Physiology

The Nervous System: Neurons and Synapses

Nervous System

- 2 types of cells in the nervous system:
  - Neurons.
  - Supporting cells.
- Nervous system is divided into:
  - Central nervous system (CNS):
    - Brain.
    - Spinal cord.
  - Peripheral nervous system (PNS):
    - Cranial nerves.
    - Spinal nerves.

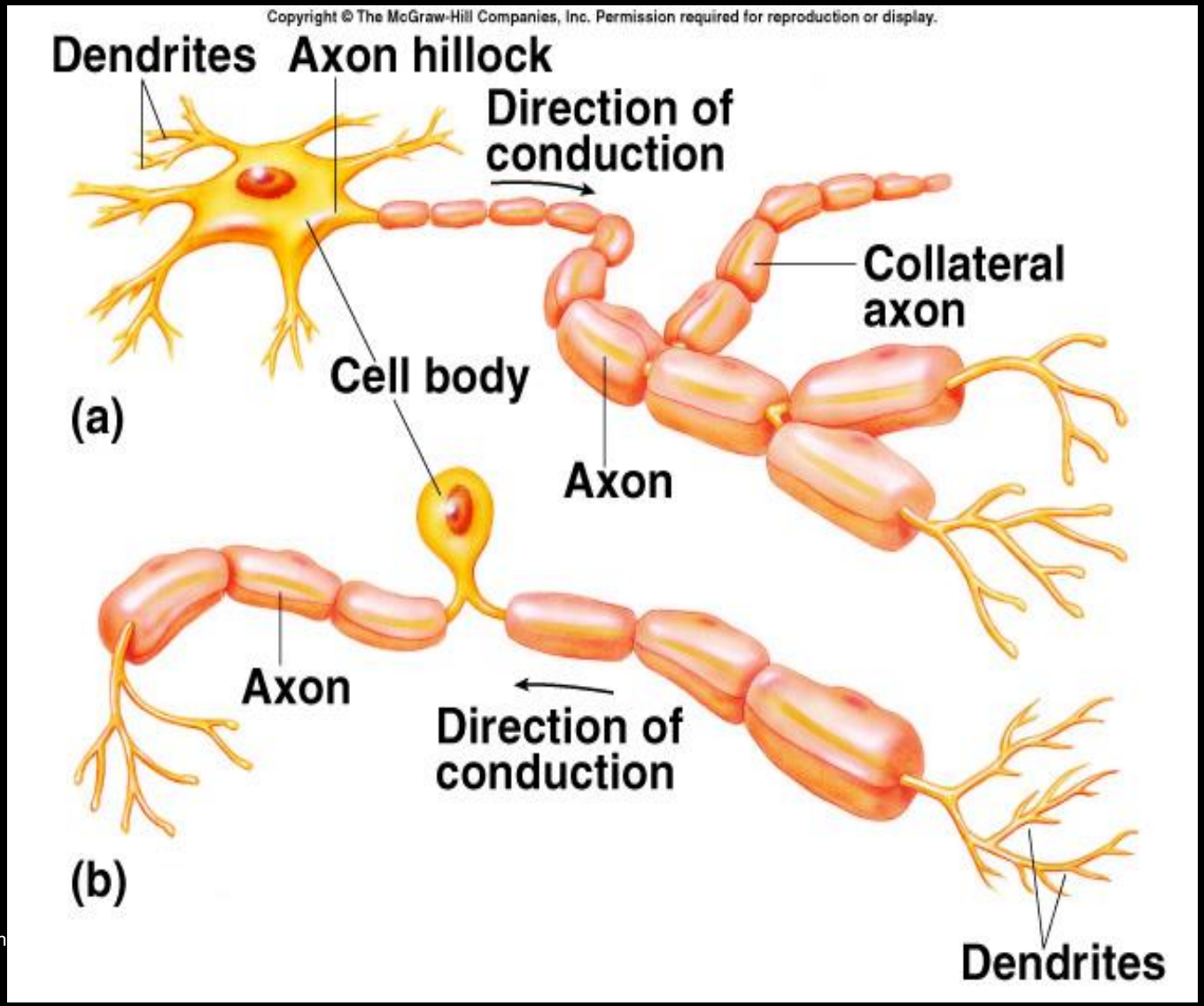
Neurons

- Basic structural and functional units of the nervous system.
  - Cannot divide by mitosis.
- Respond to physical and chemical stimuli.
- Produce and conduct electrochemical impulses.
- Release chemical regulators.
- Nerve:
  - Bundle of axons located outside CNS.
    - Most composed of both motor and sensory fibers.

Neurons (continued)

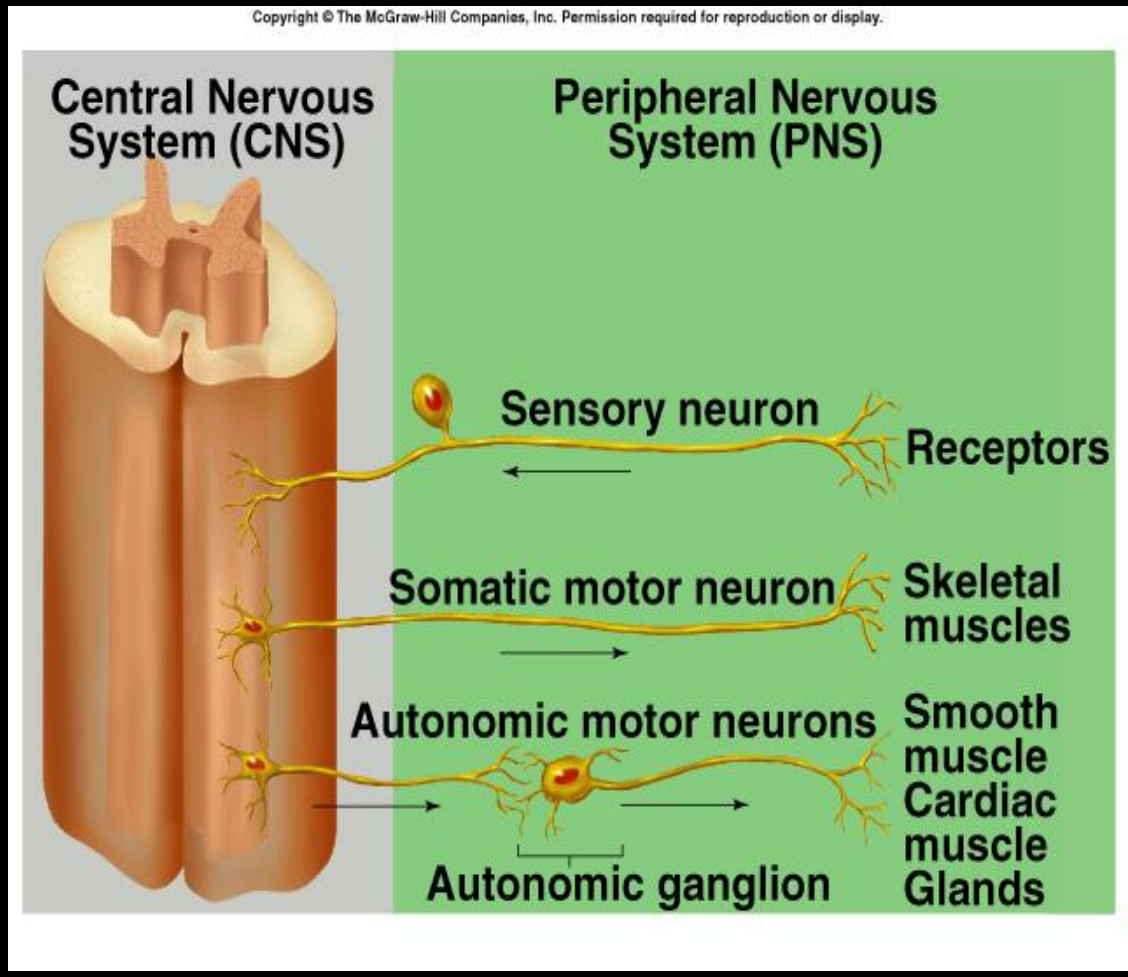
- Cell body (perikaryon):
  - "Nutrition center."
  - Cell bodies within CNS clustered into nuclei, and in PNS in ganglia.
- Dendrites:
  - Provide receptive area.
  - Transmit electrical impulses to cell body.
- Axon:
  - Conducts impulses away from cell body.
  - Axoplasmic flow:
    - Proteins and other molecules are transported by rhythmic contractions to nerve endings.
  - Axonal transport:
    - Employs microtubules for transport.
    - May occur in orthograde or retrograde direction.

Neurons (continued)



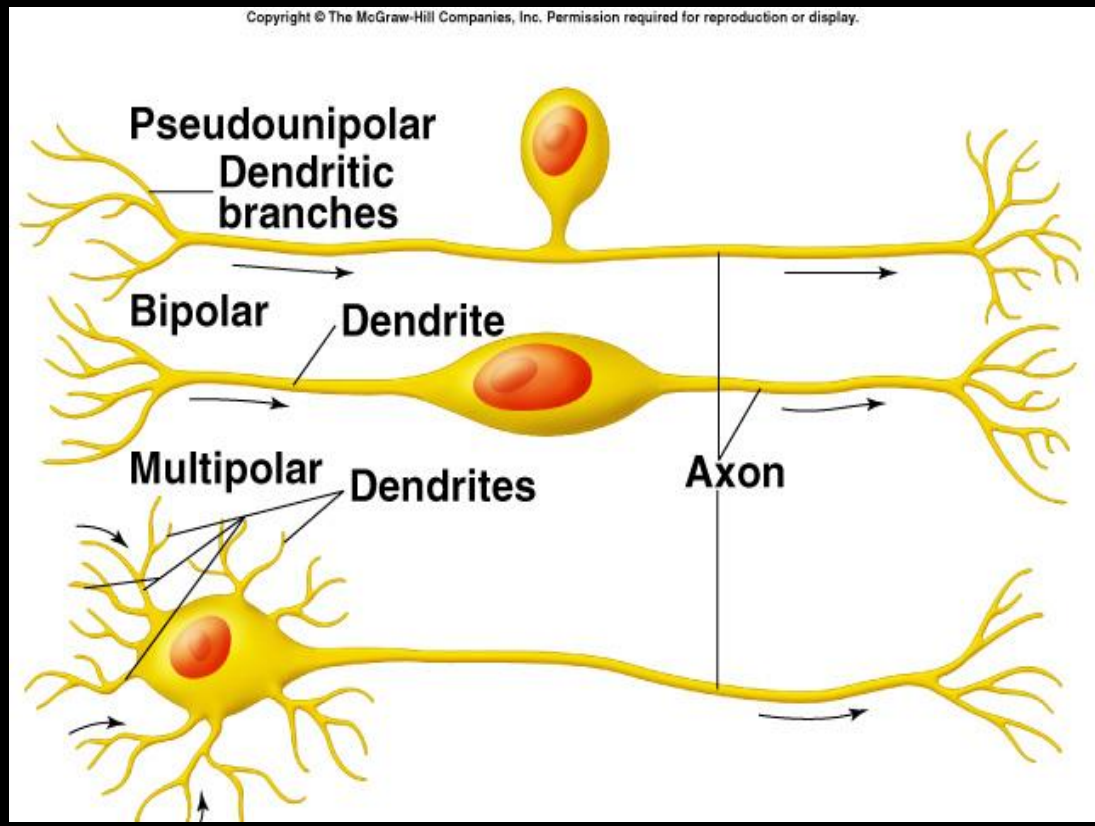
Functional Classification of Neurons

- Based upon direction impulses conducted.
- Sensory or afferent:
  - Conduct impulses from sensory receptors into CNS.
- Motor or efferent:
  - Conduct impulses out of CNS to effector organs.
- Association or interneurons:
  - Located entirely within the CNS.
  - Serve an integrative function.



Structural Classification of Neurons

- Based on the # of processes that extend from cell body.
  - Pseudounipolar:
    - Short single process that branches like a T.
      - Sensory neurons.
  - Bipolar neurons:
    - Have 2 processes.
      - Retina of the eye.
  - Multipolar:
    - Have several dendrites and 1 axon.
      - Motor neuron.

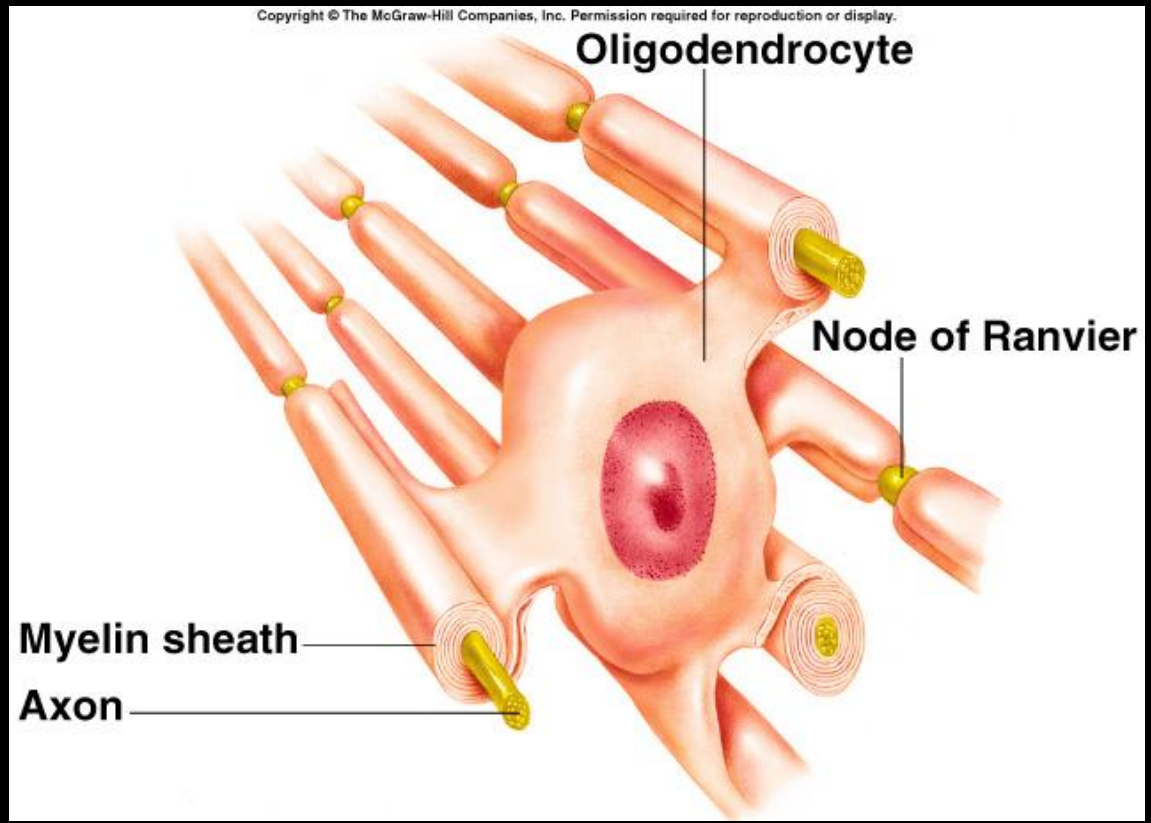


PNS Supporting Cells

- Schwaan cells:
  - Successive wrapping of the cell membrane.
  - Outer surface encased in glycoprotein basement membrane.
  - Provide insulation.
- Nodes of Ranvier:
  - Unmyelinated areas between adjacent Schwaan cells that produce nerve impulses.
- Satellite cells:
  - Support neuron cell bodies within ganglia.

CNS Supporting Cells

- Oligodendrocytes:
  - Process occurs mostly postnatally.
  - Each has extensions that form myelin sheaths around several axons.
    - Insulation.

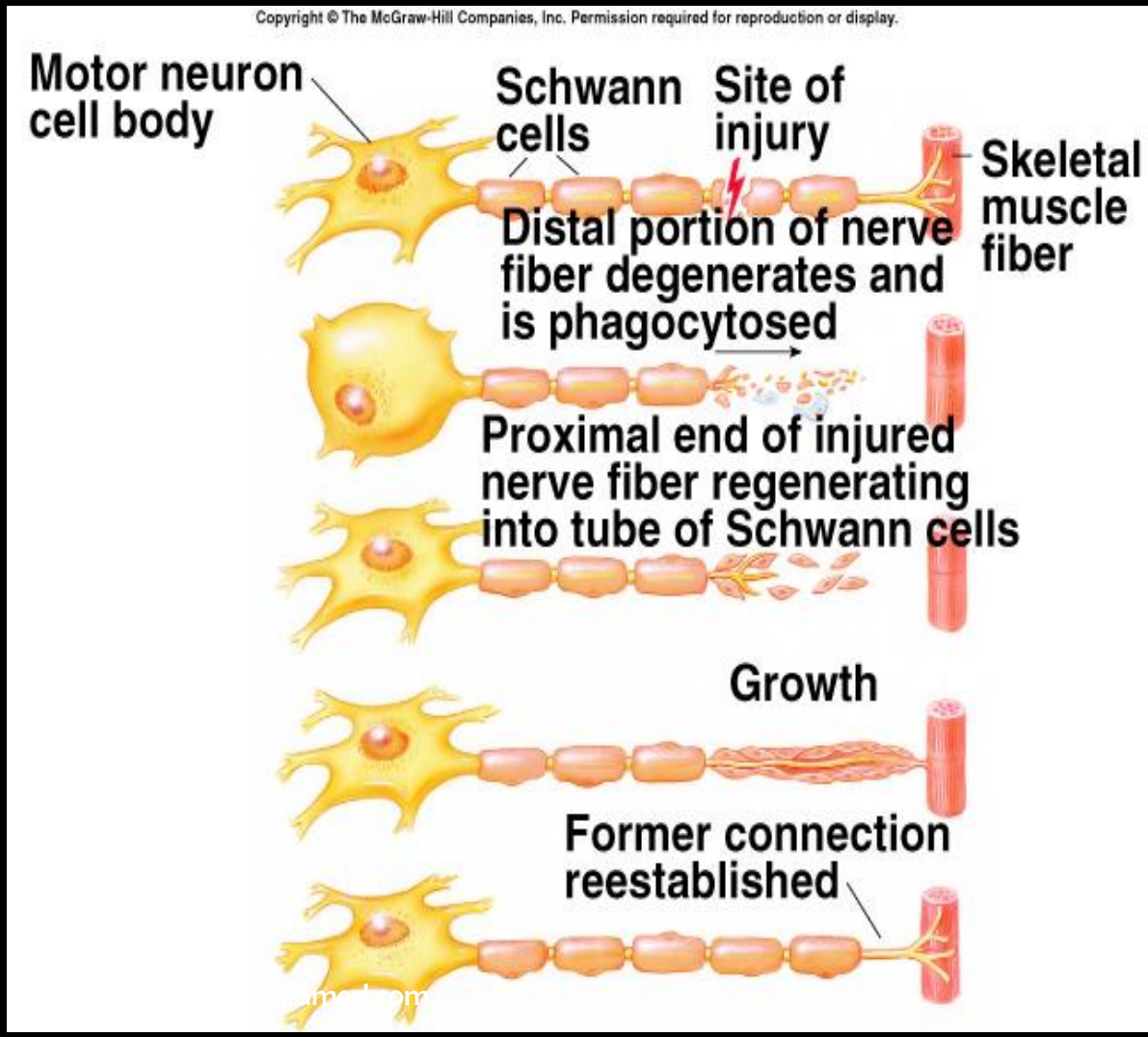


Nerve Regeneration

- Schwann cells:
  - Act as phagocytes, as the distal neuronal portion degenerates.
  - Surrounded by basement membrane, form regeneration tube:
    - Serve as guide for axon.
    - Send out chemicals that attract the growing axon.
    - Axon tip connected to cell body begins to grow towards destination.

Nerve Regeneration (continued)

- CNS has limited ability to regenerate:
  - Absence of continuous basement membrane.
  - Oligodendrocytes molecules inhibit neuronal growth.



Neurotrophins

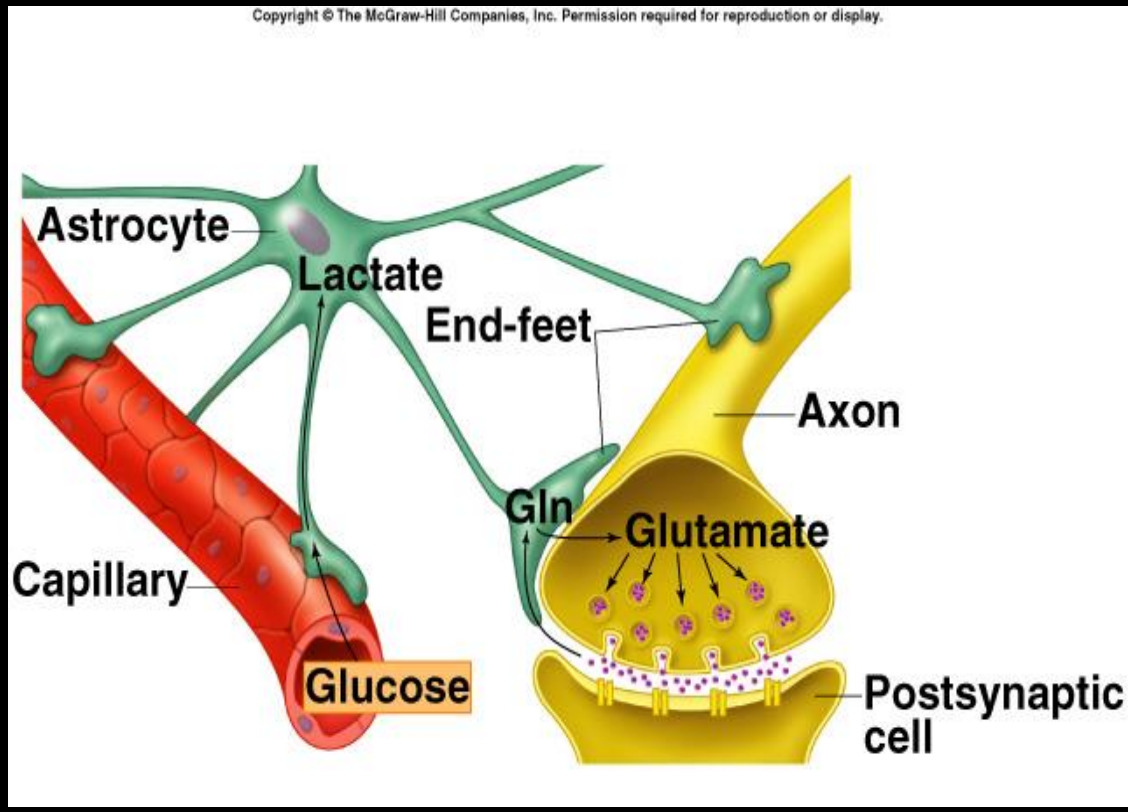
- Promote neuron growth.
- Nerve growth factors include:
  - Nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), glial-derived neurotrophic factor (GDNF), neurotrophin-3, and neurotrophin-4/5.
- Fetus:
  - Embryonic development of sensory neurons and sympathetic ganglia (NGF and neurotrophin-3).

Neurotrophins (continued)

- Adult:
  - Maintenance of sympathetic ganglia (NGF).
  - Mature sensory neurons need for regeneration.
  - Required to maintain spinal neurons (GDNF).
  - Sustain neurons that use dopamine (GDNF).
- Myelin-associated inhibitory proteins:
  - Inhibit axon regeneration.

CNS Supporting Cells (continued)

- Astrocytes:
  - Most abundant glial cell.
  - Vascular processes terminate in end-feet that surround the capillaries.
  - Stimulate tight junctions, contributing to blood-brain barrier.
  - Regulate external environment of K^+ and pH.
  - Take up K^+ from ECF, NTs released from axons, and lactic acid (convert for ATP production).
    - Other extensions adjacent to synapses.



CNS Supporting Cells (continued)

- Microglia:
  - Phagocytes, migratory.
- Ependymal cells:
  - Secrete CSF.
  - Line ventricles.
  - Function as neural stem cells.
  - Can divide and progeny differentiate.

Blood-Brain Barrier

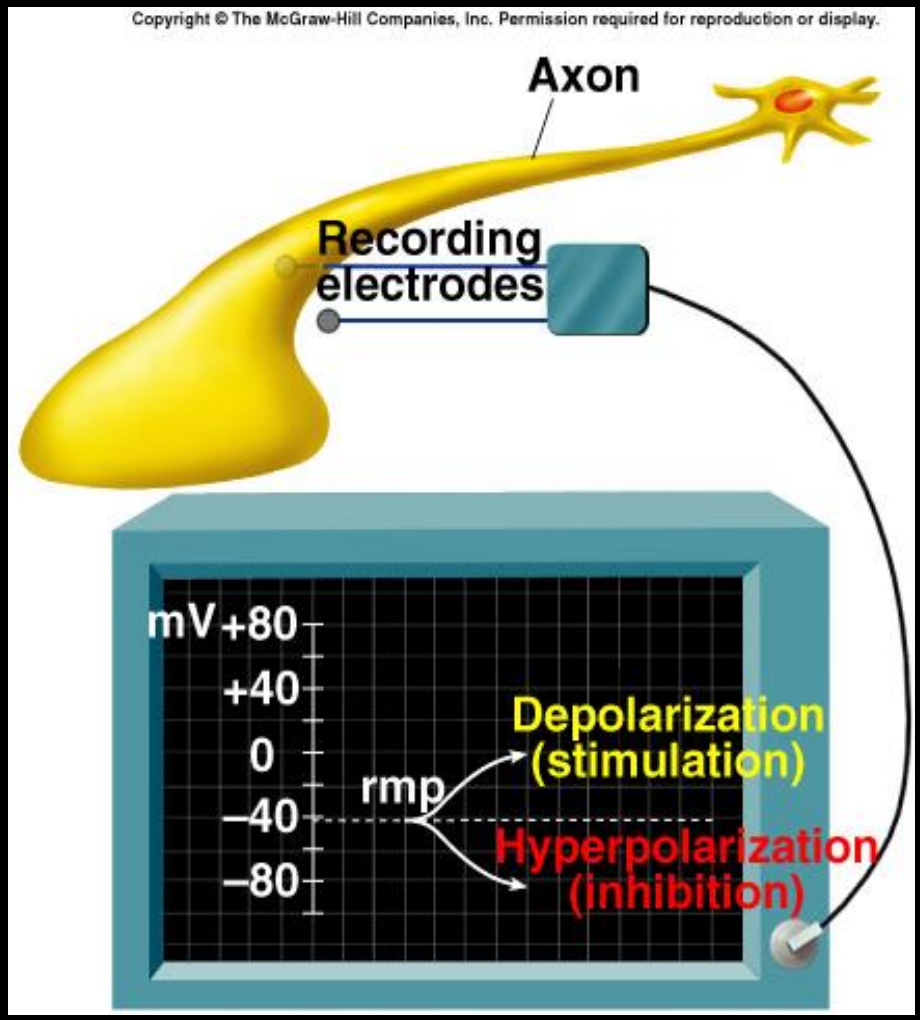
- Capillaries in brain do not have pores between adjacent endothelial cells.
  - Joined by tight junctions.
- Molecules within brain capillaries moved selectively through endothelial cells by:
  - Diffusion.
  - Active transport.
  - Endocytosis.
  - Exocytosis.

Electrical Activity of Axons

- All cells maintain a resting membrane potential (RMP):
  - Potential voltage difference across membrane.
    - Largely the result of negatively charged organic molecules within the cell.
    - Limited diffusion of positively charged inorganic ions.
  - Permeability of cell membrane:
    - Electrochemical gradients of Na^+ and K^+.
    - Na^+/K^+ ATPase pump.
- Excitability/irritability:
  - Ability to produce and conduct electrical impulses.

Electrical Activity of Axons (continued)

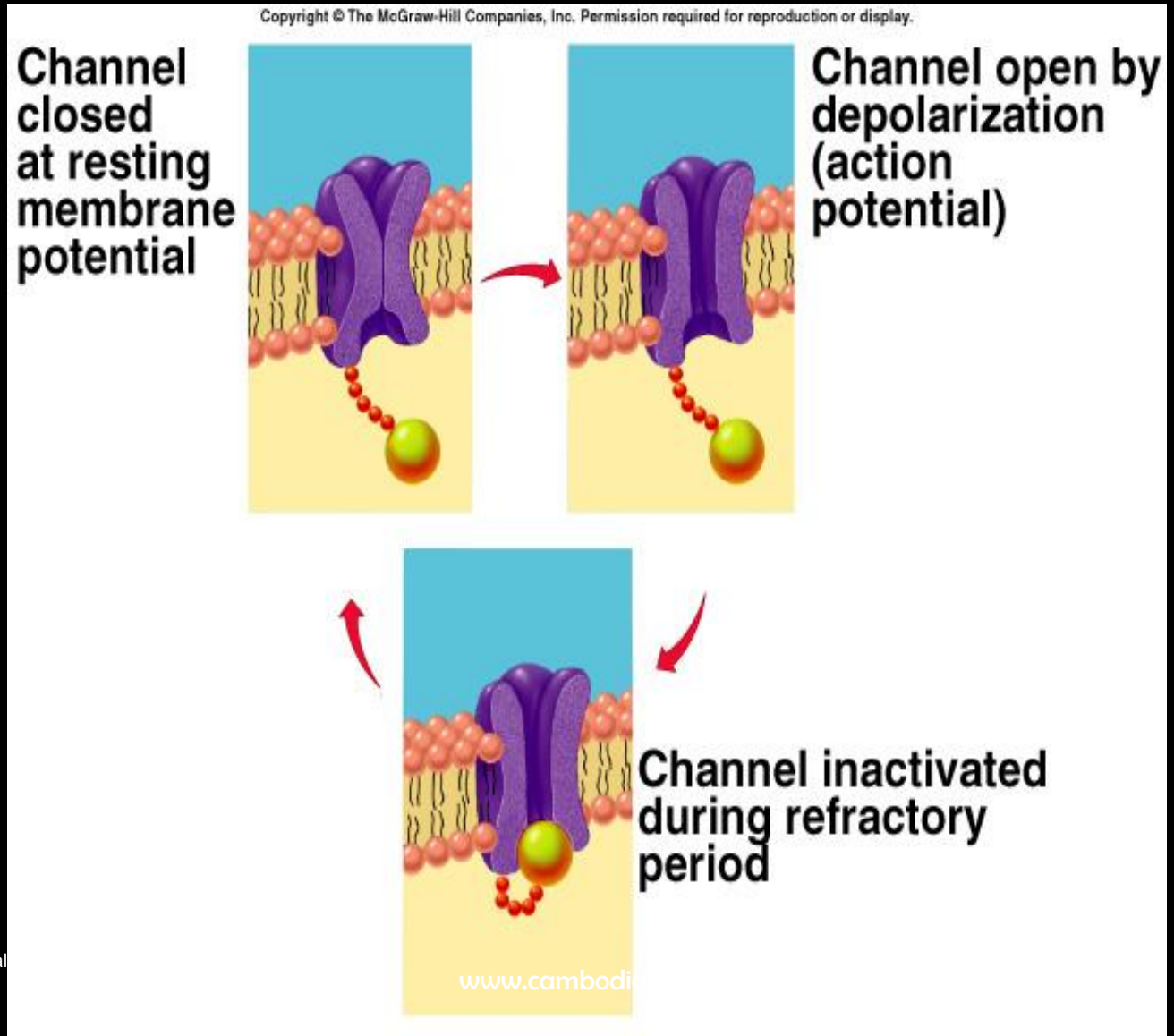
- Increase in membrane permeability for specific ion can be measured by placing 2 electrodes (1 inside and 1 outside the cell).
- Depolarization:
  - Potential difference reduced (become more positive).
- Repolarization:
  - Return to resting membrane potential (become more negative).
- Hyperpolarization:
  - More negative than RMP.



Ion Gating in Axons

- Changes in membrane potential caused by ion flow through ion channels.
- Voltage gated (VG) channels open in response to change in membrane potential.
  - Gated channels are part of proteins that comprise the channel.
    - Can be open or closed in response to change.
  - 2 types of channels for K^+:
    - 1 always open.
    - 1 closed in resting cell.
  - Channel for Na^+:
    - Always closed in resting cells.
      - Some Na^+ does leak into the cells.

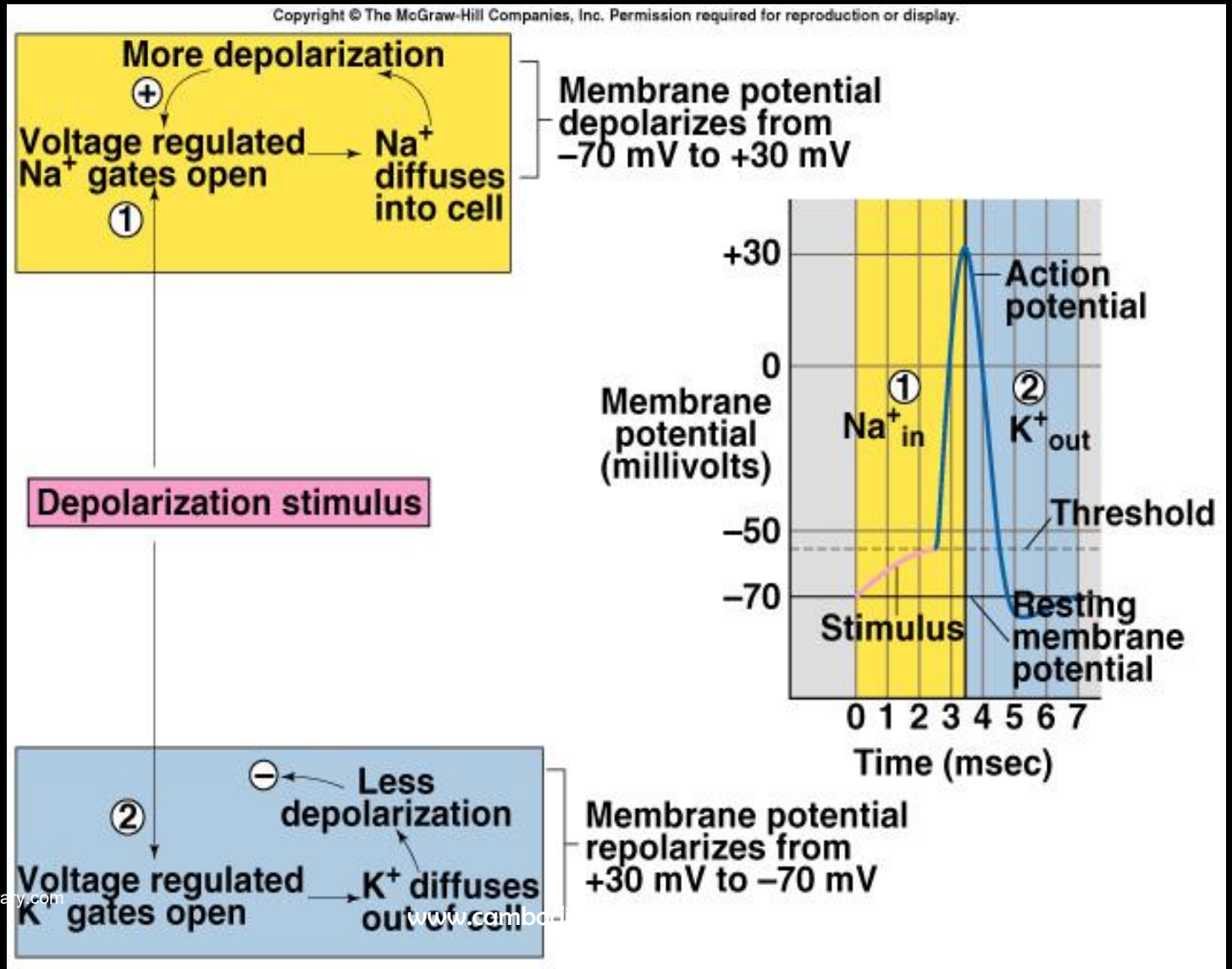
Ion Gating in Axons (continued)



Action Potentials (APs)

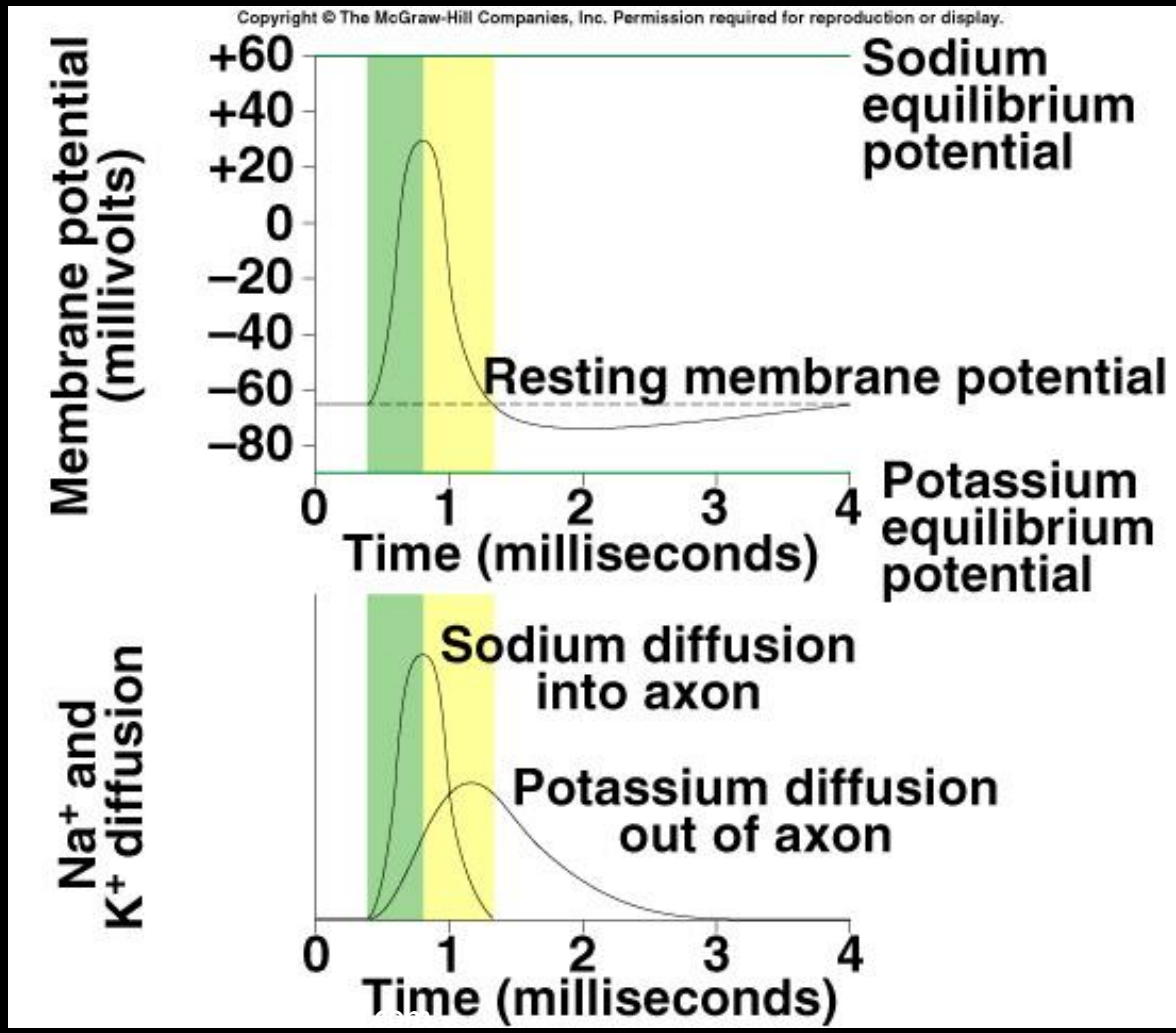
- Stimulus causes depolarization to threshold.
- VG Na^+ channels open.
  - Electrochemical gradient inward.
    - + feedback loop.
  - Rapid reversal in membrane potential from –70 to + 30 mV.
  - VG Na^+ channels become inactivated.
- VG K^+ channels open.
  - Electrochemical gradient outward.
  - - feedback loop.
  - Restore original RMP.

Action Potentials (APs) (continued)



Membrane Permeabilites

- AP is produced by an increase in Na^+ permeability.
- After short delay, increase in K^+ permeability.

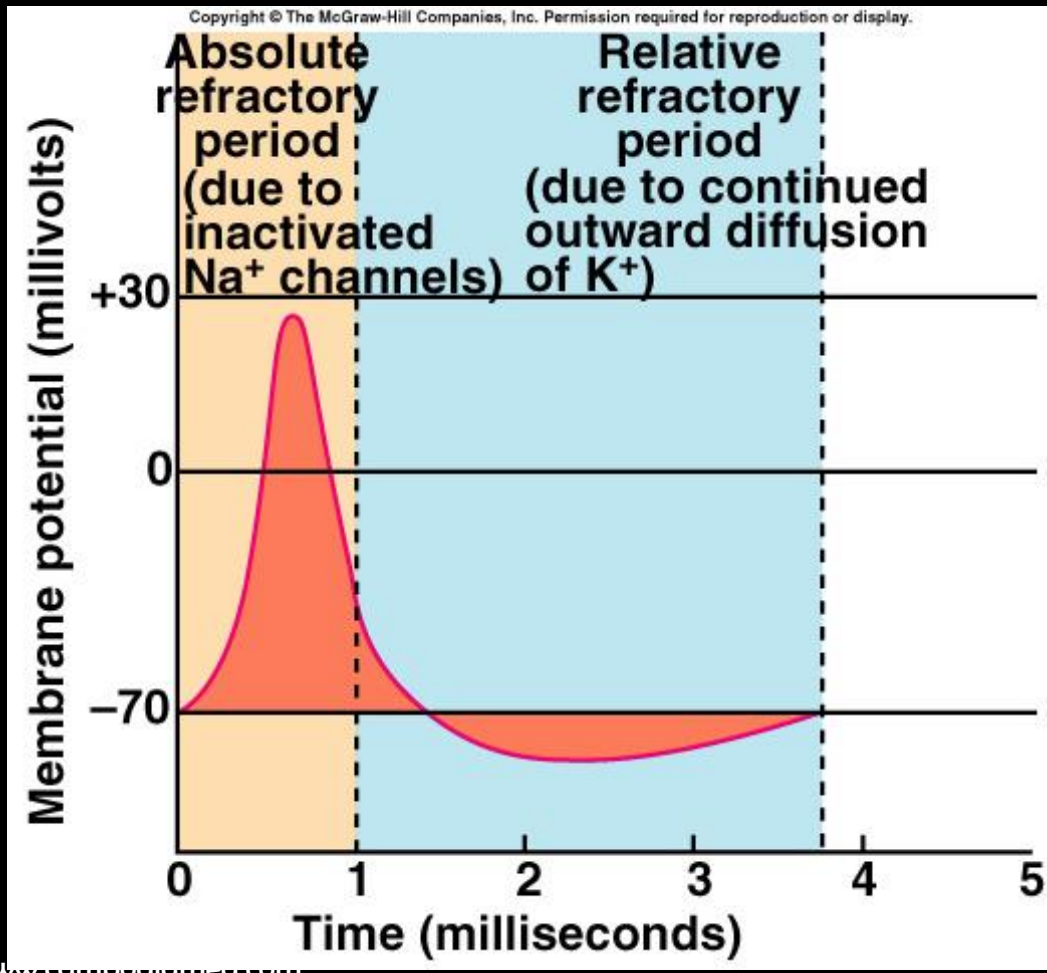


Action Potentials (APs) (continued)

- Depolarization and repolarization occur via diffusion, do not require active transport.
  - Once AP completed, Na^+/K^+ ATPase pump extrudes Na^+, and recovers K^+.
- All or none:
  - When threshold reached, maximum potential change occurs.
  - Amplitude does not normally become more positive than + 30 mV because VG Na^+ channels close quickly and VG K^+ channels open.
  - Duration is the same, only open for a fixed period of time.
- Coding for Stimulus Intensity:
  - Increased frequency of AP indicates greater stimulus strength.
- Recruitment:
  - Stronger stimuli can activate more axons with a higher threshold.

Refractory Periods

- Absolute refractory period:
  - Axon membrane is incapable of producing another AP.
- Relative refractory period:
  - VG ion channel shape alters at the molecular level.
  - VG K^+ channels are open.
  - Axon membrane can produce another action potential, but requires stronger stimulus.

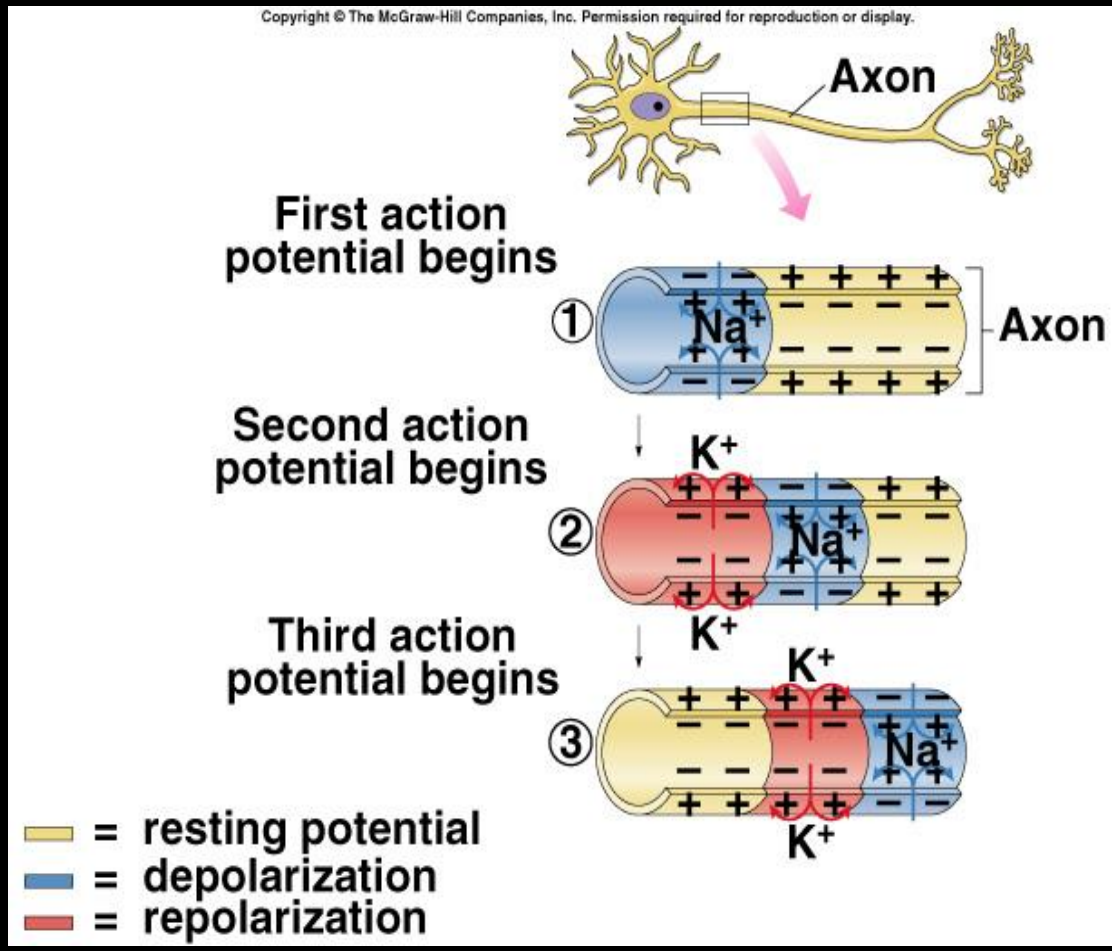


Cable Properties of Neurons

- Ability of neuron to transmit charge through cytoplasm.
- Axon cable properties are poor:
  - High internal resistance.
  - Many charges leak out of the axon through membrane.
- An AP does not travel down the entire axon.
- Each AP is a stimulus to produce another AP in the next region of membrane with VG channels.

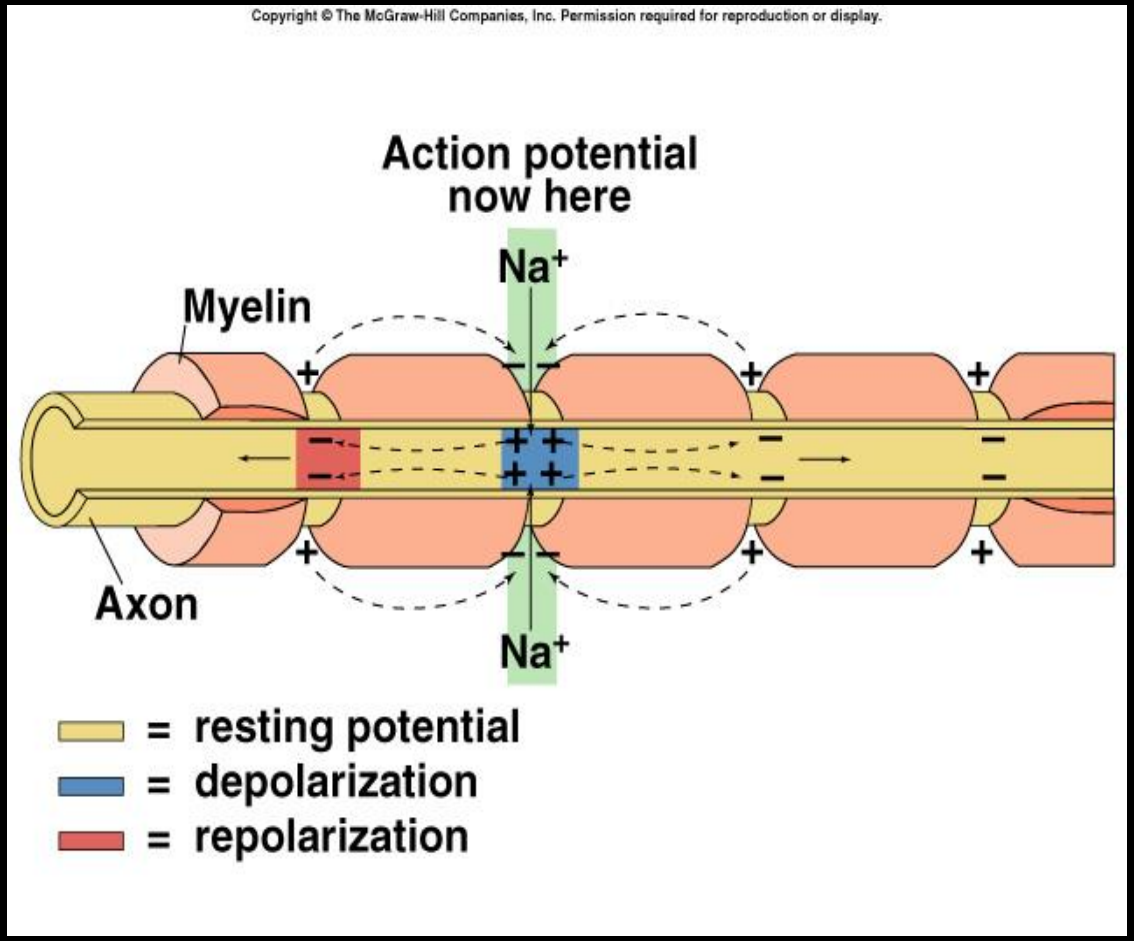
Conduction in an Unmyelinated Axon

- Cable spread of depolarization with influx of Na^+ depolarizes the adjacent region membrane, propagating the AP.
- Conduction rate is slow.
  - AP must be produced at every fraction of micrometer.
- Occurs in 1 direction; previous region is in its refractory period.



Conduction in Myelinated Axon

- Myelin prevents movement of Na^+ and K^+ through the membrane.
- Interruption in myelin (Nodes of Ranvier) contain VG Na^+ and K^+ channels.
- AP occurs only at the nodes.
  - AP at 1 node depolarizes membrane to reach threshold at next node.
- Saltatory conduction (leaps).
  - Fast rate of conduction.

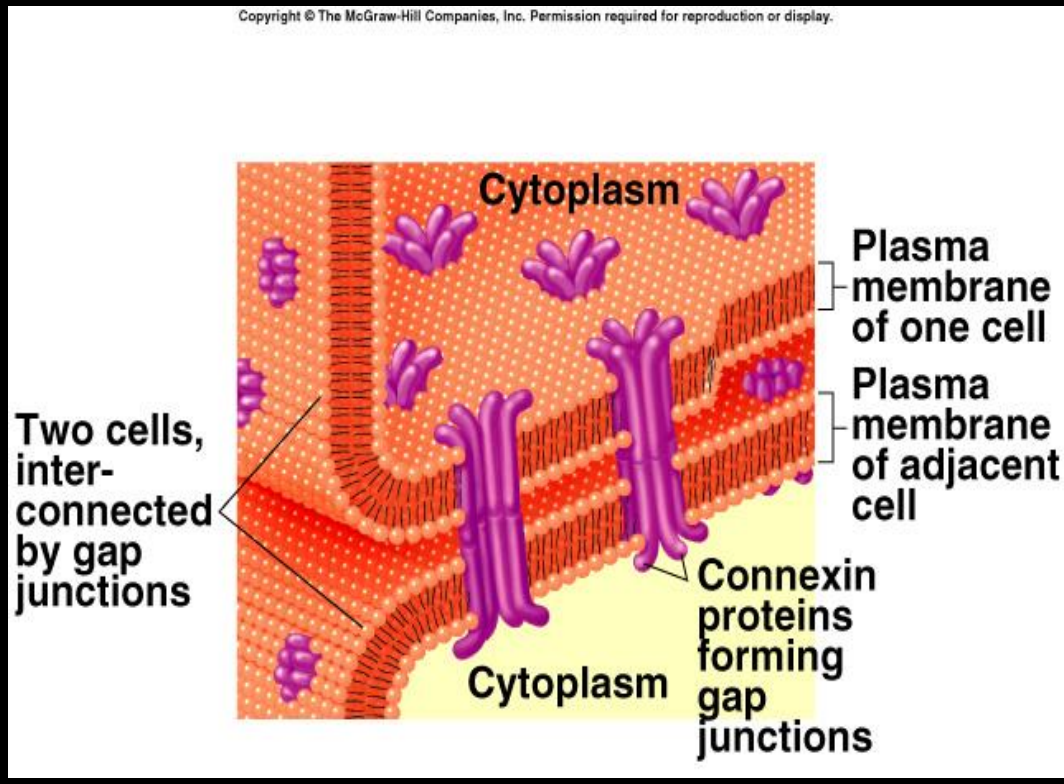


Synapse

- Functional connection between a neuron and another neuron or effector cell.
- Transmission in one direction only.
- Axon of first (presynaptic) to second (postsynaptic) neuron.
- Synaptic transmission is through a chemical gated channel.
- Presynaptic terminal (bouton) releases a neurotransmitter (NT).

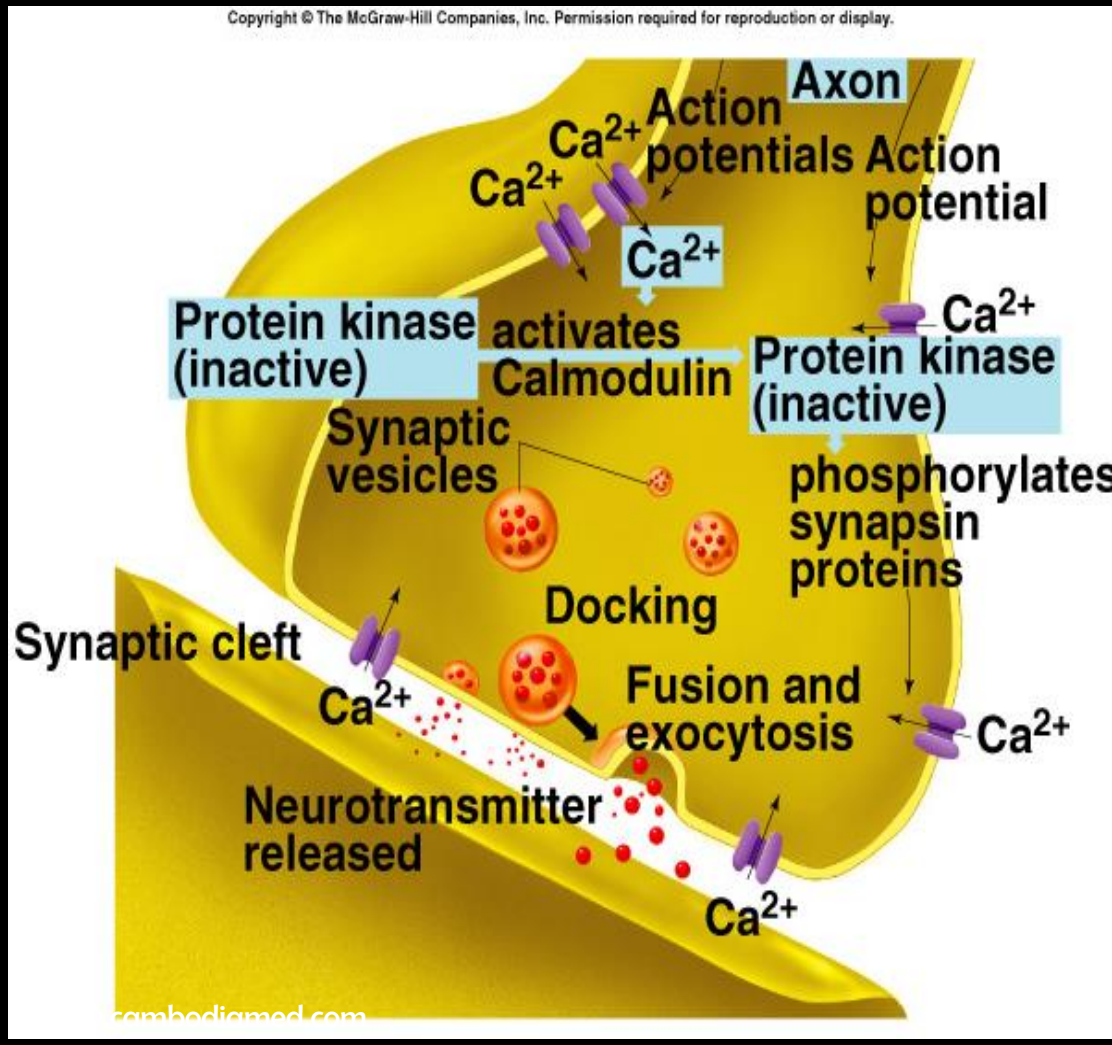
Electrical Synapse

- Impulses can be regenerated without interruption in adjacent cells.
- Gap junctions:
  - Adjacent cells electrically coupled through a channel.
  - Each gap junction is composed of 12 connexin proteins.
- Examples:
  - Smooth and cardiac muscles, brain, and glial cells.



Chemical Synapse

- Terminal bouton is separated from postsynaptic cell by synaptic cleft.
- NTs are released from synaptic vesicles.
- Vesicles fuse with axon membrane and NT released by exocytosis.
- Amount of NTs released depends upon frequency of AP.



Synaptic Transmission

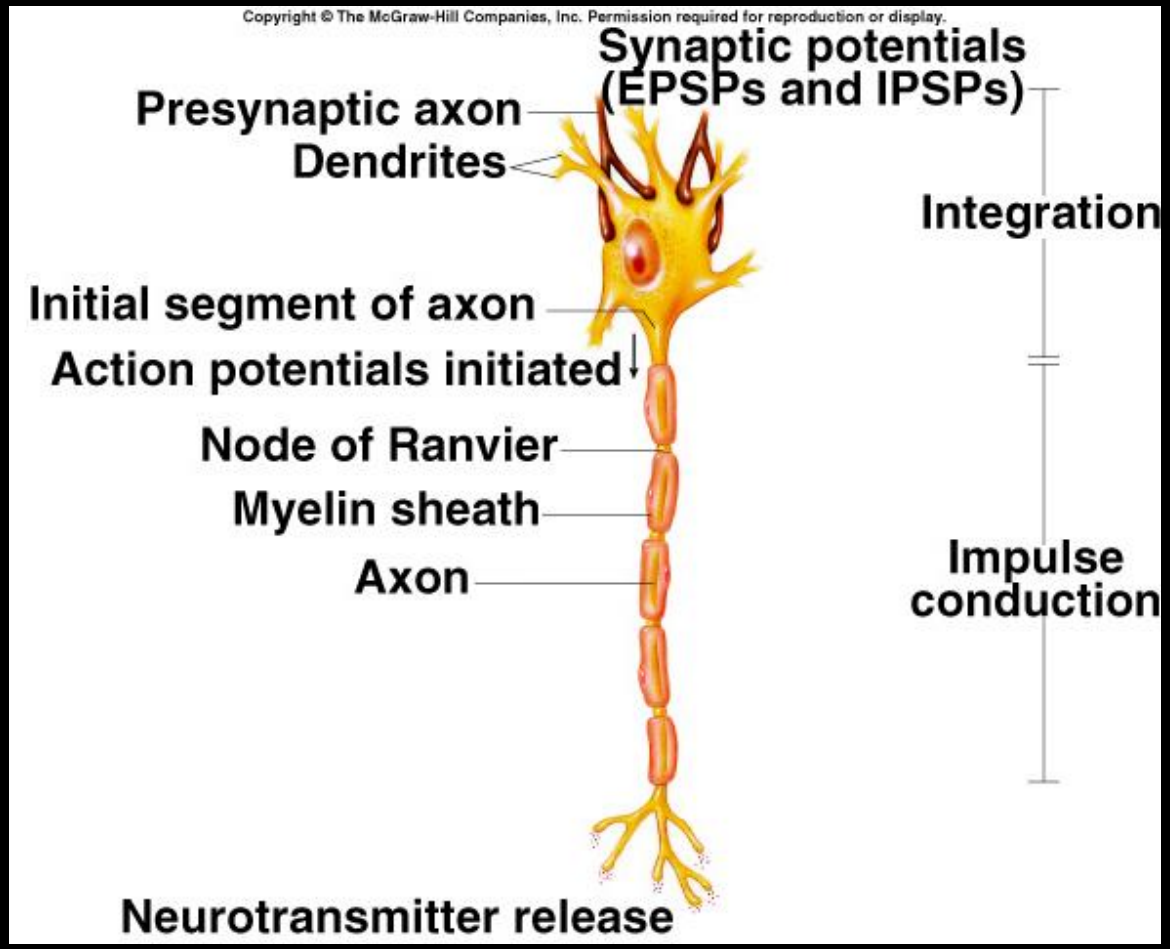
- NT release is rapid because many vesicles form fusion-complexes at "docking site."
- AP travels down axon to bouton.
- VG Ca^{2+} channels open.
  - Ca^{2+} enters bouton down concentration gradient.
  - Inward diffusion triggers rapid fusion of synaptic vesicles and release of NTs.
- Ca^{2+} activates calmodulin, which activates protein kinase.
- Protein kinase phosphorylates synapsins.
  - Synapsins aid in the fusion of synaptic vesicles.

Synaptic Transmission (continued)

- NTs are released and diffuse across synaptic cleft.
- NT (ligand) binds to specific receptor proteins in postsynaptic cell membrane.
- Chemically-regulated gated ion channels open.
  - EPSP: depolarization.
  - IPSP: hyperpolarization.
- Neurotransmitter inactivated to end transmission.

Chemical Synapses

- EPSP (excitatory postsynaptic potential):
  - Depolarization.
- IPSP (inhibitory postsynaptic potential):
  - Hyperpolarization

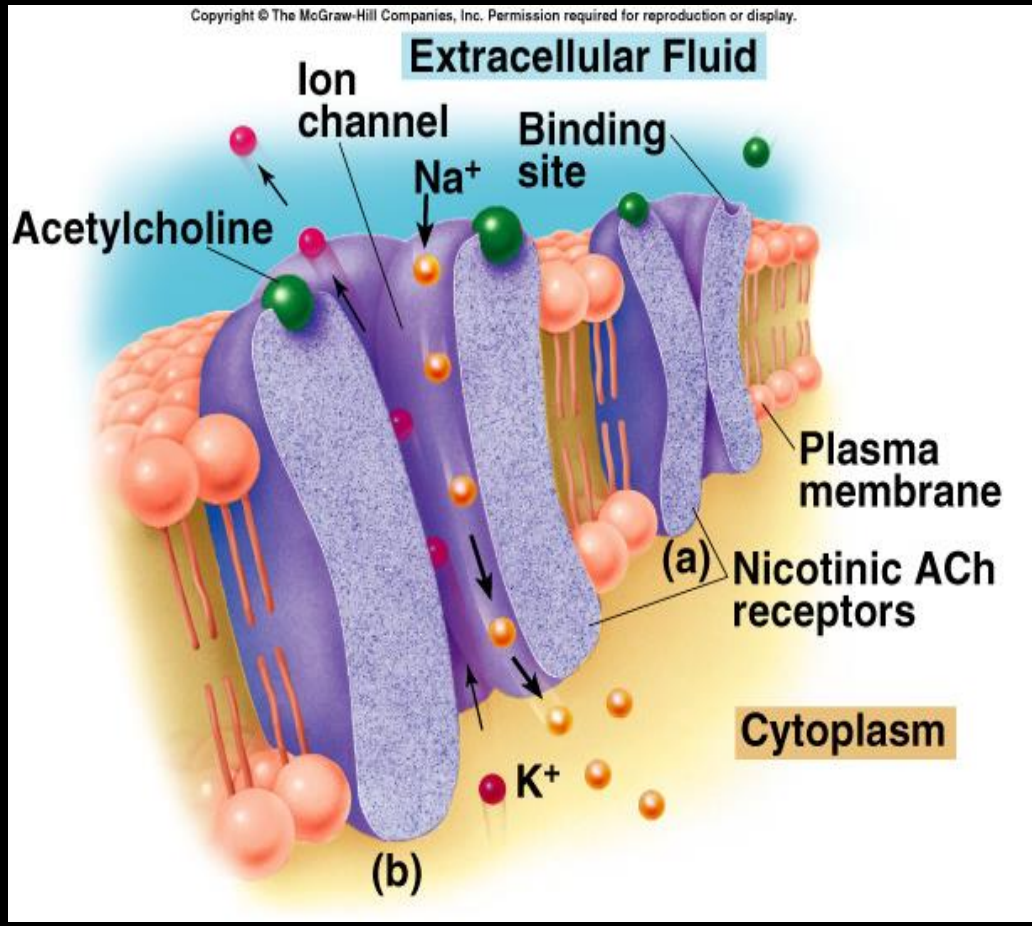


Acetylcholine (ACh) as NT

- ACh is both an excitatory and inhibitory NT, depending on organ involved.
  - Causes the opening of chemical gated ion channels.
- Nicotinic ACh receptors:
  - Found in autonomic ganglia and skeletal muscle fibers.
- Muscarinic ACh receptors:
  - Found in the plasma membrane of smooth and cardiac muscle cells, and in cells of particular glands.

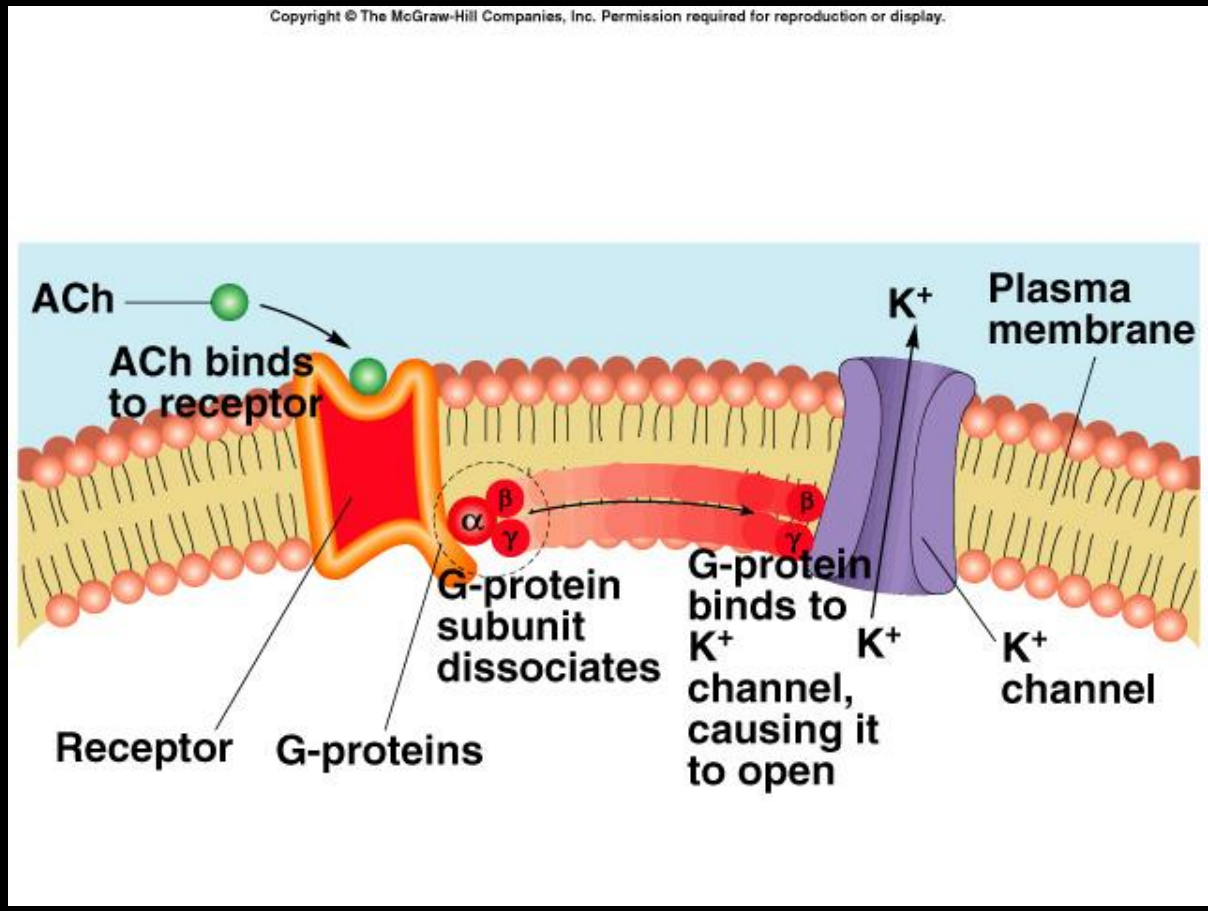
Ligand-Operated ACh Channels

- Most direct mechanism.
- Ion channel runs through receptor.
  - Receptor has 5 polypeptide subunits that enclose ion channel.
  - 2 subunits contain ACh binding sites.
- Channel opens when both sites bind to ACh.
  - Permits diffusion of Na^+ into and K^+ out of postsynaptic cell.
- Inward flow of Na^+ dominates.
  - Produces EPSPs.



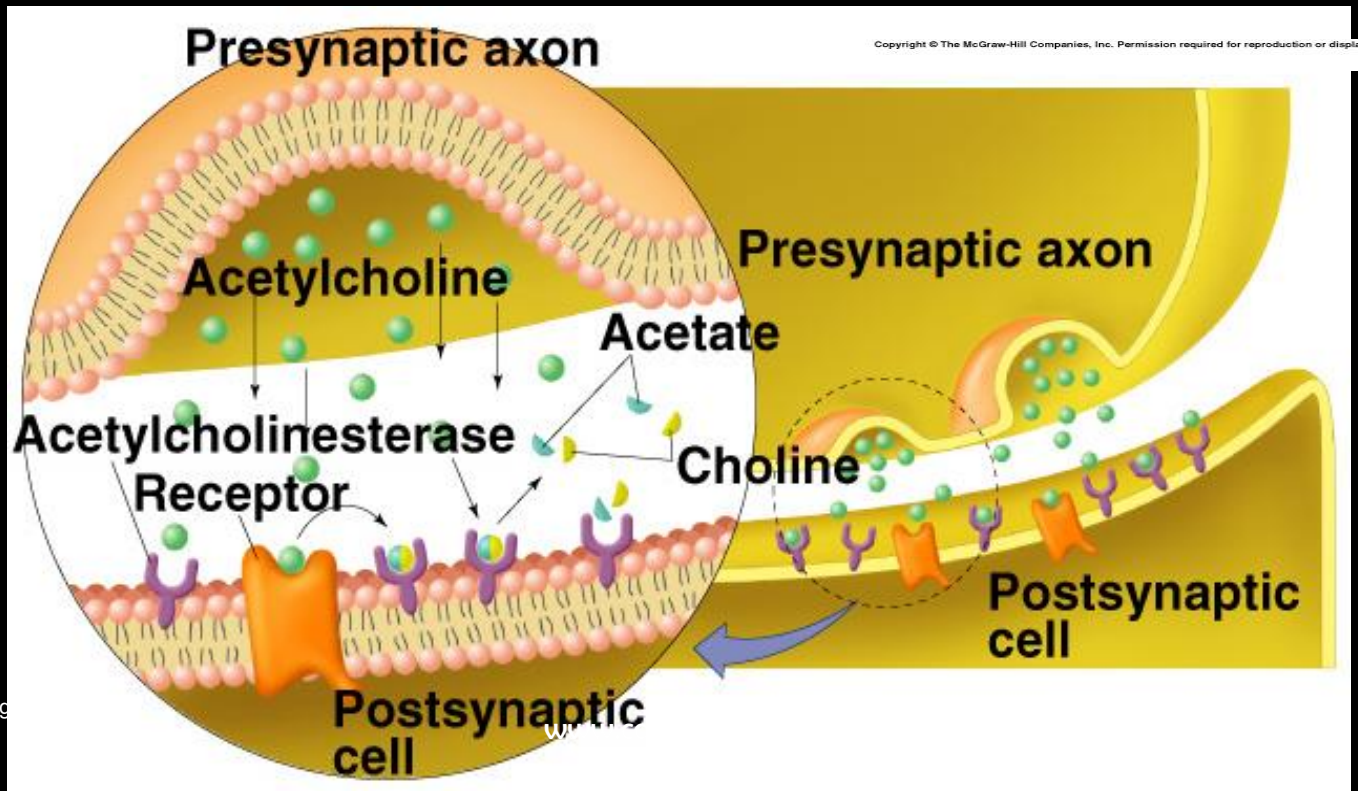
G Protein-Operated ACh Channel

- Only 1 subunit.
- Ion channels are separate proteins located away from the receptors.
- Binding of ACh activates alpha G-protein subunit.
- Alpha subunit dissociates.
- Alpha subunit or the beta-gamma complex diffuses through membrane until it binds to ion channel, opening it.



Acetylcholinesterase (AChE)

- Enzyme that inactivates ACh.
  - Present on postsynaptic membrane or immediately outside the membrane.
- Prevents continued stimulation.



ACh in CNS

- Cholinergic neurons:
  - Use ACh as NT.
  - Axon bouton synapses with dendrites or cell body of another neuron.
- First VG channels are located at axon hillock.
- EPSPs spread by cable properties to initial segment of axon.
- Gradations in strength of EPSPs above threshold determine frequency of APs produced at axon hillock.

ACh in PNS

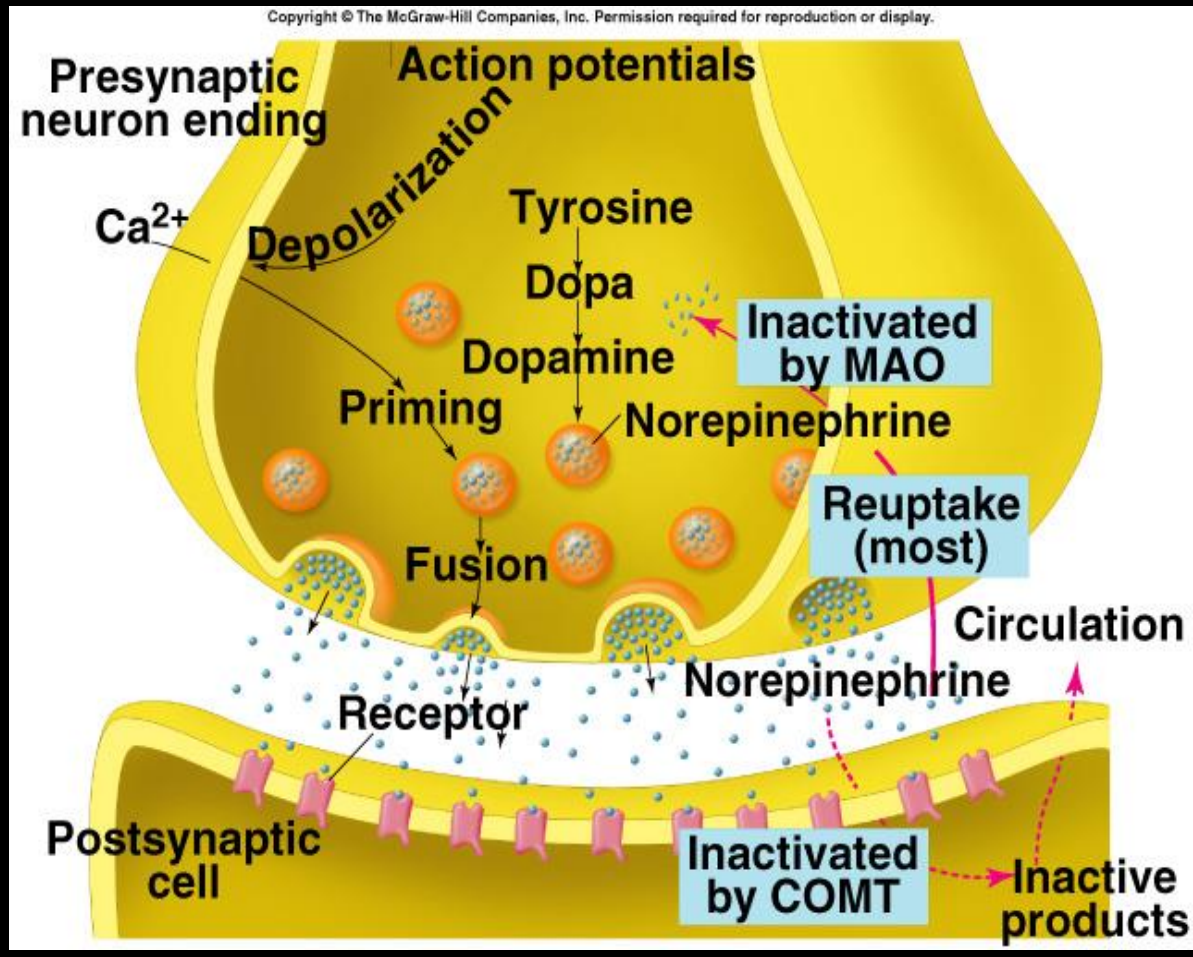
- Somatic motor neurons synapse with skeletal muscle fibers.
  - Release ACh from boutons.
  - Produces end-plate potential (EPSPs).
- Depolarization opens VG channels adjacent to end plate.

Monoamines as NT

- Monoamine NTs:
  - Epinephrine.
  - Norepinephrine.
  - Serotonin.
  - Dopamine.
- Released by exocytosis from presynaptic vesicles.
- Diffuse across the synaptic cleft.
- Interact with specific receptors in postsynaptic membrane.

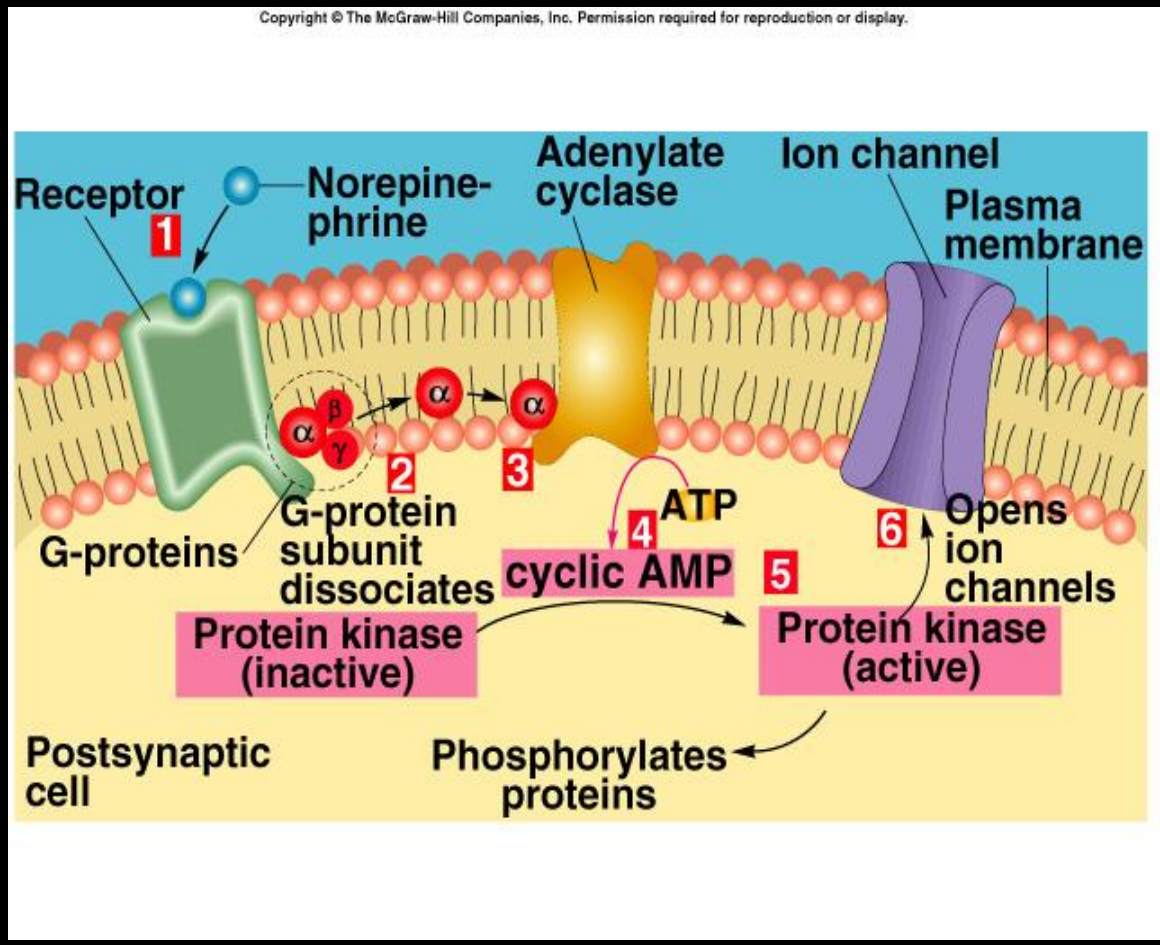
Inhibition of Monoamines as NT

- Reuptake of monoamines into presynaptic membrane.
  - Enzymatic degradation of monoamines in presynaptic membrane by MAO.
- Enzymatic degradation of catecholamines in postsynaptic membrane by COMT.



Mechanism of Action

- Monoamine NT do not directly open ion channels.
- Act through second messenger, such as cAMP.
- Binding of norepinephrine stimulates dissociation of G-protein alpha subunit.
- Alpha subunit binds to adenylate cyclase, converting ATP to cAMP.
- cAMP activates protein kinase, phosphorylating other proteins.
- Open ion channels.



Serotonin as NT

- NT (derived from L-tryptophan) for neurons with cell bodies in raphe nuclei.
- Regulation of mood, behavior, appetite, and cerebral circulation.
- SSRIs (serotonin-specific reuptake inhibitors):
  - Inhibit reuptake and destruction of serotonin, prolonging the action of NT.
  - Used as an antidepressant.
    - Reduces appetite, treatment for anxiety, treatment for migraine headaches.

Dopamine an NT

- NT for neurons with cell bodies in midbrain.
- Axons project into:
  - Nigrostriatal dopamine system:
    - Nuerons in substantia nigra send fibers to corpus straitum.
    - Initiation of skeletal muscle movement.
    - Parkinson's disease: degeneration of neurons in substantia nigra.
  - Mesolimbic dopamine system:
    - Neurons originate in midbrain, send axons to limbic system.
    - Involved in behavior and reward.
    - Addictive drugs:
      - Promote activity in nucleus accumbens.

Norepinephrine (NE) as NT

- NT in both PNS and CNS.
- PNS:
  - Smooth muscles, cardiac muscle and glands.
    - Increase in blood pressure, constriction of arteries.
- CNS:
  - General behavior.

Amino Acids as NT

- Glutamic acid and aspartic acid:
  - Major excitatory NTs in CNS.
- Glutamic acid:
  - NMDA receptor involved in memory storage.
- Glycine:
  - Inhibitory, produces IPSPs.
  - Opening of Cl^- channels in postsynaptic membrane.
    - Hyperpolarization.
  - Helps control skeletal movements.
- GABA (gamma-aminobutyric acid):
  - Most prevalent NT in brain.
  - Inhibitory, produces IPSPs.
    - Hyperpolarizes postsynaptic membrane.
      - Motor functions in cerebellum.

Polypeptides as NT

- CCK:
  - Promote satiety following meals.
- Substance P:
  - Major NT in sensations of pain.
- Synaptic plasticity (neuromodulating effects):
  - Neurons can release classical NT or the polypeptide NT.

Polypeptides as NT

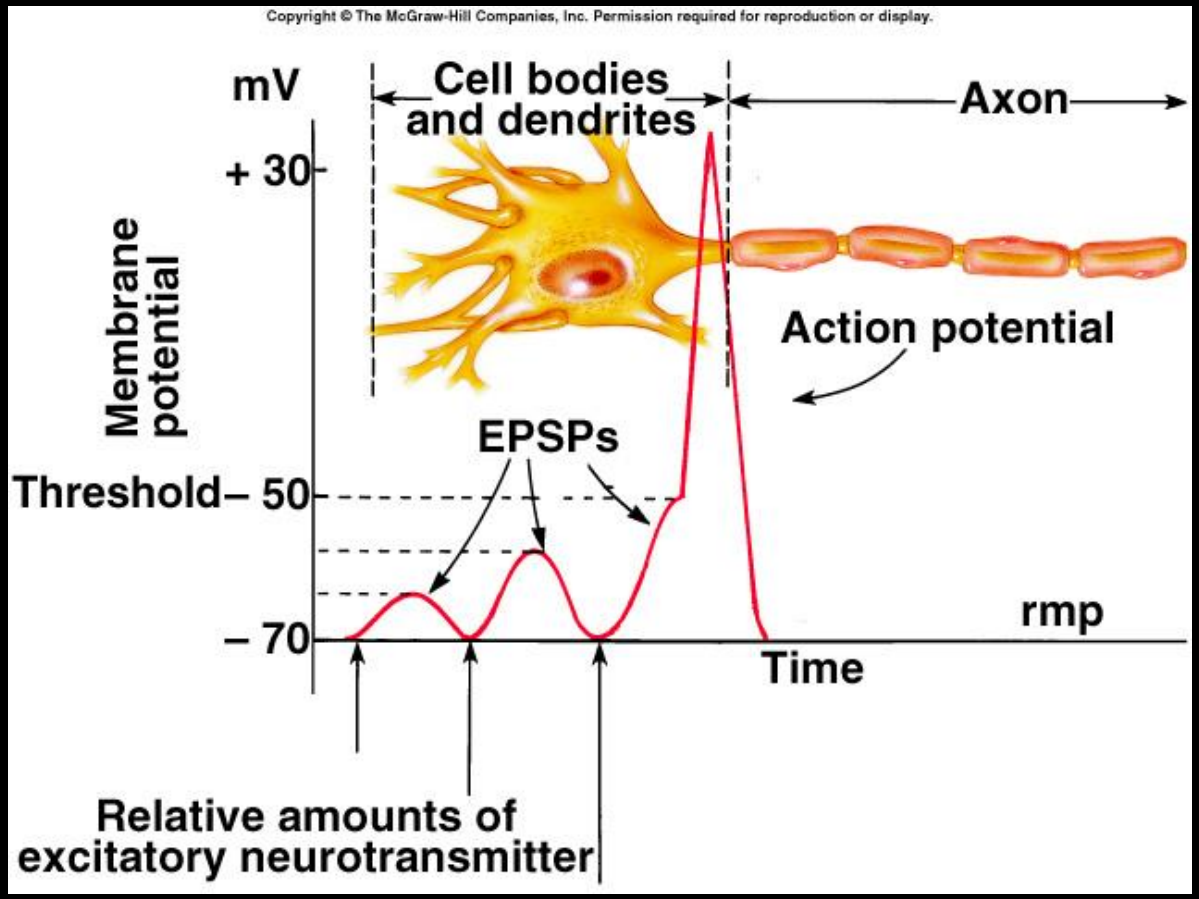
- Endogenous opiods:
  - Brain produces its own analgesic endogenous morphine-like compounds, blocking the release of substance P.
  - Beta-endorphin, enkephalins, dynorphin.
- Neuropeptide Y:
  - Most abundant neuropeptide in brain.
  - Inhibits glutamate in hippocampus.
  - Powerful stimulator of appetite.
- NO:
  - Exerts its effects by stimulation of cGMP.
  - Macrophages release NO to helps kill bacteria.
  - Involved in memory and learning.
  - Smooth muscle relaxation.

Endogenous Cannabinoids, Carbon Monoxide

- Endocannabinoids:
  - Bind to the same receptor as THC.
  - Act as analgesics.
  - Function as retrograde NT.
- Carbon monoxide:
  - Stimulate production of cGMP within neurons.
  - Promotes odor adaptation in olfactory neurons.
  - May be involved in neuroendocrine regulation in hypothalamus.

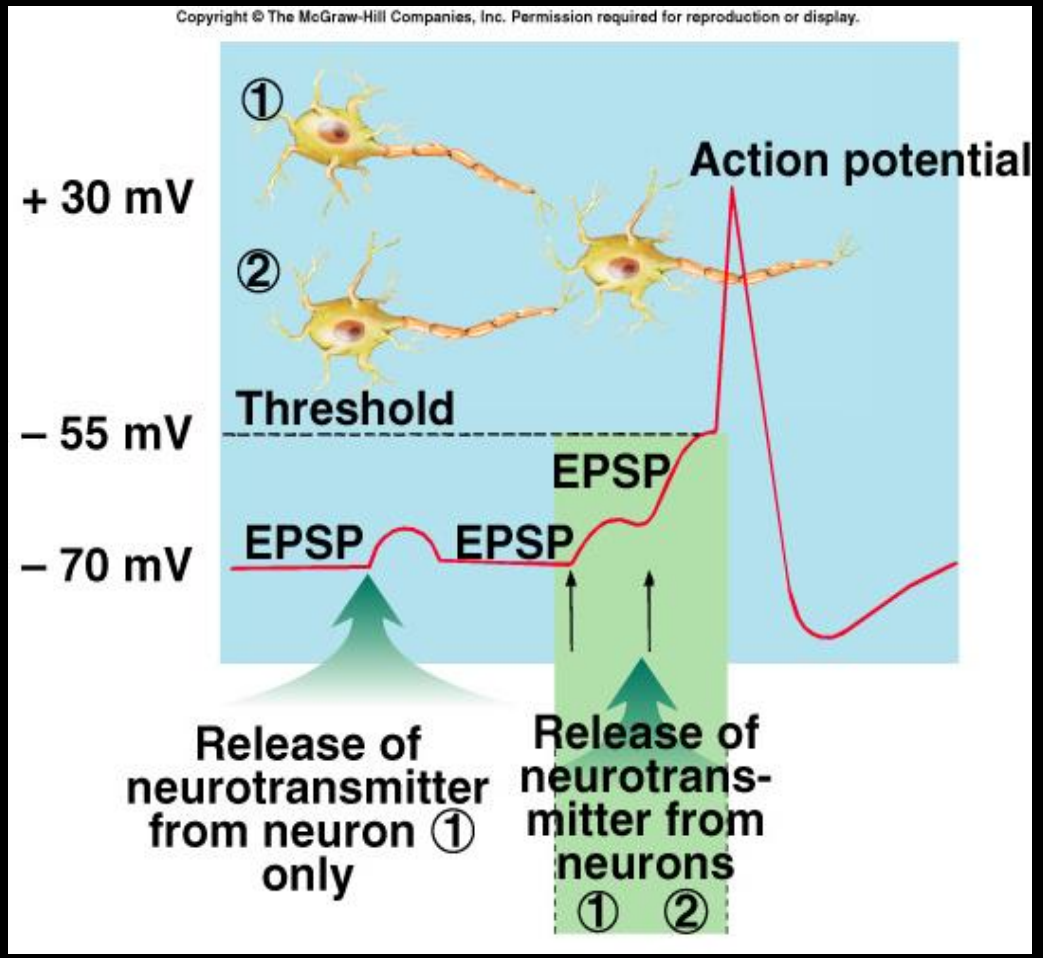
EPSP

- No threshold.
- Decreases resting membrane potential.
  - Closer to threshold.
- Graded in magnitude.
- Have no refractory period.
- Can summate.



Synaptic Integration

- EPSPs can summate, producing AP.
  - Spatial summation:
    - Numerous boutons converge on a single postsynaptic neuron (distance).
  - Temporal summation:
    - Successive waves of neurotransmitter release (time).

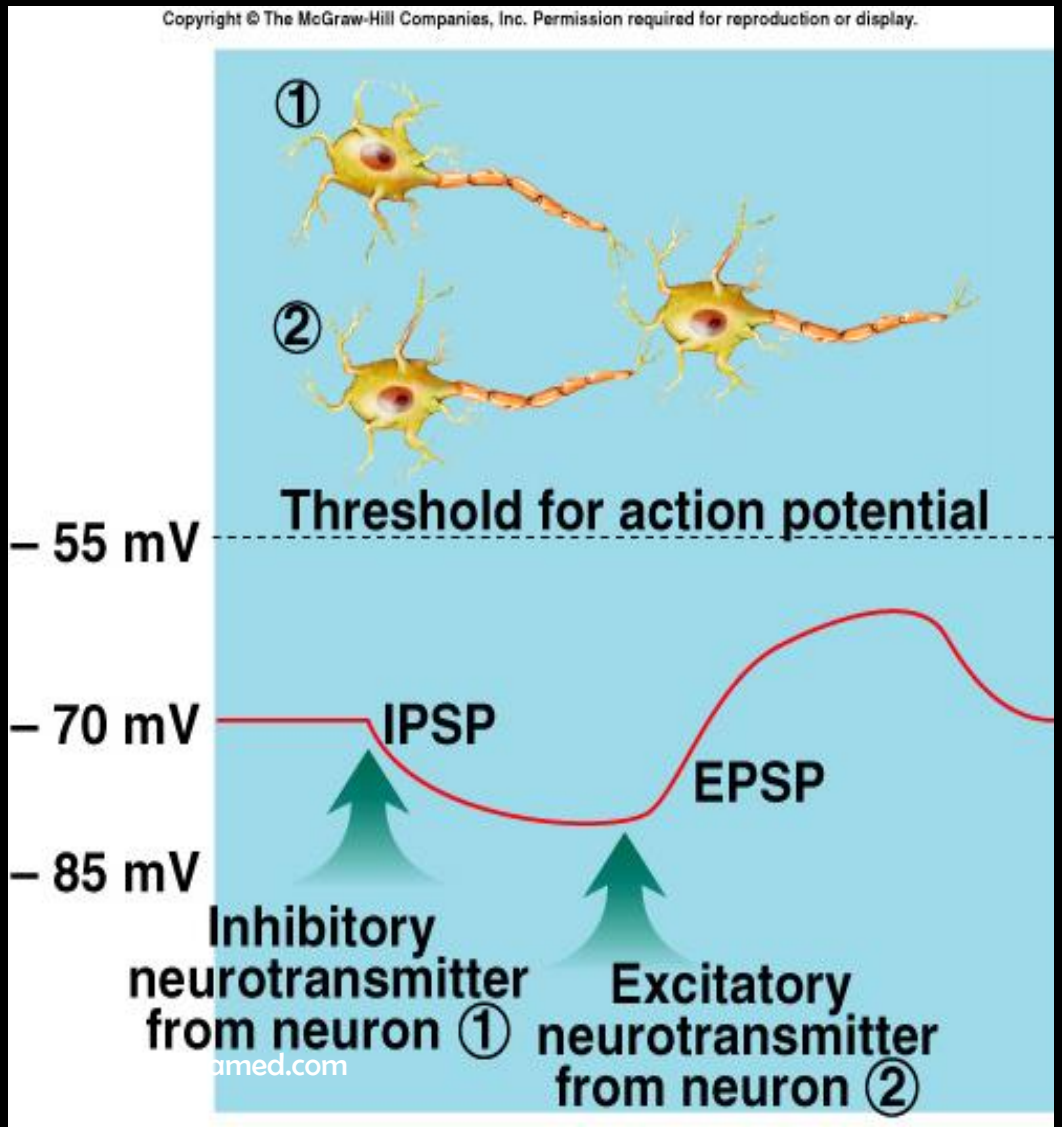


Long-Term Potentiation

- May favor transmission along frequently used neural pathways.
- Neuron is stimulated at high frequency, enhancing excitability of synapse.
  - Improves efficacy of synaptic transmission.
- Neural pathways in hippocampus use glutamate, which activates NMDA receptors.
  - Involved in memory and learning.

Synaptic Inhibition

- Presynaptic inhibition:
  - Amount of excitatory NT released is decreased by effects of second neuron, whose axon makes synapses with first neuron's axon.
- Postsynaptic inhibition
- (IPSPs):
  - No threshold.
  - Hyperpolarize postsynaptic membrane.
  - Increase membrane potential.
  - Can summate.
  - No refractory period.



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