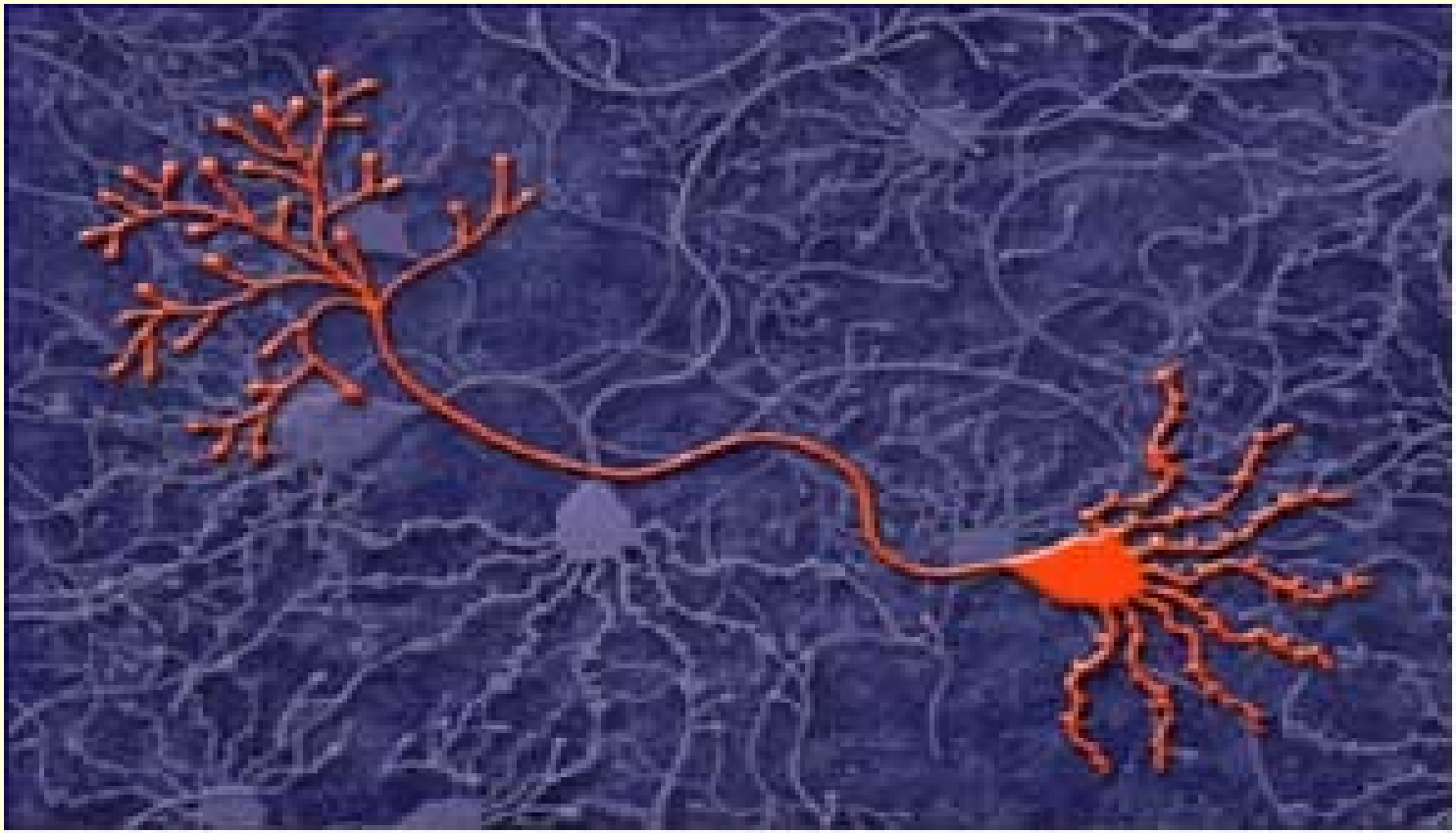
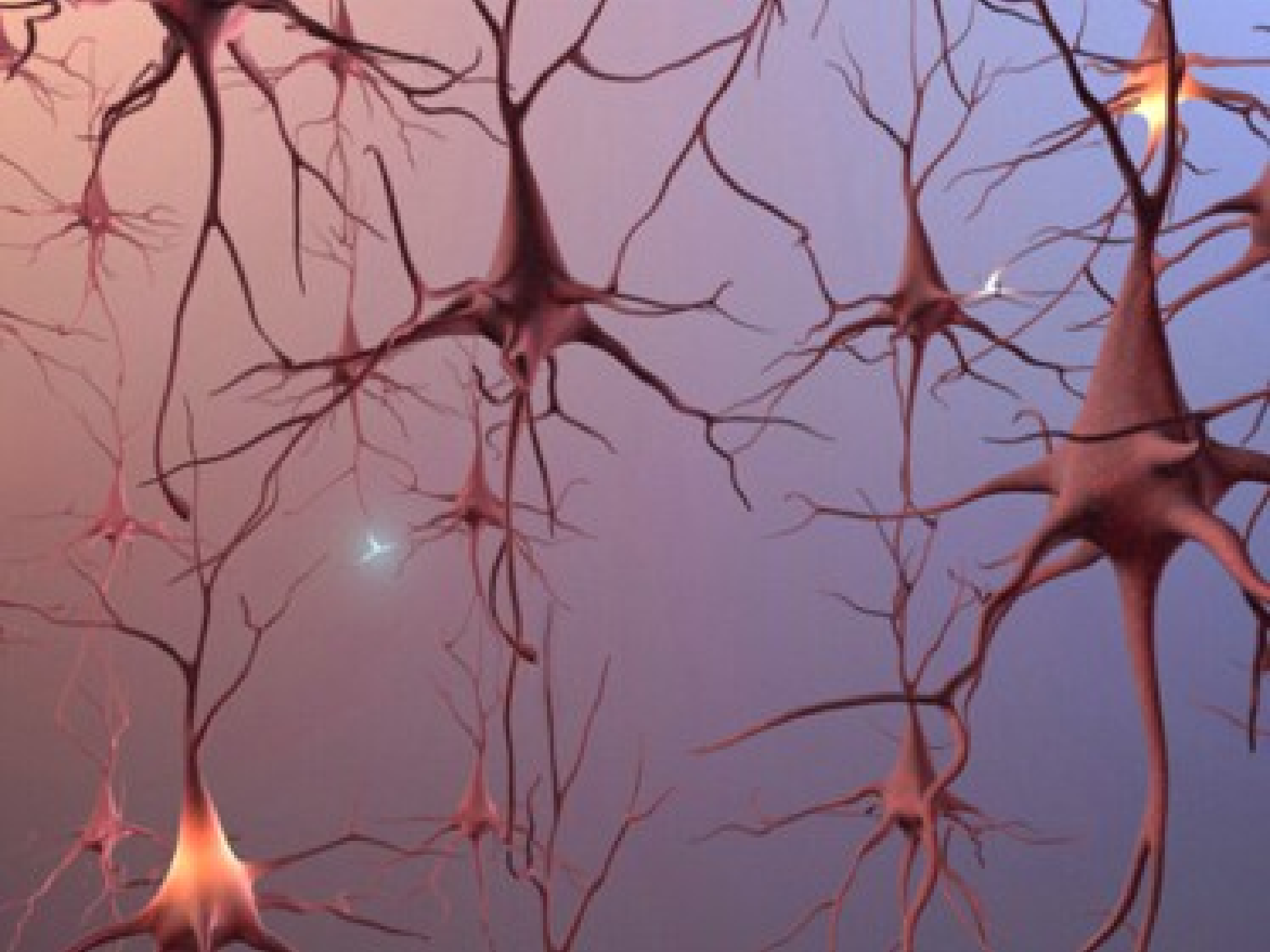
Nerve Tissue Physiology

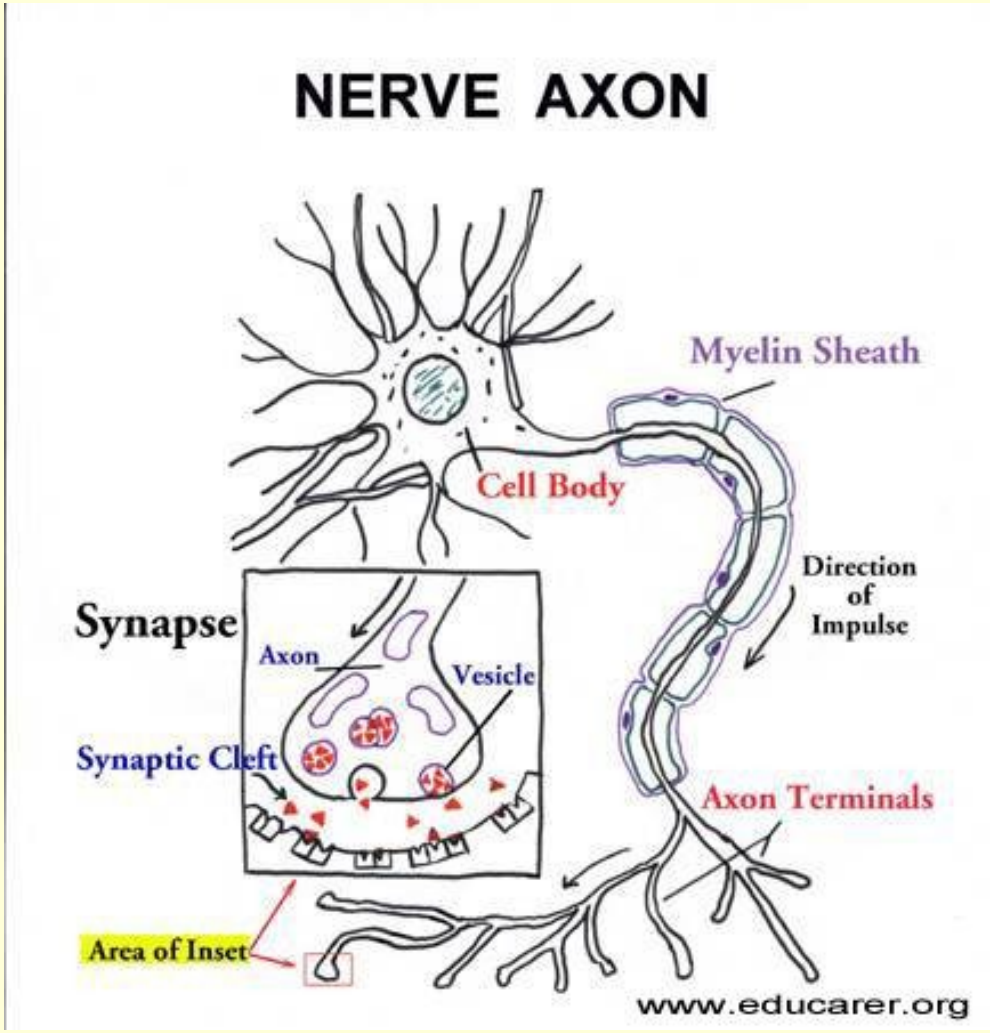


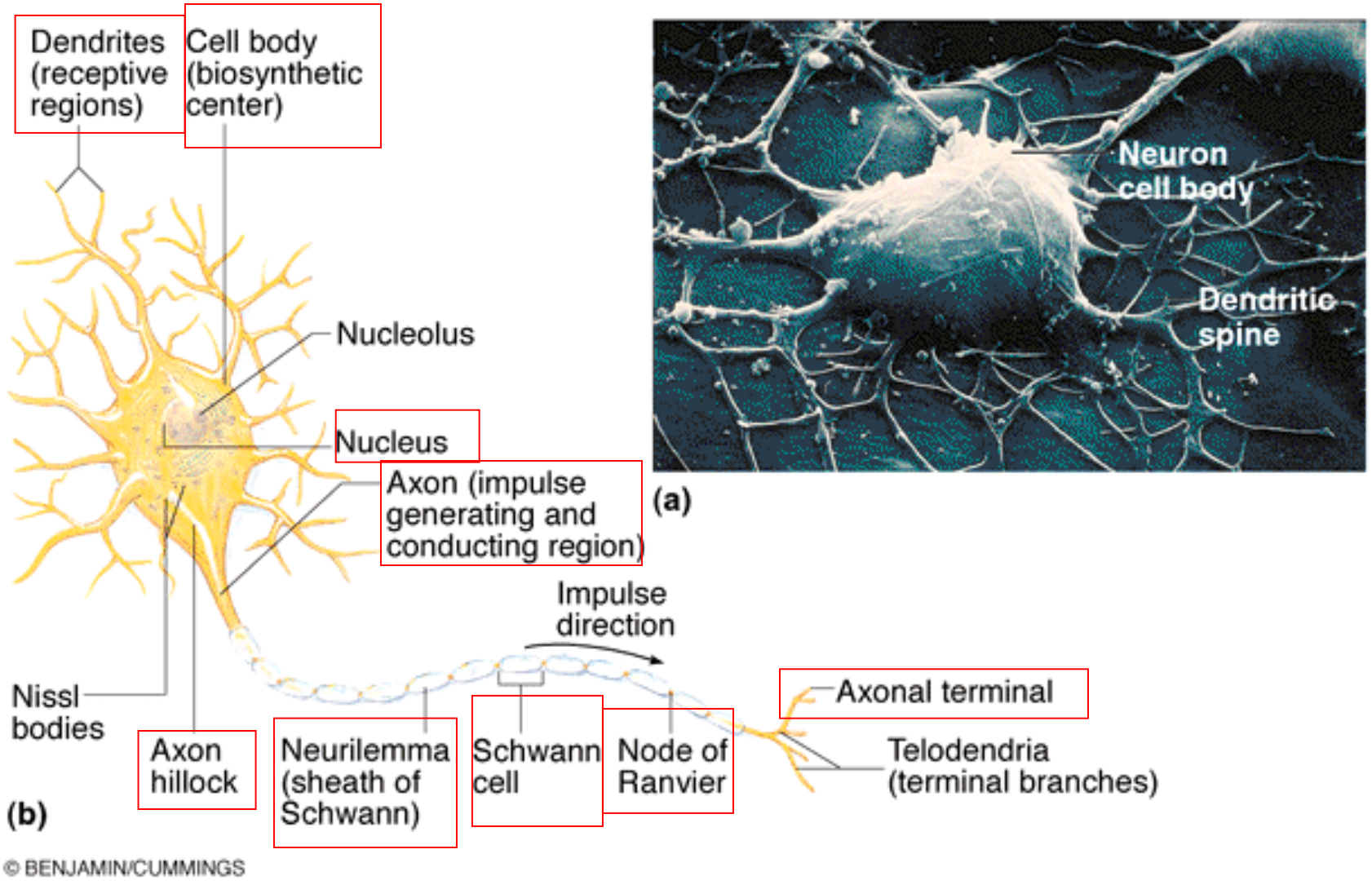


NERVE CELL STRUCTURE

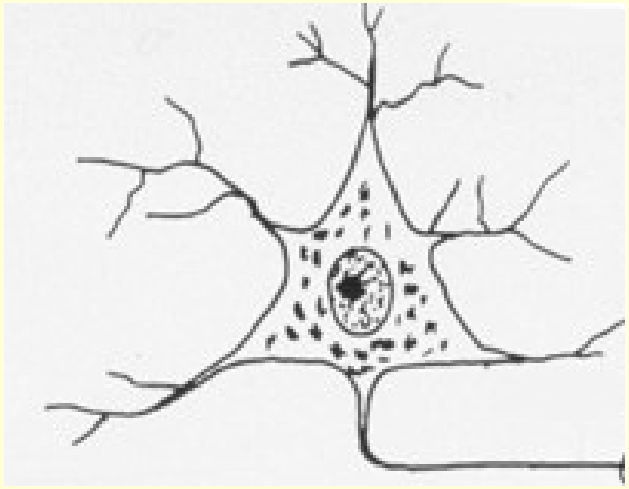
The nerve cell consists of the following structures:

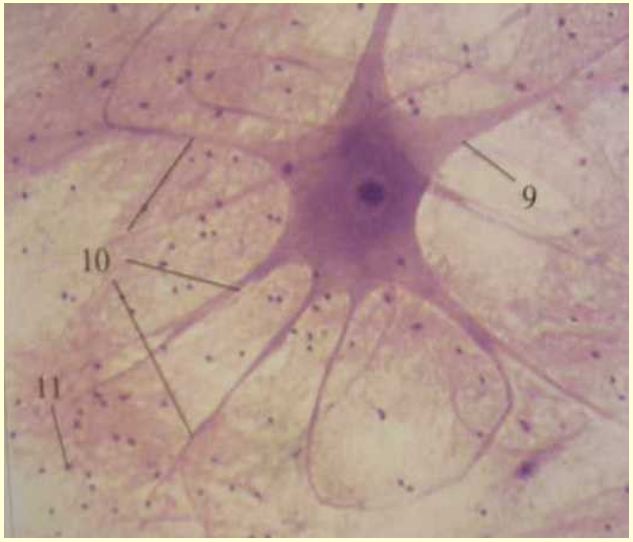
- => Dendrite
- => Cell body
- => Axon hillock
- => Axon
- => Myelin sheath (Schwann cell)
- => Nodes of Ranvier
- => Axon terminals




Dendrites (receptive regions)
Cell body (biosynthetic center)
Nucleolus
Nucleus
Axon (impulse generating and conducting region)
Impulse direction
Nissl bodies
Axon hillock
Neurilemma (sheath of Schwann)
Schwann cell
Node of Ranvier
Axonal terminal
Telodendria (terminal branches)
(b)
Neuron cell body
Dendritic spine
(a)
© BENJAMIN/CUMMINGS

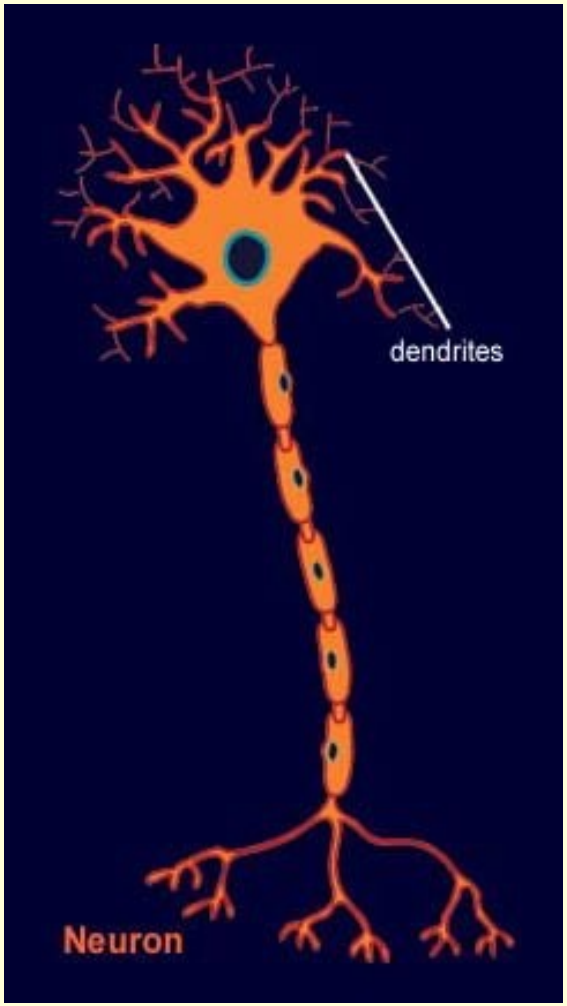
THE NERVE CELL BODY (SOMA)





- Enlarged part of the nerve cell – contains cytoplasm and cell organelles.
- Receives information from dendrites, sends messages out through the axon.
- Primary site for maintaining the life of the nerve cell; supports the dendrites and axon.

THE DENDRITE



- An incoming nerve cell process; can act as a receptor or connect to separate specialized receptors.
- Conducts stimulus information to the nerve cell body.
- Produces voltage changes in response to various stimuli and assists in nerve impulse formation.

THE AXON HILLOCK

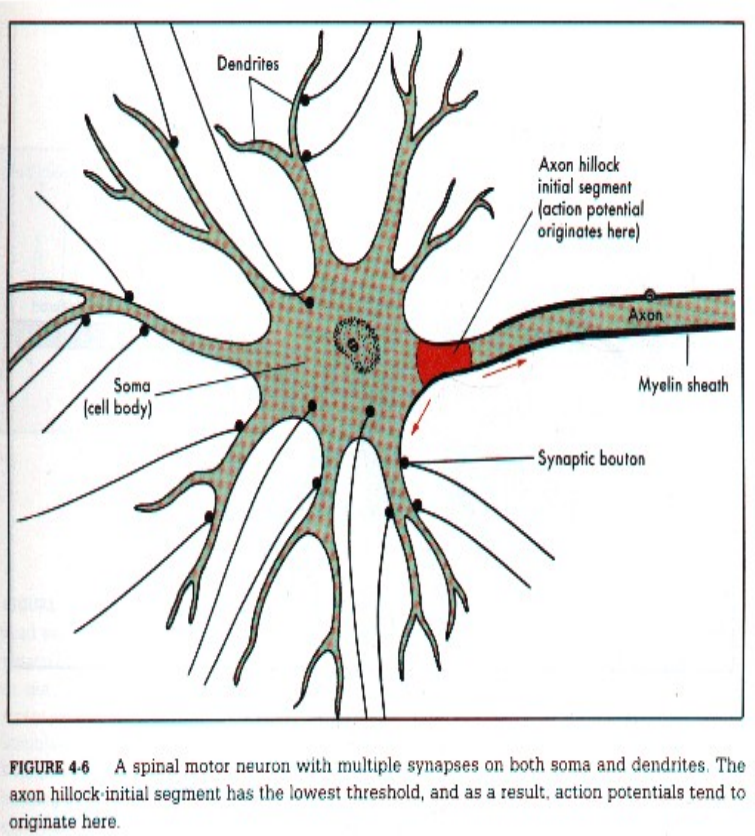


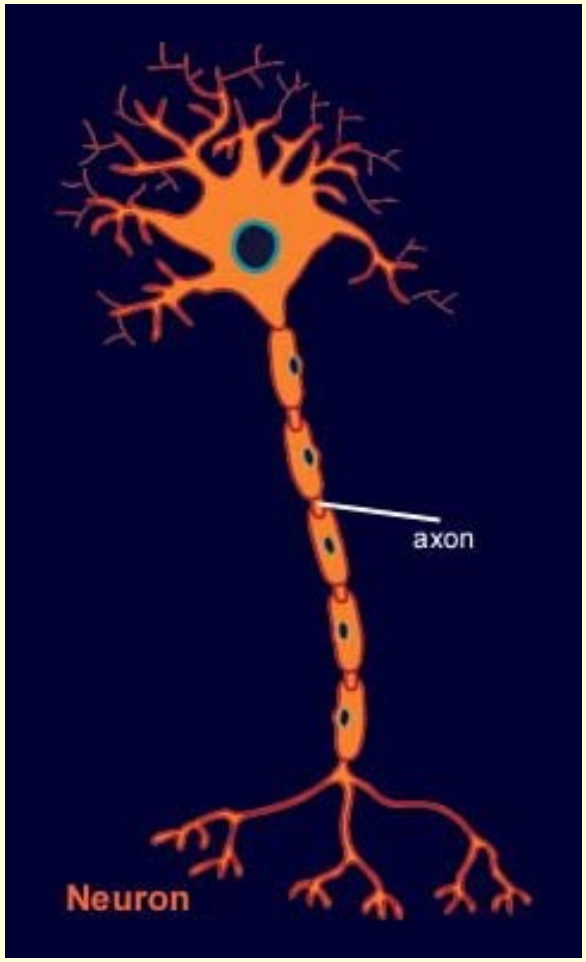
FIGURE 4-6 A spinal motor neuron with multiple synapses on both soma and dendrites. The axon hillock-initial segment has the lowest threshold, and as a result, action potentials tend to originate here.

Junction site between the nerve cell body and the axon.

Processes:

- **voltage changes, or generator potentials (GP's), from cell body and dendrites;**
- **assists formation of a transmittable nerve impulse.**

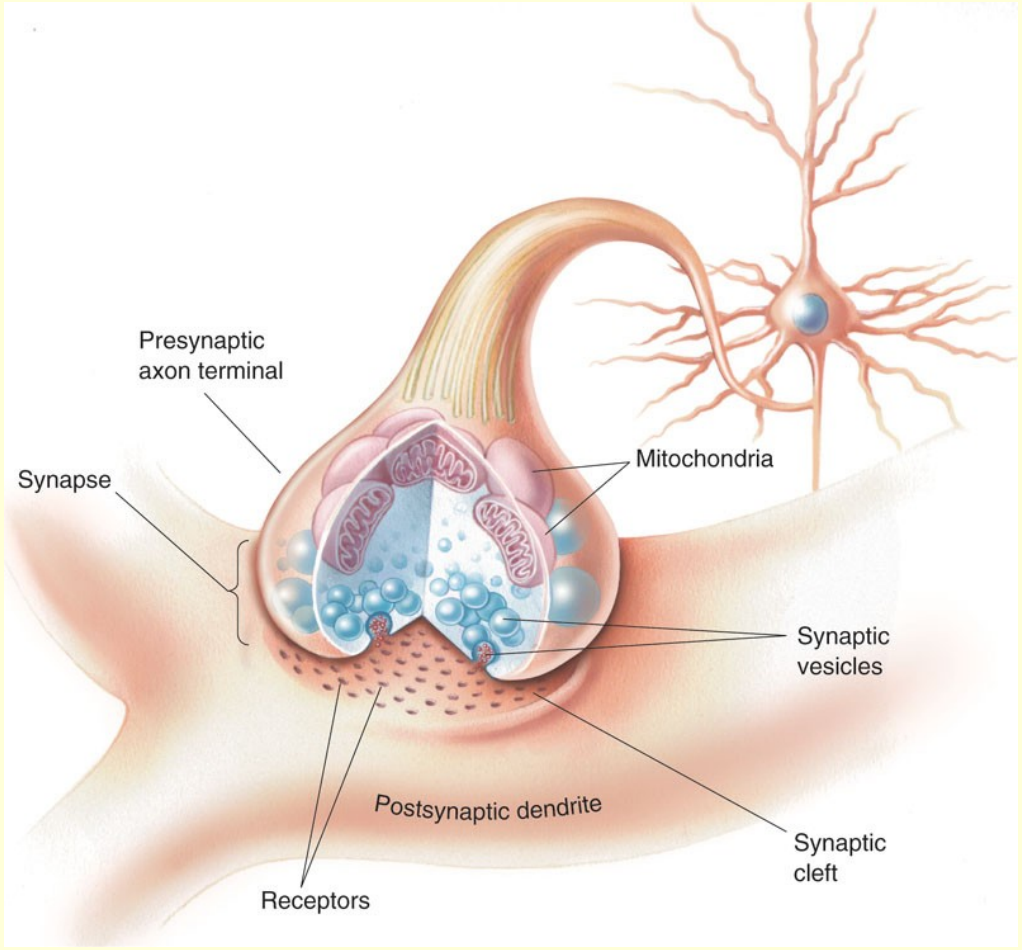
THE AXON



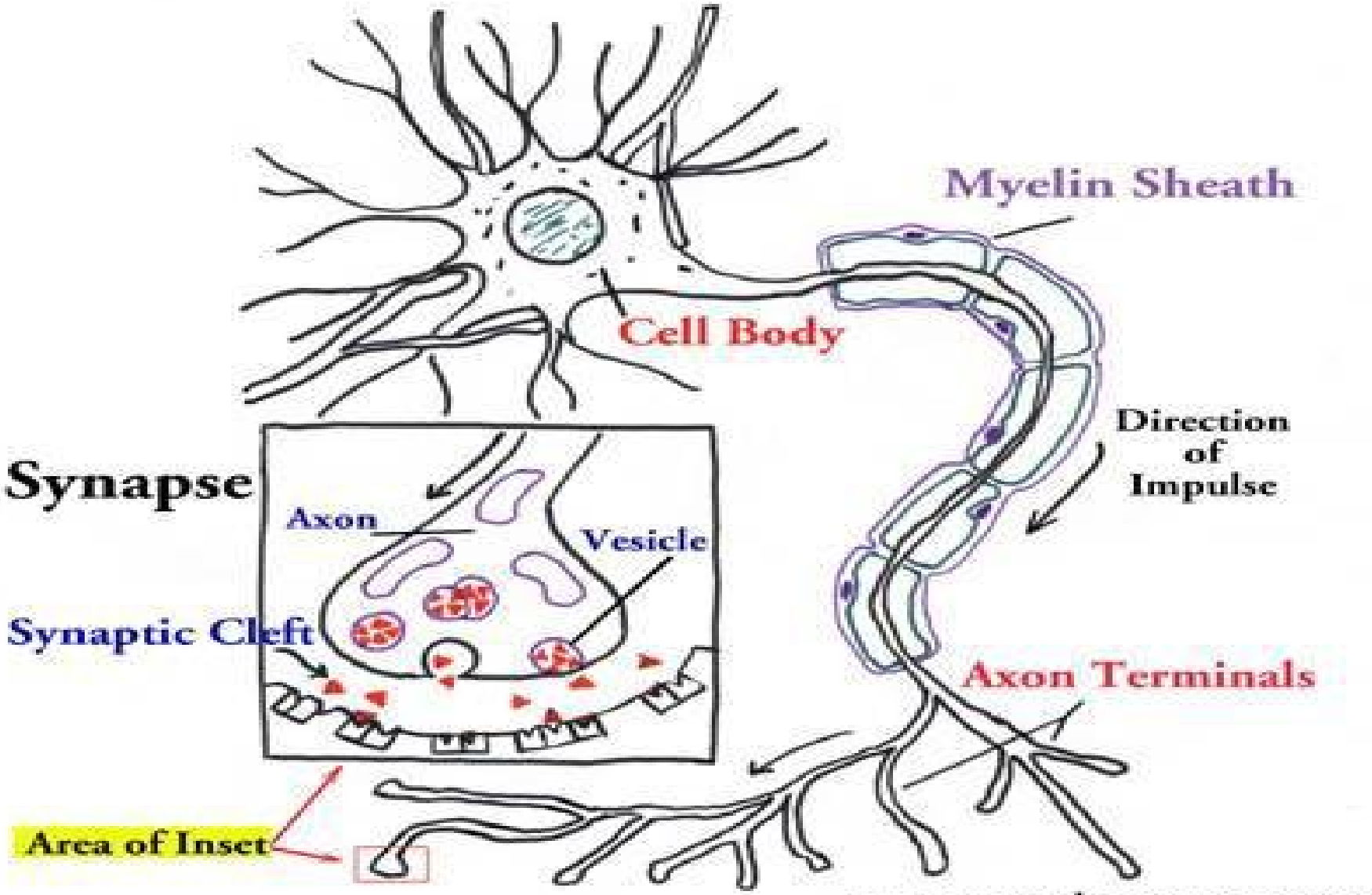
- Conducts nerve impulses away from the nerve cell to the axon terminals.
- Very small in diameter, but can be very long (e. g. the length of a leg).
- Each nerve cell has only one axon.
- If cut, distal part degenerates due a disruption of the cytoplasm extending from the cell body.

AXON TERMINALS

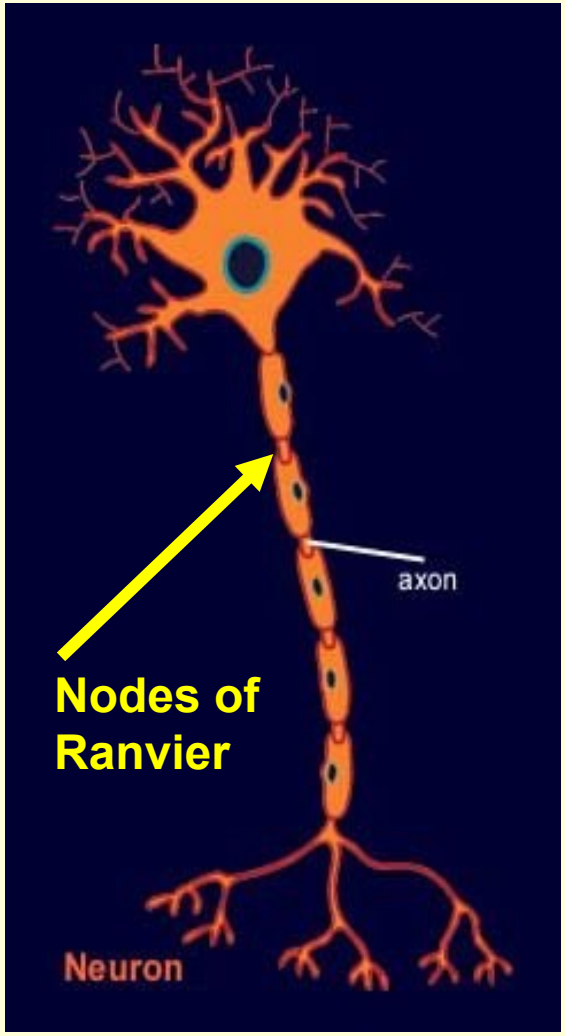
- **Bulbous distal endings of the many branches that extend from the end of an axon. Also be called synaptic knobs, boutons or even “end feet”.**
- **Serves as a secretory component that releases neurotransmitters in response to nerve impulses.**



NERVE AXON

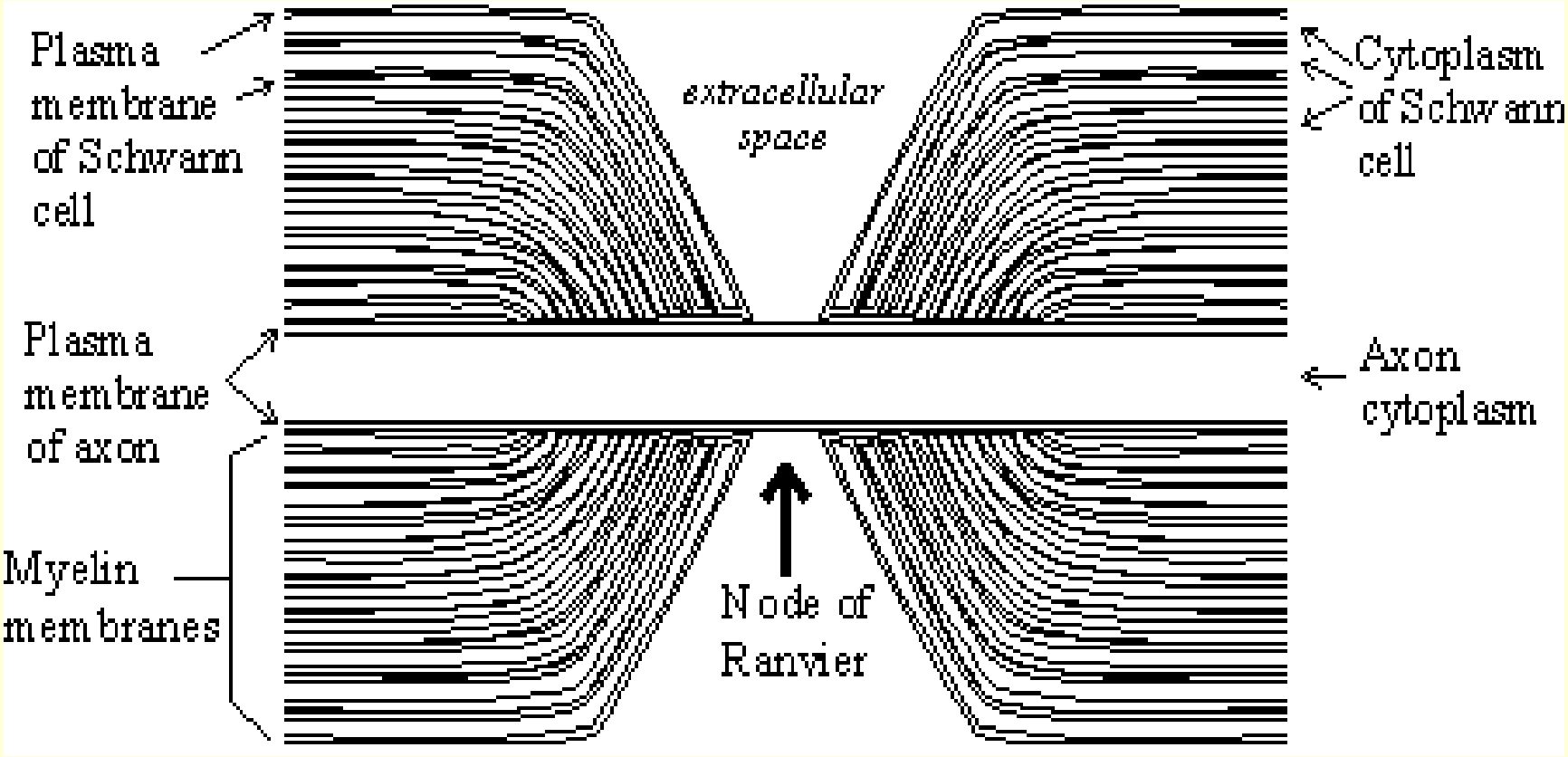


NODES OF RANVIER



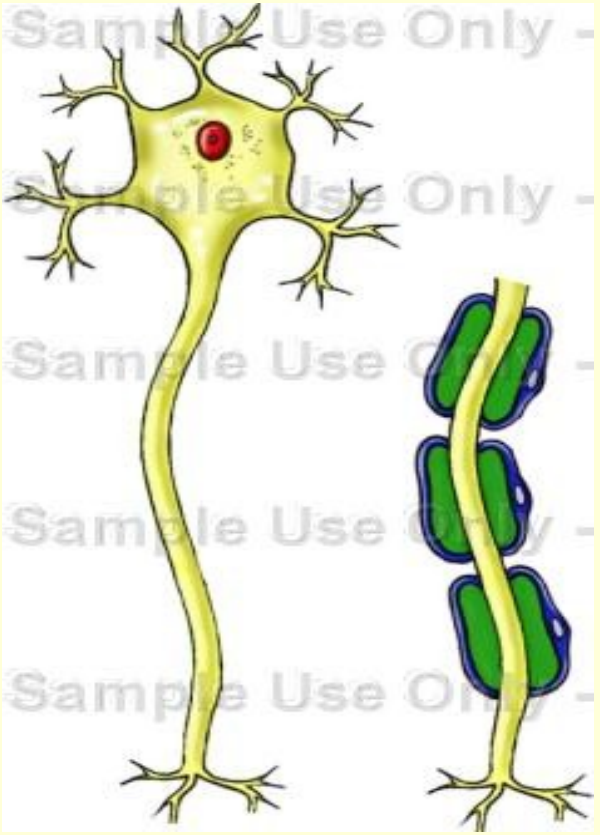
- Space or gap on a nerve cell process (axon or dendrite) between the myelin sheaths formed by Schwann Cells.
- The exposed cell membrane in the node facilitates the formation and transmission of nerve impulses.

NODE OF RANVIER



THE SCHWANN CELL

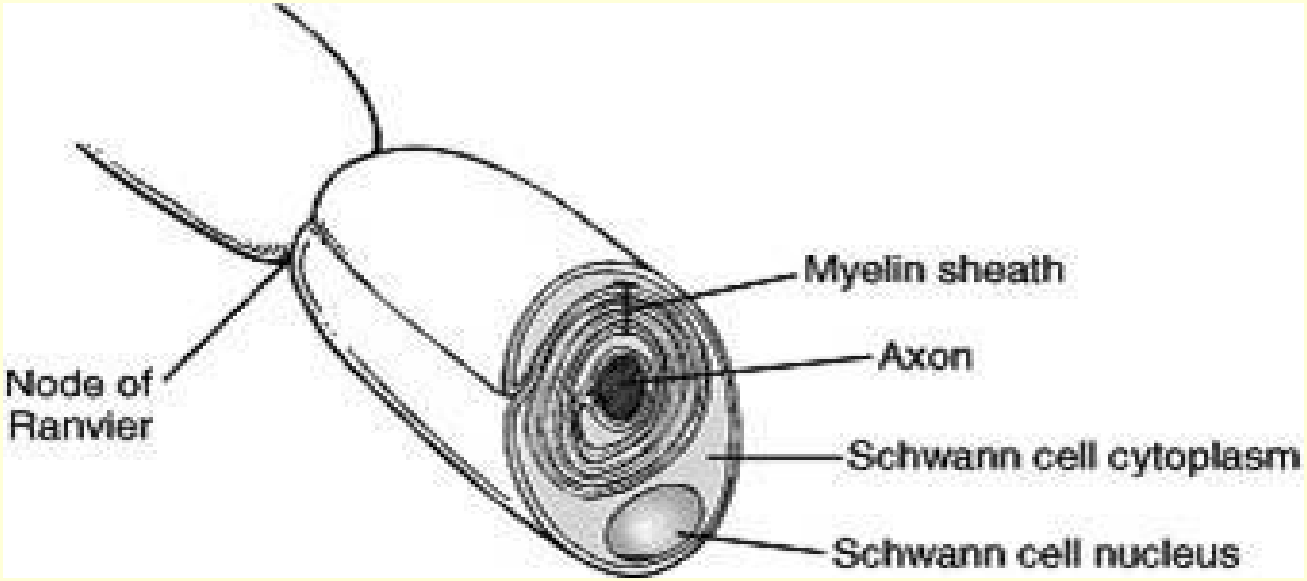
- Specialized cell that supports and maintains the fibers (axons and dendrites) of nerve cells in the peripheral nervous system. Contains myelin material.
- Assists in repair and regeneration of fibers.
- Wraps around a section of a nerve fiber and creates a protective myelin sheath.



Neuron with and without Schwann cells

THE MYELIN SHEATH

- **The Schwann cell wraps around a section of nerve cell fiber in “jellyroll” fashion resulting in a tight coil of concentric membranes called the myelin sheath.**
- **The whitish, fatty myelin material insulates and protects the nerve cell fiber.**

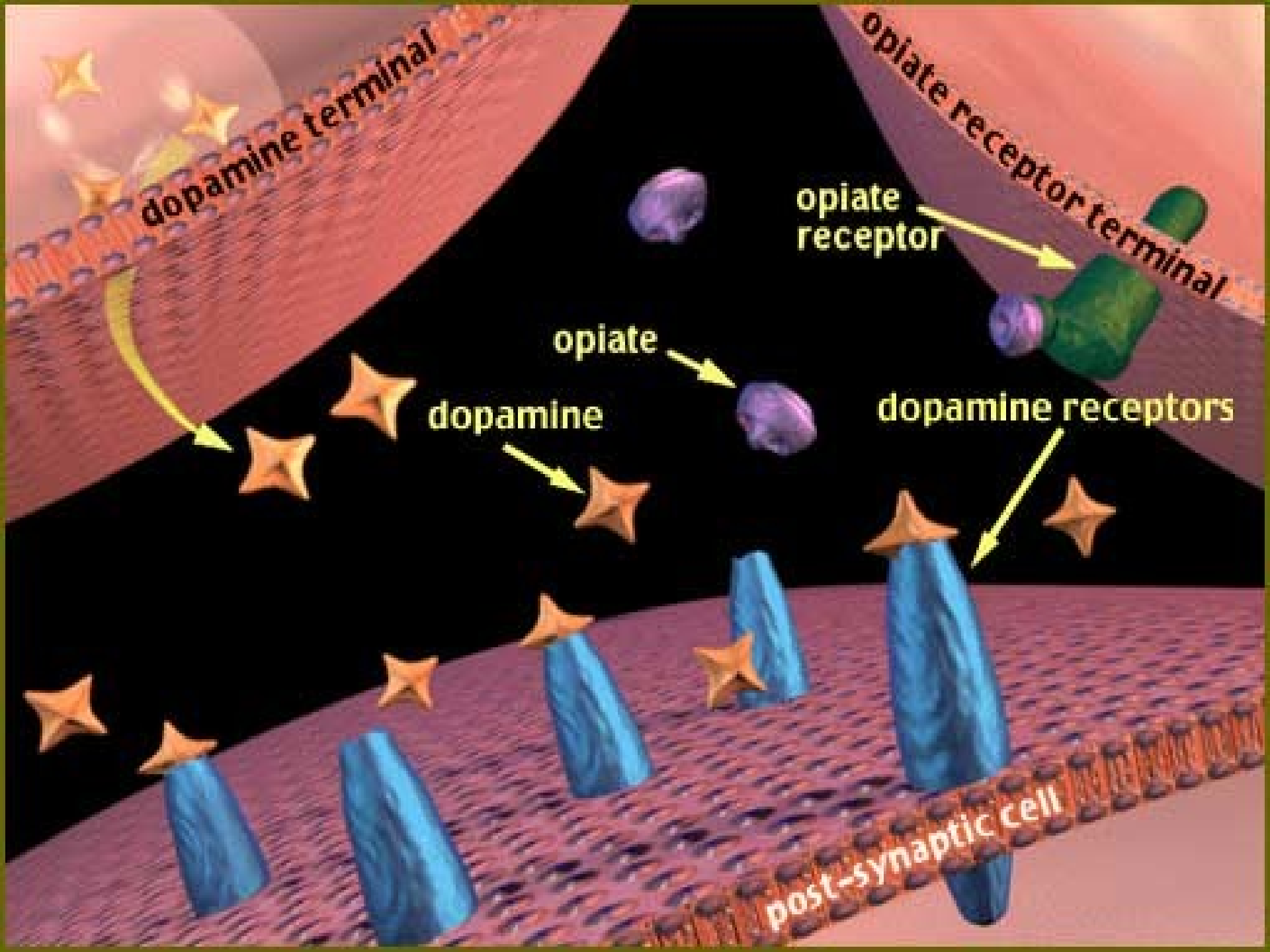


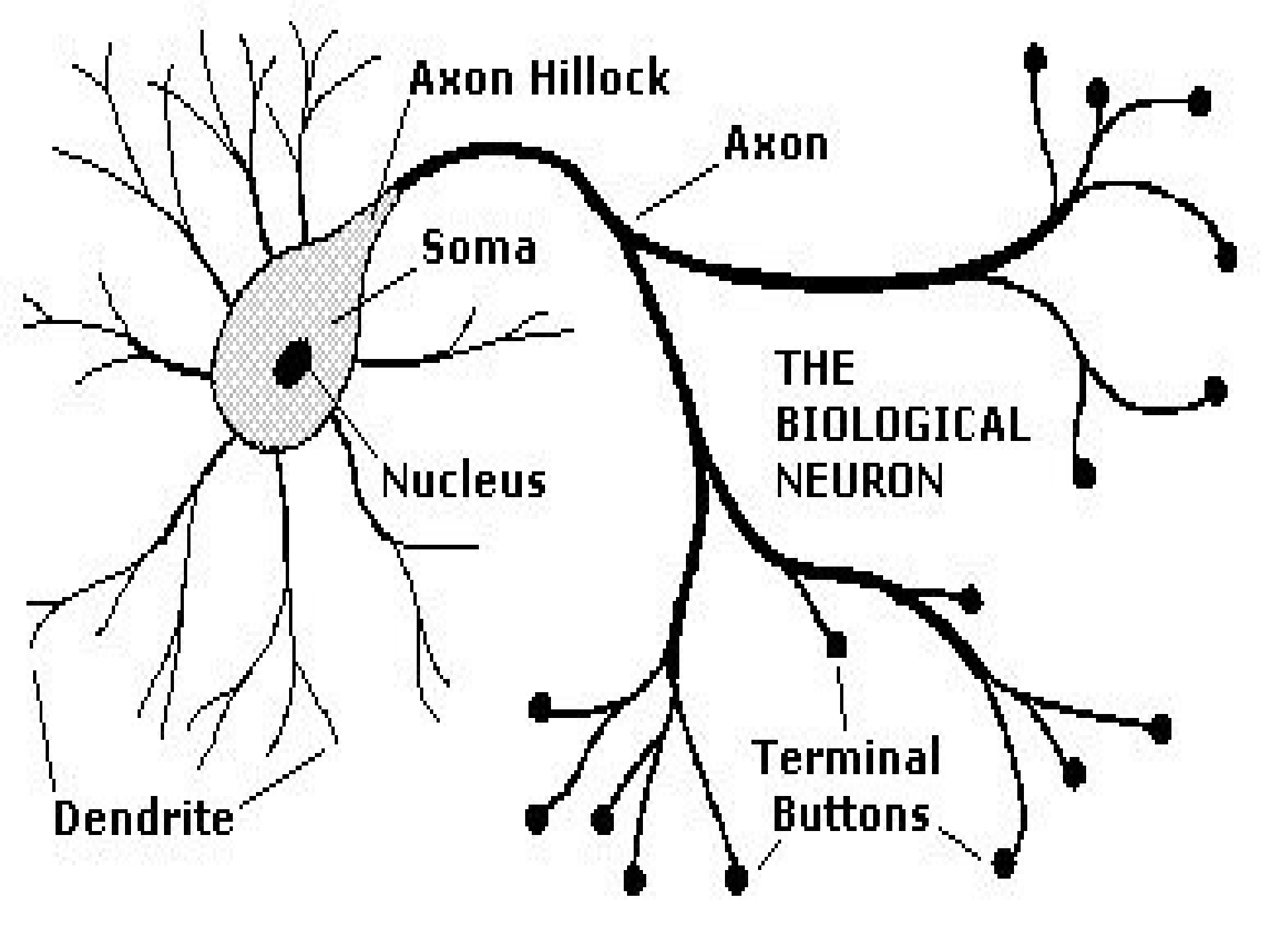
THE NEURILEMMA

- The most external portion of the plasma or cell membrane of the Schwann cell.
- This specialized membrane surrounds the myelin sheath.
- The neurilemma is sometimes called the sheath of the Schwann cell or a neuron “husk”.

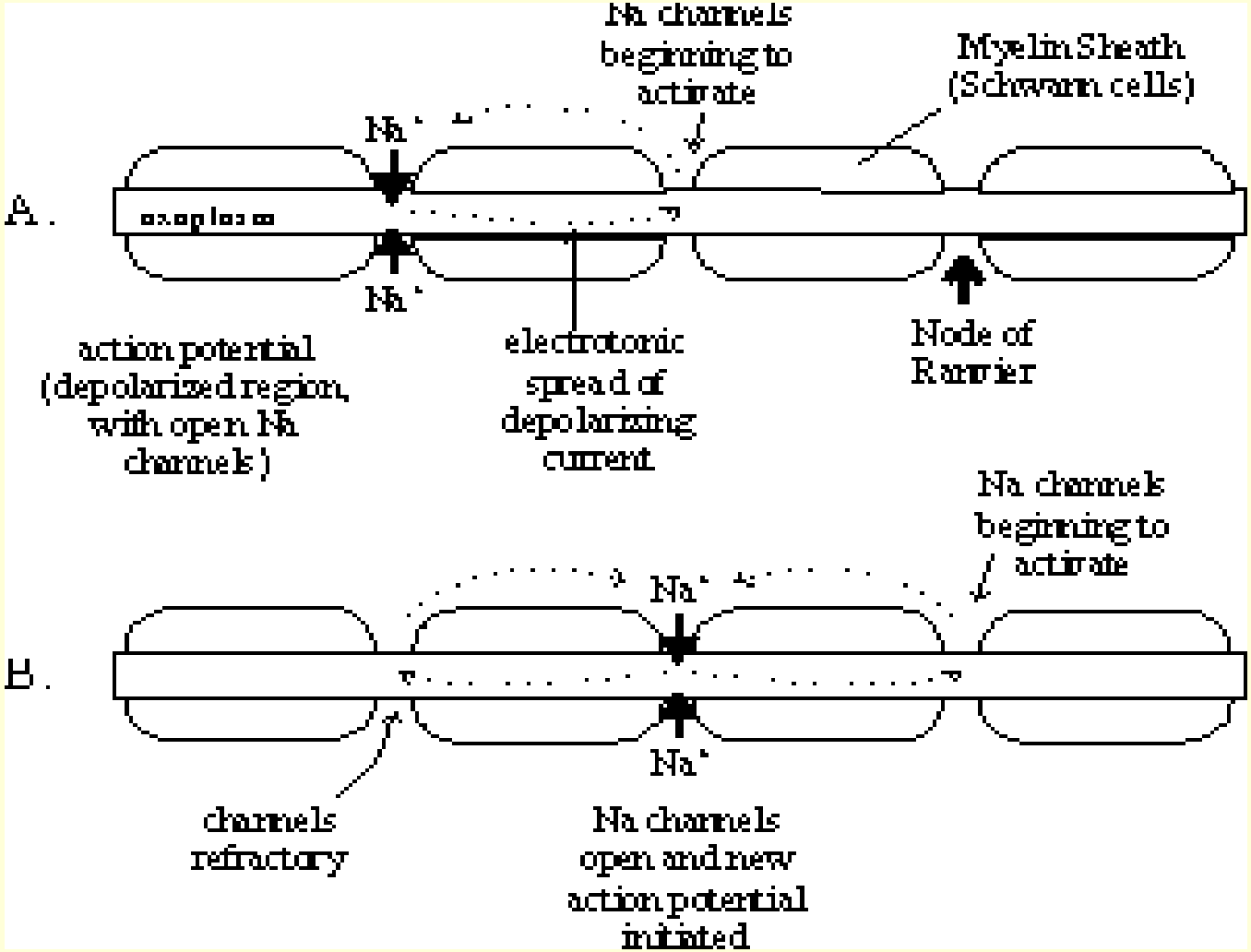
RECEPTOR

- A specialized part of a nerve cell or the nervous system - detects stimuli and produces voltage changes that can lead to nerve impulses.
- Tips of dendrites, the nerve cell body, and sections of the axon can have receptors.
- The voltage produced by receptors are called graded or generator potentials.

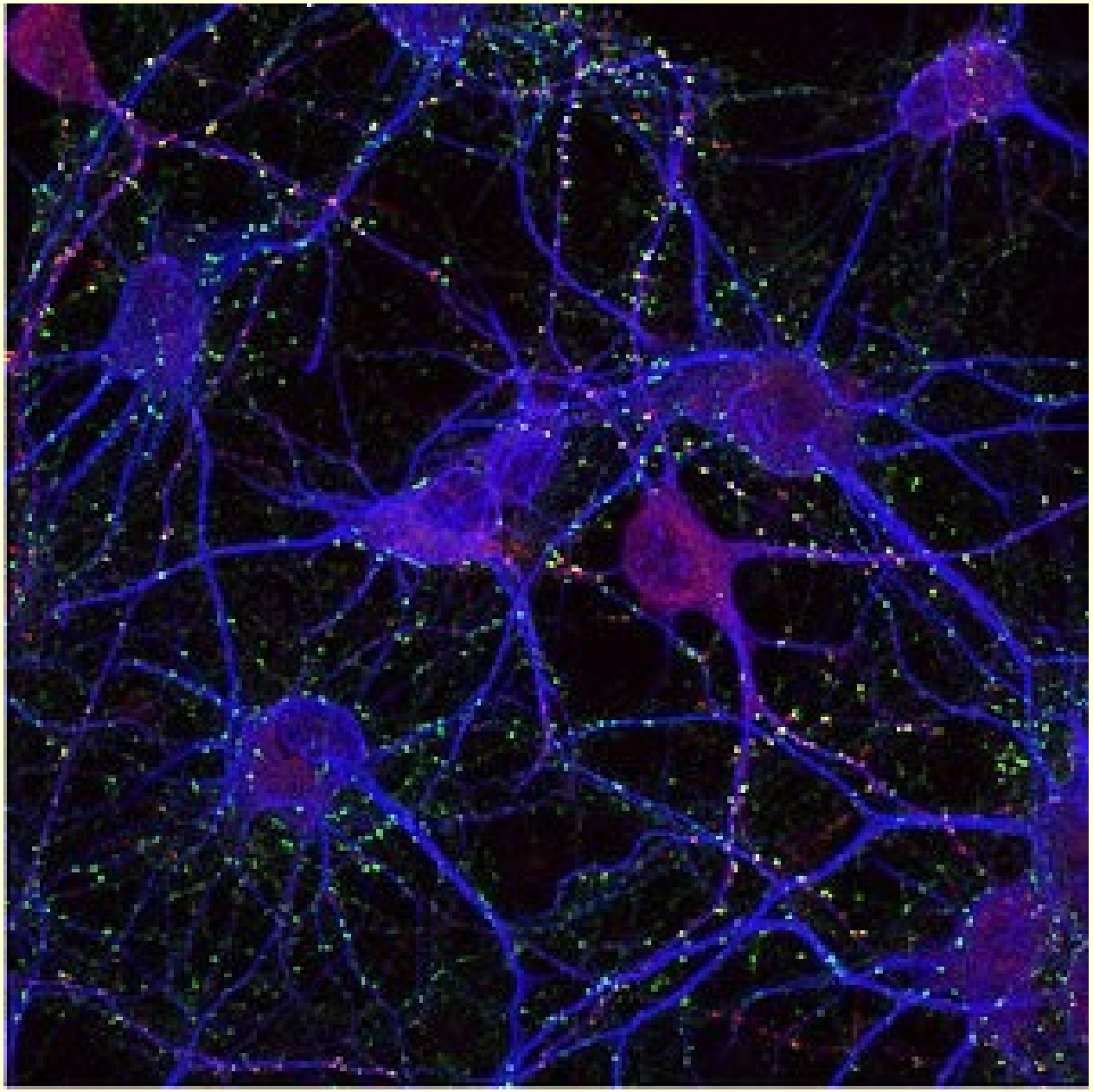

dopamine terminal
opiate receptor terminal
opiate receptor
opiate
dopamine
dopamine receptors
post-synaptic cell


Axon Hillock
Axon
Soma
THE
BIOLOGICAL
NEURON
Nucleus
Terminal
Buttons
Dendrite

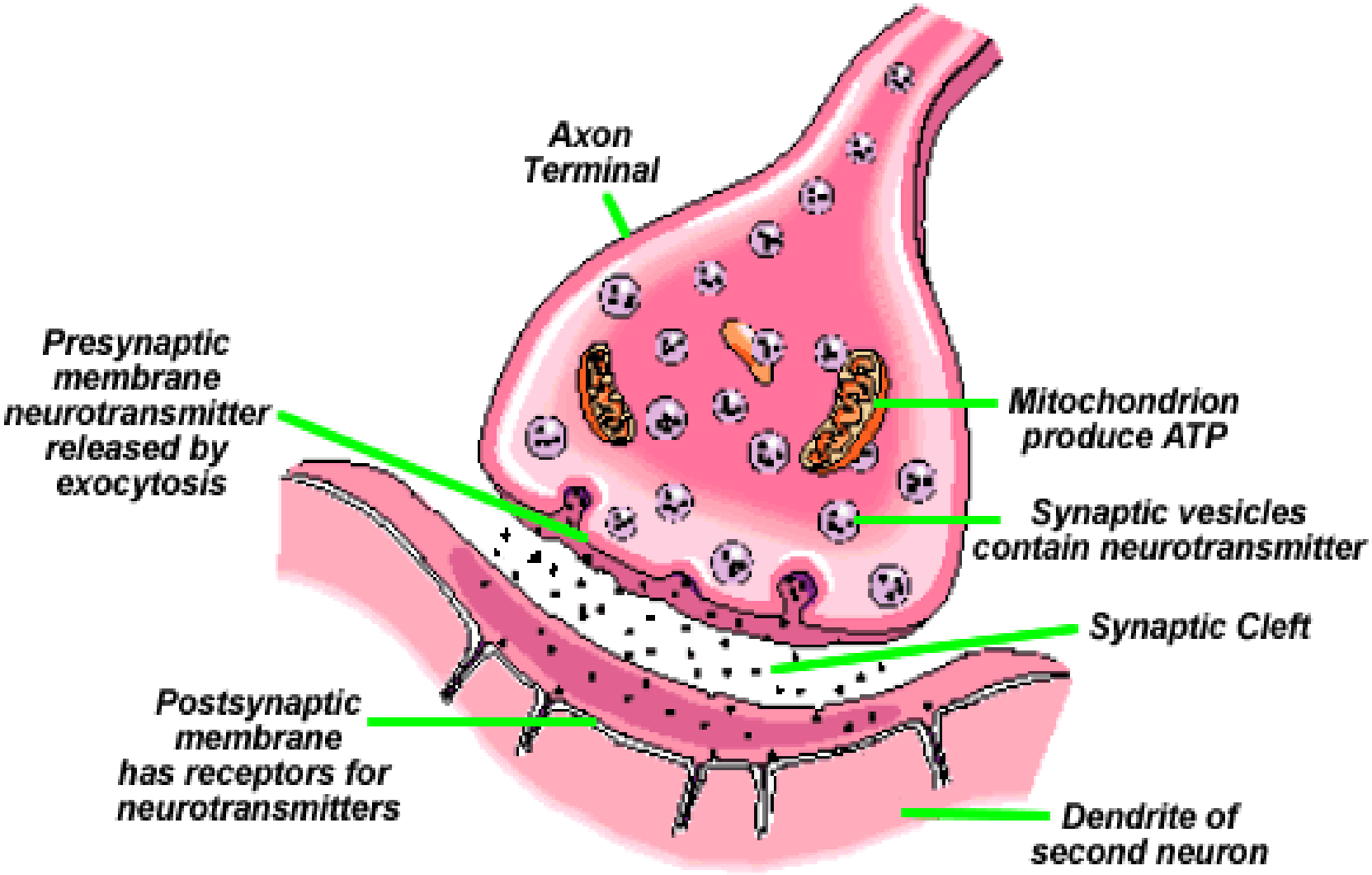
CONDUCTION OF INFORMATION ALONG NERVE FIBRES



SYNAPSE



A SYNAPSE


Axon Terminal
Presynaptic membrane neurotransmitter released by exocytosis
Mitochondrion produce ATP
Synaptic vesicles contain neurotransmitter
Synaptic Cleft
Postsynaptic membrane has receptors for neurotransmitters
Dendrite of second neuron

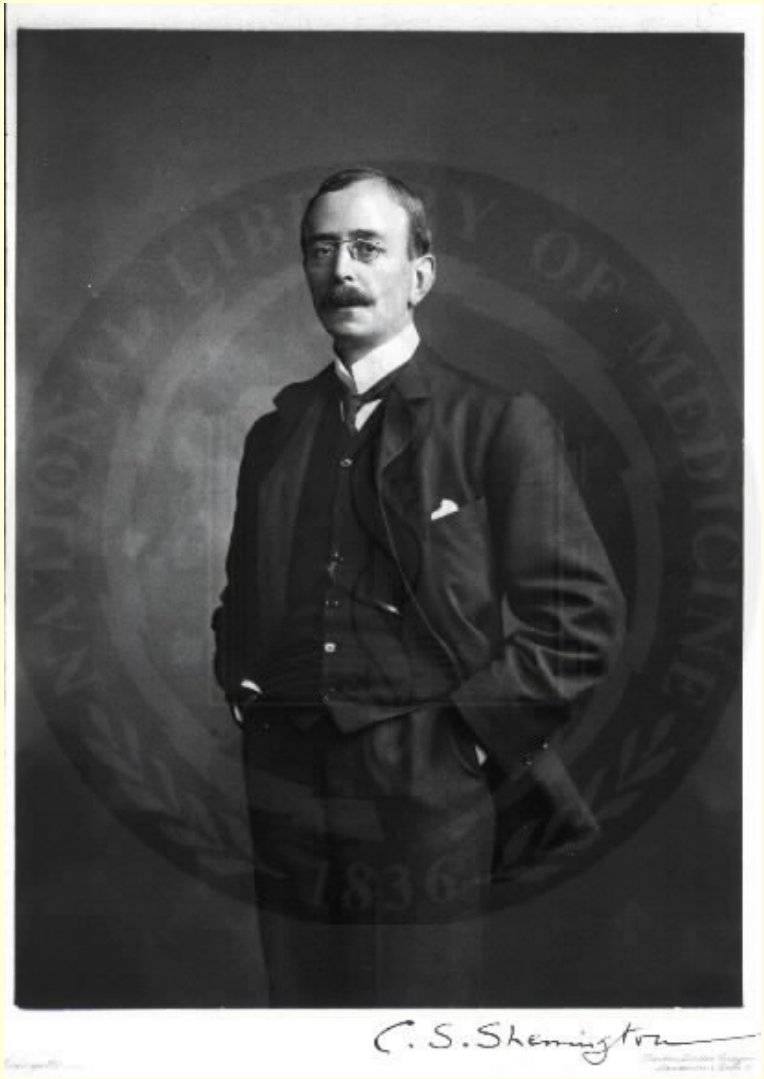
DEFINITION

SYNAPSE **- a specialized junction where transmission of information takes place between a nerve fiber and another nerve, muscle or gland cell.**

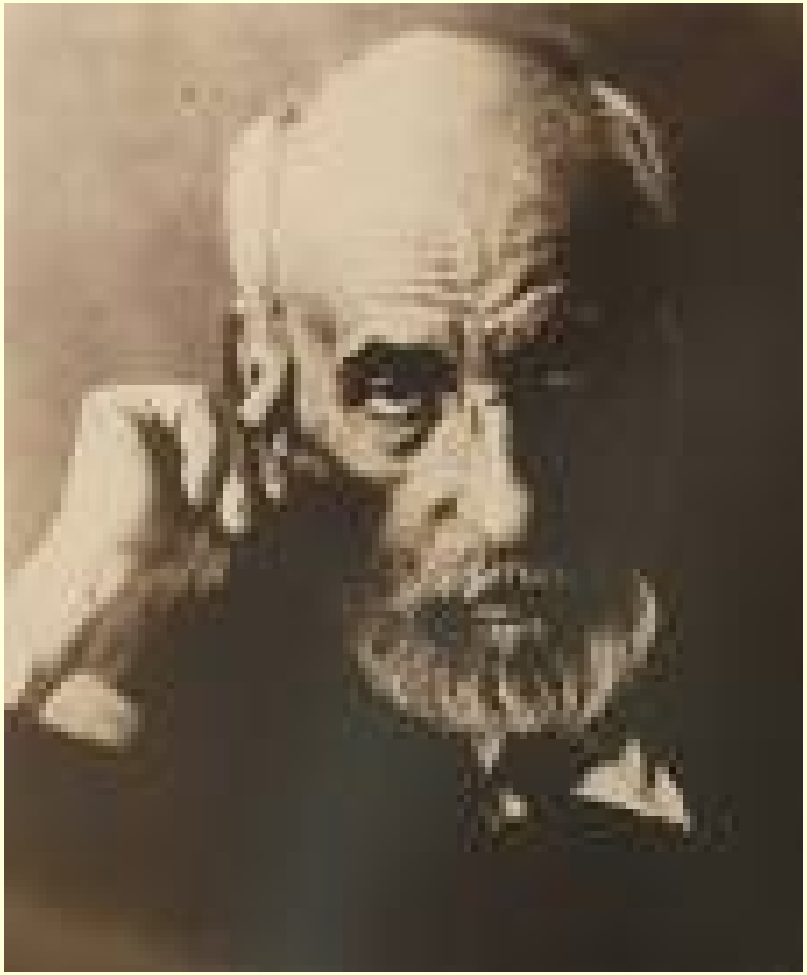
- **The term was introduced at the end of the nineteenth century by the British neurophysiologist Charles Sherrington.**
- **He argued, on the basis of his own observations of reflex responses and the studies of the great Spanish anatomist, Ramón y Cajal, that a special form of transmission takes place at the contact between one cell and the next.**

HISTORY

Charles Sherrington

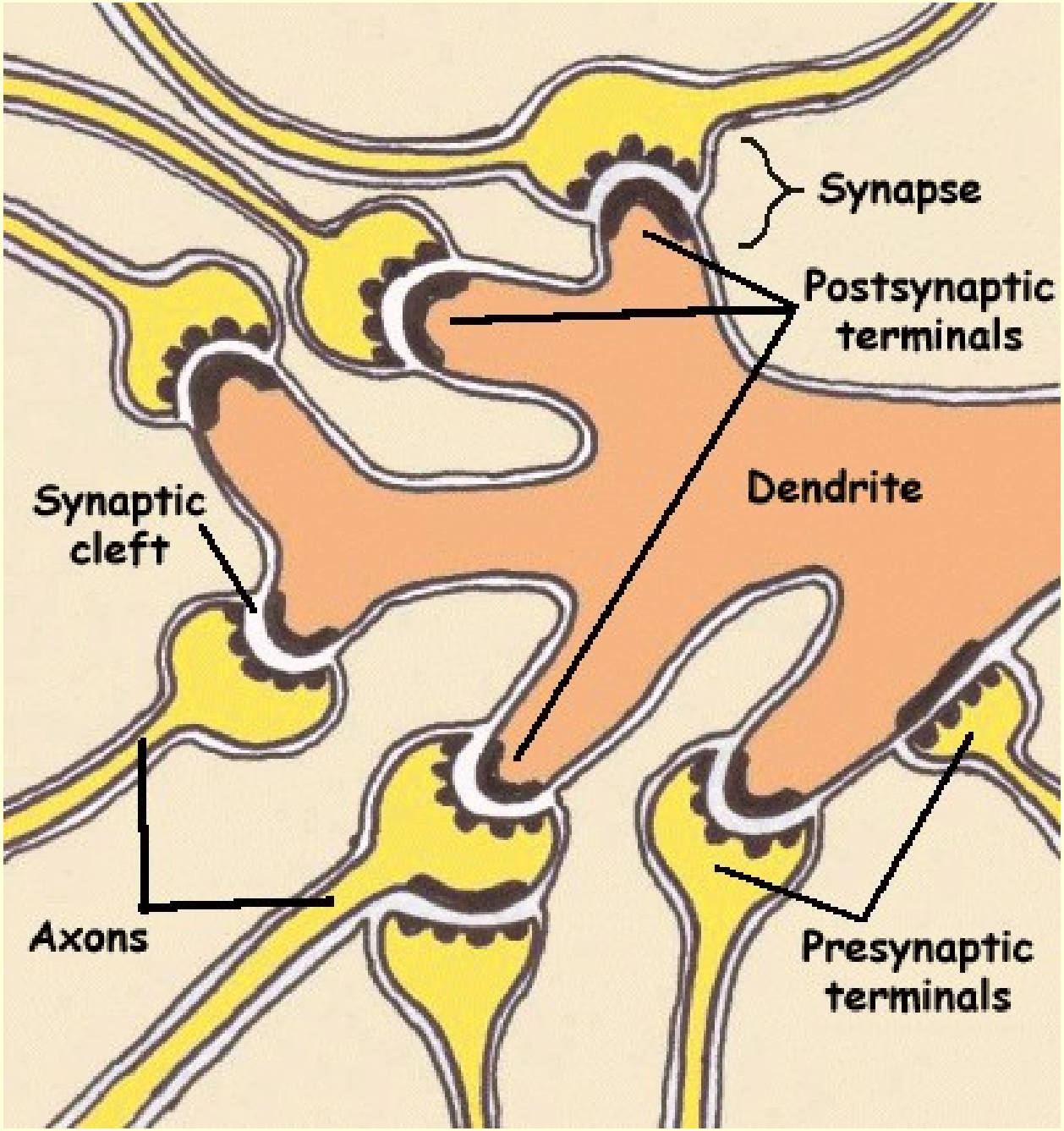


Ramón y Cajal



ELECTRICAL & CHEMICAL SYNAPSE

- **The information contained in action potentials in a nerve (*presynaptic cell*) are transferred to certain neighboring cells (*postsynaptic cells*) either by direct current flow at an *electrical synapse*, or indirectly by release of a chemical transmitter from vesicles in the ending of the presynaptic cell, at a *chemical synapse*.**


Synapse
Postsynaptic terminals
Dendrite
Synaptic cleft
Axons
Presynaptic terminals

NERVE-MUSCLE SYNAPSE

- The nerve-muscle synapse at the neuromuscular junction is a typical chemical synapse that uses acetylcholine (ACh) as the transmitter.
- Specialized receptors on the muscle bind ACh, causing ionic channels to open. Sodium and potassium ions flow through these channels, depolarizing the muscle cell, and causing an action potential to be generated across the muscle cell membrane.
- Transmitter action is terminated by rapid destruction of ACh by acetylcholinesterase (AChE).

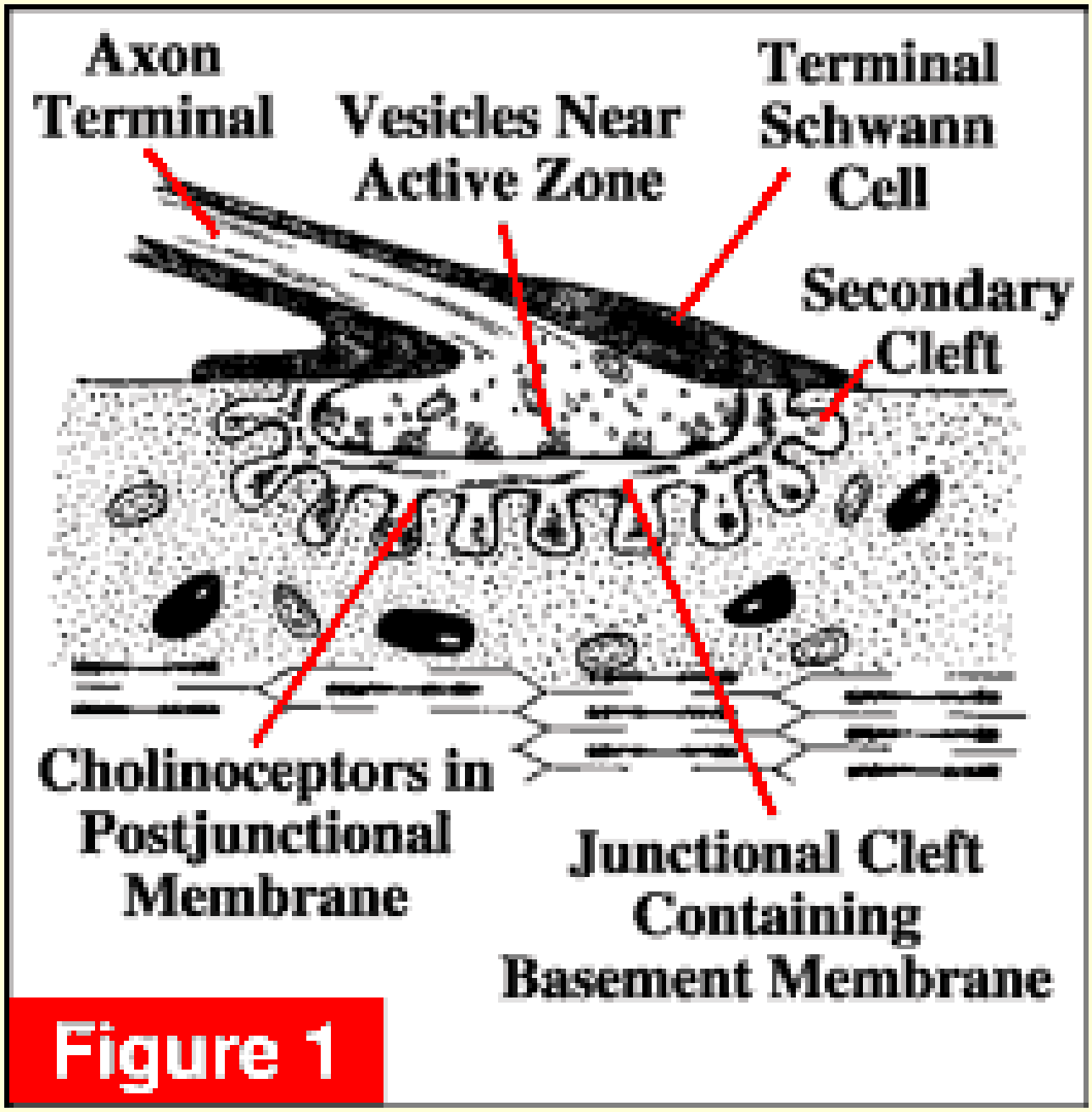
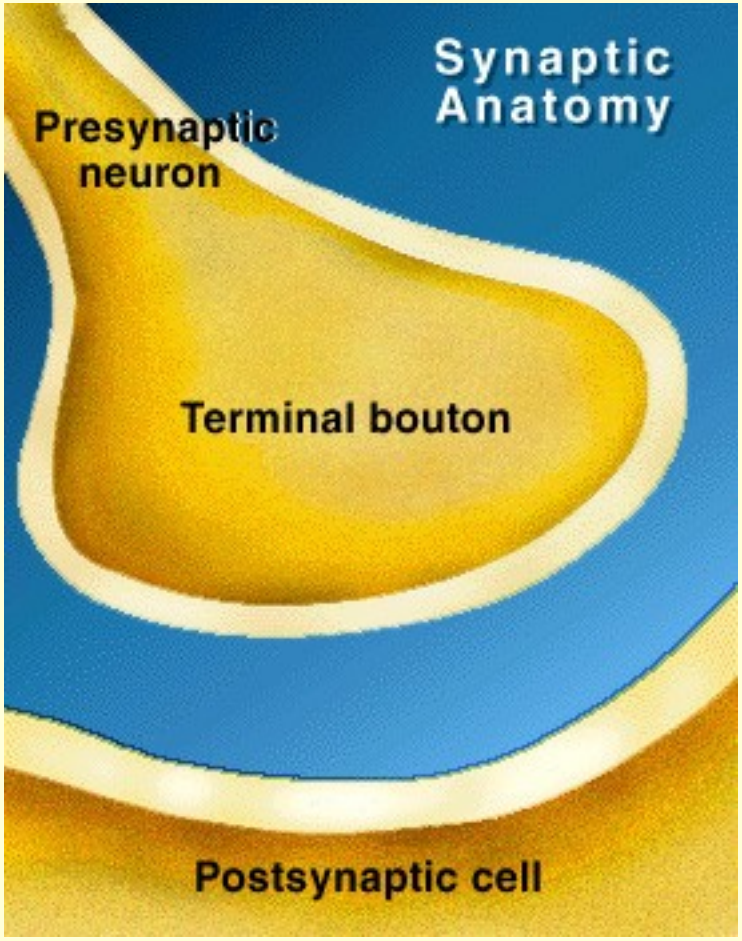
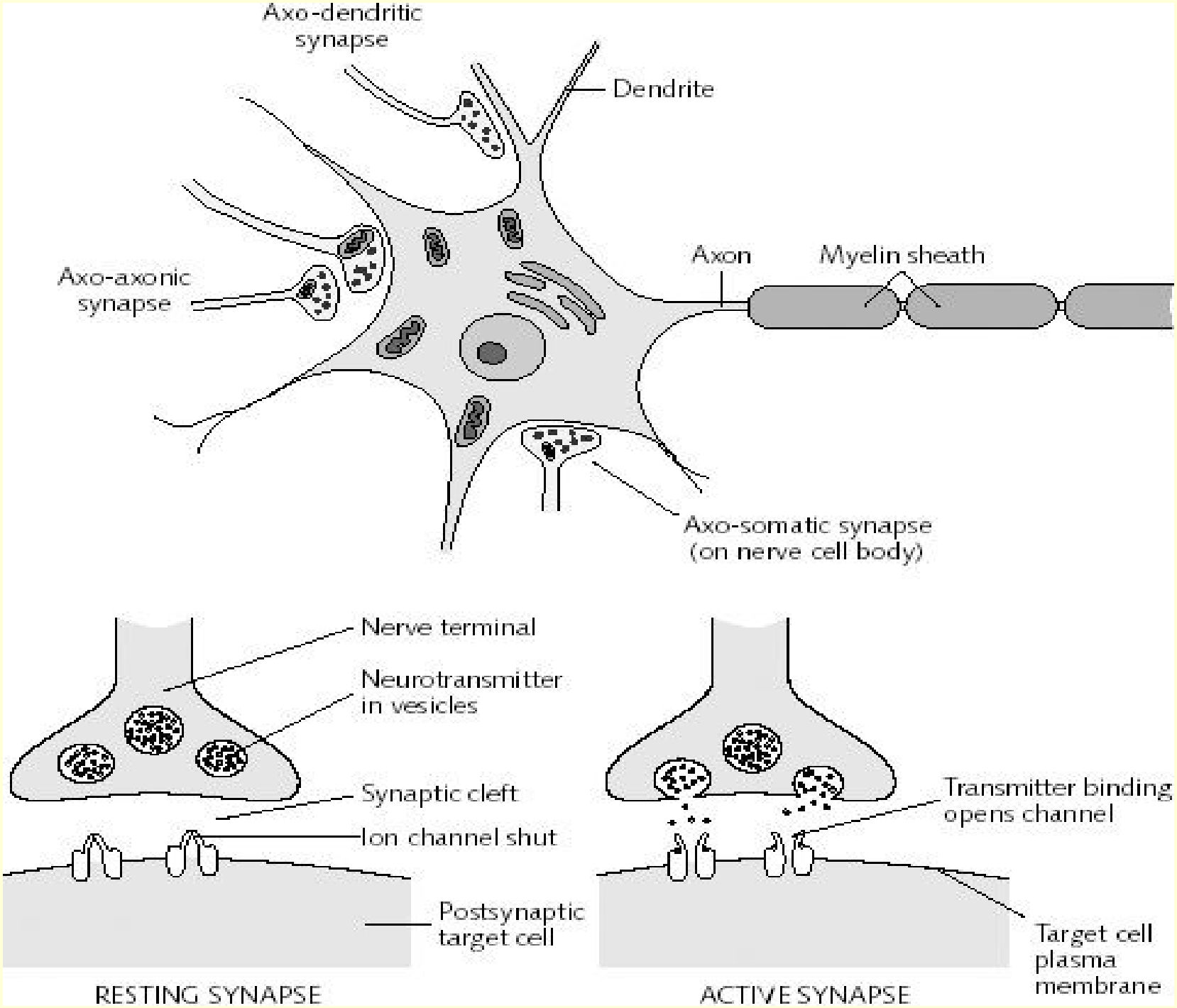

Axon Terminal
Vesicles Near Active Zone
Terminal Schwann Cell
Secondary Cleft
Cholinoceptors in Postjunctional Membrane
Junctional Cleft Containing Basement Membrane

Figure 1

SYNAPTIC ANATOMY



- The synapse is made up of a presynaptic neuron, which forms a terminal bouton, and a postsynaptic cell.
- The postsynaptic cell may be another nerve, a muscle cell, or a glandular cell.


Axo-dendritic synapse
Dendrite
Axo-axonic synapse
Axon
Myelin sheath
Axo-somatic synapse (on nerve cell body)
Nerve terminal
Neurotransmitter in vesicles
Synaptic cleft
Ion channel shut
Postsynaptic target cell
RESTING SYNAPSE
Transmitter binding opens channel
Target cell plasma membrane
ACTIVE SYNAPSE

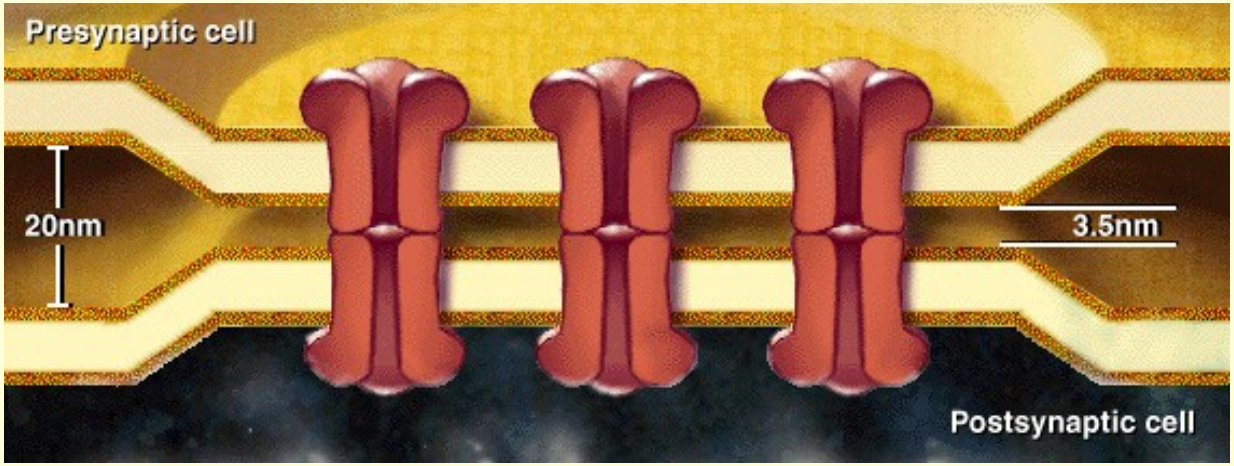
Electrical vs. Chemical Transmission

- There are two basic mechanisms by which electrical signals are transmitted between the pre- and postsynaptic cells at a synapse.
- At an electrical synapse, the current associated with the action potential of the presynaptic cell flows into the postsynaptic cell. This current flow leads to depolarization of the postsynaptic cell.

Electrical vs. Chemical Transmission

- At a chemical synapse, current associated with the action potential of the presynaptic cell does not flow into the postsynaptic cell.
- The presynaptic action potential causes the release of a chemical transmitter from the presynaptic cell.
- This chemical, in turn, causes channels to open in the membrane of the postsynaptic cell.
- Current flowing through these channels then leads to electrical changes across the membrane of the postsynaptic cell.

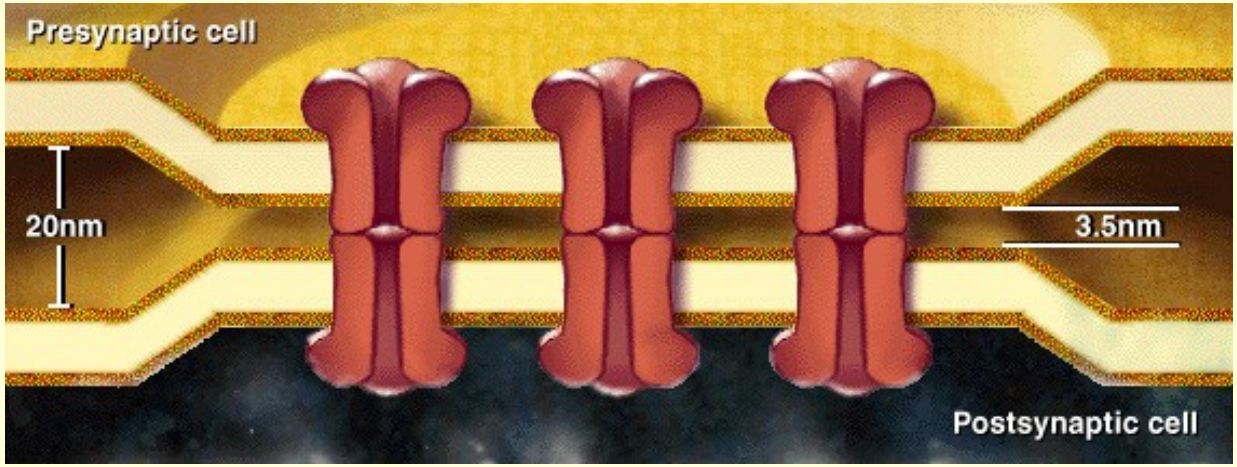
Electrical Transmission



An electrical synapse is widespread in invertebrates and submammalian vertebrates. There is only a small gap (3.5 nm) between the pre-synaptic and the postsynaptic cells. This gap is bridged by channels. This region of close apposition between the pre- and post-synaptic membranes is termed a *gap junction*.

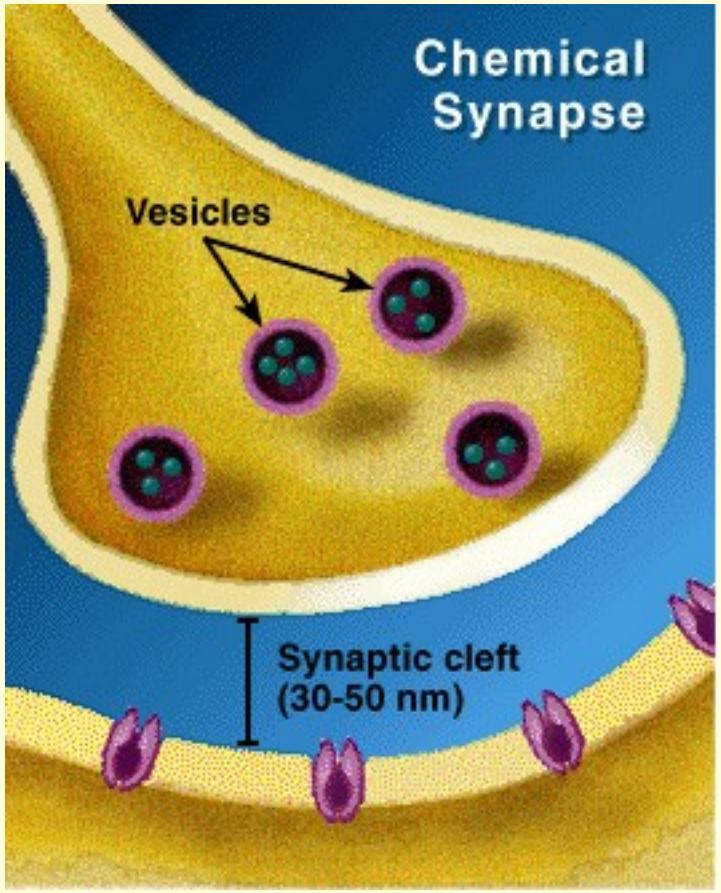
Electrical Transmission

The channels in the gap junctions form low resistance pathways between the two cells that permit current to flow so that depolarization of the presynaptic cell leads to depolarization of the postsynaptic cell. Likewise, depolarization of the postsynaptic cell may cause depolarization of the presynaptic cell. Thus information transmission can be bidirectional at an electrical synapse.



CHEMICAL TRANSMISSION

- This is the typical chemical synapse found in mammals.
- The presynaptic cell and the postsynaptic cell are separated by an obvious gap or synaptic cleft (about 30 to 50 nanometers wide).
- The terminal bouton of the presynaptic nerve also contains numerous small organelles called vesicles.
- Chemical transmitter molecules are packaged within these vesicles.



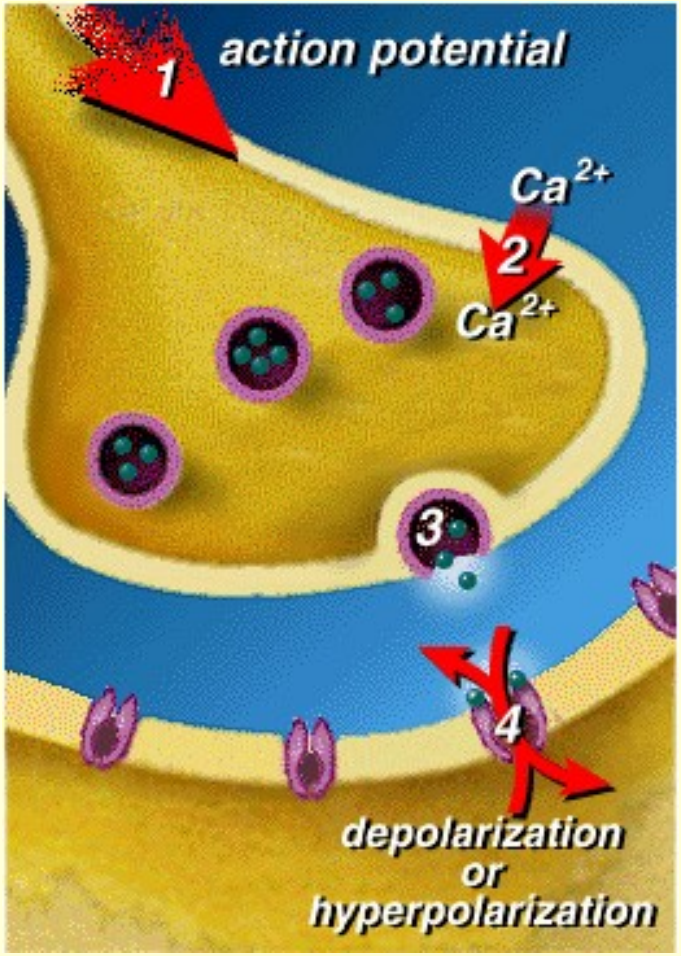
Steps in Transmission at a Chemical Synapse

Step 1

The action potential in the presynaptic nerve causes the terminal bouton to depolarize.

Step 2

This depolarization opens voltage-gated calcium channels in the terminal. Calcium (Ca2+) flows down its electrochemical gradient and enters the presynaptic terminal.



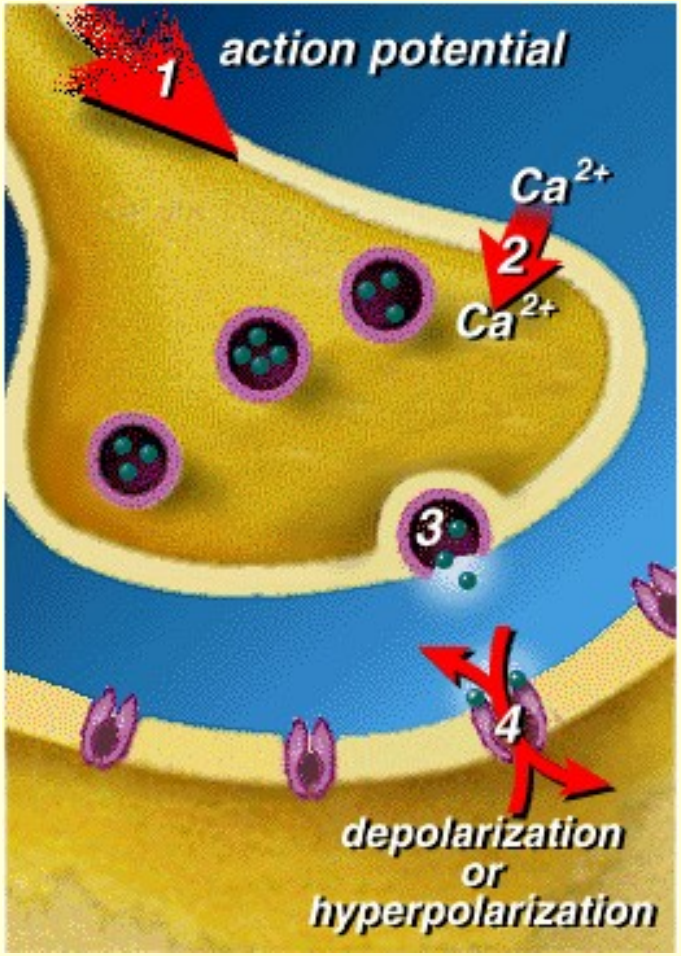
Steps in Transmission at a Chemical Synapse

Step 3

The rise in intracellular calcium causes the membranes of the vesicles to fuse with the membrane of the terminal bouton in the region of the synaptic cleft. The contents of each vesicle (transmitter molecules) are released by exocytosis into the synaptic cleft.

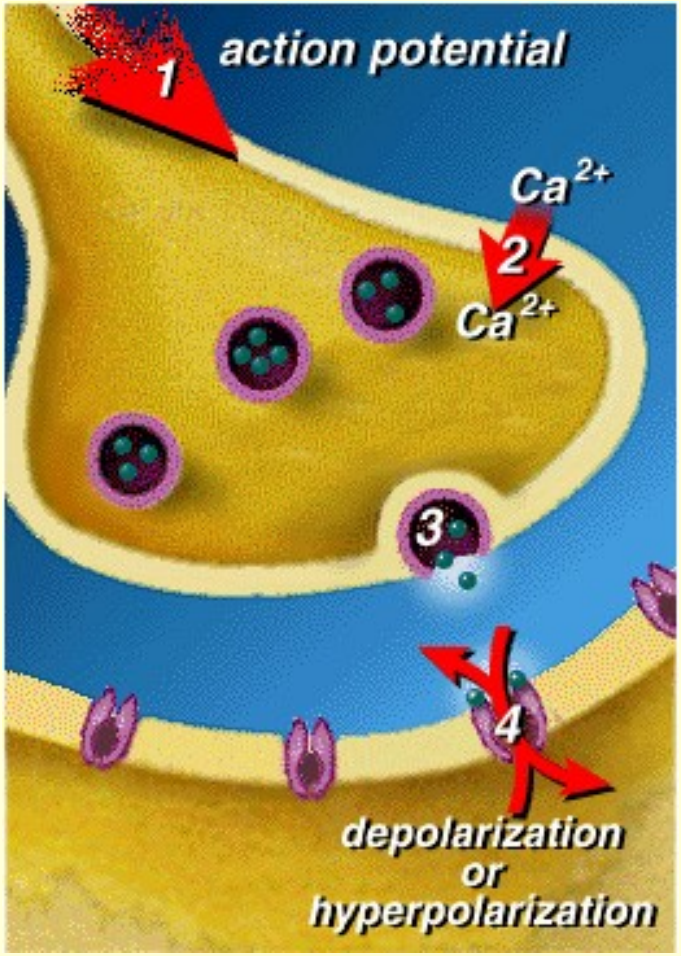
Step 4

Transmitter molecules diffuse across the synaptic cleft and bind to receptors on the postsynaptic membrane.



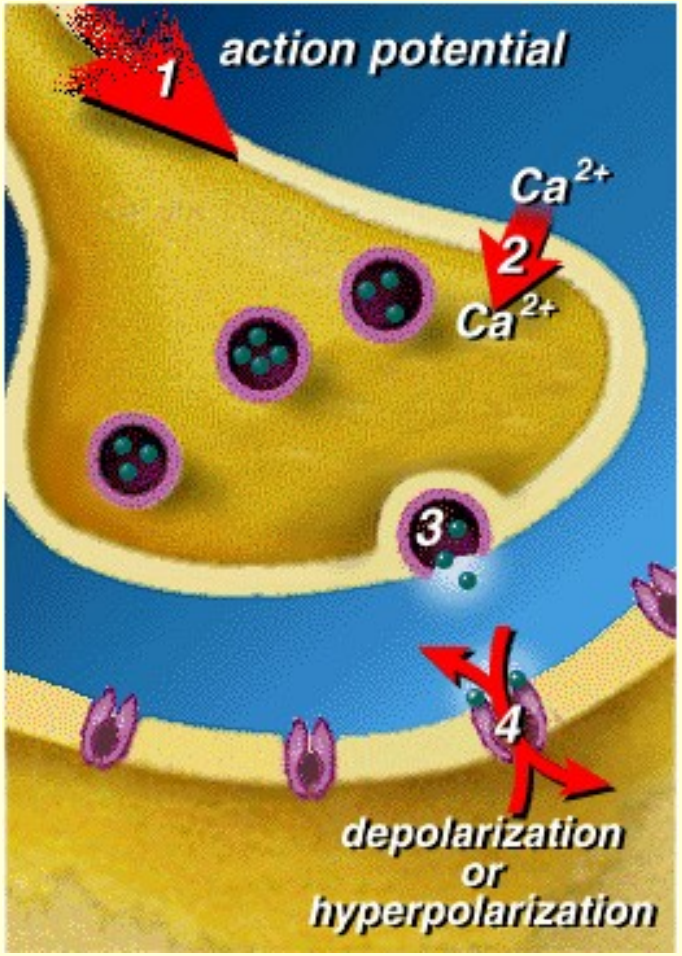
Transmission at a Chemical Synapse

- At some synapses, these receptors are actually a part of an ion channel molecule in the postsynaptic membrane.
- In these directly gated channels, binding of transmitter to the receptor causes the ion channels to open through molecular rearrangement.
- Ionic currents then flow through the channel.

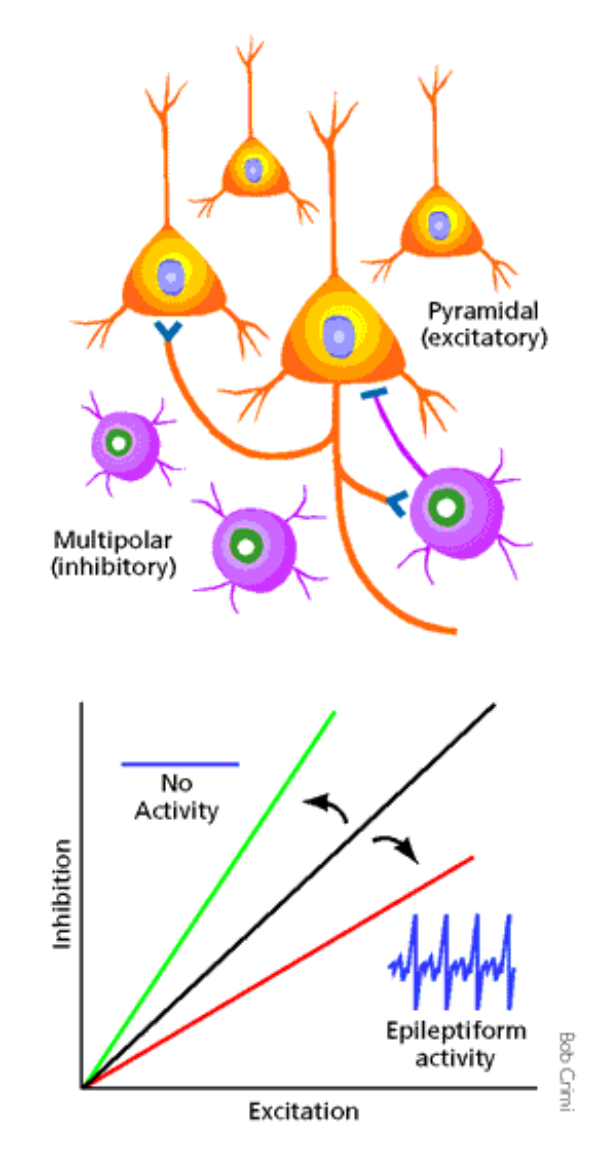


Transmission at a Chemical Synapse

- At some synapses the receptor gates the channels indirectly.
- Here binding of the transmitter causes the production of a second messenger (cyclic-AMP).
- The second messenger then causes gating of a separate ion channel.

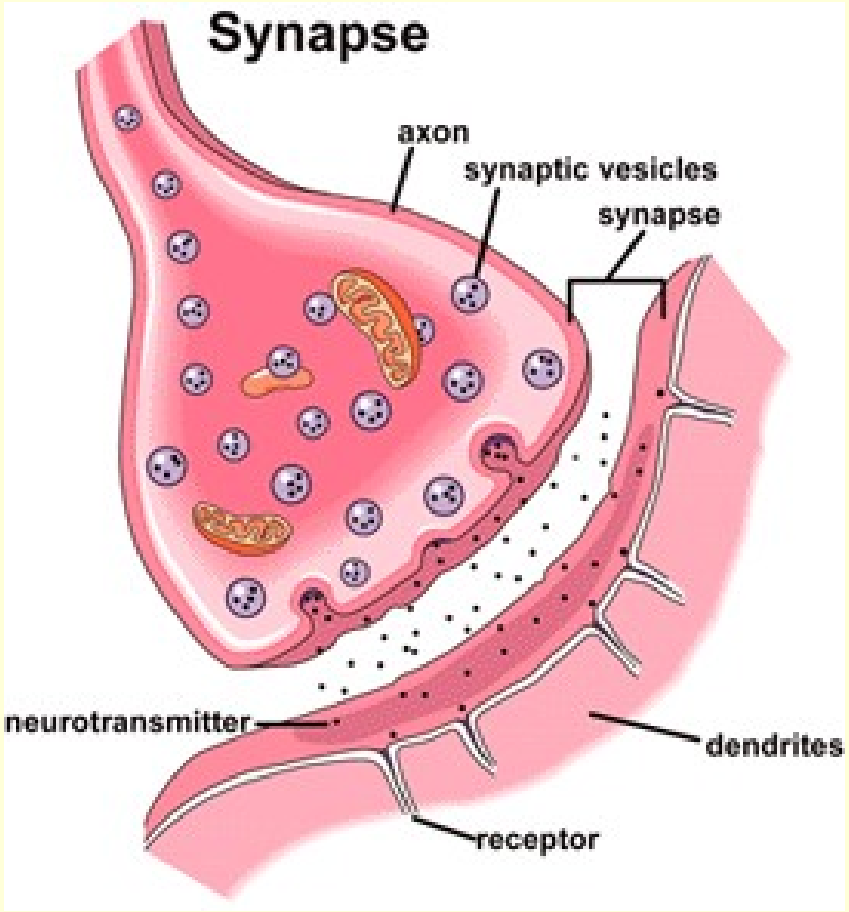


EXCITATORY & INHIBITORY SYNAPSES



- At an *excitatory synapse*, ionic currents flowing through the ion channels cause a net depolarization of the postsynaptic cell.
- At an *inhibitory synapse*, ionic currents flowing through the ion channels cause a net hyperpolarization of the postsynaptic cell.

UNIDIRECTIONAL TRANSMISSION



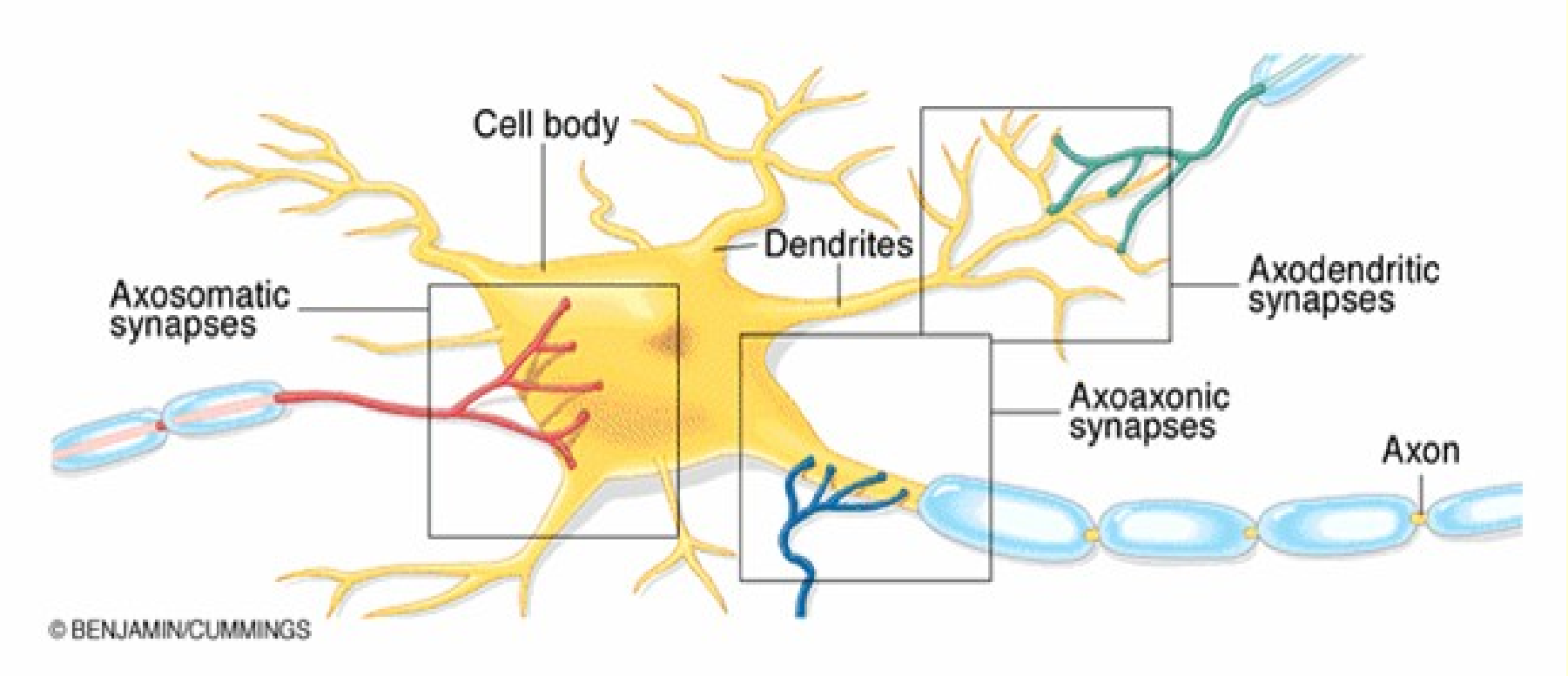
- **Vesicles containing transmitter are only found in the presynaptic cell and receptors for the transmitter are only found on the postsynaptic cell.**
- **This ensures information transmission only occurs from presynaptic cell to postsynaptic cell, i.e., transmission is exclusively - *unidirectional*.**

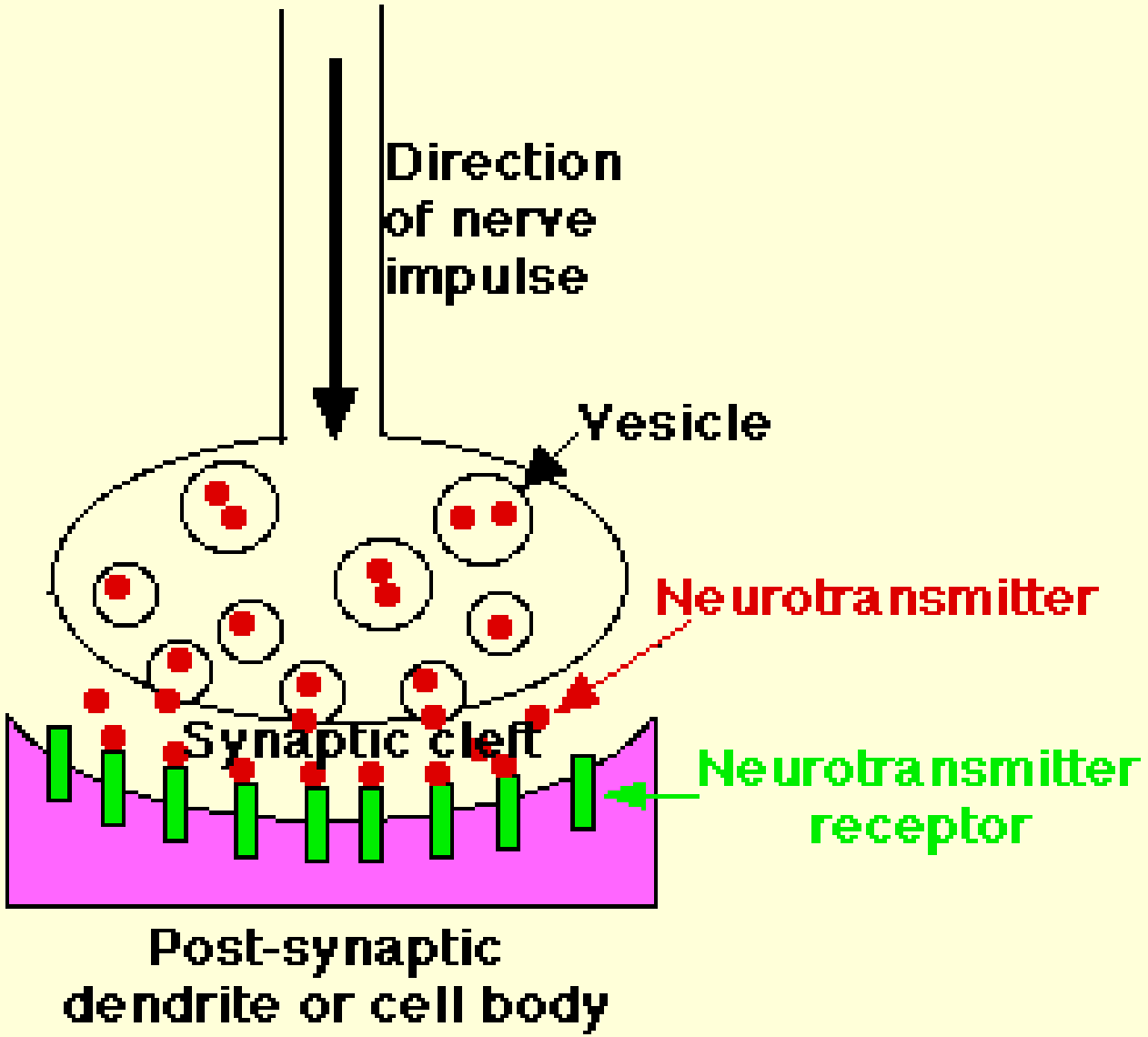
PROPERTIES OF SINGLE CHEMICAL AND ELECTRICAL SYNAPSES

Property	Chemical synapses	Electrical synapses
1. Rectification (correction)	Always	Sometimes, usually not
2. Amplification (enhancement)	Yes	No
3. Delay	Yes	No
4. Inhibition	Yes	Yes
5. Summation	Yes	Yes, but over shorter time
6. Influenced by membrane potential	Yes	No

THE SYNAPSE TYPES

The synapse operates as an on/off switch and as a filter for information flow.

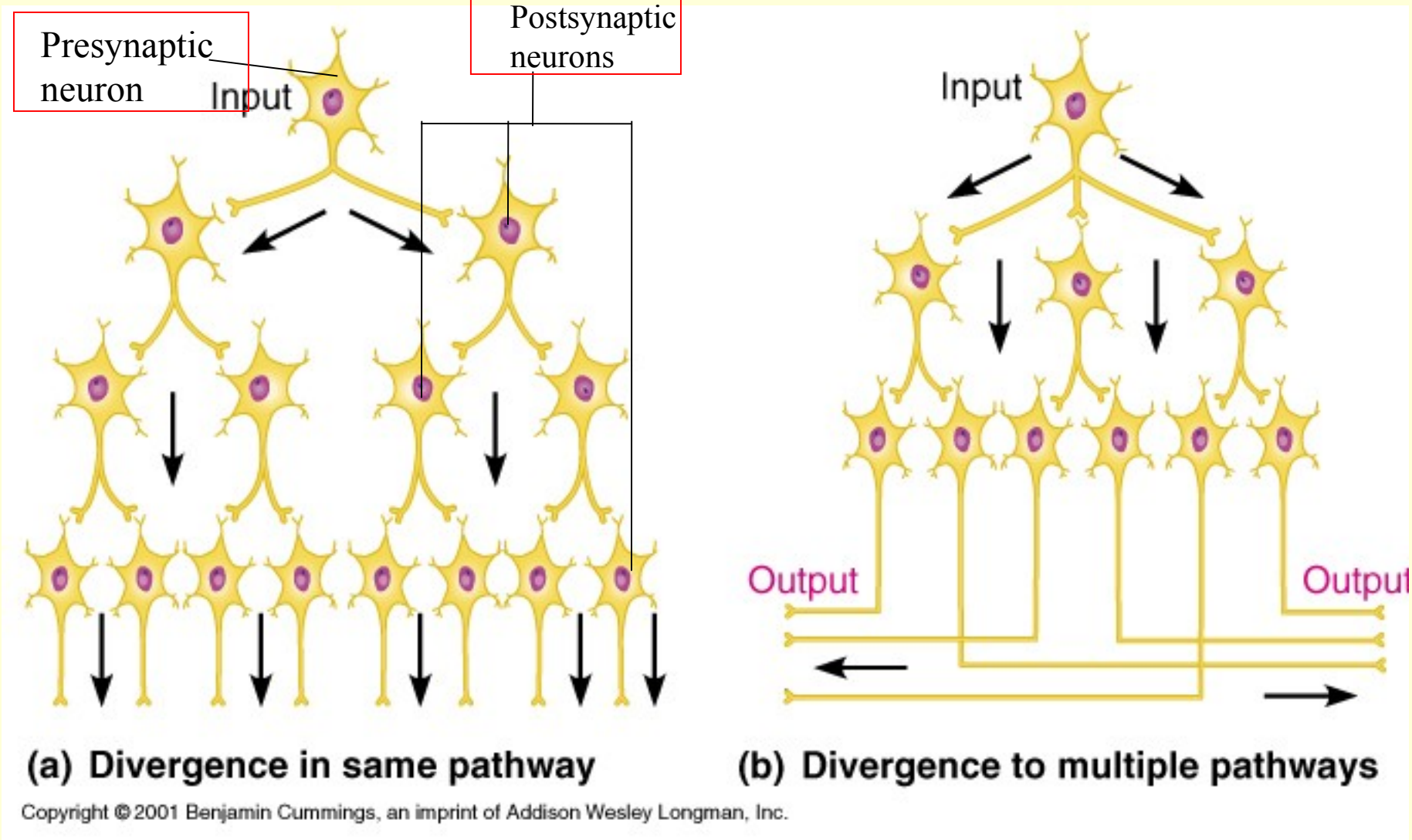



Direction
of nerve
impulse
Vesicle
Neurotransmitter
Synaptic cleft
Neurotransmitter
receptor
Post-synaptic
dendrite or cell body

DIVERGENT SYNAPSE

- A junction that occurs between a presynaptic neuron and two or more postsynaptic neurons (ratio of pre to post is less than one).
- The stimulation of the postsynaptic neurons depends on the rapid accumulation of neurotransmitter by the presynaptic neuron over time (e.g. temporal summation).

DIVERGENT SYNAPSE



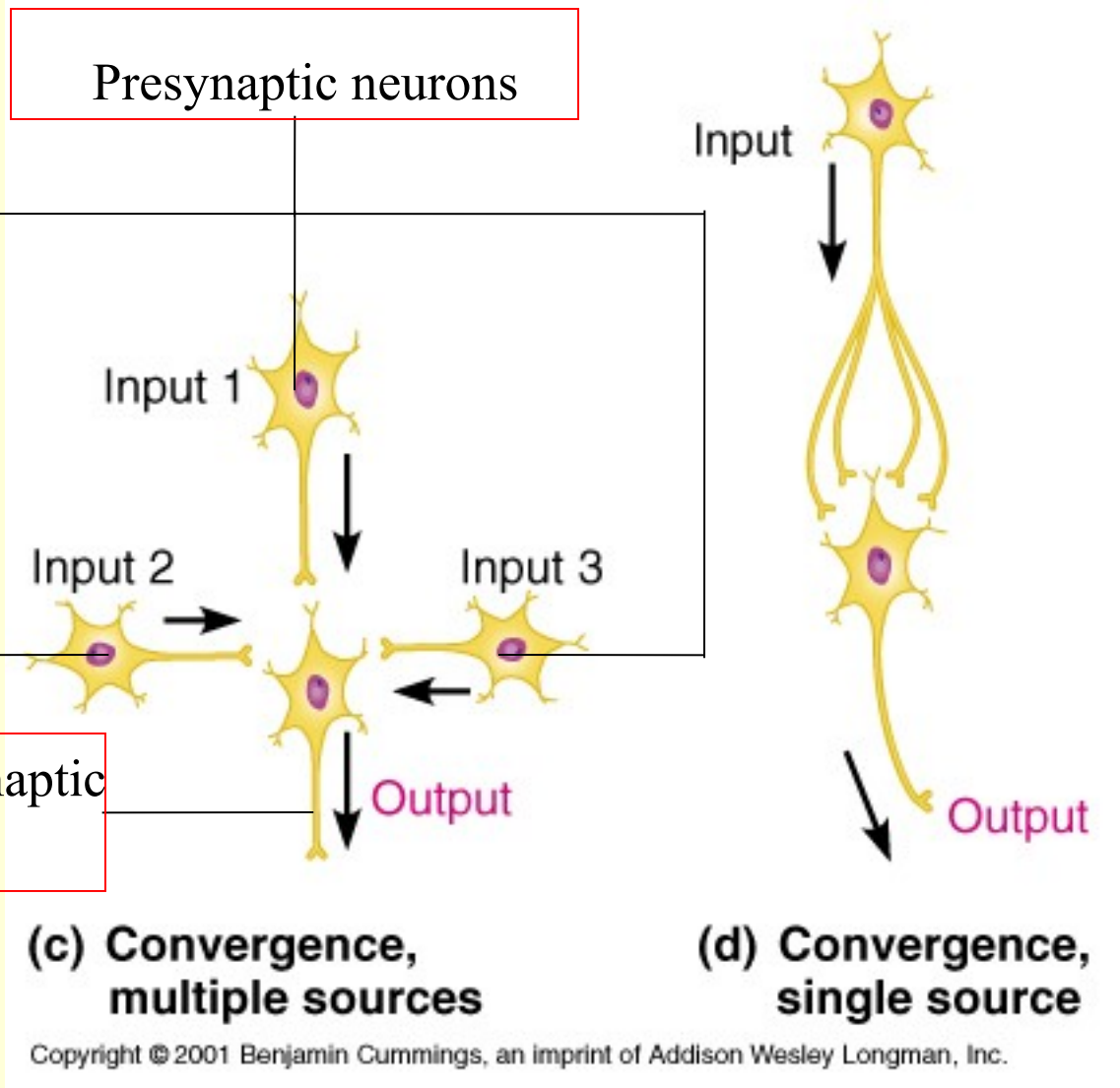
TEMPORAL SUMMATION

- The accumulation of neurotransmitters in a synapse due to the rapid activity of a presynaptic neuron over a given time period.
- Occurs in a divergent synapse.
- Is a time (temporal) dependent process.

CONVERGENT SYNAPSE

- A junction between two or more presynaptic neurons and a postsynaptic neuron (the ratio of pre to post is greater than one).
- The stimulation of the postsynaptic neuron depends on the accumulation of neurotransmitter from the presynaptic neurons (e. g. spatial summation).

CONVERGENT SYNAPSE



SPATIAL SUMMATION

- **The accumulation of neurotransmitter in the synapse due the combined activity of several presynaptic neurons entering the area (space) of a convergent synapse.**
- **A space (spatial) dependent process.**

NEUROTRANSMITTERS

The neurotransmitter substances can be classified into two main groups.

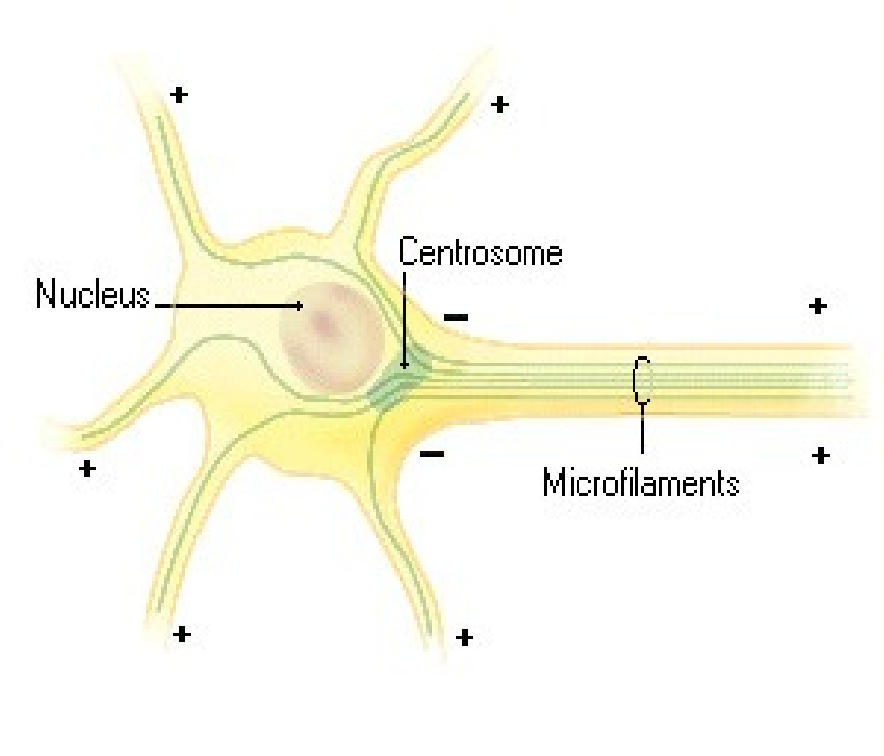
1. *small-molecule transmitters*:

acetylcholine; amino acids such as glycine, glutamate, and gamma aminobutyric acid (GABA); and biogenic amines such as norepinephrine, serotonin, and dopamine.

2. *neuroactive peptides*:

substance P, enkephalin, endorphin, and insulin.

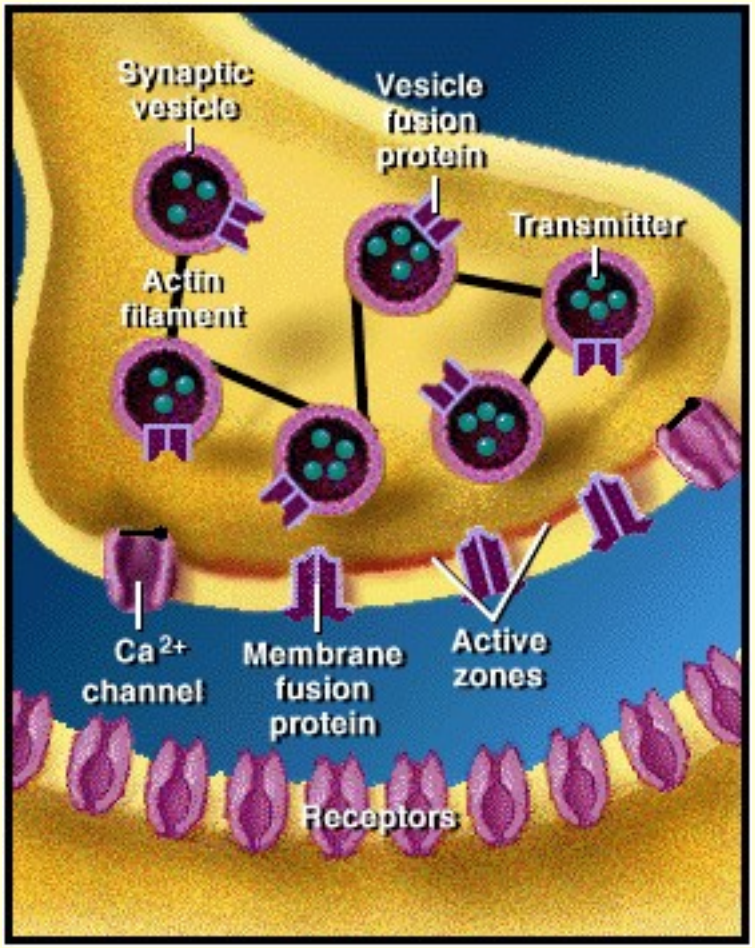
AXOPLASMIC TRANSPORT OF ENZYMES



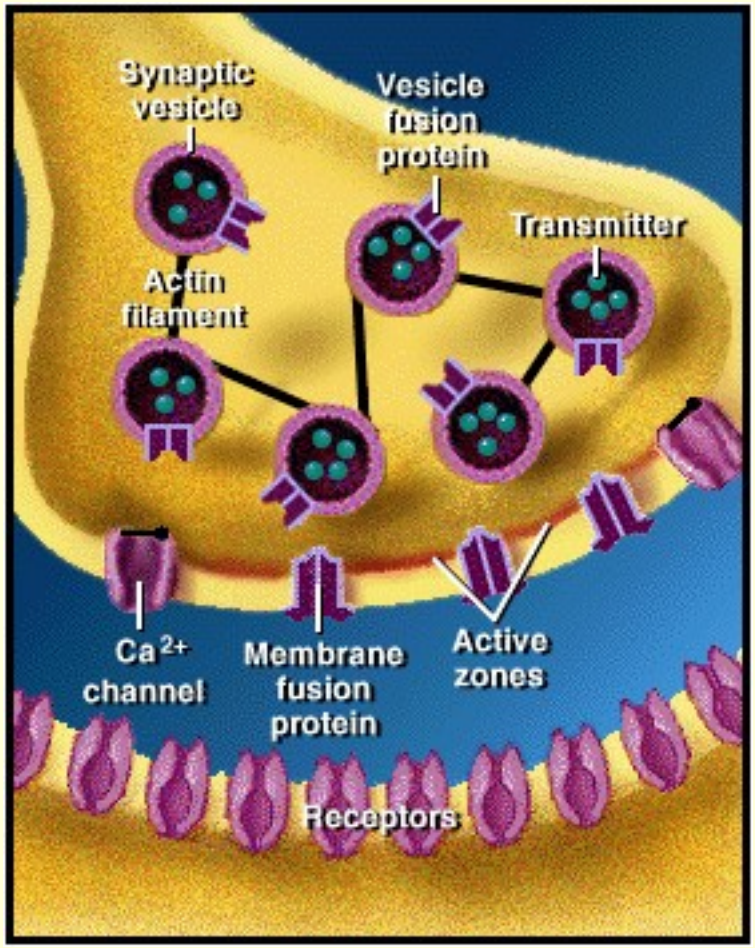
- The enzymes involved in the synthesis of the transmitter and the packaging of the transmitter into vesicles are produced in the cell body, which may be quite distant from the nerve endings.
- These enzymes are transported from the cell body to the nerve endings by a process called *axoplasmic transport*.
- Any interruption of axoplasmic transport will have inhibitory effects on synaptic transmission.

NEUROMUSCULAR JUNCTION: RELEASE OF ACETYLCHOLINE

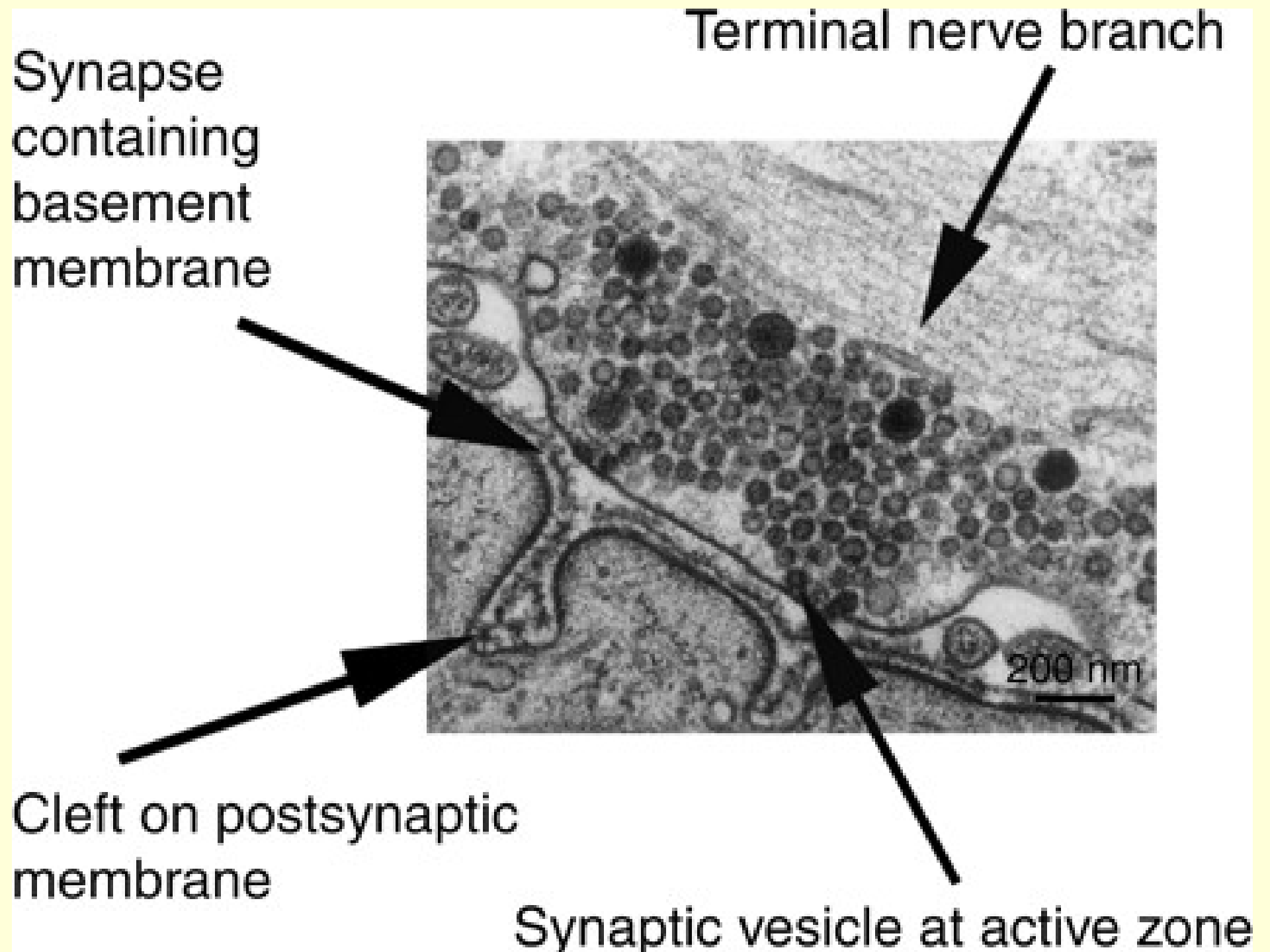
- The neuromuscular junction is the connection between a motor nerve (neuron) and a skeletal muscle cell.
- At the neuromuscular junction, the transmitter is *acetylcholine* (ACh). Thus this synapse is termed a *cholinergic* synapse.



NEUROMUSCULAR JUNCTION: RELEASE OF ACETYLCHOLINE

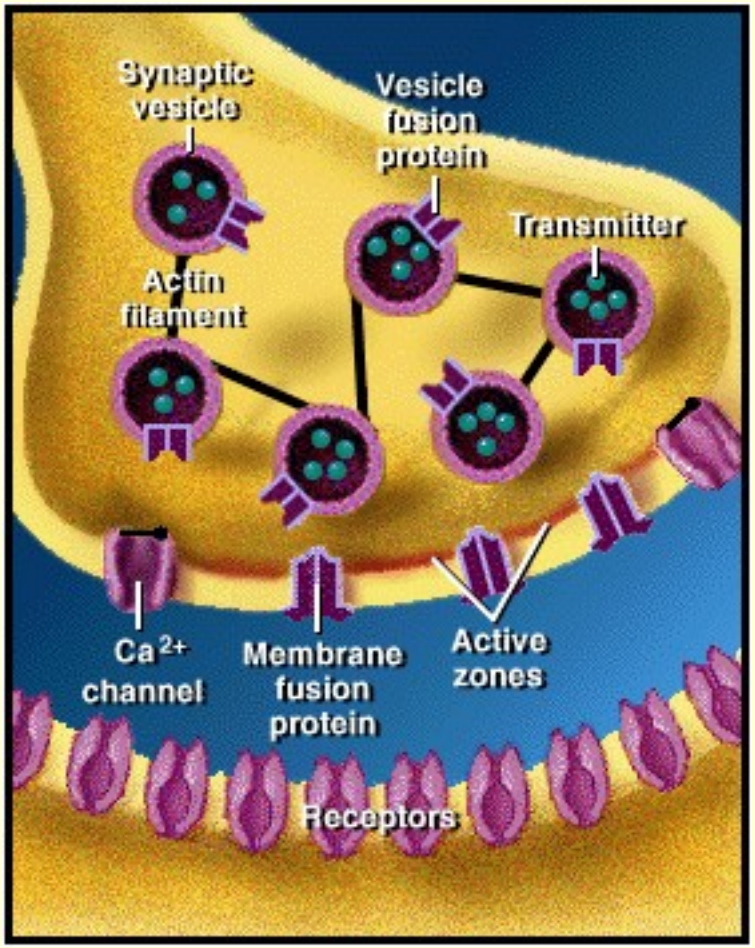


- The action potential in the motor nerve depolarizes the presynaptic nerve ending, causing an influx of calcium into the terminal bouton.
- This causes vesicles to fuse to the presynaptic membrane facing the synaptic cleft.
- The vesicles are anchored to actin filaments that keep the vesicles clustered around regions called *active zones* (voltage-sensitive calcium channels are localized in this region).

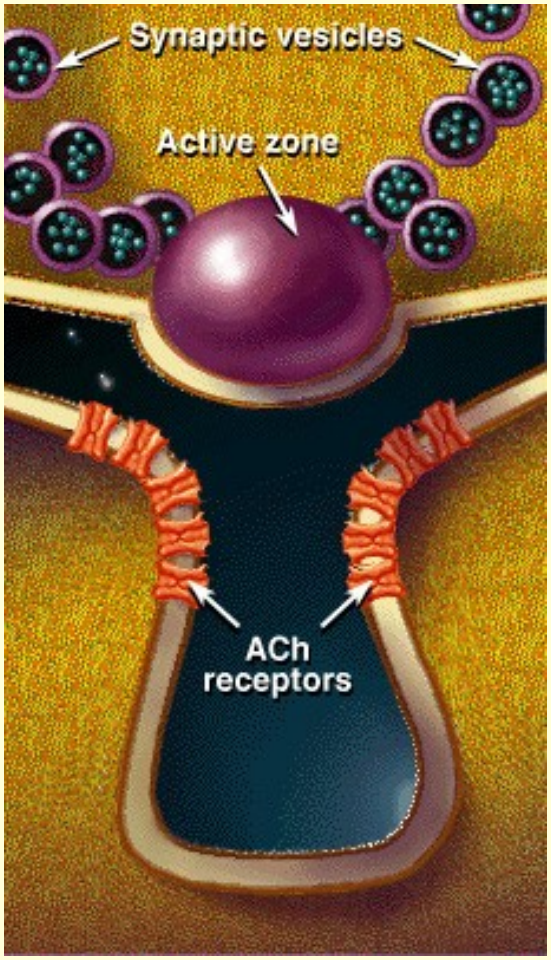

Terminal nerve branch
Synapse containing basement membrane
200 nm
Cleft on postsynaptic membrane
Synaptic vesicle at active zone

NEUROMUSCULAR JUNCTION: RELEASE OF ACETYLCHOLINE

- Calcium entry leads to severing of some of the actin filaments, which facilitates movement of the vesicles toward the junctional membrane.
- Calcium also helps the vesicles dock with specialized regions of the presynaptic membrane.
- When the vesicles dock, fusion pores are formed between the vesicle interior and the junctional cleft. This causes rapid release of the transmitter into the synaptic cleft.

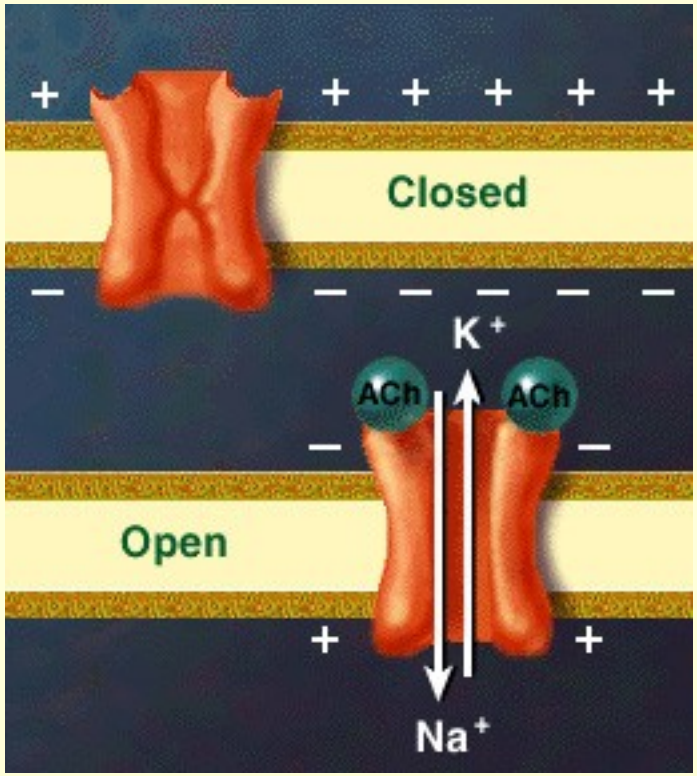


POSTSYNAPTIC EXCITATORY EVENTS



- The acetylcholine diffuses across the synaptic cleft and binds to nicotinic ACh receptors on the postsynaptic membrane of the skeletal muscle cell. This region is called the motor end-plate.
- The postsynaptic membrane of the neuromuscular junction has many *junctional folds*. The ACh receptors are localized at the apex of the junctional folds and in close proximity to the active zones.

POSTSYNAPTIC EXCITATORY EVENTS



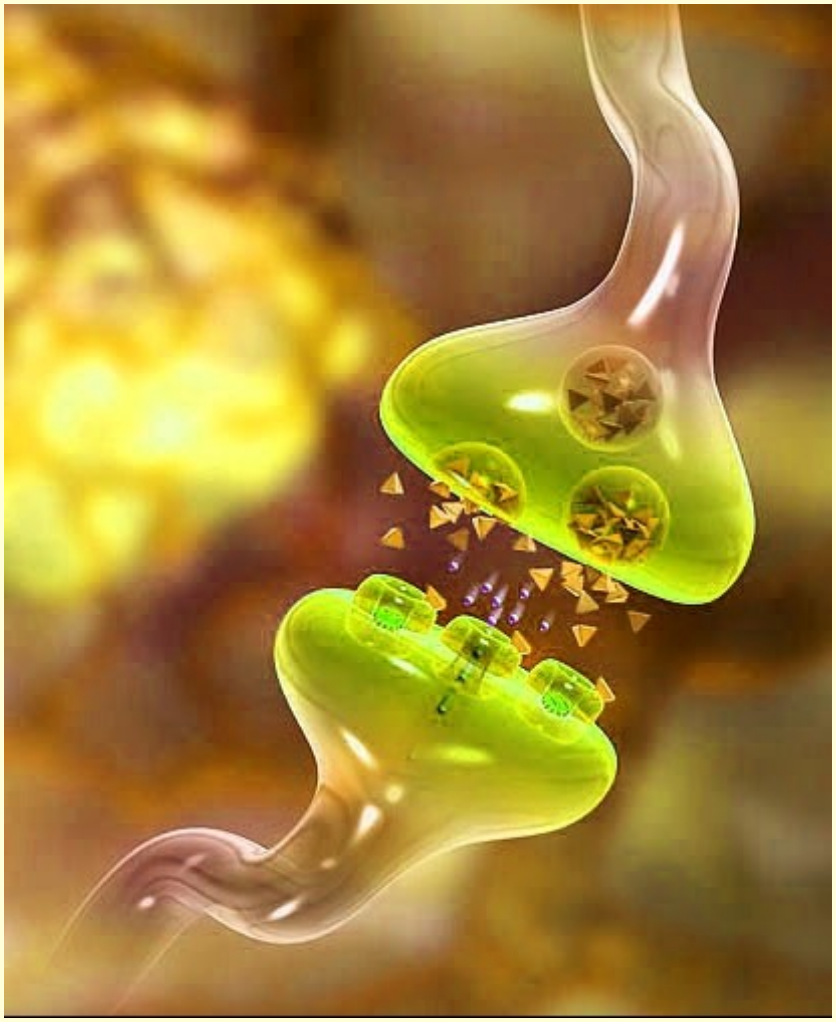
- Binding of ACh to the receptor causes directly gated channels in the end-plate region to open.
- When opened, they are permeable to small cations (mainly sodium and potassium).
- Flux of small cations through these channels leads to a depolarization of the end-plate region towards an equilibrium potential of approximately 0 mV.
- This potential is called an *end-plate potential* (EPP).

POSTSYNAPTIC EXCITATORY EVENTS

- The end-plate region of post-synaptic membrane containing the ACh receptors and their associated channels is a specialized, chemically sensitive membrane.
- The motor end plate is surrounded by voltage-sensitive membrane containing voltage-sensitive channels for sodium and potassium (similar to those in nerve membranes).
- Depolarization of the end-plate by current through the ACh-gated channels gives rise to local-circuit currents that cause the surrounding voltage-sensitive membrane to depolarize and generate an action potential.
- This action potential causes the skeletal muscle to contract.

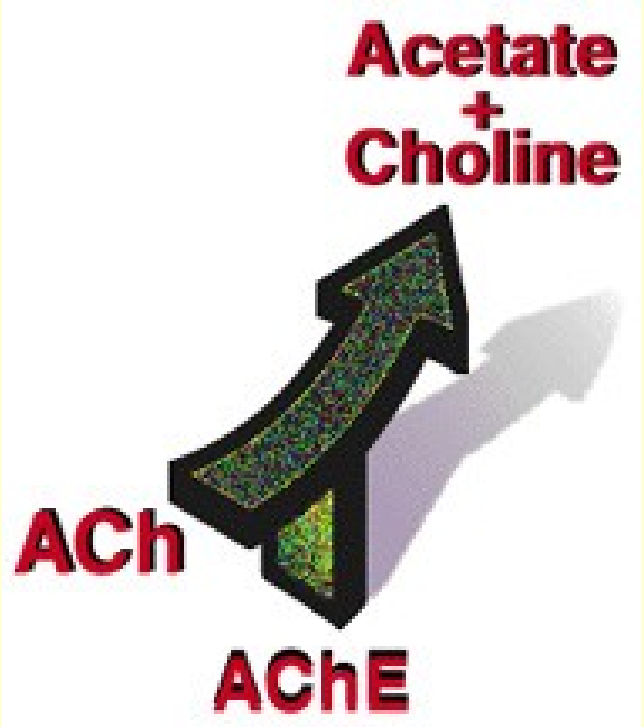
SINGLE AP IN THE MOTOR NERVE – SINGLE AP IN THE MUSCLE

- One action potential in the motor nerve normally leads to one and only one action potential across the muscle membrane.
- This ensures that the central nervous system has complete control of muscular activity.
- Neuromuscular transmission has a very high safety factor – an action potential in the motor nerve always causes a single action potential in the muscle.

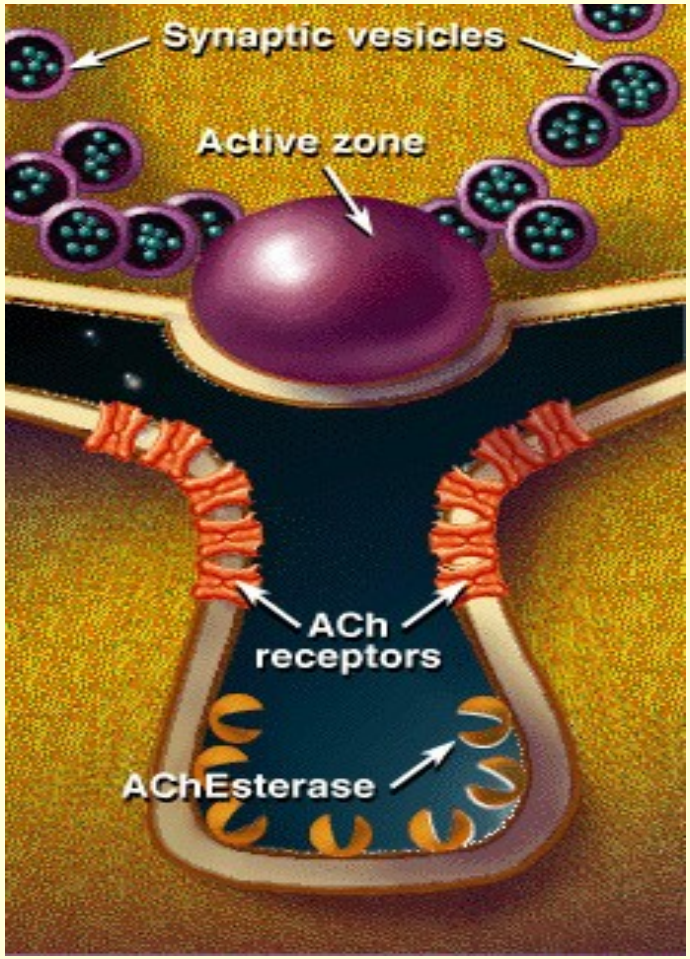


TERMINATION OF TRANSMITTER

- To ensure that only one action potential is generated across the muscle membrane, the transmitter action must be brief.
- This is accomplished when acetylcholinesterase (AChE) destroys the transmitter.

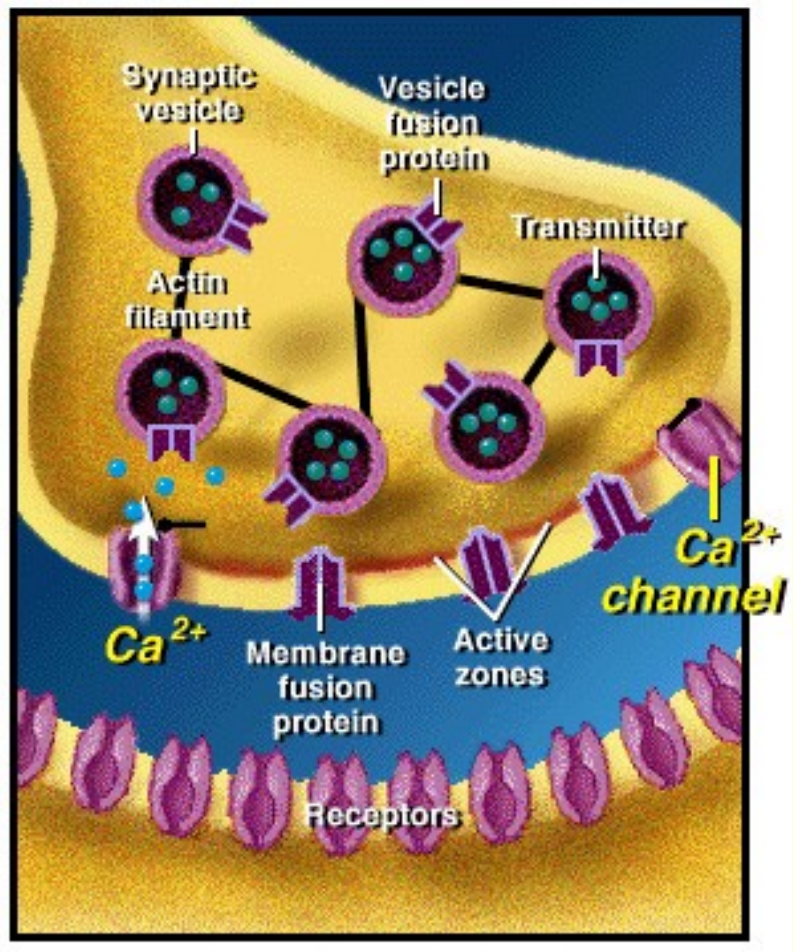


ACTION BY ACETYLCHOLINESTERASE



- AChE is located on the postsynaptic membrane lining the postjunctional folds.
- The choline is transported back into the nerve terminals for use in resynthesis of ACh.

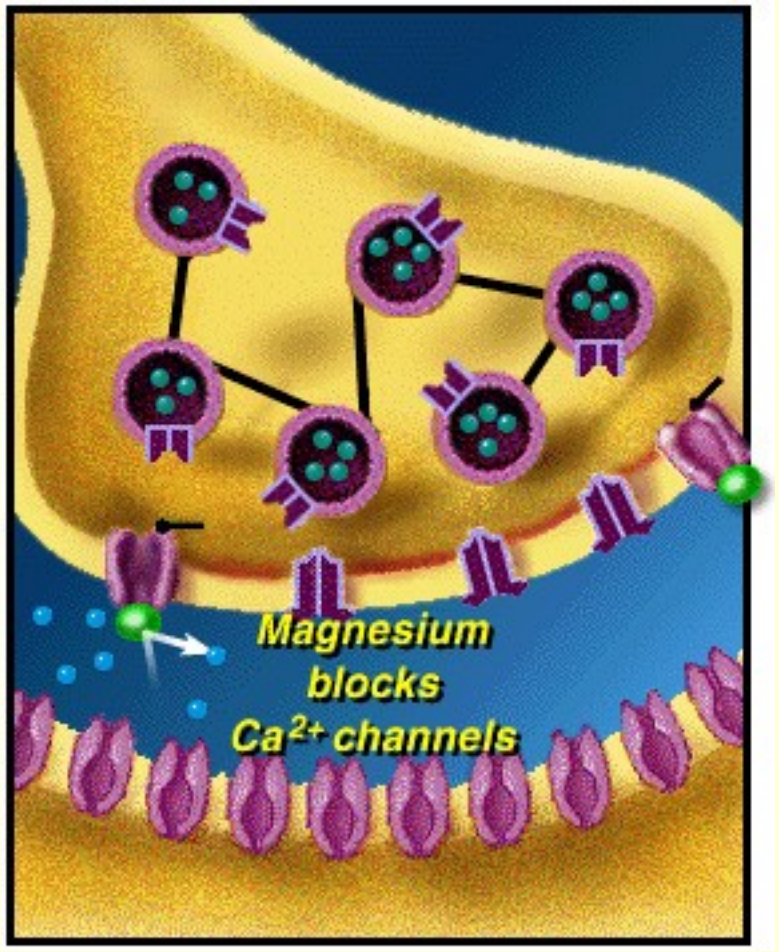
EXTRACELLULAR CALCIUM



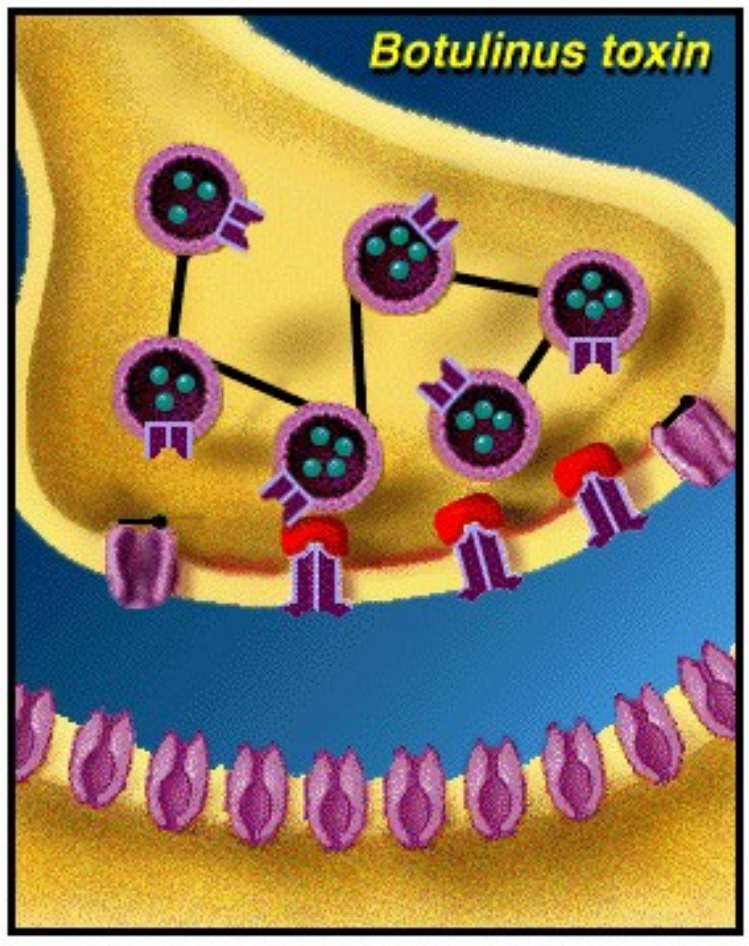
- Because entry of calcium from the extracellular medium is required for vesicle mobilization and fusion with the presynaptic membrane, altering the extracellular calcium concentration affects the number of vesicles released by each nerve action potential.
- Increasing extracellular calcium concentration increases the number of vesicles released.
- Conversely, decreasing extracellular calcium concentration decreases the number of vesicles released, and, if extracellular calcium is too low, can impair neuromuscular transmission.

EXTRACELLULAR MAGNESIUM

- Extracellular magnesium acts just the opposite to calcium.
- Increasing extracellular magnesium decreases the number of vesicles released by a nerve action potential, most likely by inhibiting the entry of calcium into the nerve terminal.
- Thus, high extracellular magnesium, as might be seen in patients using large quantities of magnesium-containing salts can lead to impaired neuromuscular transmission.
- Conversely, decreased extracellular magnesium increases the number of vesicles released.



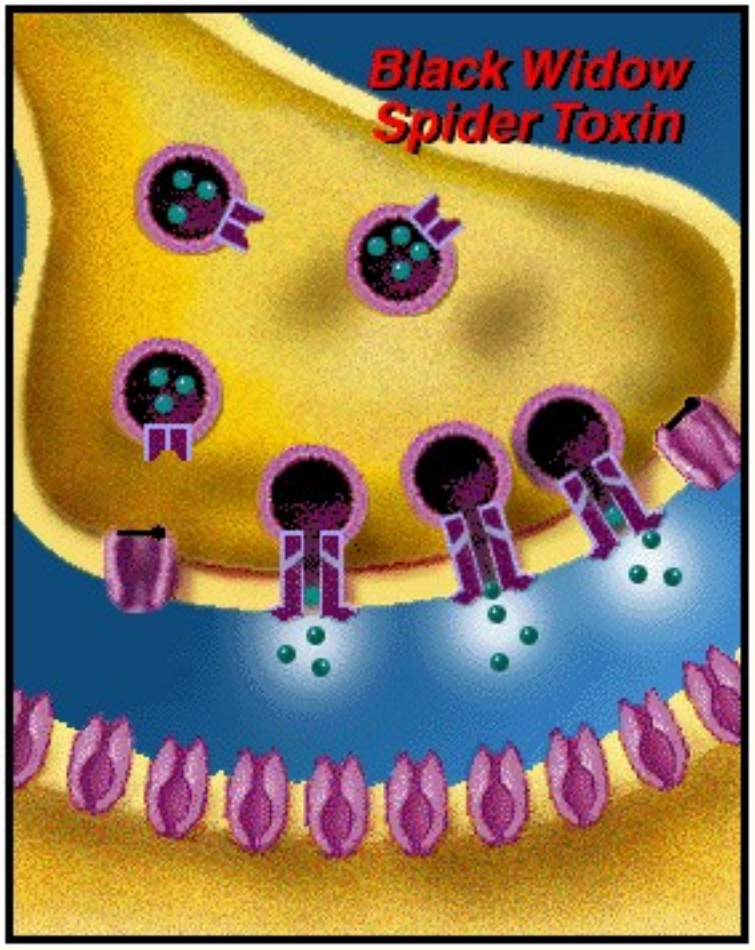
BOTULINUS TOXIN



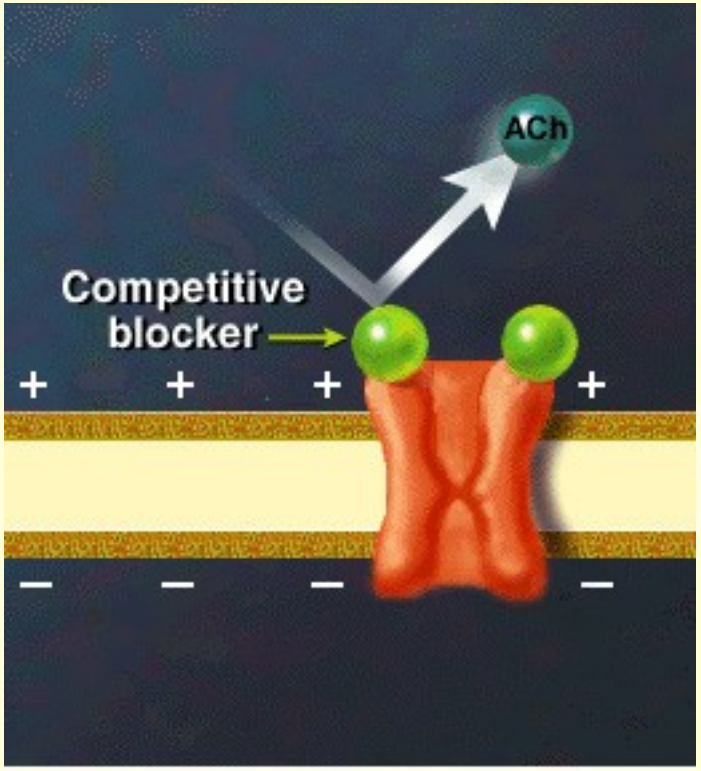
- **Botulinus toxin is produced by the anaerobic bacillus *Clostridium botulinum*, which may be found in improperly canned food, and is one of the most potent toxins known.**
- **This toxin (the agent responsible for botulism) blocks the release of vesicles.**
- **This leads to muscle paralysis and, if the diaphragm becomes affected, can be fatal.**

Black Widow Spider Toxin

- Black widow spider toxin, like botulinus toxin, affects the release of transmitter. However, its effect is opposite to that of botulinus toxin.
- Black widow spider toxin causes an excessive release of vesicles.
- This causes muscle spasms, cramping pain, and generalized nervous excitation.

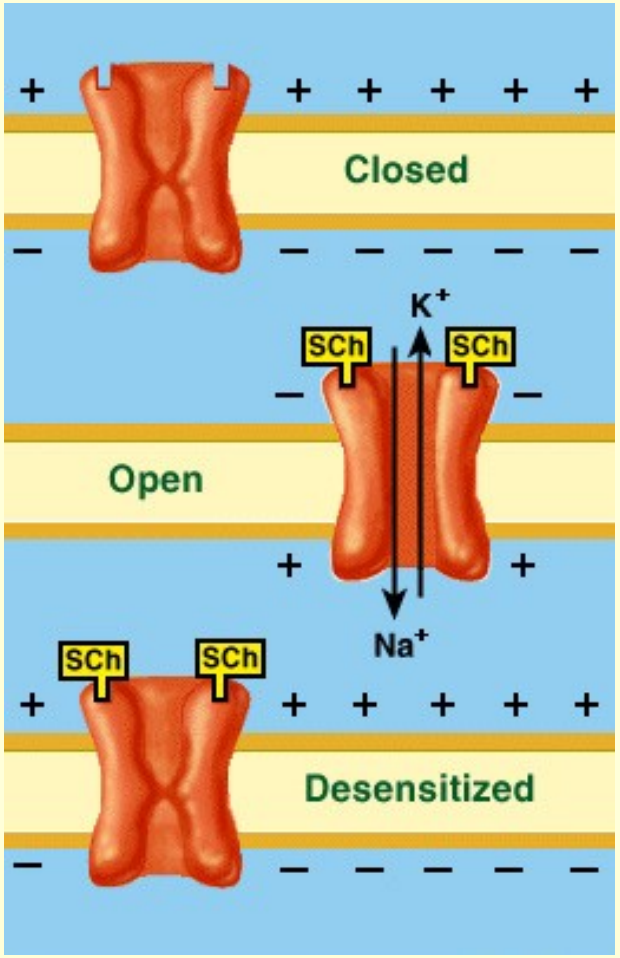


Postsynaptic AChReceptors: Competitive Blockers



- Chemical agents that bind to the ACh receptor but do not cause the associated channels to open are called "competitive" blockers, because they compete with ACh for the receptors.
- An example is d-tubocurarine (curare). High doses occupy enough ACh receptors to cause muscle paralysis.
- The safety factor in normal neuromuscular transmission is so high, however, that more than 75% of the receptors can be blocked before the reliable generation of a muscle action potential is impaired.

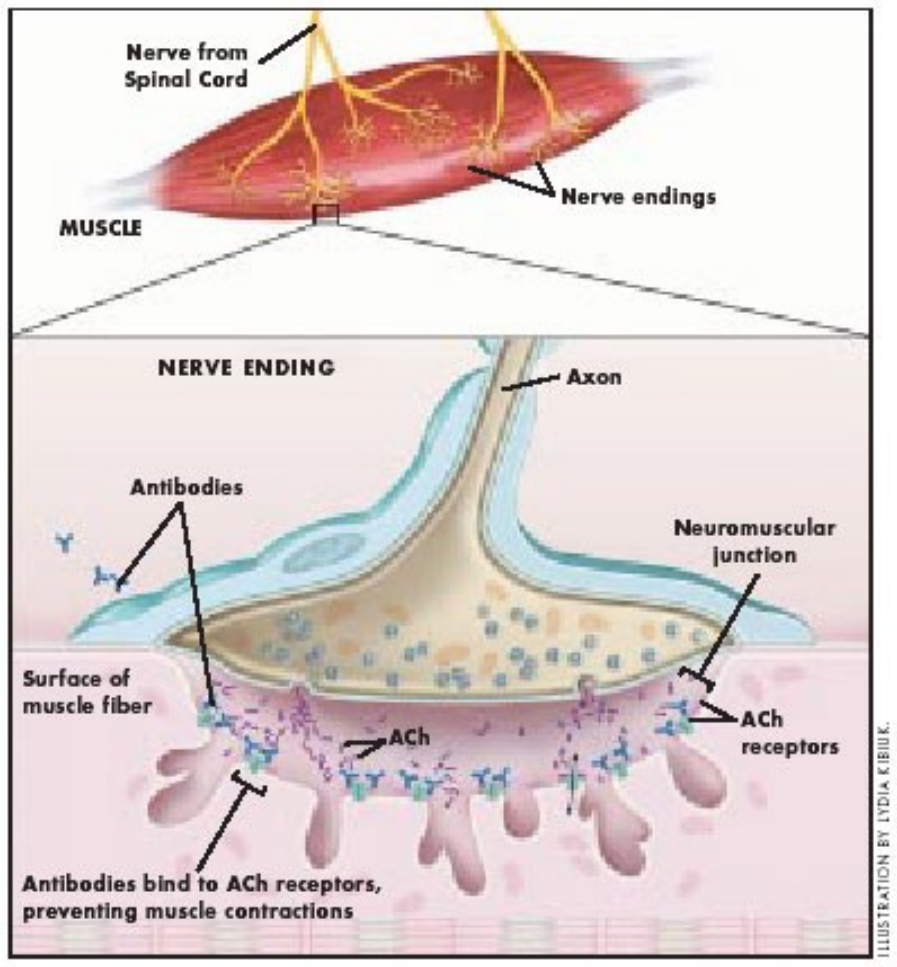
Postsynaptic AChReceptors: Depolarizing Blockers



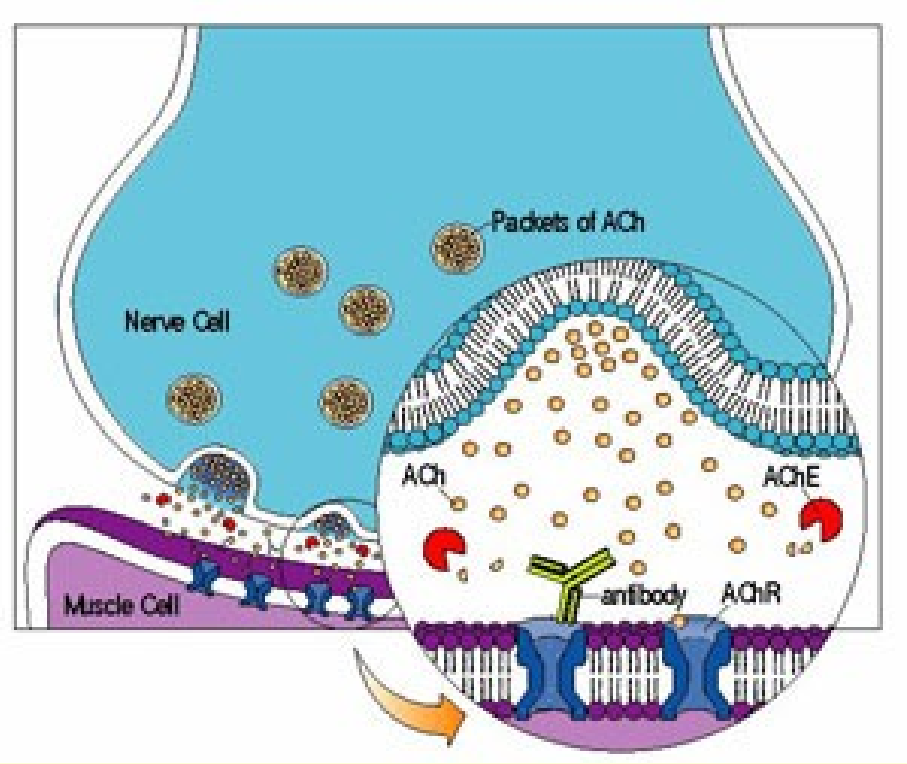
- Chemical agents that bind to the ACh receptor and, like ACh, cause channel opening (i.e, agonists of ACh) can also inhibit neuromuscular transmission.
- To do so, they must be less readily destroyed by the AChE.
- Such agents are called "depolarizing" blockers, an example of which is *succinylcholine*. Like ACh, these agents cause depolarization of the end-plate region.
- Both competitive and depolarizing neuromuscular blockers are used clinically to relax muscles for surgery or tracheal intubation.

Factors Affecting Neuromuscular Transmission: Myasthenia Gravis

- Patients afflicted with the autoimmune disease myasthenia gravis exhibit neuromuscular problems, especially muscle weakness.
- These individuals have antibodies to their own ACh receptors.
- As the disease progresses, the patients have fewer and fewer ACh receptors at their motor end-plates because the autoimmune process destroys receptor proteins.
- At some point, there are too few receptors to ensure reliable neuromuscular transmission.

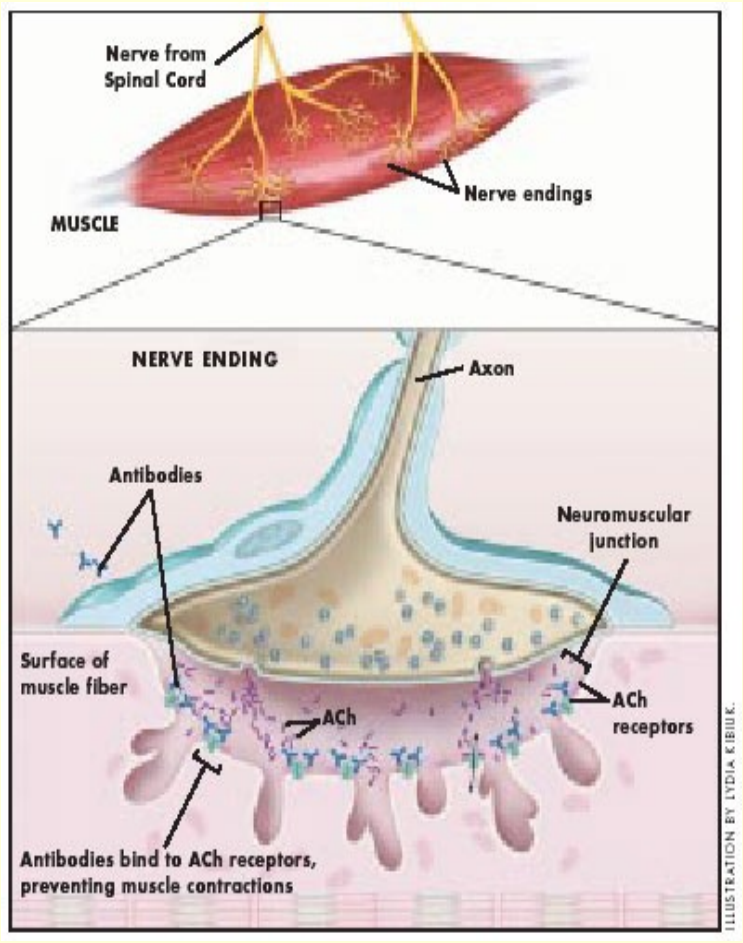


MYASTHENIA GRAVIS



- Muscle weakness in patients with myasthenia gravis is especially obvious when they attempt a sustained muscular contraction.
- Normally, the decrease in vesicles released by each action potential in a series of nerve stimuli has no adverse effect.
- More than enough transmitter is released to saturate enough ACh receptors to adequately depolarize the muscle membrane to threshold for firing of an action potential.

MYASTHENIA GRAVIS



- Presynaptic release of transmitter in patients with myasthenia is normal, and decreases with repeated nerve stimuli.
- However, they have so few ACh receptors that this normal decrease in vesicular release means an insufficient number of postsynaptic channels open to adequately depolarize the muscle membrane surrounding the motor end-plate.
- Neuromuscular transmission fails, the muscle action potentials do not fire reliably, and the patient experiences progressive muscle weakness.

CONCLUSION

- ***Step 1***: **The action potential reaches an axon bulb and causes calcium ion gates to open and calcium ions move into the axon bulb.**
- ***Step 2***: **The rise in calcium ions in the axon bulb causes synaptic vesicles containing neurotransmitter to move towards the presynaptic membrane.**
- ***Step 3***: **Synaptic vesicles merge with the presynaptic membrane and exocytosis of neurotransmitters into the synaptic cleft occurs (requires ATP energy). The axon bulb contains many mitochondria to produce ATP.**
- ***Step 4***: **Neurotransmitters diffuse across the synaptic cleft (a very short distance) and bind to receptor proteins on the postsynaptic membrane. Excitatory neurotransmitters cause sodium ions to move through receptor proteins depolarizing the membrane. Inhibitory neurotransmitters do not depolarize the postsynaptic membrane.**
- ***Step 5***: **If sufficient excitatory neurotransmitter binds to receptors, an action potential is produced in the postsynaptic membrane and travels along the length of the second neuron.**
- ***Step 6***: **To prevent continuous stimulation or inhibition of the postsynaptic membrane, neurotransmitters are broken down by enzymes or are reabsorbed through the presynaptic membrane by endocytosis (also requires ATP energy).**

BRITANNICA ENCYCLOPEDIA: SYNAPSE

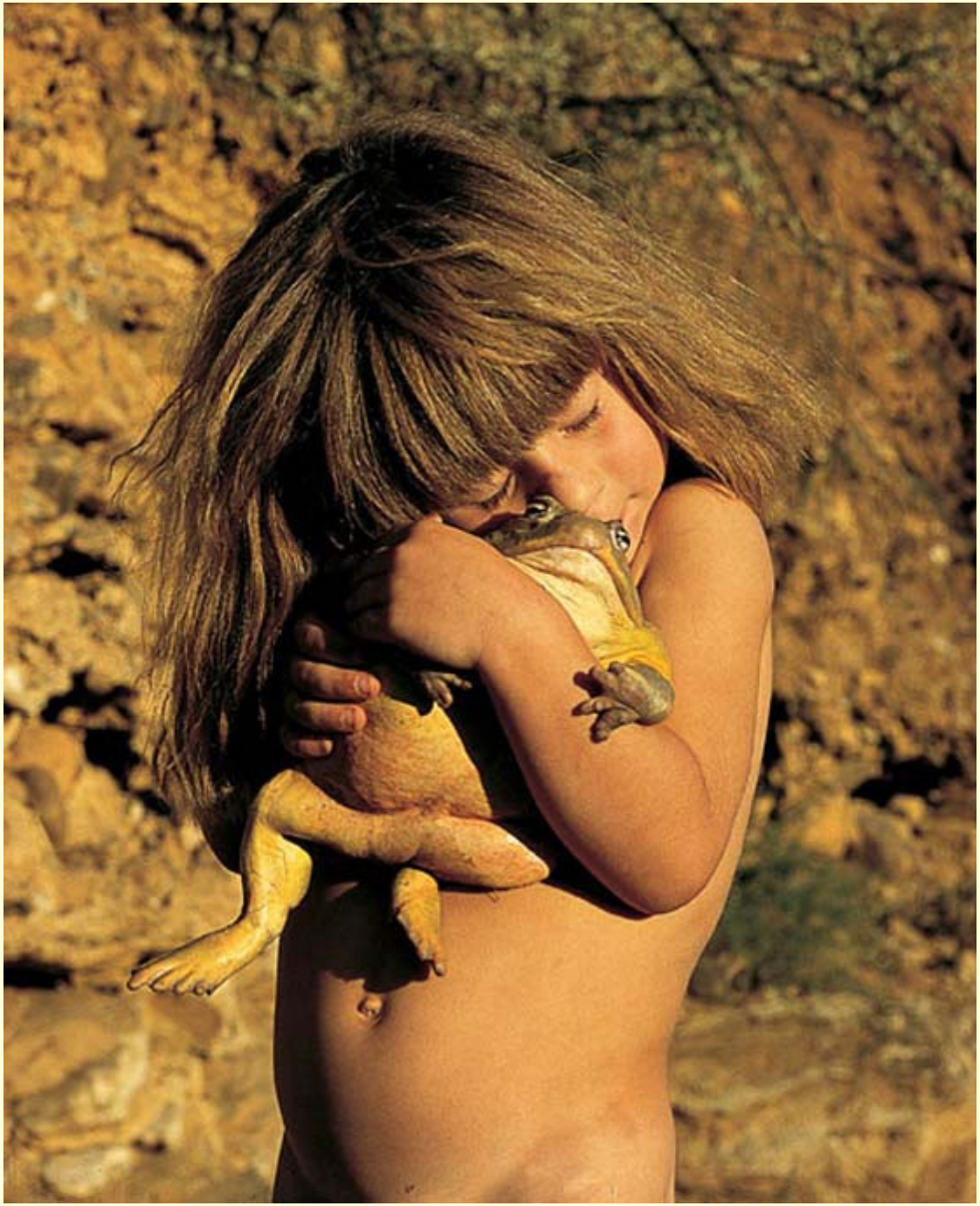
"Site of transmission of electric nerve impulses between two nerve cells or between a nerve cell and a gland or muscle cell.

At chemical synapses, impulses are transmitted across microscopic spaces via chemical substances called neurotransmitters.

In electric synapses, direct communication between nerve cells whose membranes are fused is possible because ions flow between the cells through channels.

Electric synapses are found mainly in invertebrates and lower vertebrates; they transmit messages faster than chemical synapses.

Chemical transmission seems to have evolved in large, complex vertebrate nervous systems, in which multiple messages must be transmitted over long distances".



I thank all of you for your patience!