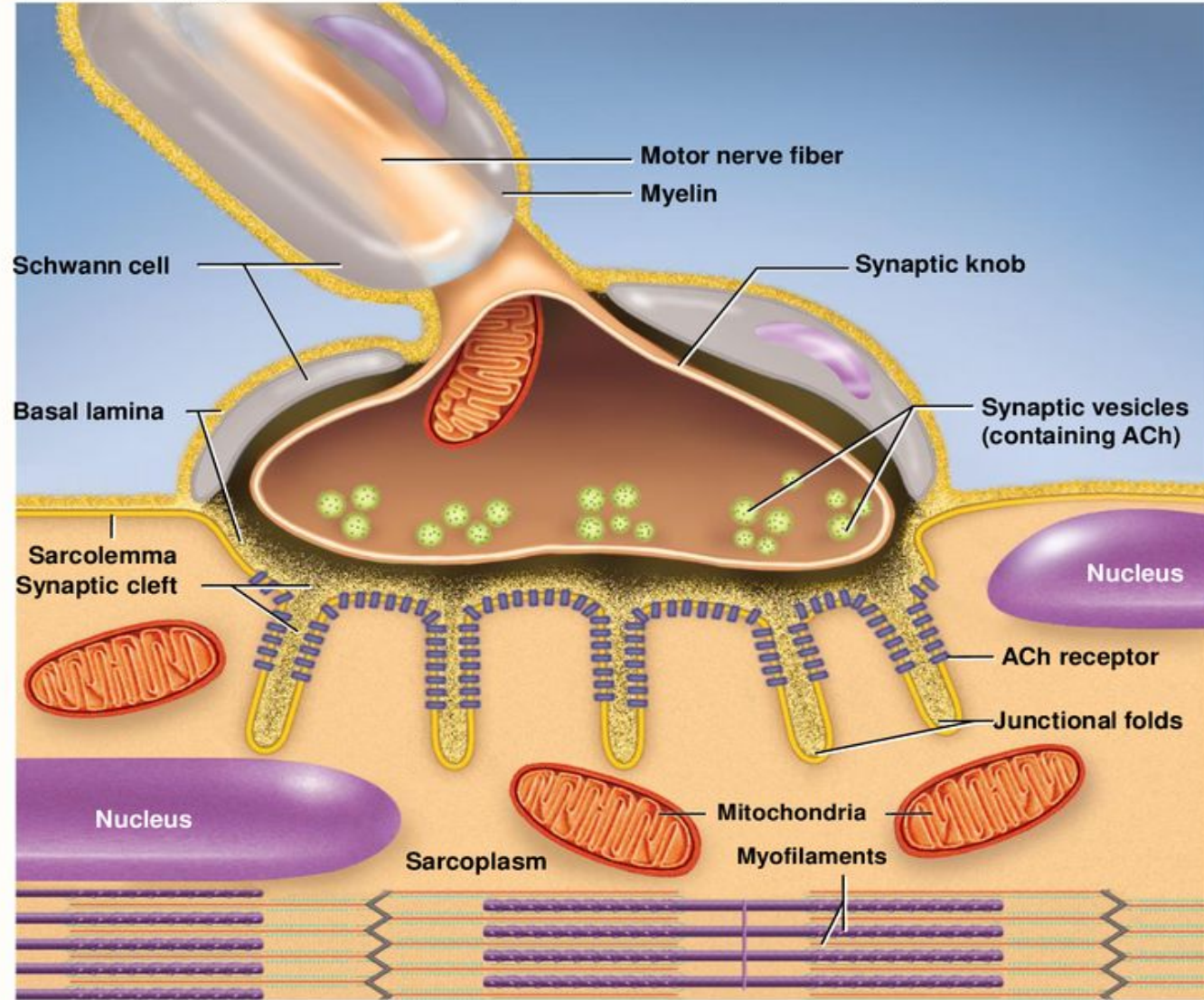
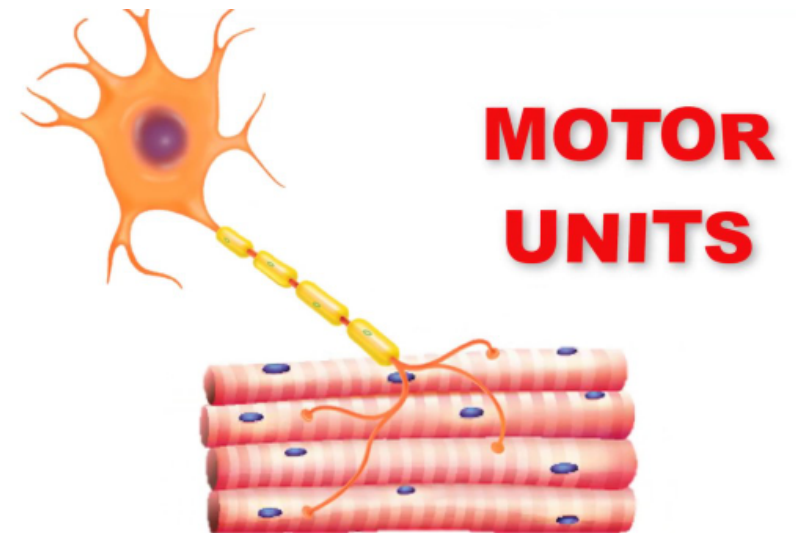


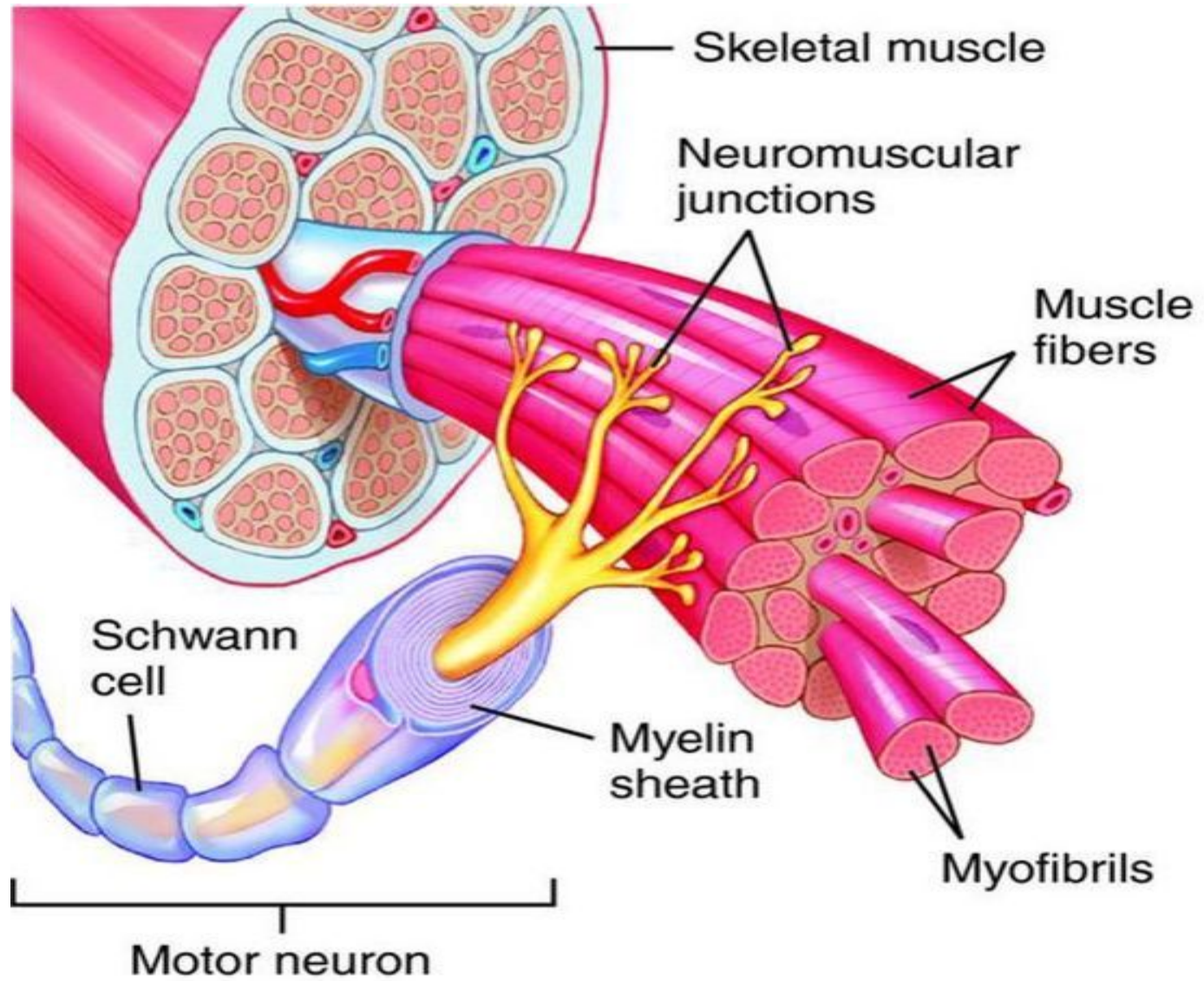
Figure 11.7b

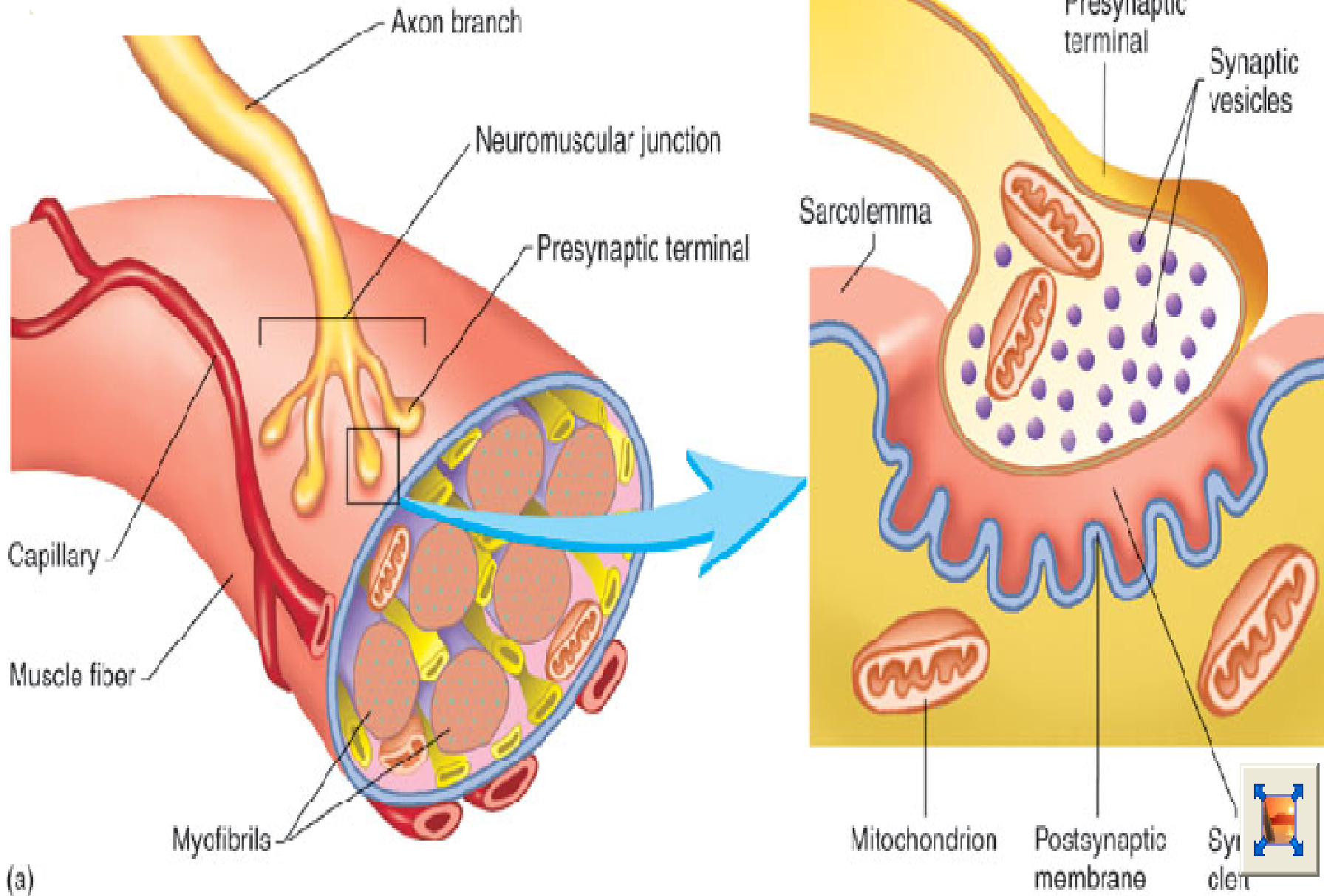
(b)

MOTOR UNIT

- A single motor neuron and all of the muscle fibers it innervates is called a motor unit
- When an AP occurs in a motor neuron all muscle fibers in it's motor unit contract as one







(a)

MOTOR END PLATE

The nerve fiber forms a **complex of branching nerve terminals that invaginate into the surface of the muscle fiber but lie outside the muscle fiber plasma membrane**

Entire structure - *motor endplate*.

Covered by one or more **Schwann cells** that insulate it from the surrounding fluids.

Neurotransmitter vesicles

Myelin

Axon of motor neuron

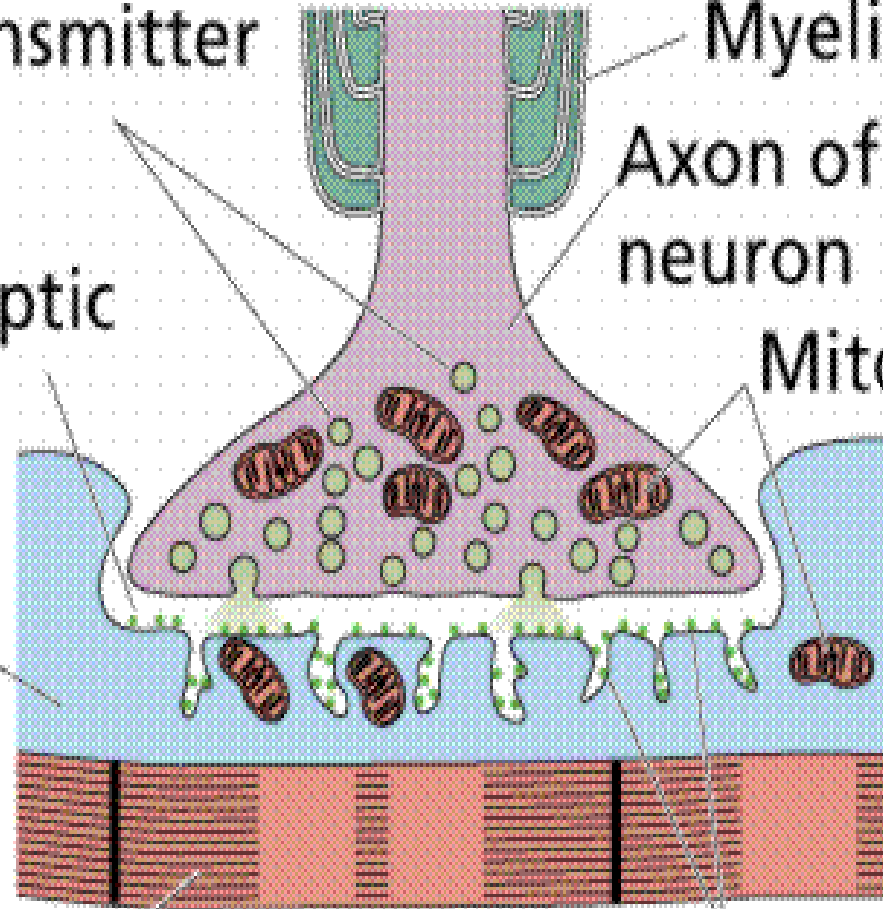
Synaptic cleft

Mitochondria

Motor end plate

Skeletal muscle fiber

Neurotransmitter receptors



PHYSIOLOGICAL ANATOMY OF THE NMJ (MOTOR ENDPLATE)

Neuromuscular junction or motor endplate

- **Axon of motor neuron branches, loses the myelin sheath and forms several axon terminals**
- **Axon terminals contain vesicles resembling vesicles found at synaptic interfaces**
- **Axon terminals contain the neurotransmitter acetylcholine (ACh)**

PHYSIOLOGICAL ANATOMY OF THE NMJ (MOTOR ENDPLATE)

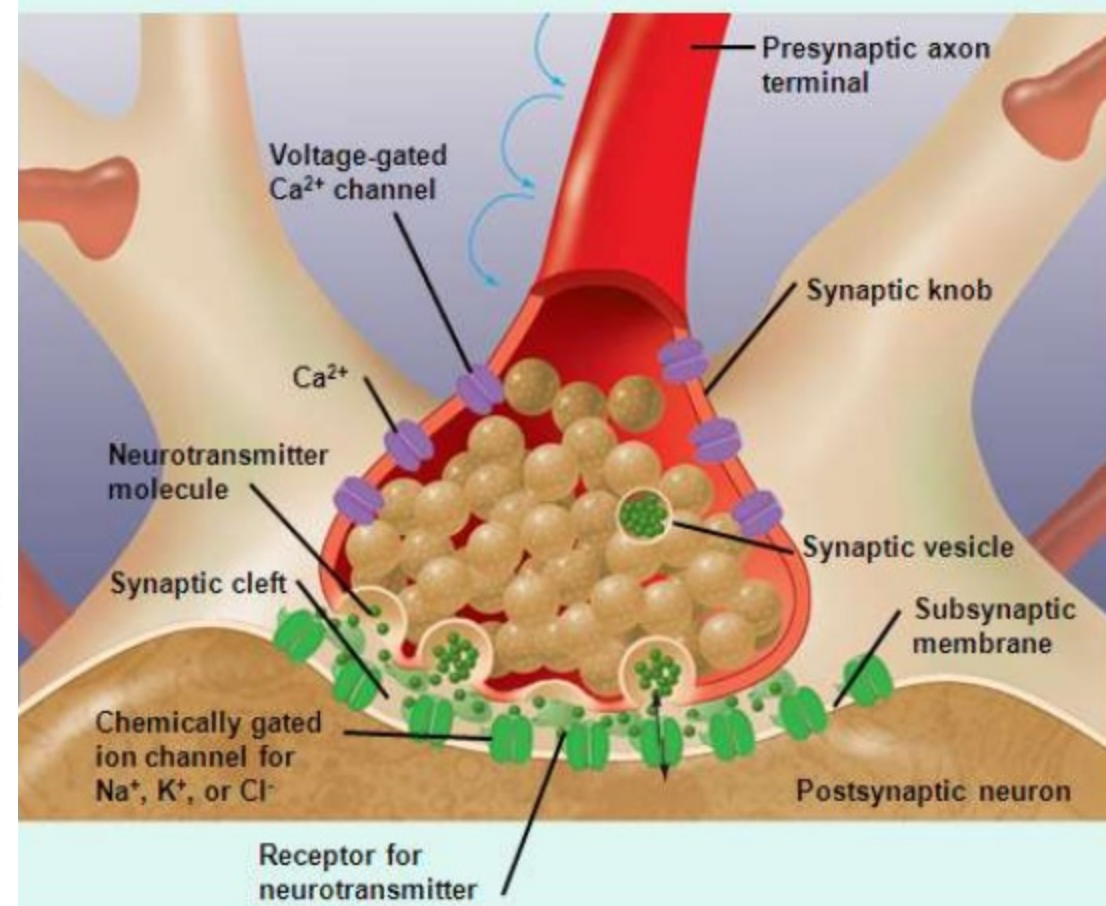
2. Axon terminals invaginate into the muscle fiber
 - ▶ Axon terminal and muscle fiber do not physically touch
 - ▶ Muscle fiber membrane (postsynaptic) is specialized and is different from the plasma membrane on the rest of the muscle fiber
3. Junction is covered by Schwann cells, this insulates the junctional cleft from surrounding fluids and prevents some of the loss of neurotransmitter by diffusion from the cleft

PHYSIOLOGICAL ANATOMY OF THE NMJ (MOTOR ENDPLATE)

- **Synaptic gutter or trough** - Invagination of the membrane beneath the axon terminal (postsynaptic membrane)
- **Synaptic cleft** - space between axon terminal and synaptic trough
 - 20 to 30 nm wide
 - Space filled with ECF, a gel of carbohydrate rich amorphous material

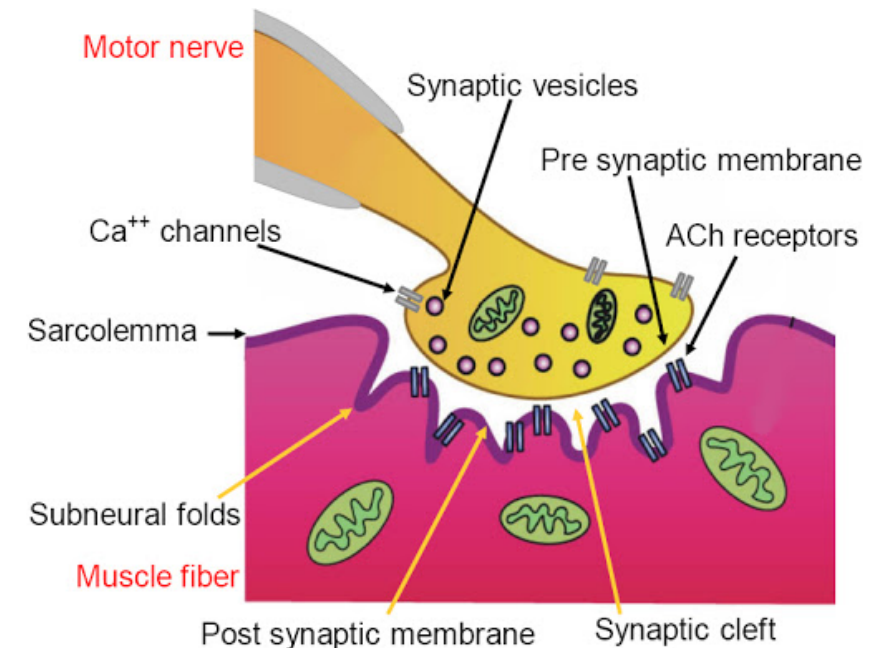
SYNAPTIC VESICLES

- **Size** 40 nanometers
- **Formed by** the Golgi apparatus in the cell body of the motor neuron in the spinal cord.
- **Transported by** axoplasm to the neuromuscular junction at the tips of the peripheral nerve fibers.
- About **300,000** of these small vesicles collect in the nerve terminals of a single skeletal muscle end plate.



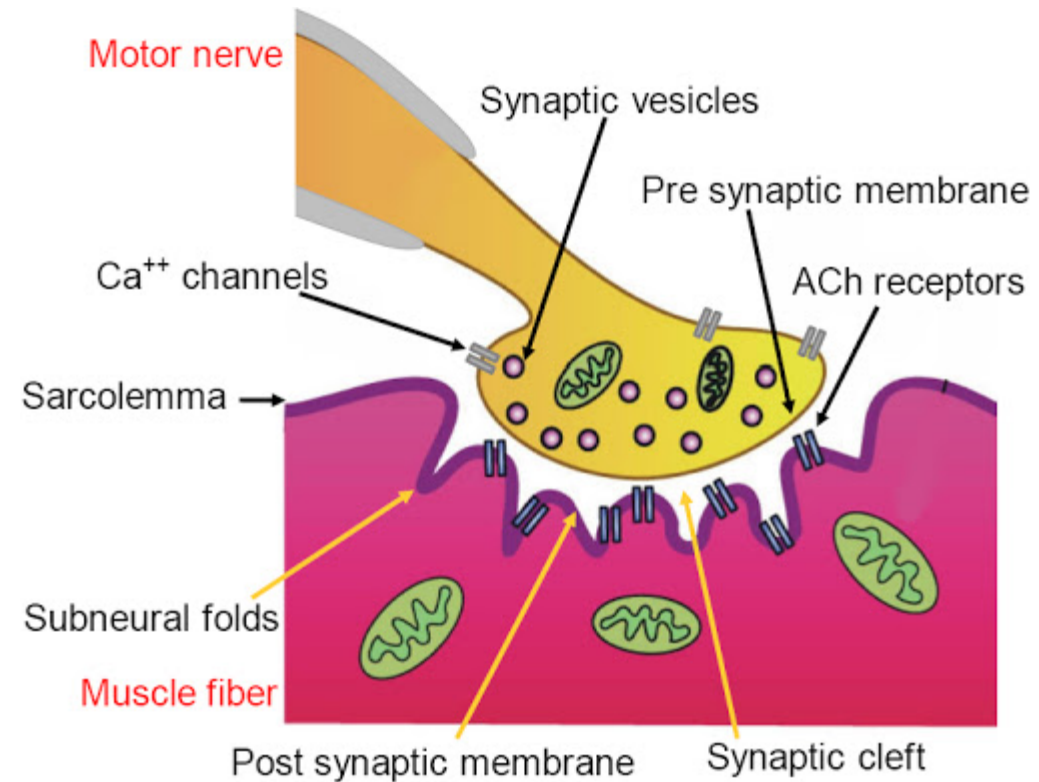
THE POSTSYNAPTIC MEMBRANE

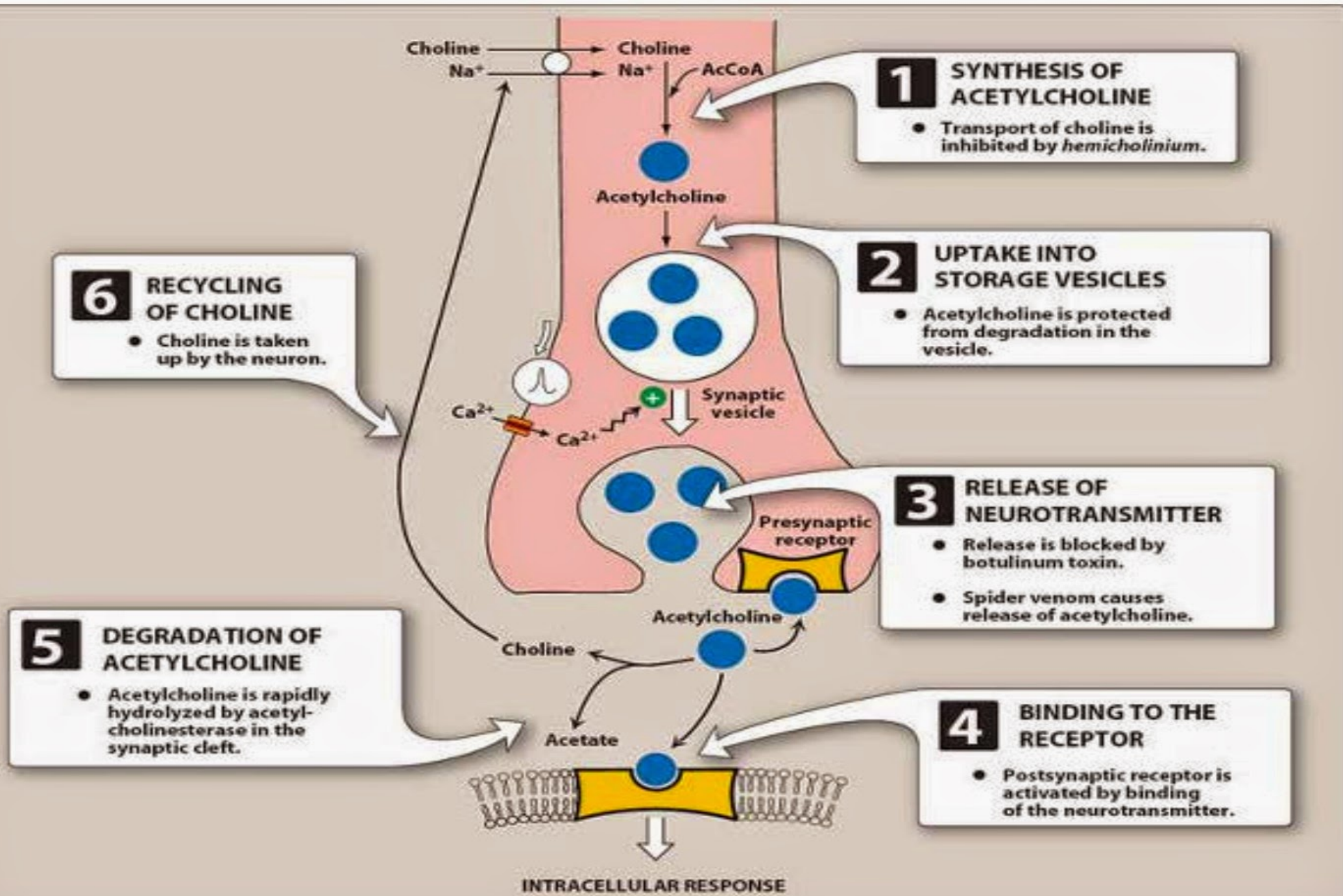
- the **membrane** that receives a signal (binds neurotransmitter) from the presynaptic cell and responds via depolarisation or hyperpolarisation.
- The **postsynaptic membrane** is separated from the presynaptic membrane by the synaptic cleft.
- Has Ach receptor which are Ach-gated channels located near the mouths of sub-neural clefts.



SUB NEURAL CLEFTS OR FOLDS

- ▶ **Folds of the synaptic trough**
- ▶ **Increase postsynaptic surface area**
- ▶ **Location of the majority of the acetylcholine receptors (ligand gated Na⁺& K⁺ channels)**
- ▶ **Basal lamina and postsynaptic membrane contain many molecules of acetylcholinesterase (splits acetylcholine into acetylCoA and choline)**
- ▶ **Active zone of axon terminal is located over the subnerural folds**





1 SYNTHESIS OF ACETYLCHOLINE

- Transport of choline is inhibited by *hemicholinium*.

2 UPTAKE INTO STORAGE VESICLES

- Acetylcholine is protected from degradation in the vesicle.

3 RELEASE OF NEUROTRANSMITTER

- Release is blocked by botulinum toxin.
- Spider venom causes release of acetylcholine.

4 BINDING TO THE RECEPTOR

- Postsynaptic receptor is activated by binding of the neurotransmitter.

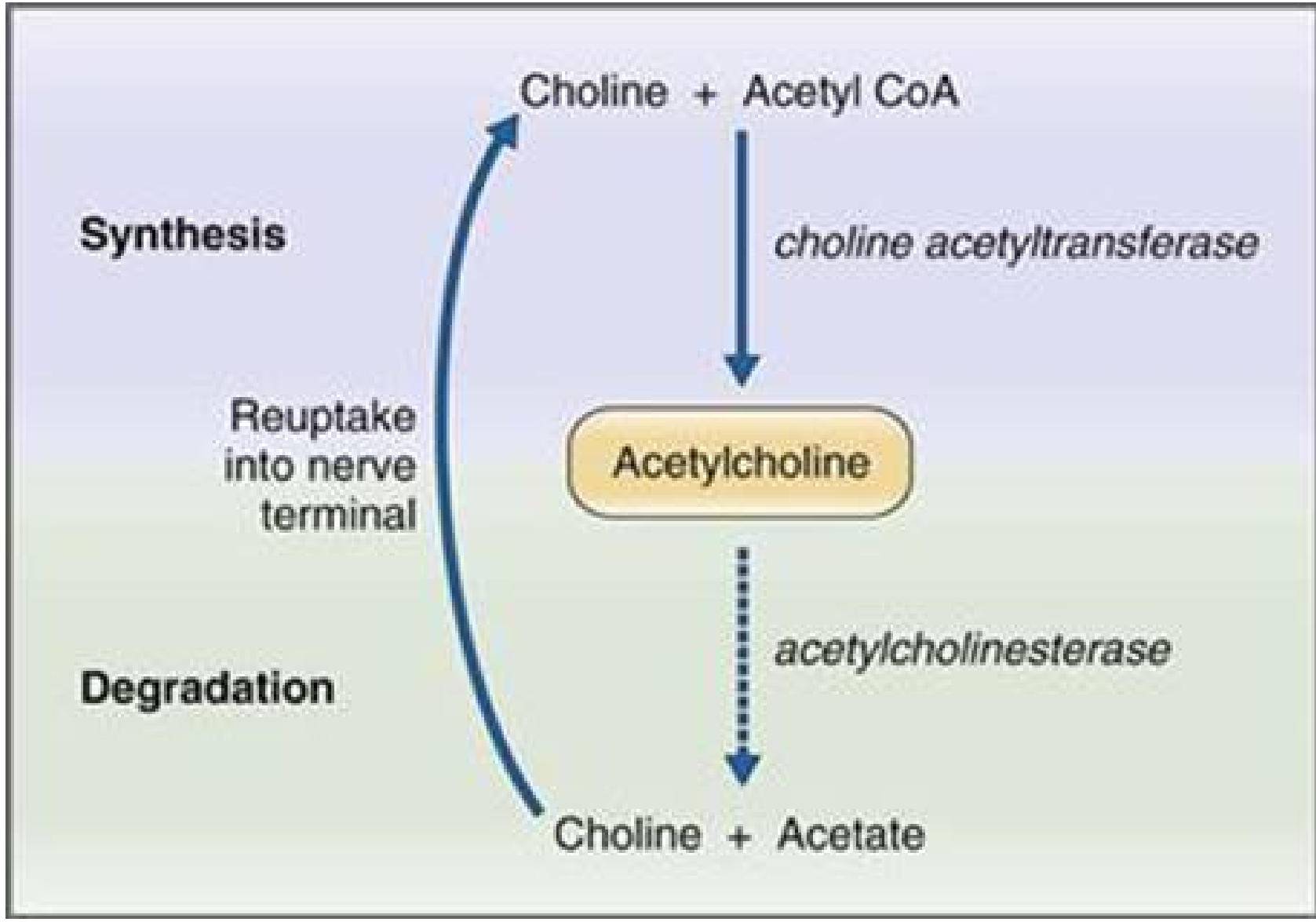
6 RECYCLING OF CHOLINE

- Choline is taken up by the neuron.

5 DEGRADATION OF ACETYLCHOLINE

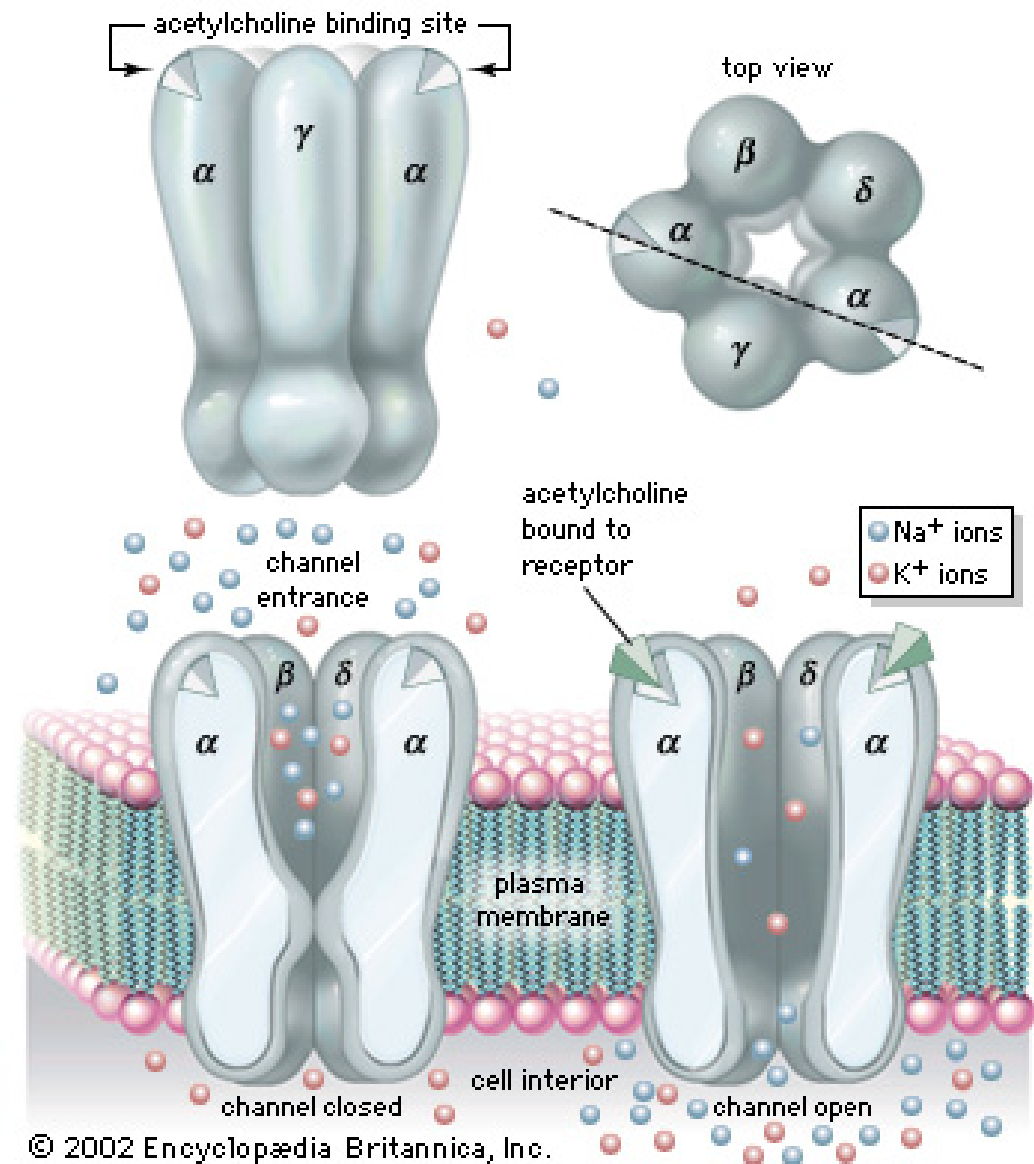
- Acetylcholine is rapidly hydrolyzed by acetylcholinesterase in the synaptic cleft.

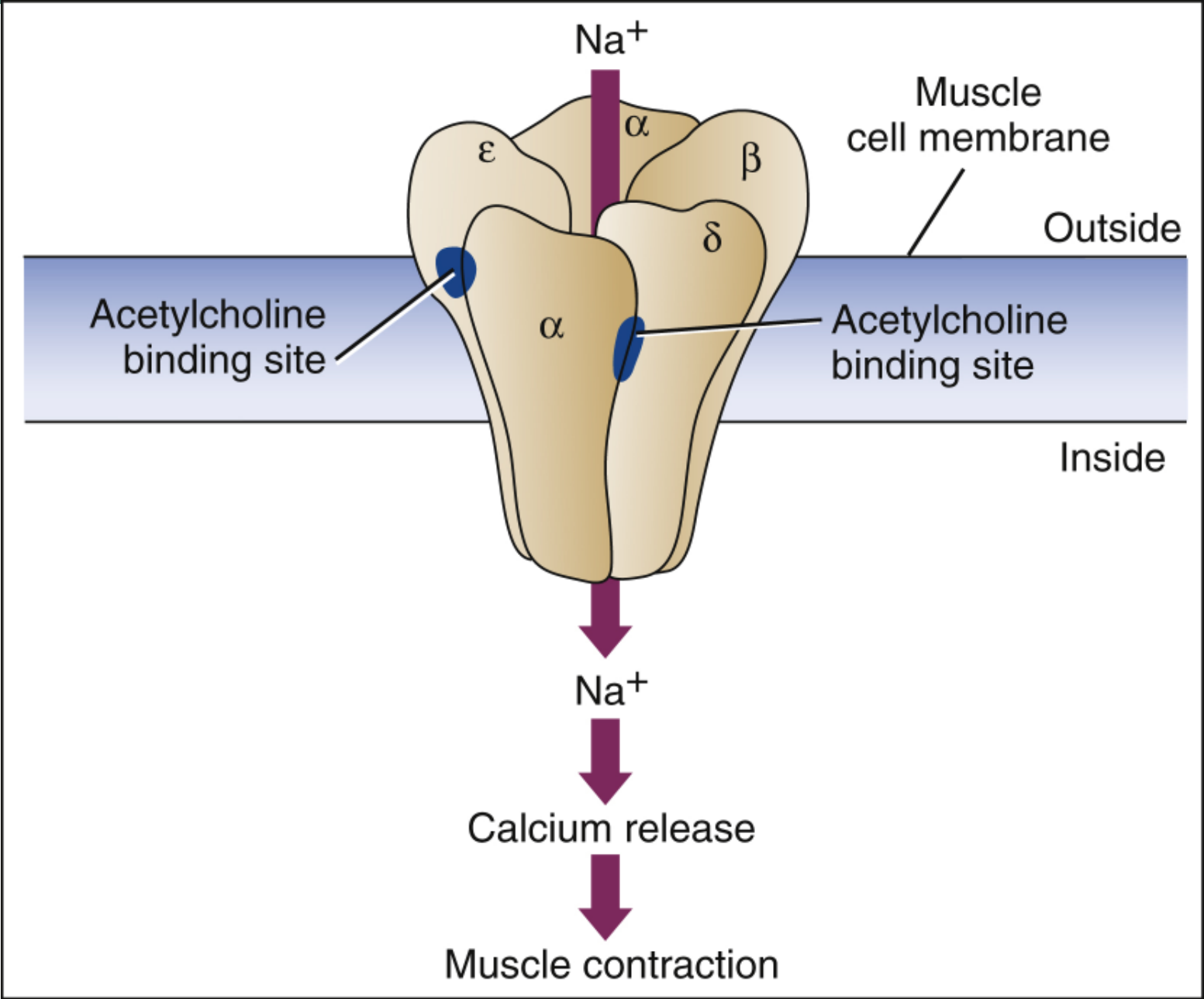
INTRACELLULAR RESPONSE



Nicotinic receptors

- 5 subunits
 - 2 α
 - 1 β
 - 1 δ
 - 1 γ







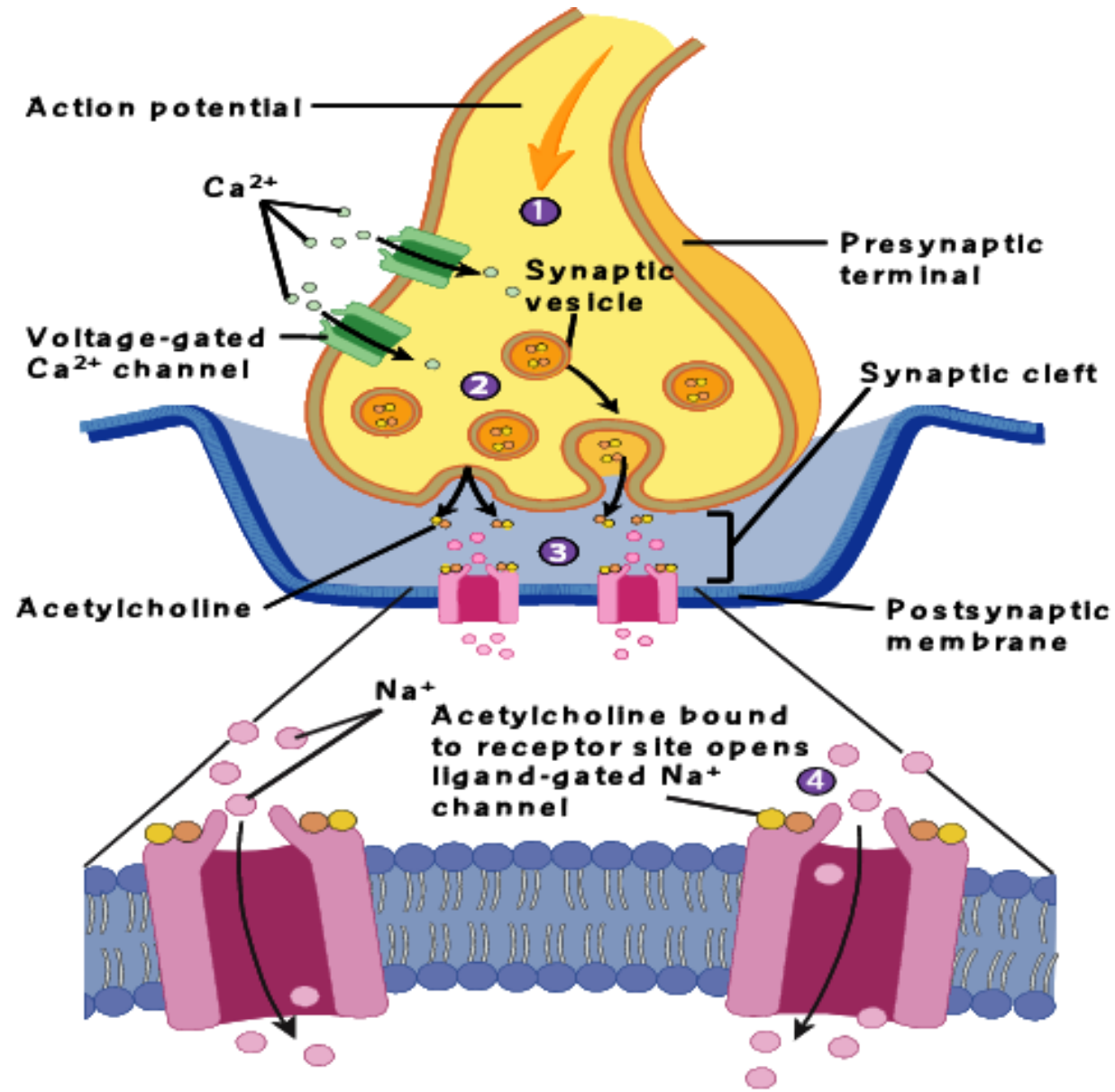
PART 2- NEUROMUSCULAR TRANSMISSION



EVENTS OF NEUROMUSCULAR JUNCTION

1. Propagation of an action potential to a terminal button of motor neuron.
2. Opening of voltage-gated Ca^{2+} channels.
3. Entry of Calcium into the terminal button.
4. Release of acetylcholine (by exocytosis).
5. Diffusion of Ach across the space.
6. Binding of Ach to a receptor on motor end plate

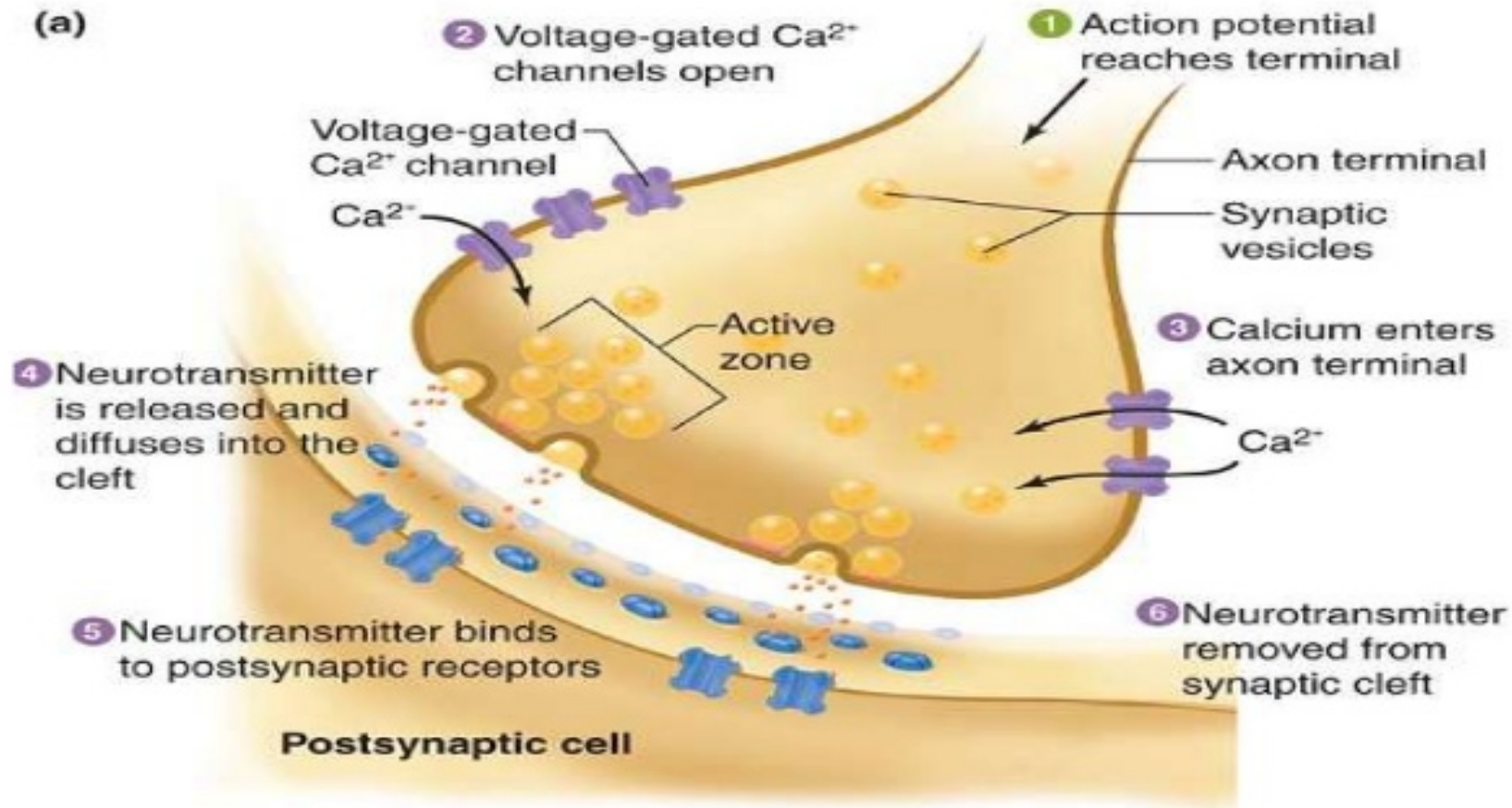
Sequence Of Events At Neuromuscular Junction




SECRETION OF ACH BY AXON TERMINALS

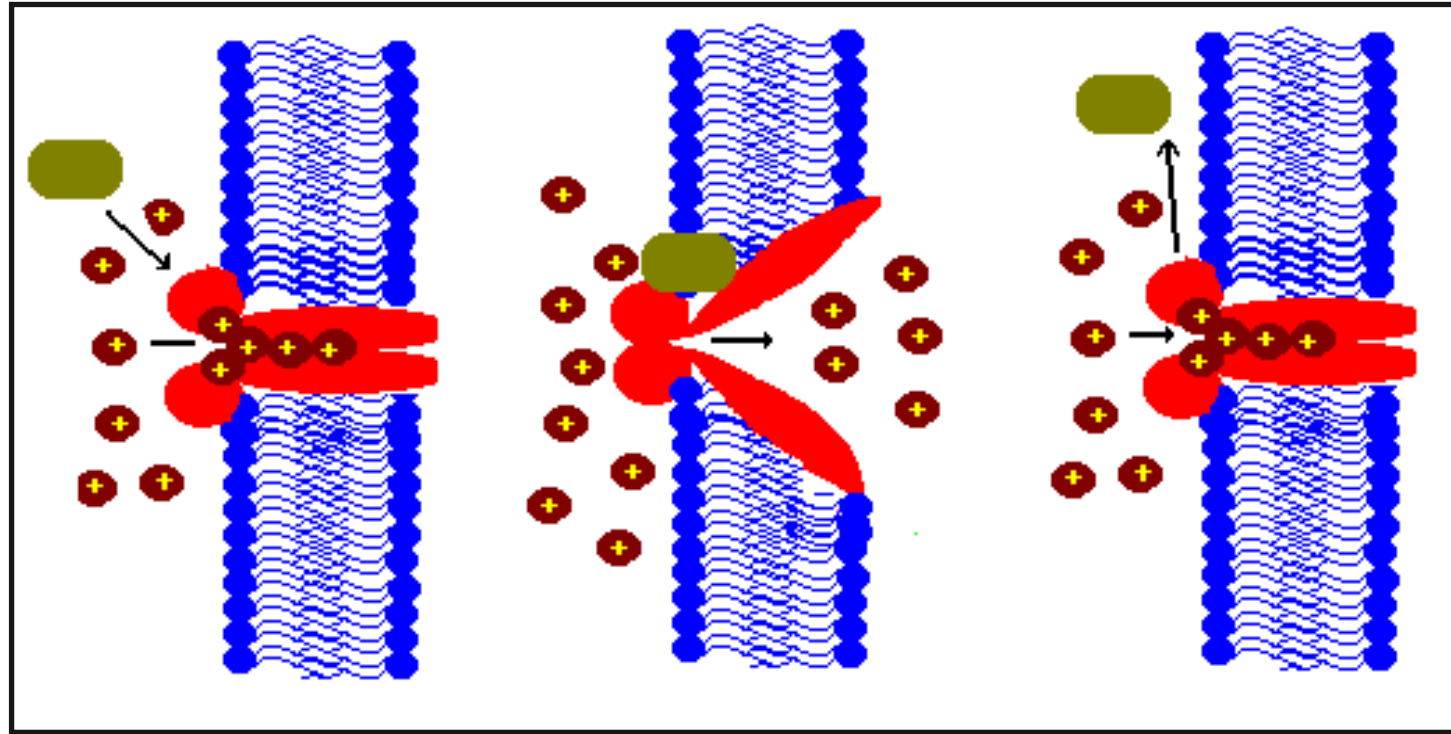
- 1. AP along the axon of motor neuron is propagated to axon terminal
- 2. Depolarization of the axon terminal opens voltage-gated calcium channels
 - a. Calcium release causes Ach vesicles to fuse with the axon terminal membranes at the active sites
 - b. Ach quanta are released into the synaptic cleft

Release of acetylcholine



- 
- ▶ **3. Acetylcholine diffuses across the synaptic cleft and binds with nicotinic ligand-gated channels that allow calcium, sodium, and potassium to move across the postsynaptic membrane**
 - ▶ **a. Electrochemical gradient across membrane favors more sodium flux inward than potassium flux outward, very little calcium moves across the membrane**
 - ▶ **b. Depolarization of the postjunctional membrane occurs and is called an EPP (end-plate potential)**

NMJ (MOTOR ENDPLATE) LIGAND GATING



DESTRUCTION OF RELEASED ACH BY ACETYLCHOLINESTERASE

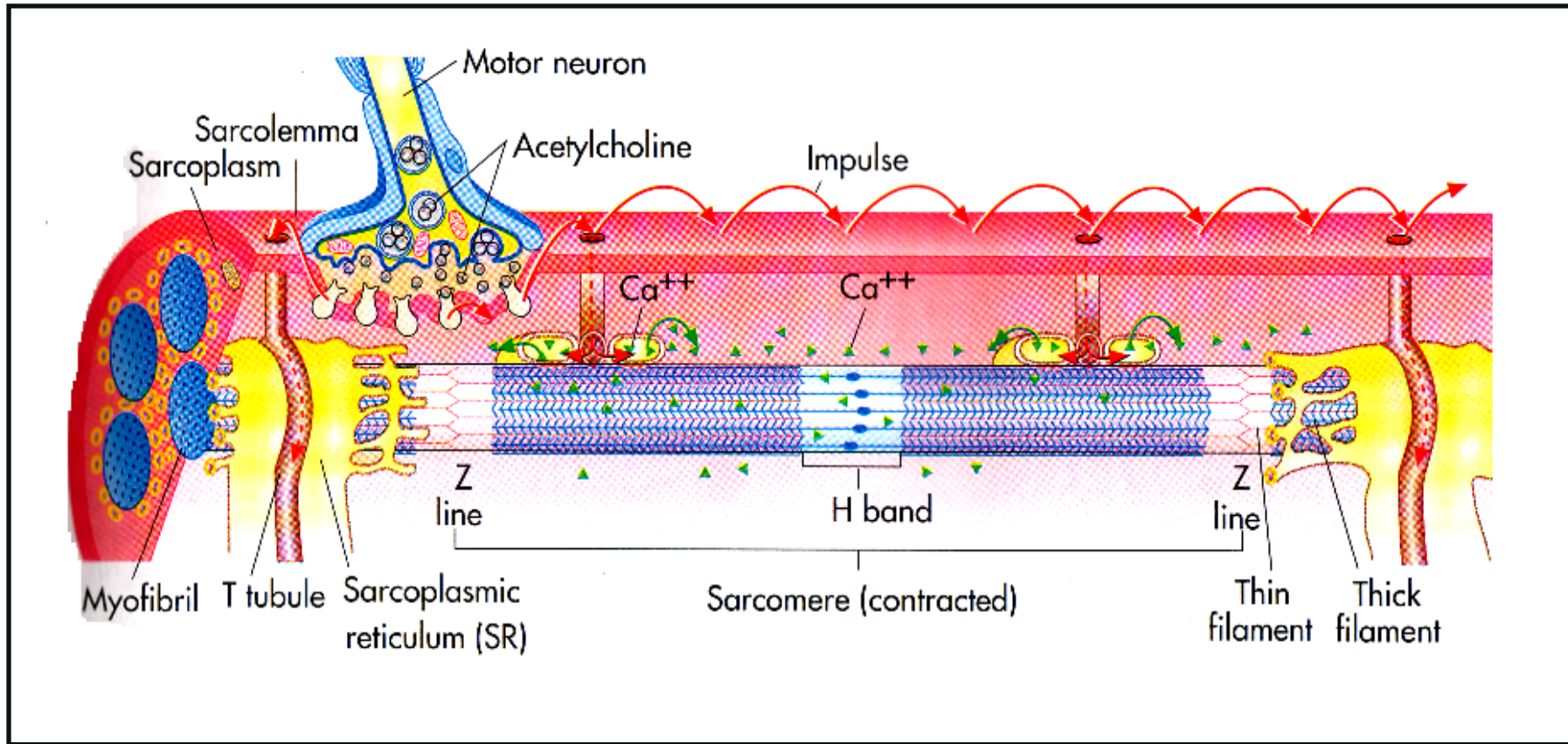
- Acetylcholine is rapidly removed by two mechanisms
 1. **Acetylcholinesterase** is located on the postsynaptic membrane and the external basal lamina most Ach is broken down by this mechanism
 2. **Diffusion** - small amounts of Ach diffuse out of the synaptic cleft

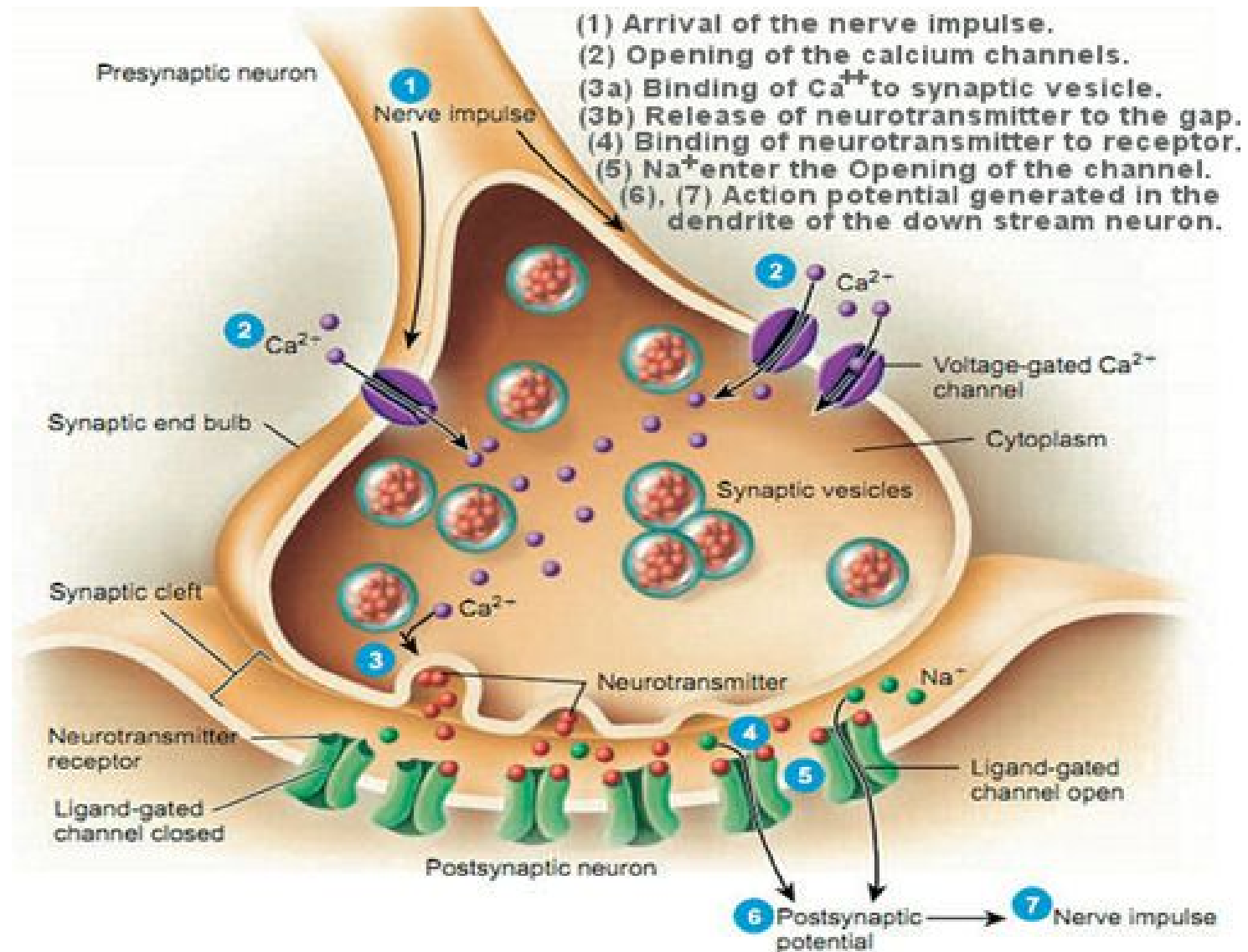
EPP AND EXCITATION OF MUSCLE FIBER

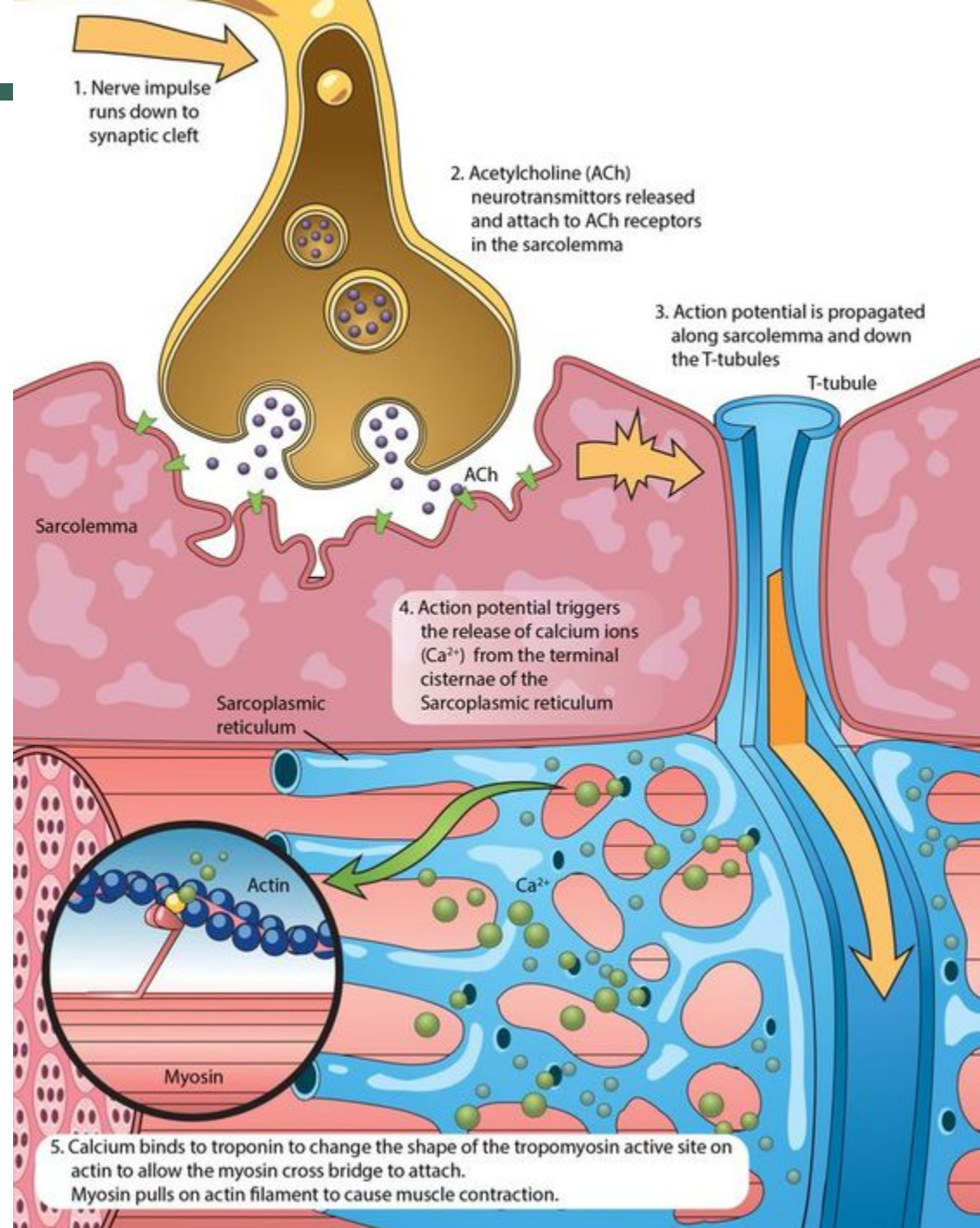
- NMJ postsynaptic membrane is Not electrically excitable and does not fire an AP
- EPP is a local graded potential
 - 1. EPP is analogous to an EPSP but much larger, all NMJ potentials are excitatory and cause an AP on the adjacent postsynaptic membrane every time

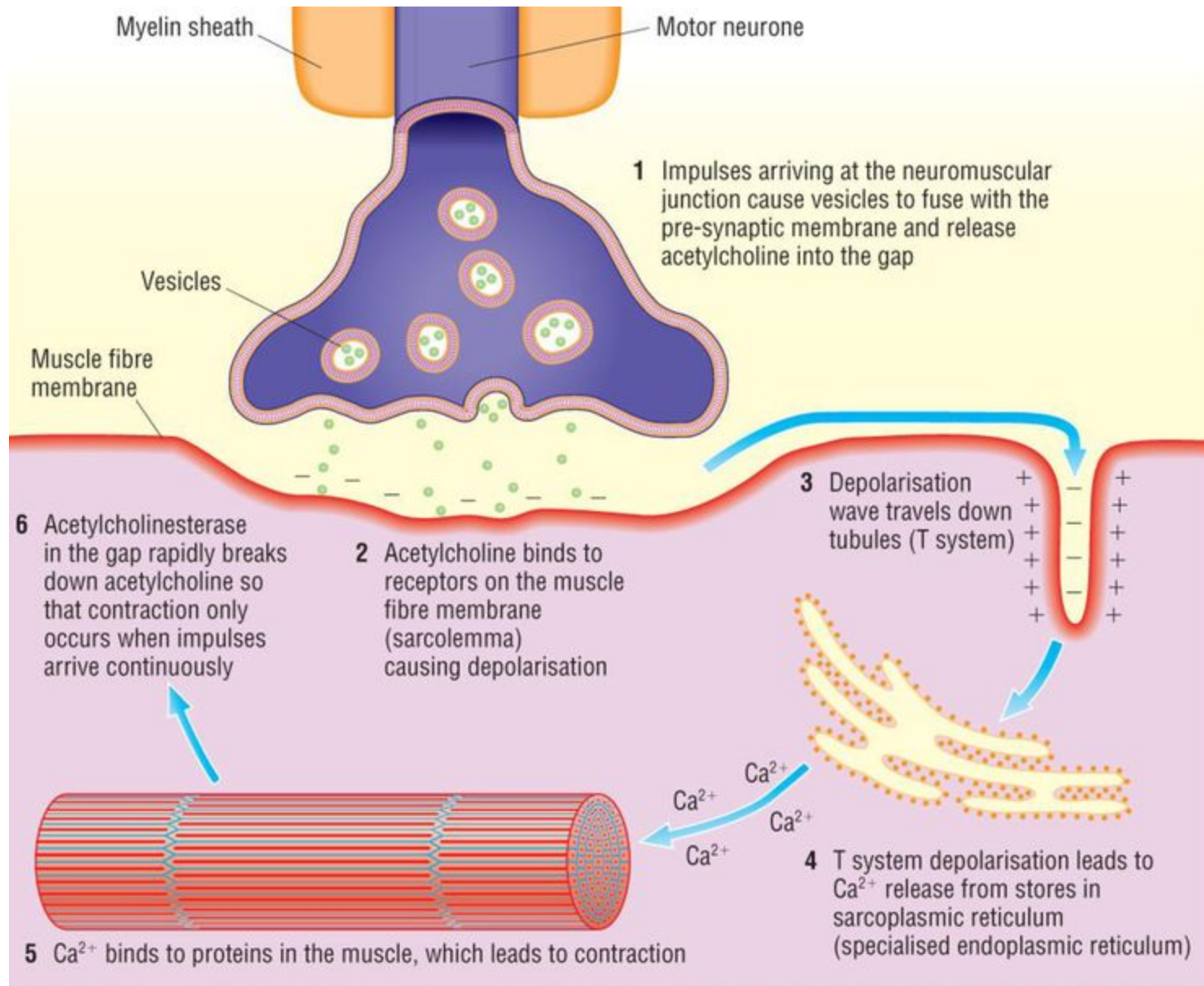
PHYSIOLOGICAL ANATOMY OF THE NMJ (MOTOR ENDPLATE)

- 2. One EPP is normally more than sufficient to cause AP generation on adjacent skeletal muscle membrane
- 3. AP is propagated on skeletal muscle fibers from center toward both ends so that center sarcomeres contract first (prevents excess strain on skeletal muscle fibers and produces a stronger response faster)

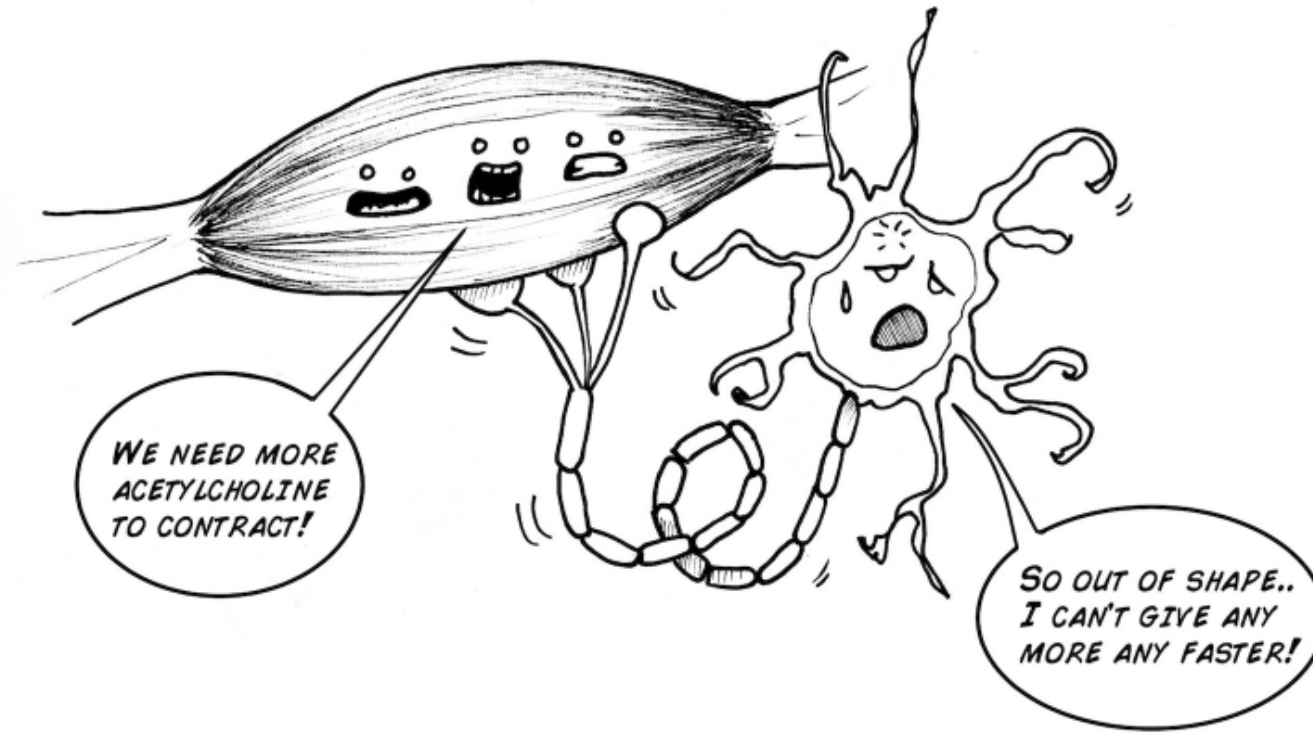


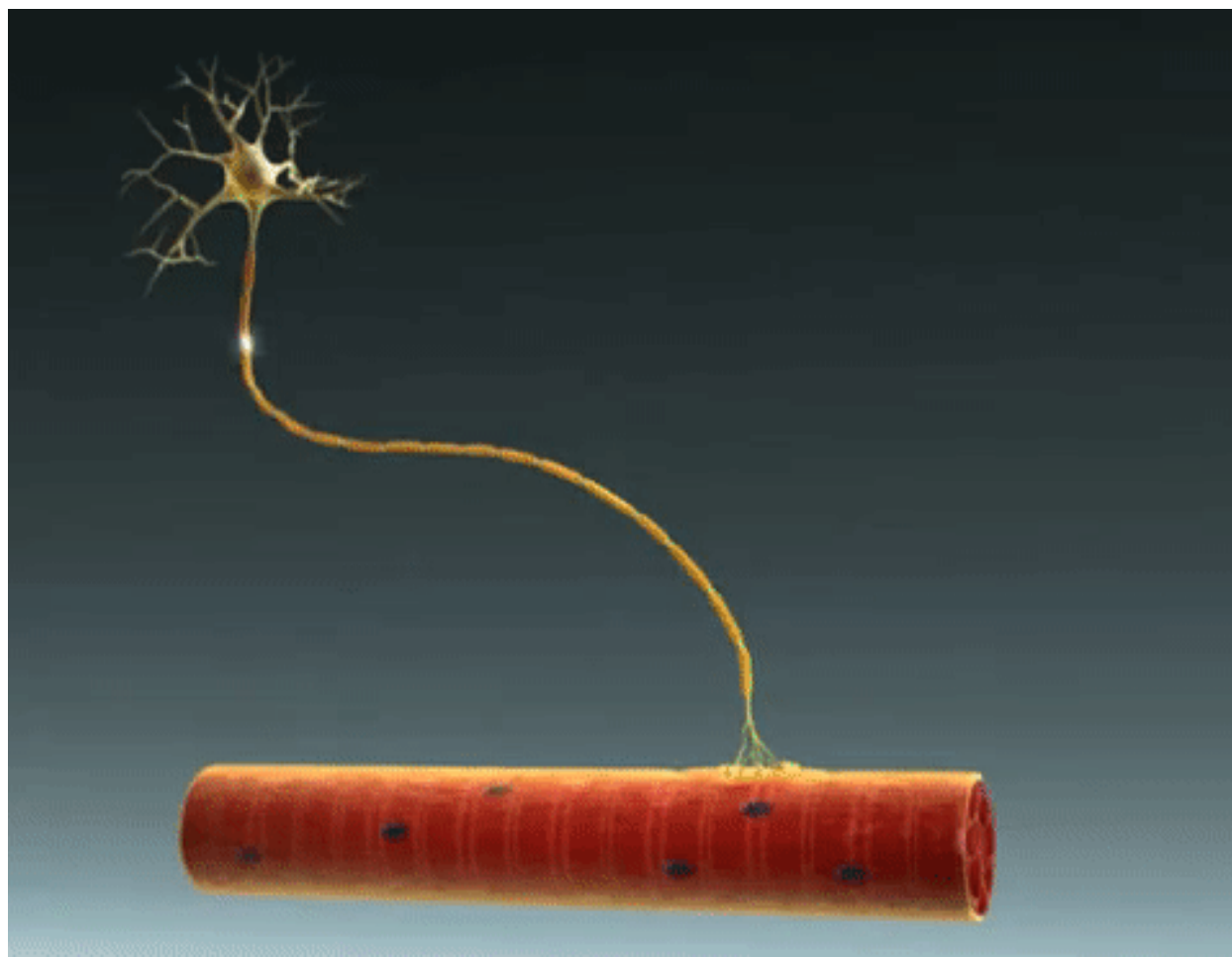


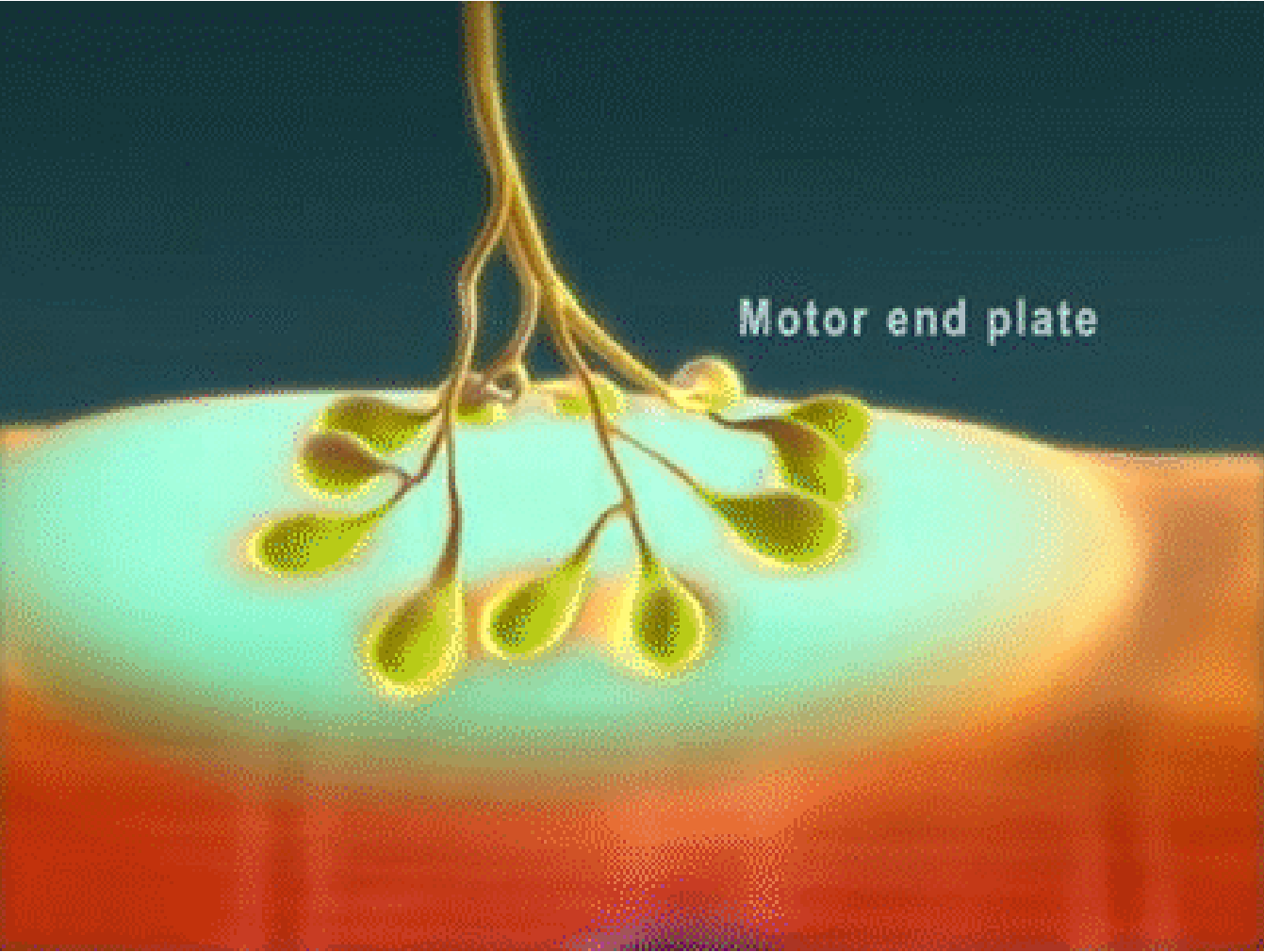




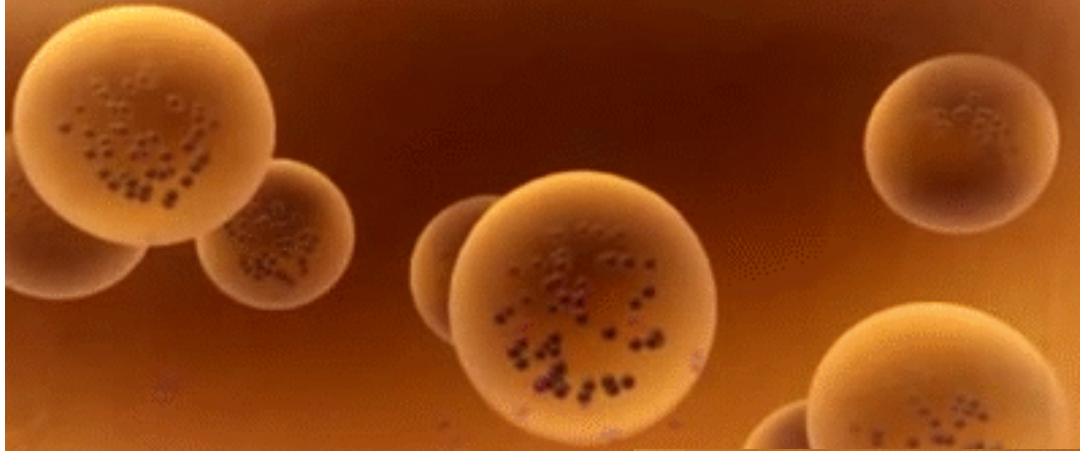
NEUROMUSCULAR FATIGUE



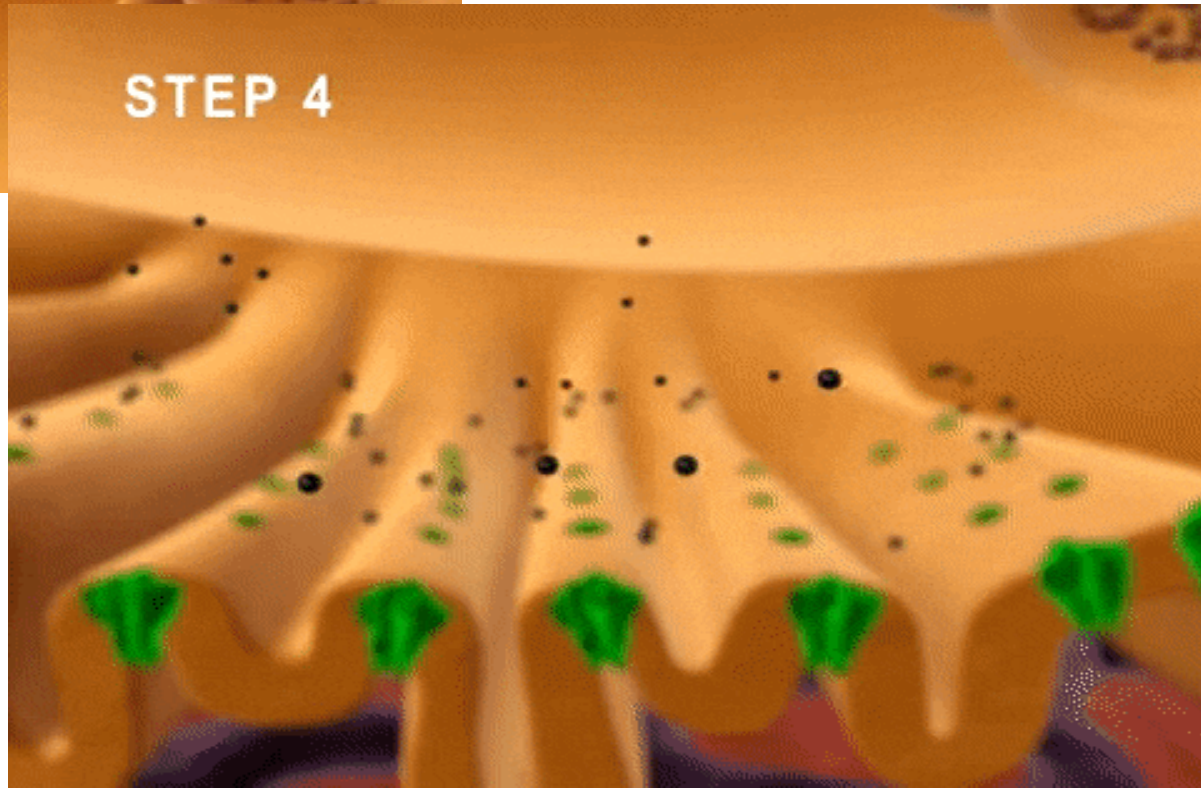


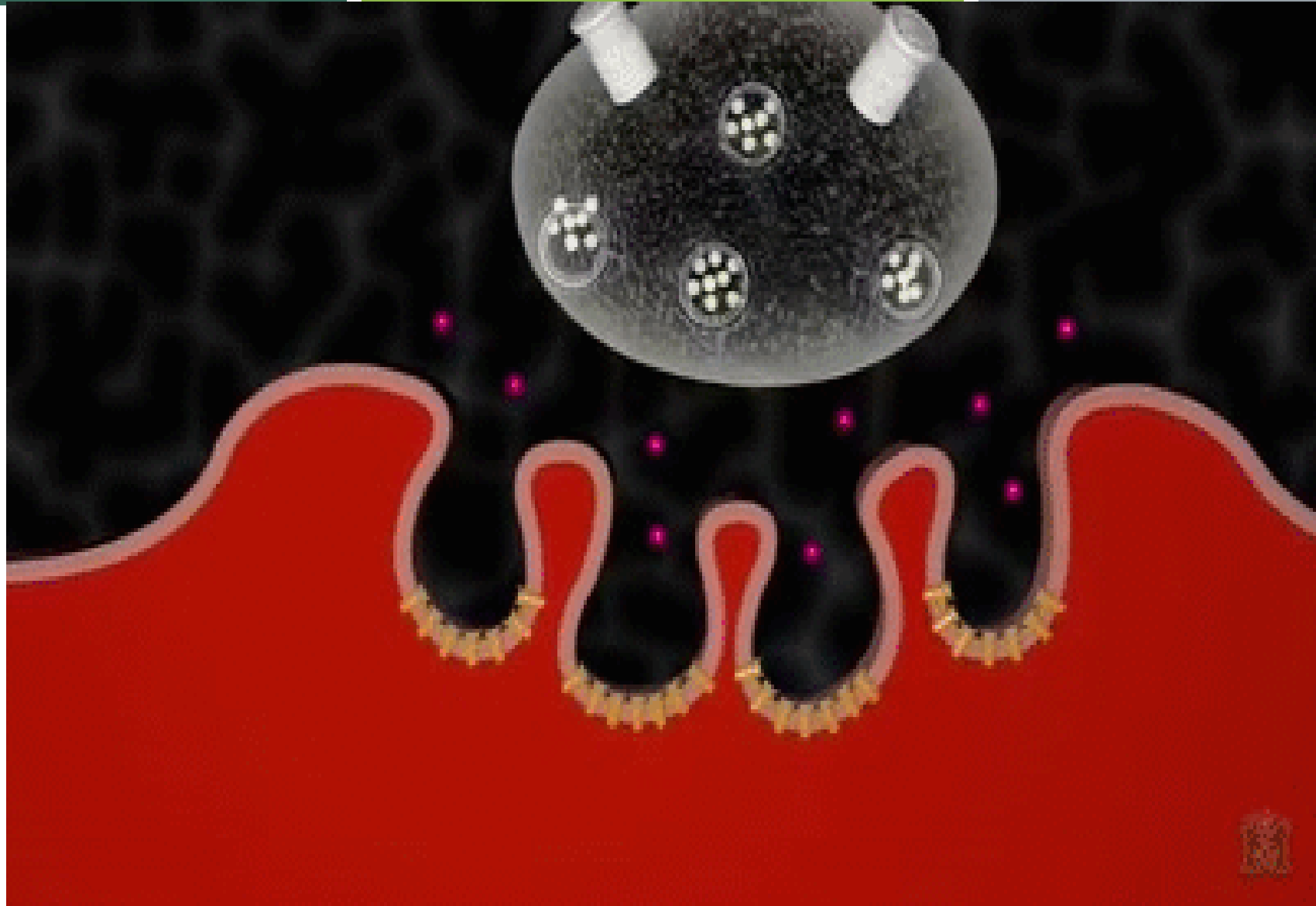


STEP 3



STEP 4





Myasthenia Gravis is an autoimmune
Disease that is
characterized by a decrease in
number of AChR



Any Questions?

“Because
answers
exist only
to *questions...*”

Mungara Tarou Krishnamurti
26 Jan 2013 2:17 am

**Questions ,
Comments,
Feedback?**

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RECOMMENDED BOOKS / RESOURCES

- Text book of Medical Physiology-Guyton and Hall
- Principles of human Physiology-Lauralee Sherwood
- Color Atlas of human Physiology
- Dr najeeb lecture on NMJ

[https://www.youtube.com/
watch?v=h7fQa0GaVkE](https://www.youtube.com/watch?v=h7fQa0GaVkE)



That's all Folks!