Chapter 4 細胞及環境的互動

4-1　細胞外環境

4-2　細胞間的溝通

4-3　物質通過細胞膜的運輸方式

✓4-4　細胞的興奮性 (p.110-114)

Chapter 5 神經傳訊

5-1　神經組織

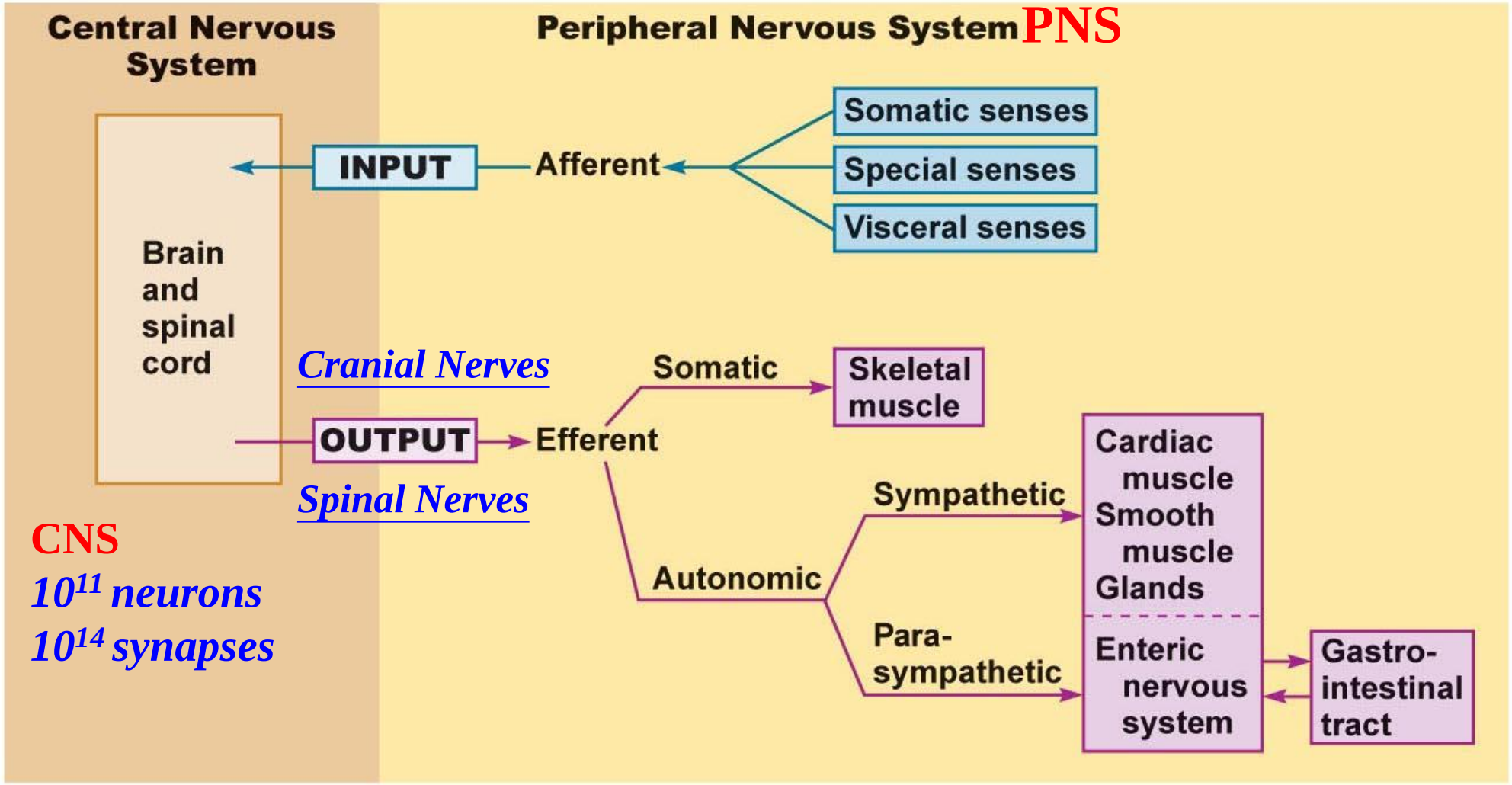
5-2　動作電位

5-3　突 觸

5-4　神經傳遞物質

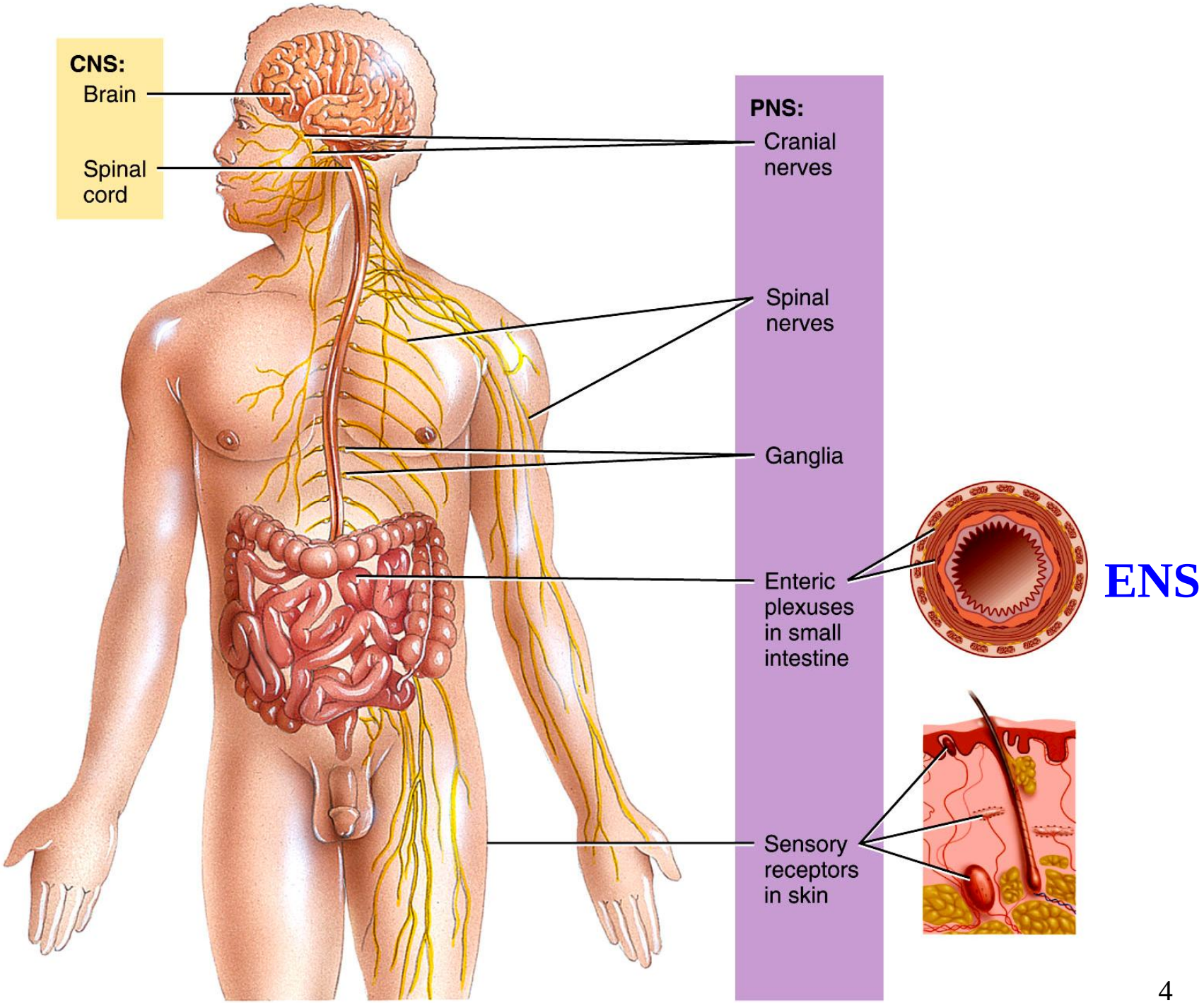
Overview of the Nervous System

Controls and integrates all body activities within limits that maintain life



Subdivisions of the PNS

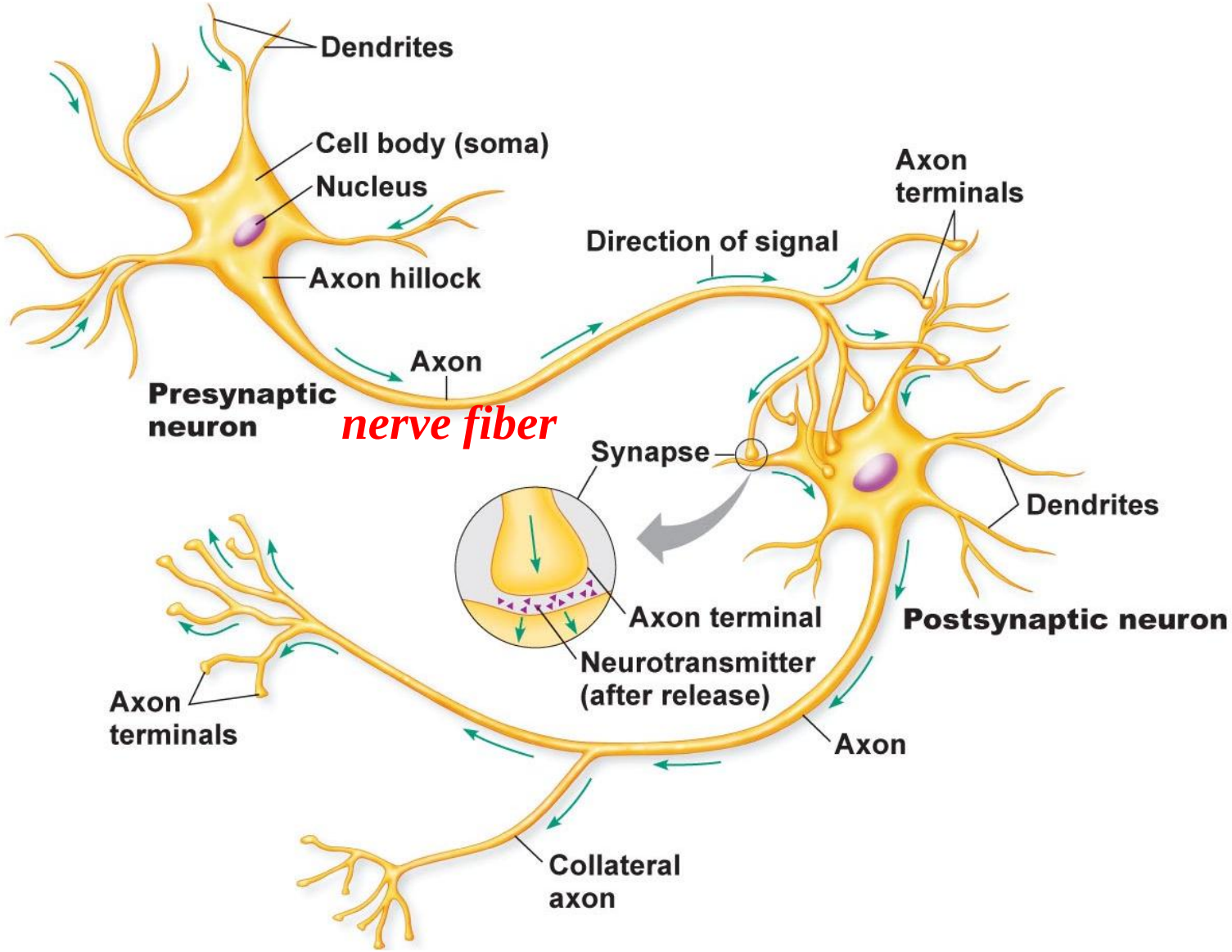
- **Somatic (voluntary) nervous system (SNS)**
  --neurons from cutaneous and special sensory receptors to the CNS (input)
  --motor neurons to skeletal muscle tissue (output)
- **Autonomic (involuntary) nervous systems (ANS)**
  --sensory neurons from visceral organs to CNS
  --motor neurons to smooth & cardiac muscle and glands
    - **sympathetic** division (speeds up heart rate)
    - **parasympathetic** division (slow down heart rate)
- **Enteric nervous system (ENS)**
  --involuntary sensory & motor neurons control GI tract
  --neurons function independently of ANS & CNS


CNS:
Brain
Spinal cord
PNS:
Cranial nerves
Spinal nerves
Ganglia
Enteric plexuses in small intestine
Sensory receptors in skin
ENS

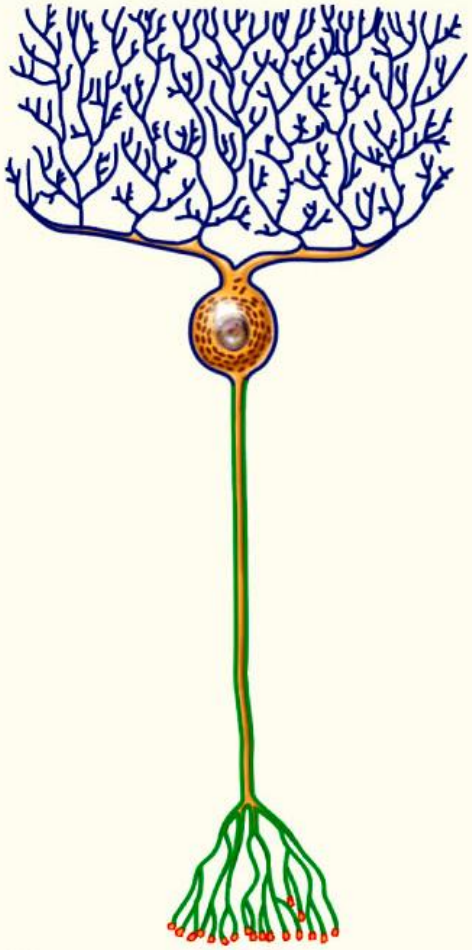
Cells of the Nervous System

***Neurons*: conduct impulses (excitable cells)**

***Glial cells*: support the neurons (support cells)**



Summary of Neuronal Structure and Function

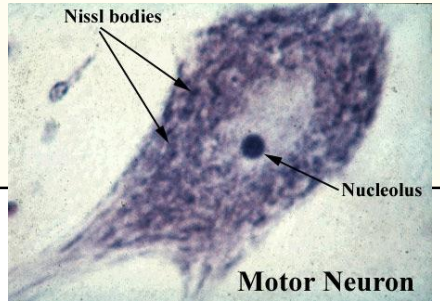


STRUCTURE	FUNCTIONS
Dendrites	Receive stimuli through activation of ligand-gated or mechanically gated ion channels; in sensory neurons, produce generator or receptor potentials; in motor neurons and interneurons, produce excitatory and inhibitory postsynaptic potentials (EPSPs and IPSPs).
Cell body	Receives stimuli and produces EPSPs and IPSPs through activation of ligand-gated ion channels.
Junction of axon hillock and initial segment of axon	Trigger zone in many neurons; integrates EPSPs and IPSPs and, if sum is a depolarization that reaches threshold, initiates action potential (nerve impulse).
Axon	Propagates nerve impulses from initial segment (or from dendrites of sensory neurons) to axon terminals in a self-regenerating manner; impulse amplitude does not change as it propagates along the axon.
Axon terminals and synaptic end bulbs (or varicosities)	Inflow of Ca^{2+} caused by depolarizing phase of nerve impulse triggers exocytosis of neurotransmitter from synaptic vesicles.

Key:

- Plasma membrane includes chemically gated channels
- Plasma membrane includes voltage-gated Na^+ and K^+ channels
- Plasma membrane includes voltage-gated Ca^{2+} channels

- ***Nissl bodies (chromatophilic substance) --rough ER (with ribosomes) for protein synthesis***



Axonal Transport

- **Cell body is location for most protein synthesis**

  --neurotransmitters & repair proteins

- **Axonal transport system moves substances**

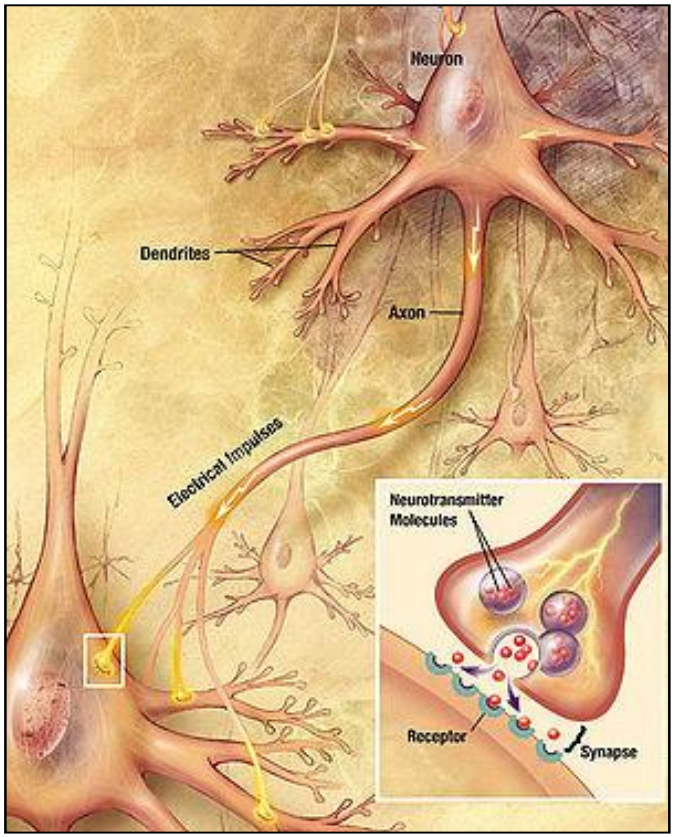
  --Slow axonal flow

  - movement in one direction only -- away from cell body
  - movement at 1-5 mm per day

  --Fast axonal flow

  - moves organelles & materials along surface of microtubules
  - at 200-400 mm per day
  - transports in either direction
  - for use or for recycling in cell body

Cellular Communication

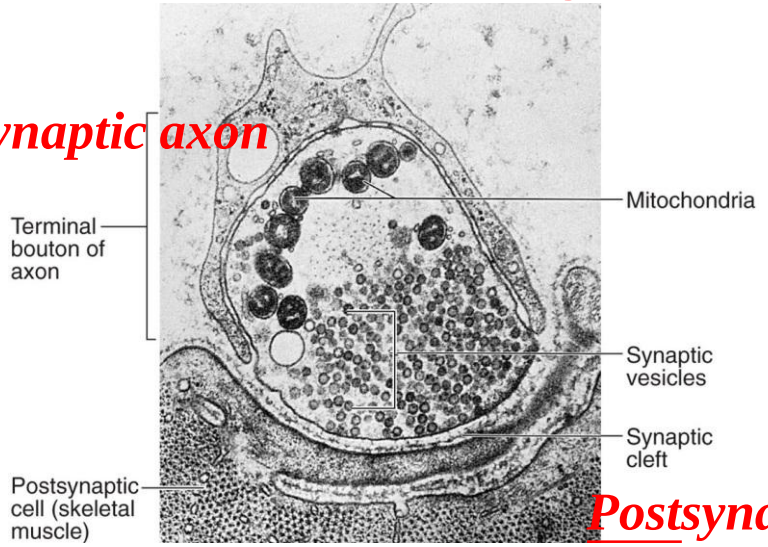


Intracellular communication

Impulses

Intercellular communication

Chemical messengers



Synapses

--***Chemical synapses:*** Site of communication between two neurons (CNS) or between a neuron and an effector organ (PNS)

--***Electrical synapses:*** Occur in smooth muscle and cardiac muscle, between some neurons of the brain, and between glial cells **(gap junction)**

Localization of Ion Channels: Neuron

- **Leak (non-gated) channels**

  --always open, responsible for resting membrane potential
  --found in the cell membrane throughout a neuron

- **Ligand-gated channels**

  --Open or close in response to ligand binding

  --Most located in the **dendrite and soma**

- **Voltage-gated channels**

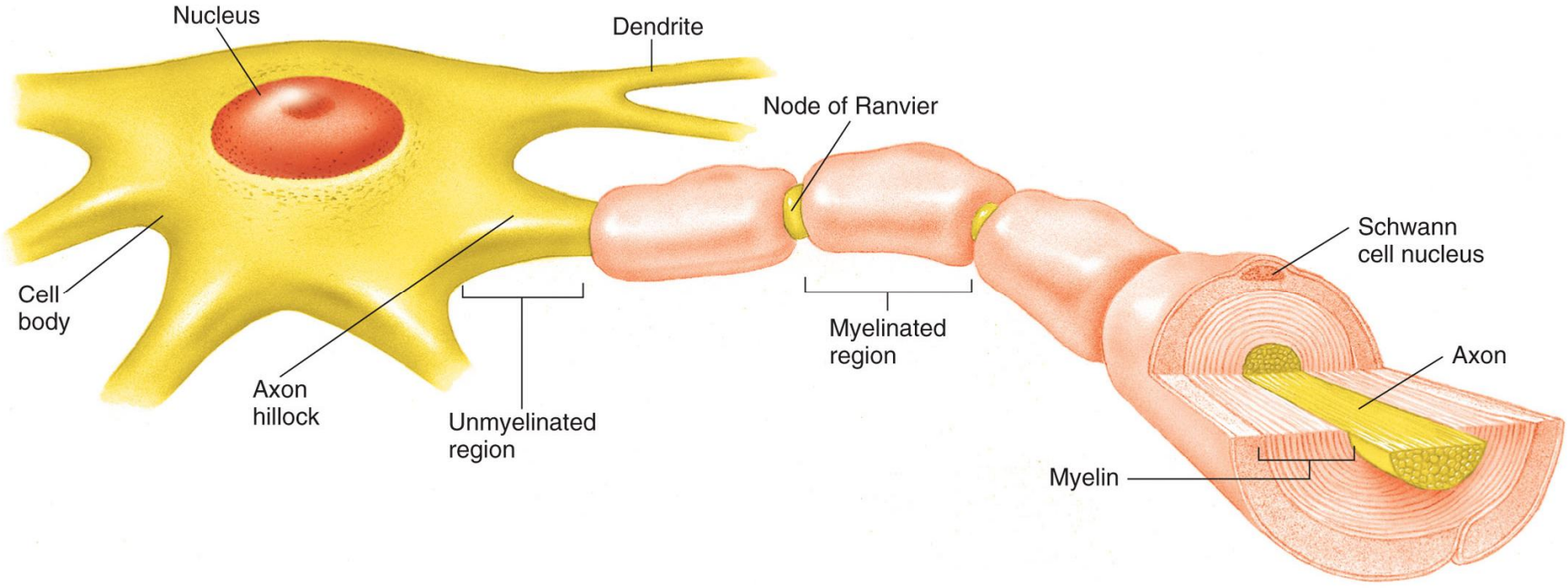
  --Open or close in response to change in membrane potential

  --located in throughout the neuron, most densely in the **axon hillock and axon**

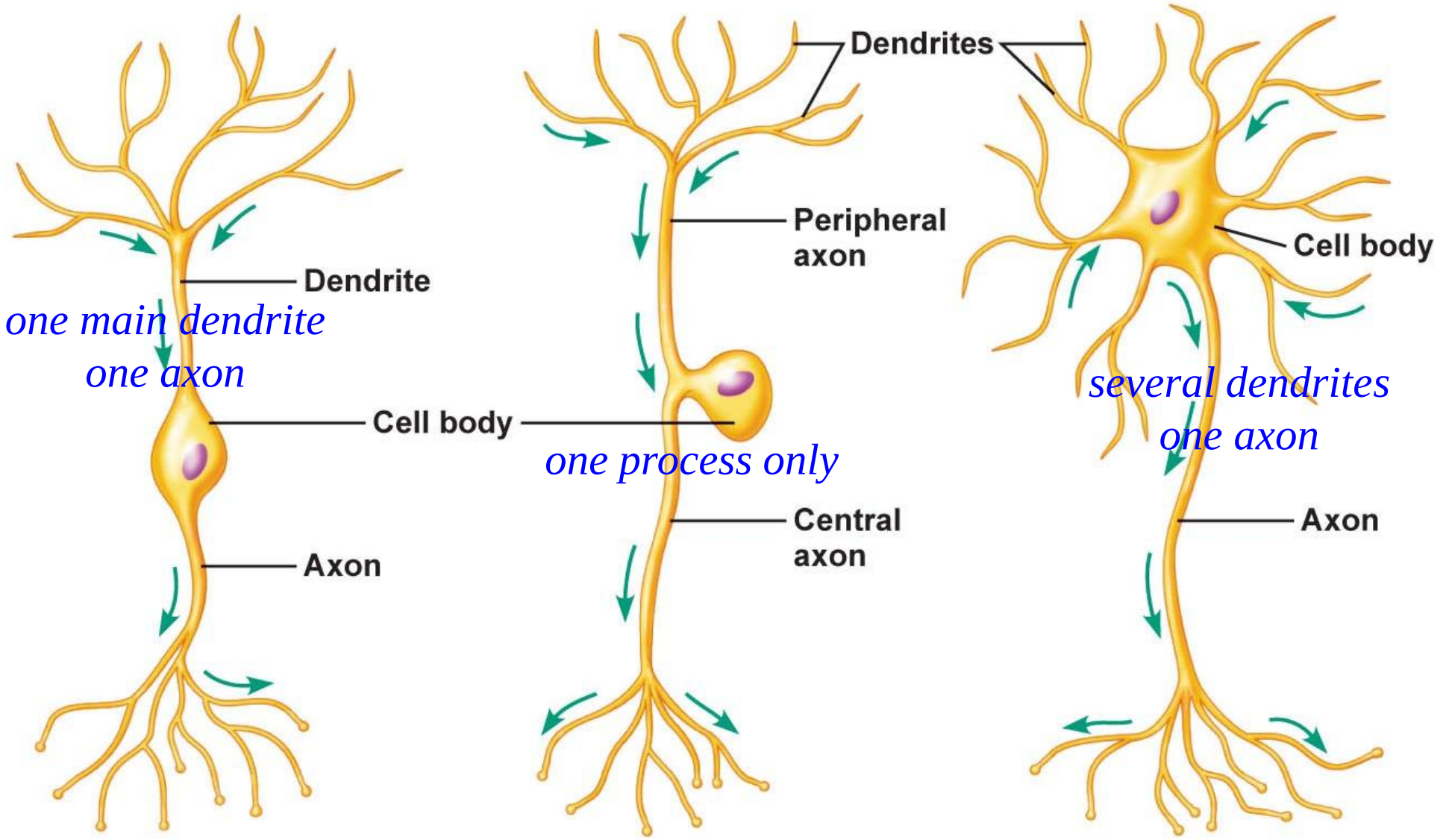
Localization of Ion Channels: Neuron

Ion Channels in Neurons

TYPE OF ION CHANNEL	DESCRIPTION	LOCATION
Leakage channels	Gated channels that randomly open and close.	Found in nearly all cells, including the dendrites, cell bodies, and axons of all types of neurons.
Ligand-gated channels	Gated channels that open in response to the binding of a ligand (chemical) stimulus.	Dendrites of some sensory neurons such as pain receptors and dendrites and cell bodies of interneurons and motor neurons.
Mechanically gated channels	Gated channels that open in response to the binding of a mechanical stimulus (such as touch, pressure, vibration, and tissue stretching).	Dendrites of some sensory neurons such as touch receptors, pressure receptors, and some pain receptors.
Voltage-gated channels	Gated channels that open in response to a voltage stimulus (change in membrane potential).	Axons of all types of neurons.



Structural Classes of Neurons



one main dendrite
one axon

one process only

several dendrites
one axon

(a) Bipolar

Olfaction (smell)
Vision (retina)

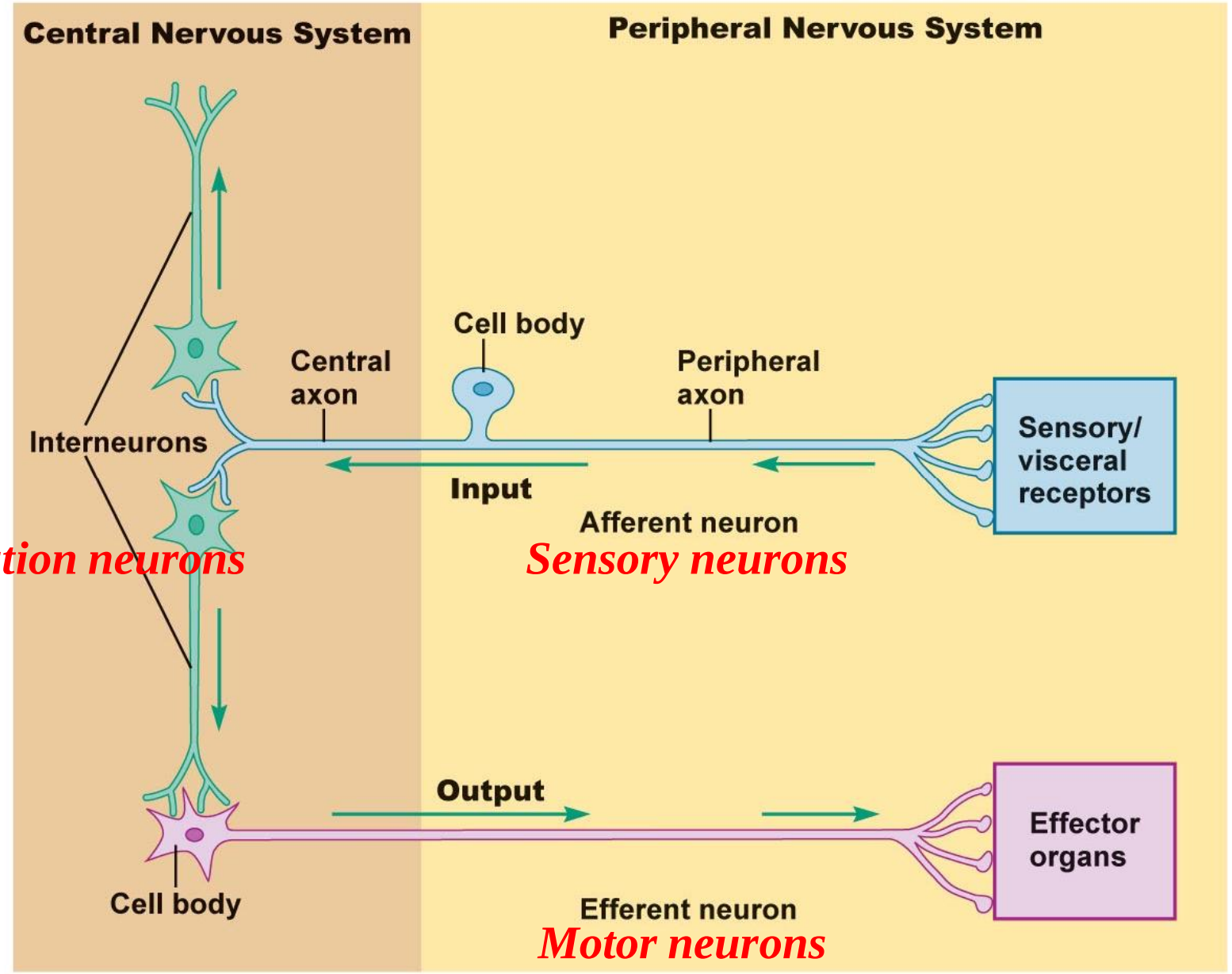
(b) Pseudo-unipolar

Most sensory neurons

(c) Multipolar

Most common neurons

Functional Classes of Neurons

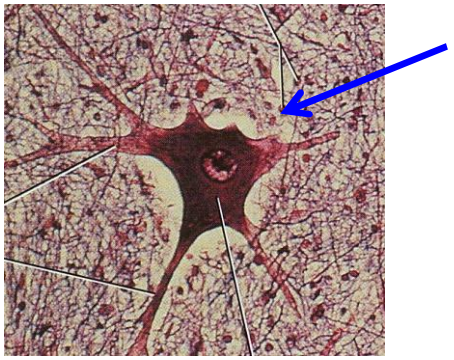


Terminology of the Nervous System

Term	Definition
Central nervous system (CNS)	Brain and spinal cord
Peripheral nervous system (PNS)	Nerves, ganglia, and nerve plexuses (outside of the CNS)
Association neuron (interneuron)	Multipolar neuron located entirely within the CNS
Sensory neuron (afferent neuron)	Neuron that transmits impulses from a sensory receptor into the CNS
Motor neuron (efferent neuron)	Neuron that transmits impulses from the CNS to an effector organ; for example, a muscle
Nerve	Cablelike collection of many axons in the PNS; may be "mixed" (contain both sensory and motor fibers)
Somatic motor nerve	Nerve that stimulates contraction of skeletal muscles
Autonomic motor nerve	Nerve that stimulates contraction (or inhibits contraction) of smooth muscle and cardiac muscle and that stimulates glandular secretion
Ganglion	Grouping of neuron cell bodies located outside the CNS
Nucleus	Grouping of neuron cell bodies within the CNS **(Gray matter)**
Tract	Grouping of axons that interconnect regions of the CNS **(White matter)**

Glial (Latin for "glue") Cells

- 90% of CNS composed of glia (neuroglial cells)
- Smaller cells than neurons
- 50X more numerous
- Cells can divide



  --rapid mitosis in tumor formation (gliomas)

- 4 cell types in **CNS**

  --Astrocytes, oligodendrocytes, microglia & ependymal cells

- 2 cell types in **PNS**

  --Schwann and satellite cells

知識小補帖 Knowledge Supplements

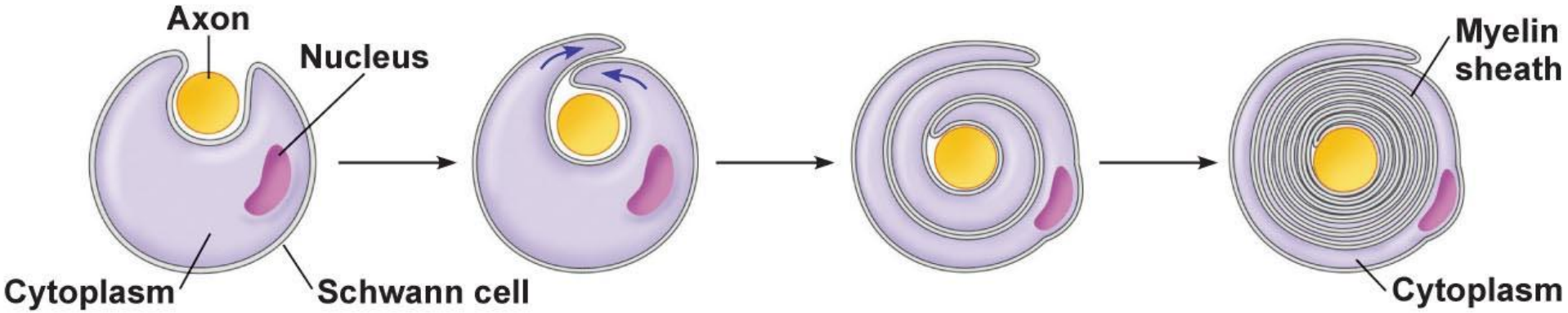
神經膠細胞瘤 (glioma) 是中樞神經系統原發性腫瘤（俗稱腦瘤）中最常見者。主要包括星形膠細胞瘤 (astrocytoma)、寡突膠細胞瘤 (oligodendroglioma) 及室管膜瘤 (ependymoma)，其中又以星形膠細胞瘤最常見。而神經膠母細胞瘤 (glioblastoma multiforme) 則為分化最差、最為惡性的腦瘤。

神經膠細胞瘤的臨床症狀主要有兩方面的表現：一是顱內壓增高和其他一般症狀，如頭痛、嘔吐、視力減退、複視、癲癇發作和精神症狀等；另一是腦組織受腫瘤的壓迫、浸潤、破壞所產生的局部症狀，造成神經功能缺失。其生長特點為浸潤性生長，與正常腦組織無明顯界限，因此預後普遍不佳。

Functional Classes of Glia Cells

支持細胞	位置	功能
許旺氏細胞 (Schwann cells)	PNS	➢ Myelin-Forming Cells =neurolemmocytes ➢ One Schwann cell forms one **myelin sheath (**around the axons of PNS neurons**)** ➢ Regeneration
寡樹突細胞 (Oligodendrocytes)	CNS	➢ Myelin-Forming Cells ➢ One cell forms several **myelin sheath (**around the axons of CNS neurons=white matter**)**
衛星細胞 (Satellite cells)	PNS	➢ Ganglionic gliocytes ➢ Support cell bodies within the ganglia of the PNS
星形細胞 (Astrocytes)	CNS	➢ Most common glial cell type ➢ Form **blood-brain barrier (BBB)** by covering blood capillaries ➢ Development of neural connections ➢ Possibly modulate synaptic activity ➢ Remove neurotransmitter from synaptic cleft ➢ Communicate to neurons through chemical messengers ➢ Maintain **normal electrolyte composition of ISF** in CNS ➢ Protect neurons against toxic substances and oxidative stress
小神經膠細胞 (Microglial cells)	CNS	➢ Protect CNS from foreign matter through **phagocytosis** (bacteria & dead or injured cells) ➢ Protect CNS from oxidative stress (overactive⟶ROS↑)
室管膜細胞 (Ependymall cells)	CNS	➢ Line the ventricles and **secrete cerebrospinal fluid (CSF)**

Schwann Cells & Oligodendrocytes



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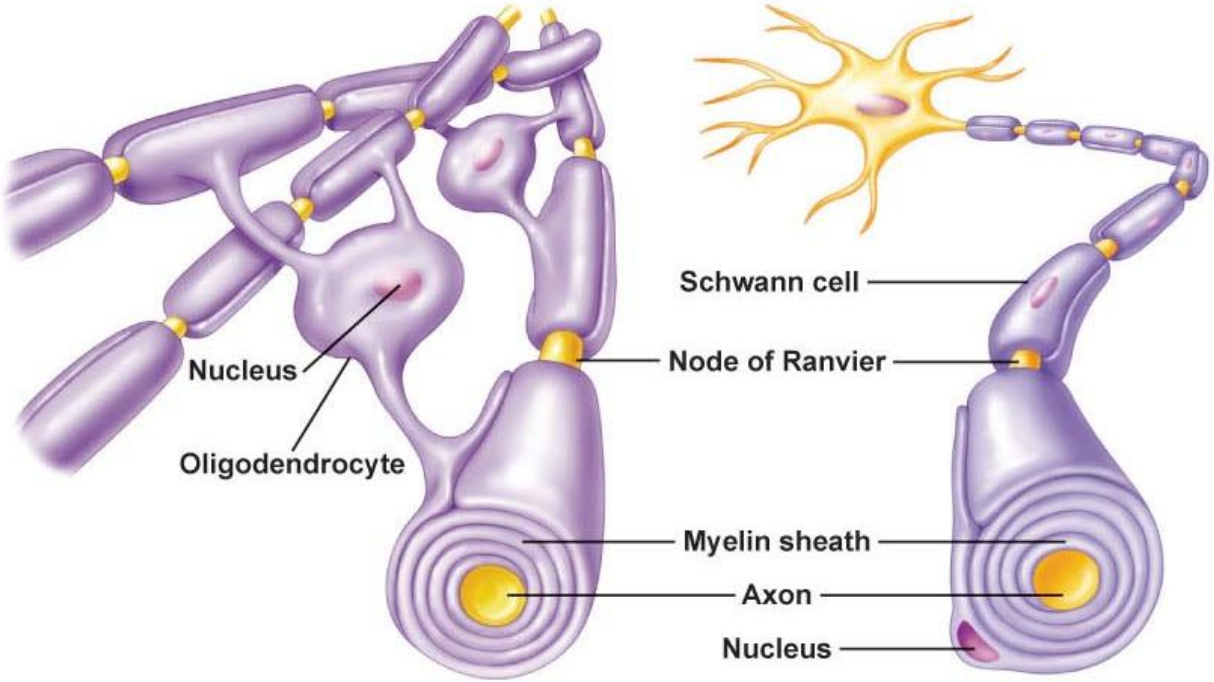

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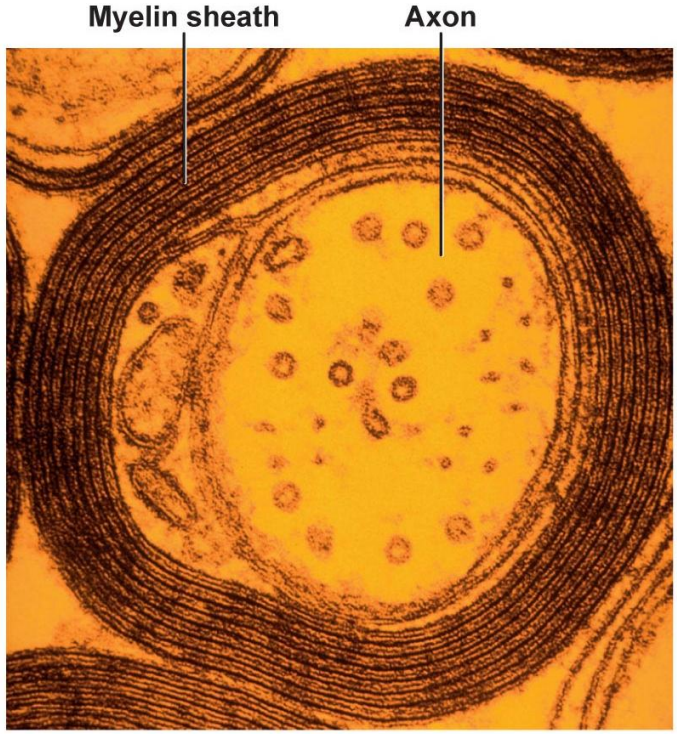
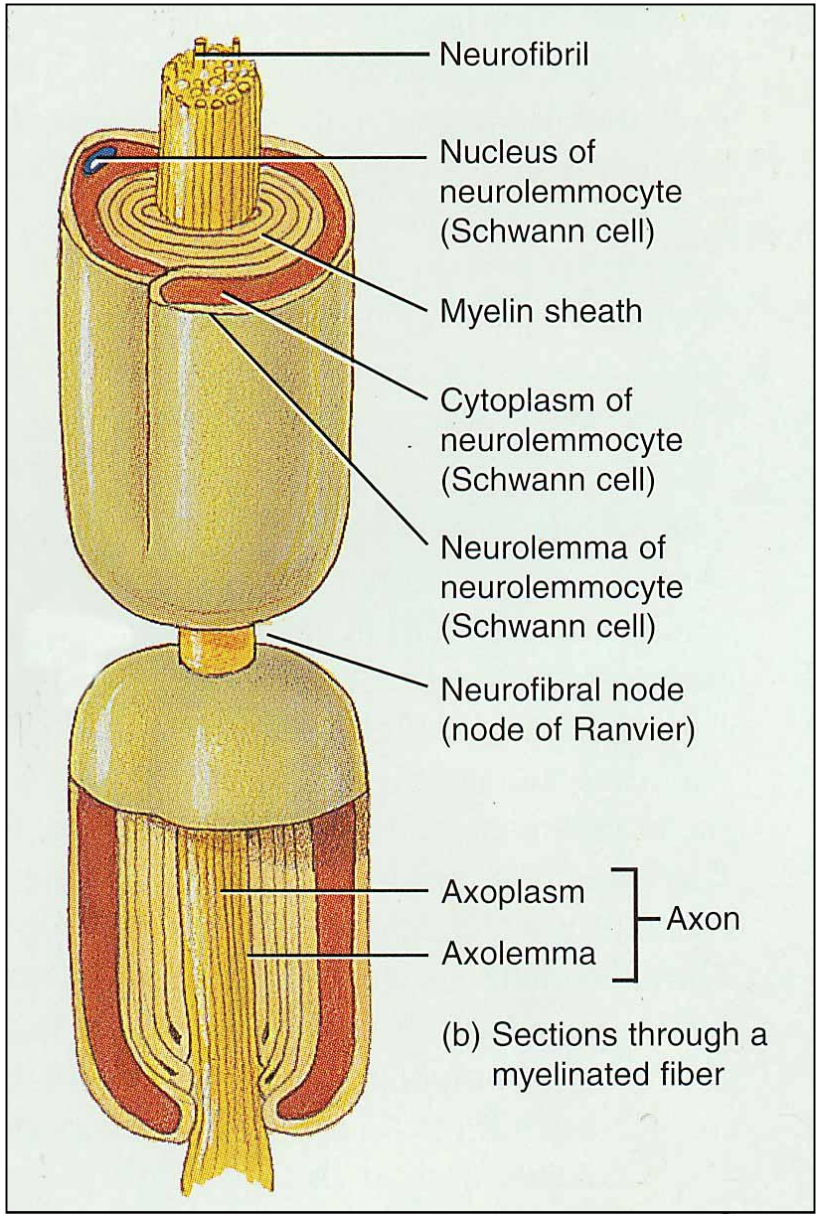


(d)

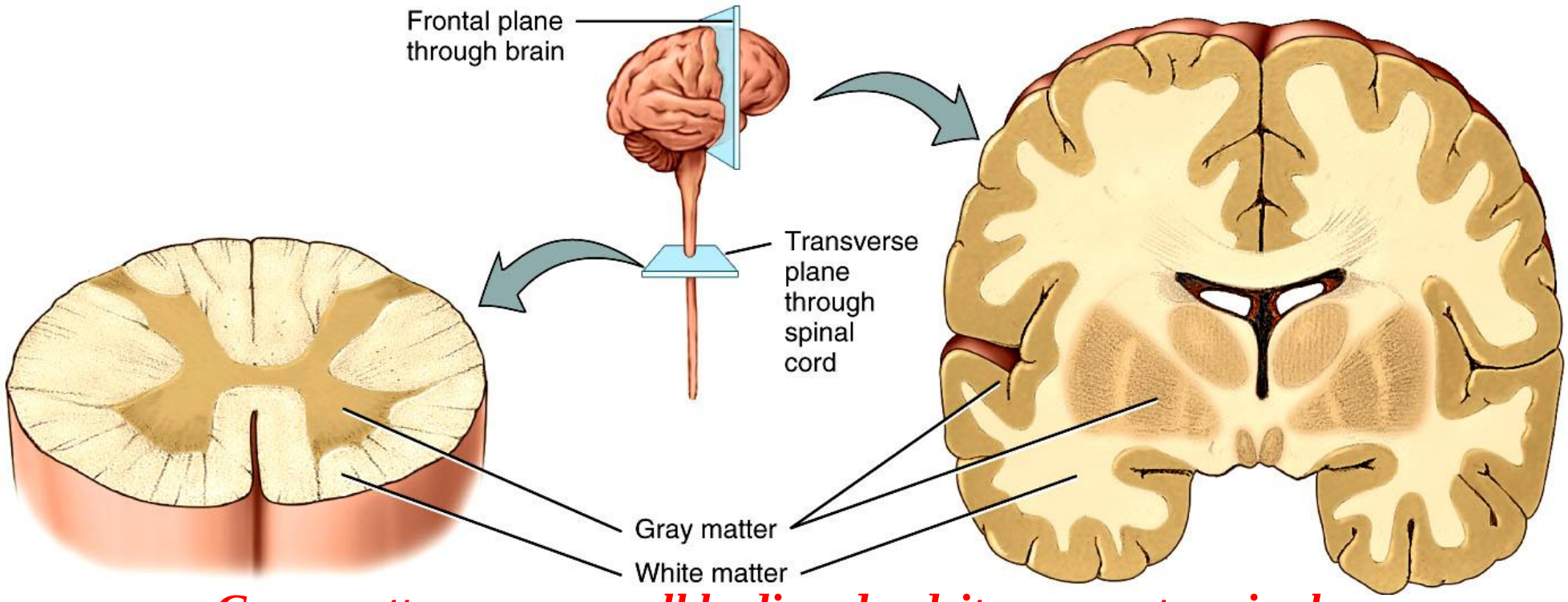
Myelination in the PNS

- Schwann cells myelinate (wrap around) axons in the PNS during fetal development
- Neurolemma is cytoplasm & nucleus of Schwann cell
  --gaps called nodes of Ranvier
- Myelinated fibers appear white
  --jelly-roll like wrappings made of lipoprotein = myelin
  --acts as electrical insulator
  --speeds conduction of nerve impulses
- Unmyelinated fibers
  --slow, small diameter fibers
  --only surrounded by neurolemma but no myelin sheath wrapping



Myelination in the CNS

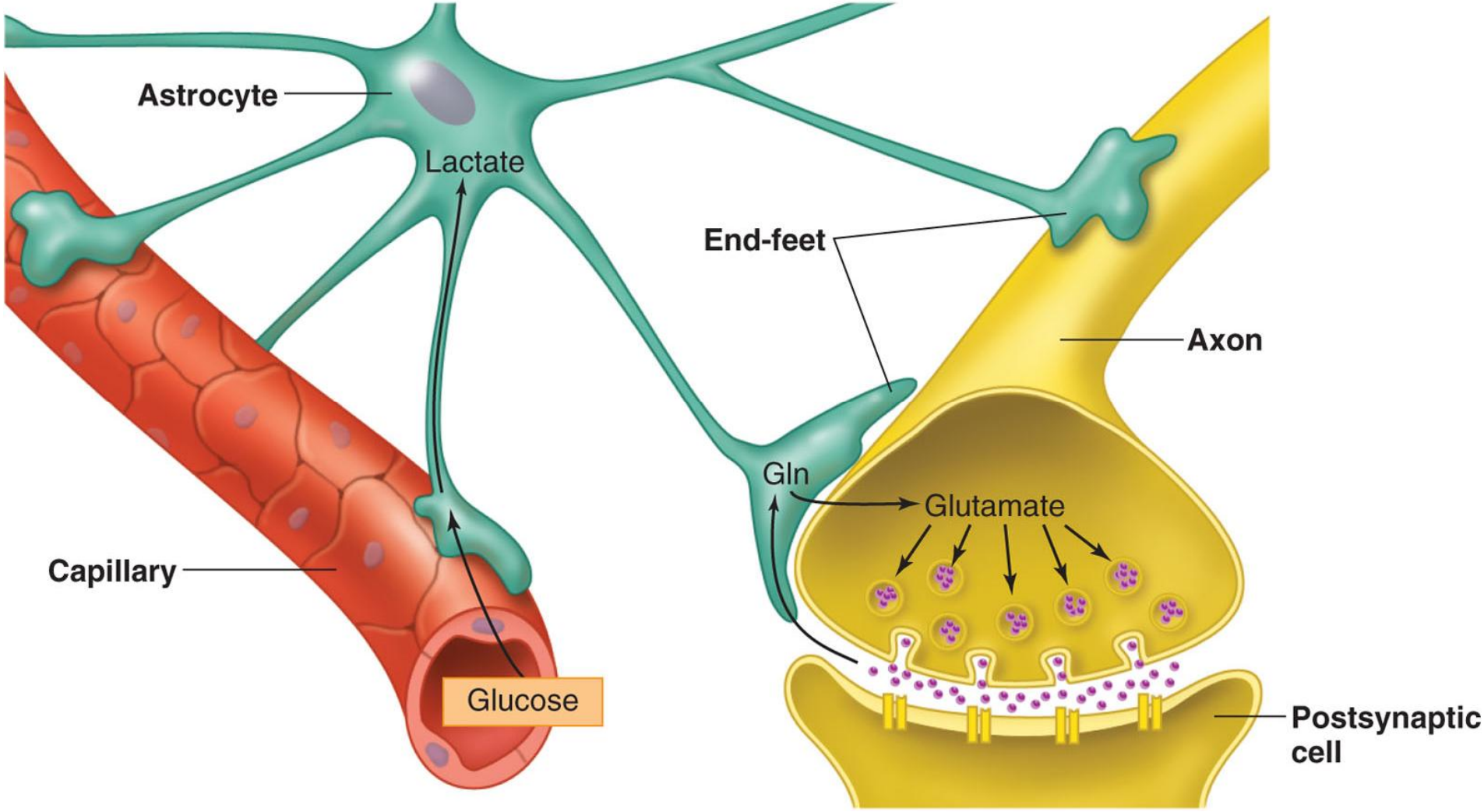
- Oligodendrocytes myelinate axons in the CNS (**white matter**)
- Broad, flat cell processes wrap about CNS axons, but the cell bodies do not surround the axons
- No neurolemma is formed
- Little regrowth after injury is possible due to the lack of a distinct tube or neurolemma



Gray matter = nerve cell bodies, dendrites, axon terminals, bundles of unmyelinated axons and neuroglia (gray color)

Astrocytes

Processes with end-feet associate with blood capillaries (BBB) and axon terminals (Remove neurotransmitters)



Astrocytes Functions

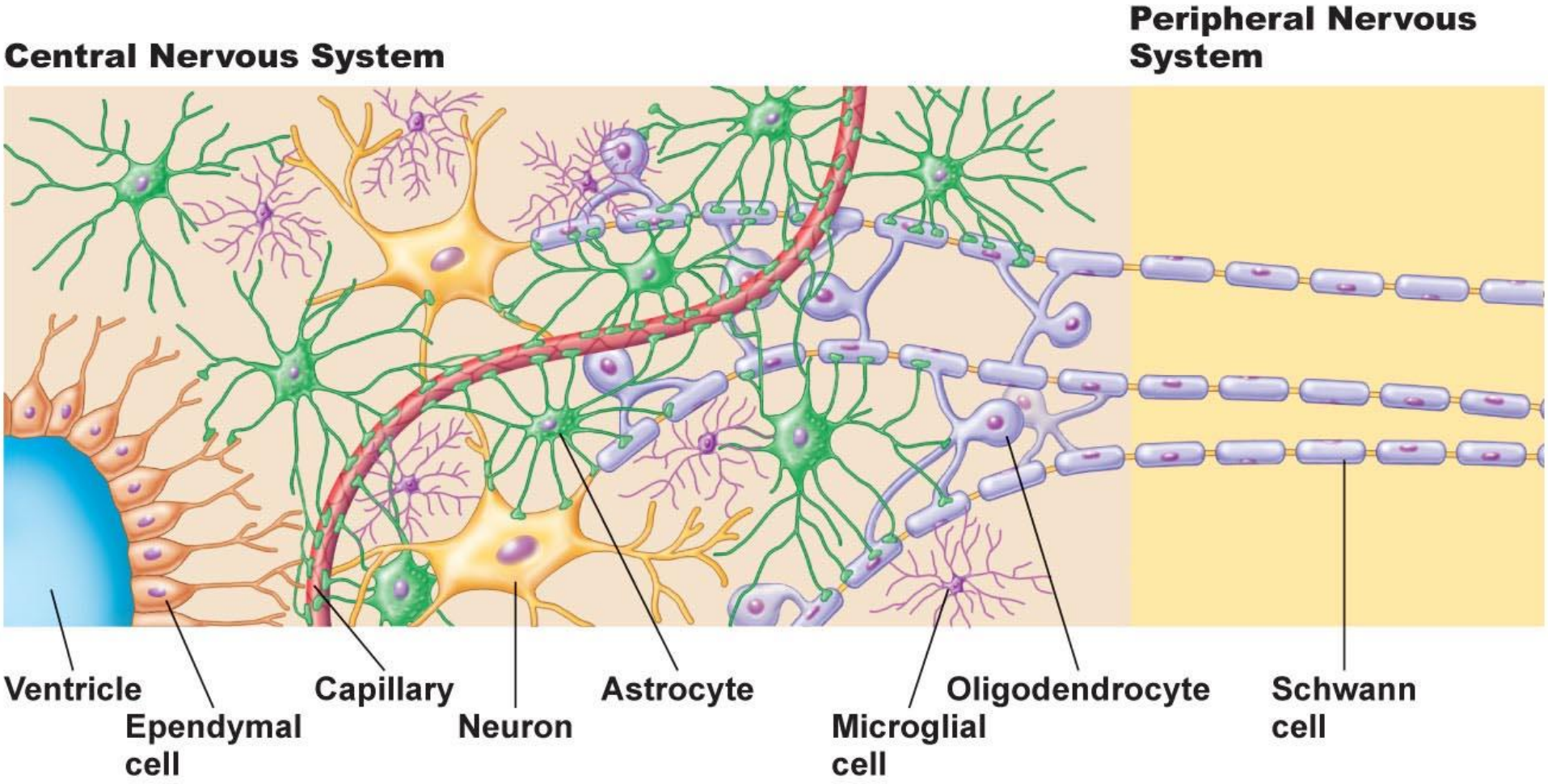
- Form the blood-brain barrier (**BBB**); plasma Glu (GLUT1)→brain

  --Parkinson's disease (L-dopa) and Meningitis (some antibiotics)

  --Influence the production of ion channels and enzymes that can destroy toxic substances by secreting glial-derived neurotrophic factor

- Take up **K^+ from the ECF** to maintain ionic environment for neurons
- Take up **extra neurotransmitter (Glu)** released from axon terminal. Chemicals are recycled
- End-feet around capillaries **take up glucose** from blood for use by neurons to make ATP (PET scans, fMRI—brain metabolic atcivity)
- Needed for the **formation of synapses** in the CNS
- Regulate **neurogenesis** in the adult brain (stem cells/hippocampus)
- Release **transmitter molecules** that can stimulate (glutamate) or inhibit neurons (ATP)

Functional Classes of Glia Cells



Electrical Signals in Neurons

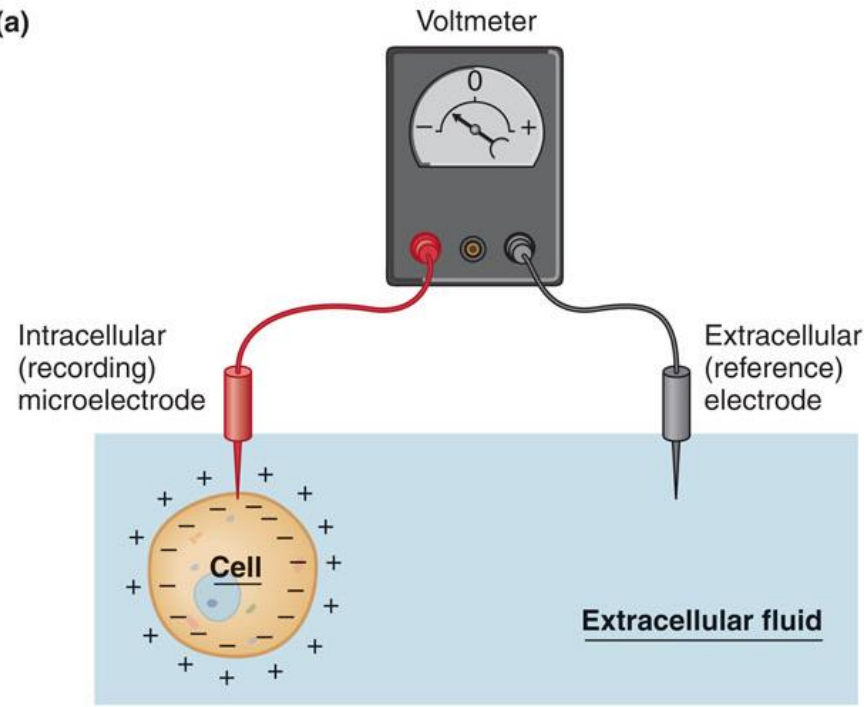
- Neurons are **electrically excitable** due to the voltage difference across their membrane
- Communicate with 2 types of electric signals

  --***Action potentials*** that can travel long distances

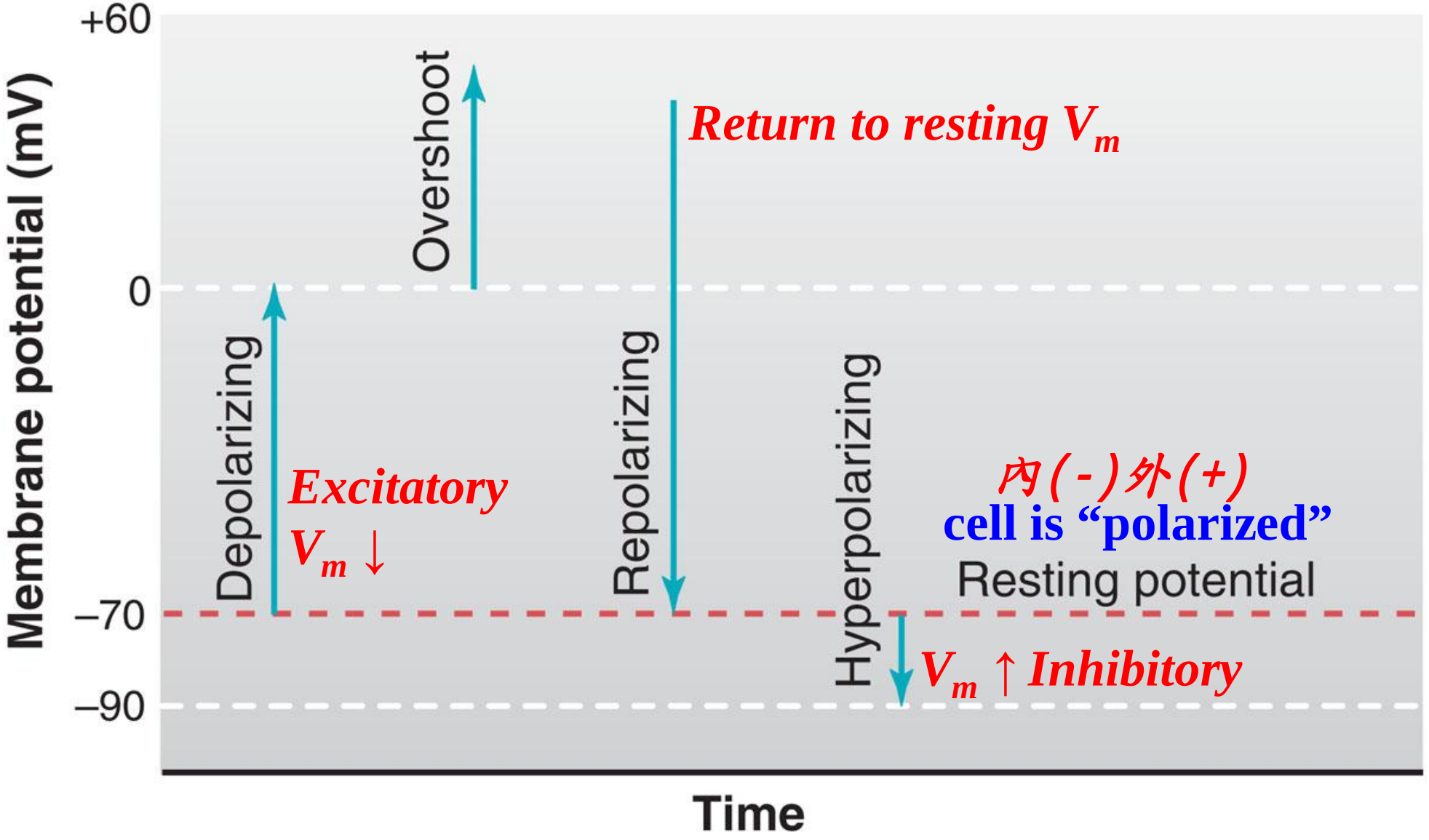
  --***Graded potentials*** that are local membrane changes only
- In living cells, a flow of ions occurs through ion channels in the cell membrane

➢***Gated channels open and close in response to a stimulus***

--results in neuron excitability



Change in Membrane Potential=V_m



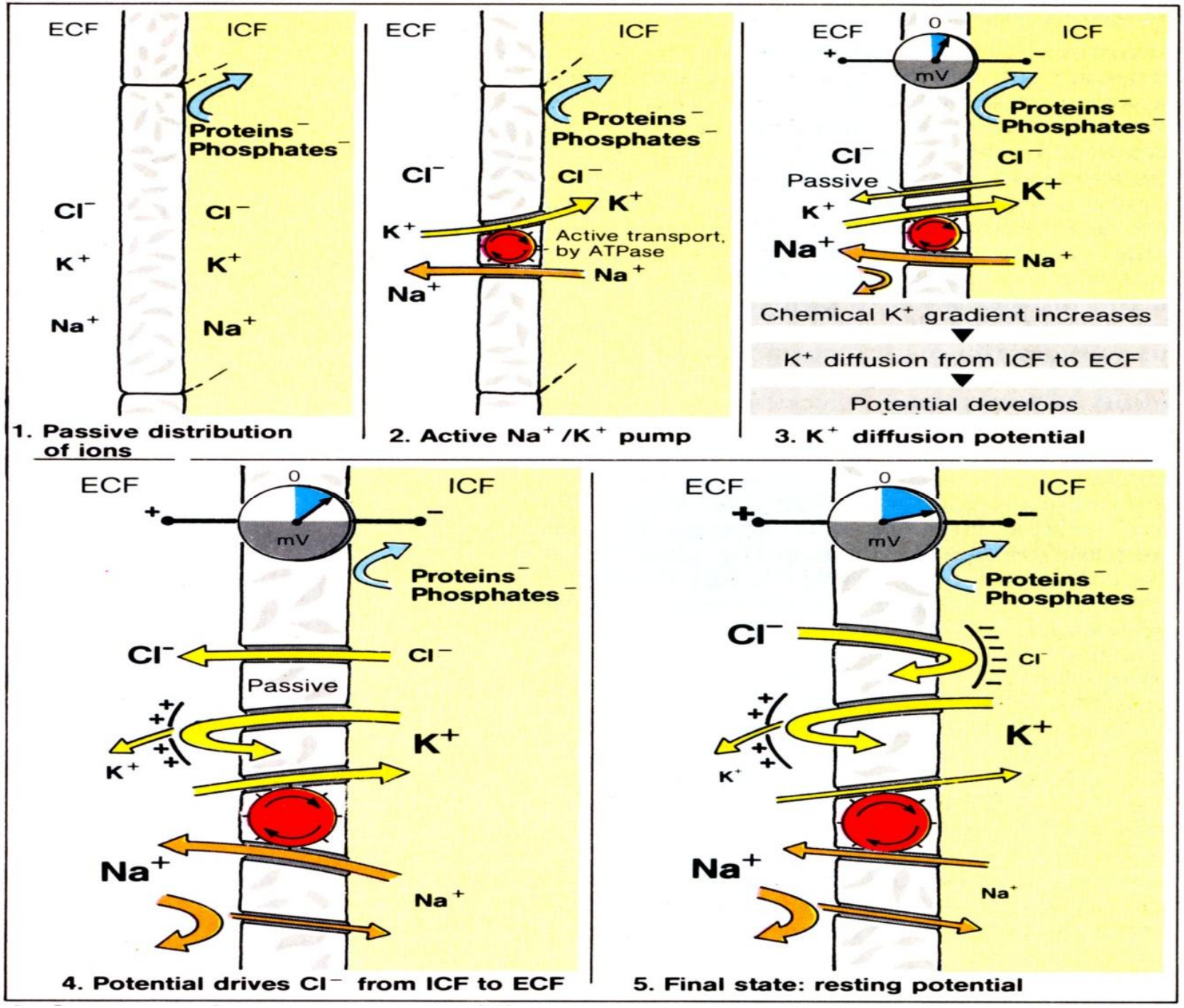
Types of Electrical Potentials

Potential	Definition
Potential difference = E	Difference in voltage between two points
Membrane potential = V_m	Difference in voltage across the plasma membrane; always given in terms of voltage inside the cell relative to voltage outside the cell
Resting V_m	Difference in voltage across the plasma membrane when a cell is at rest (not receiving or sending signals)
Graded potential	A relatively small change in the membrane potential produced by some type of stimulus that triggers the opening or closing of ion channels; strength of graded potential is relative to strength of stimulus
Synaptic potential	Graded potentials produced in the post-synaptic cell in response to neurotransmitters binding to receptors
Receptor potential	Graded potentials produced in response to a stimulus acting on a sensory receptor
Action potential	A large, rapid change in the membrane potential produced by depolarization of an excitable cell's plasma membrane to threshold
Equilibrium potential	The membrane potential that counters the chemical forces acting to move an ion across the membrane, thereby putting the ion at equilibrium

Establishment of Resting V_m

- Neurons have a resting potential of **−70 mV**
  - **--Large negative molecules inside the cell**
  - **--Na^+/K^+ pumps (ion concentration gradients)**
  - **--Membrane is highly permeable to K^+** (K^+50X >Na^+)
    - ➢ K^+ has two types of channels:
      - Not gated (always open); sometimes called "leaky" K^+ channels
      - Voltage-gated K^+ channels; open when a particular membrane potential is reached
- At rest, there is a high concentration of K^+ inside the cell and Na^+ outside the cell

Establishment of Resting V_m



Resting V_m

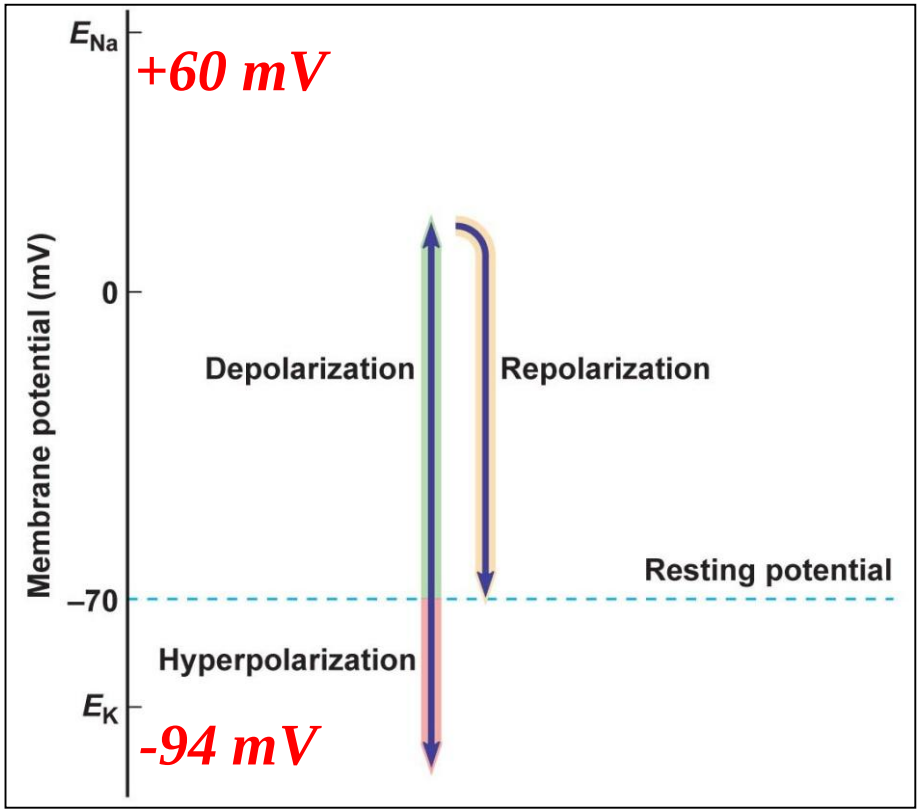
The resting membrane potential is closer to the potassium equilibrium potential

Nernst equation:

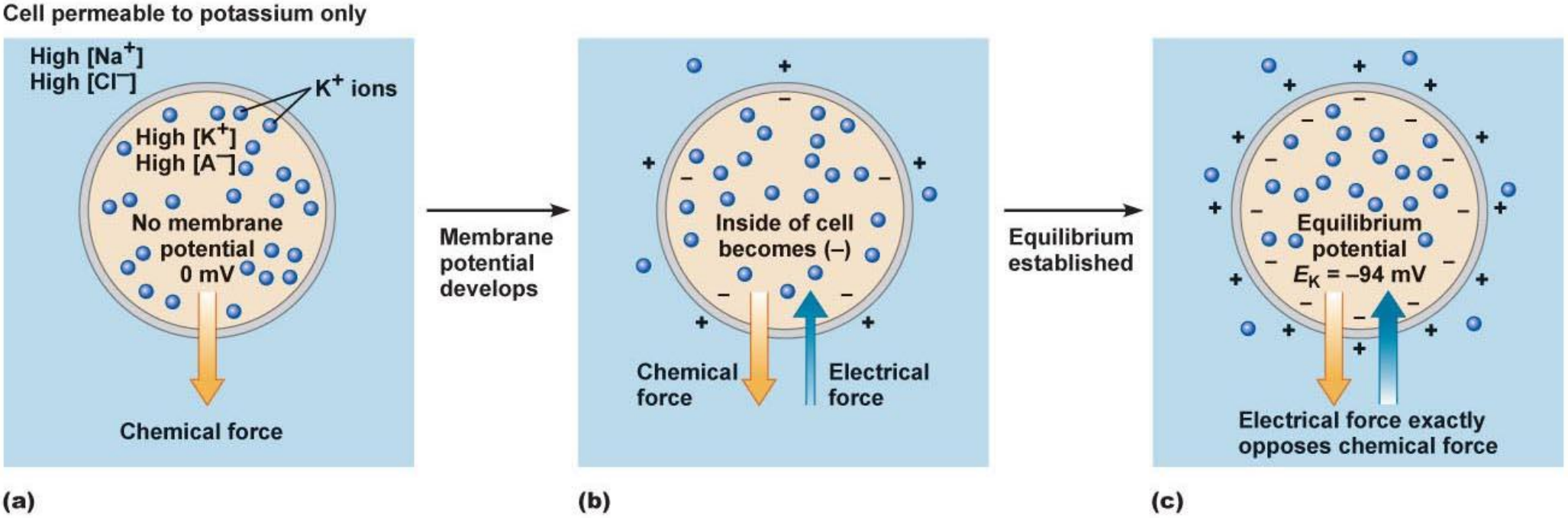
$$E_{X^+} = 61.55 \quad \log \frac{[X^+]_o}{[X^+]_i} \text{ (mV)}$$

$$\mathbf{E_K} = 61 \text{ mV x log } \frac{4 \text{ mM}}{140 \text{ mM}} = \mathbf{-94 \text{ mV}}$$

When membrane potential = -94 mV, potassium is at equilibrium.



Establishment of K^+ Equilibrium Potential



Equilibrium Potential is ***Chemical force = negative electrical force***

Or ***electrochemical force = 0***

➢ **K^+ Equilibrium Potential (E_K):**

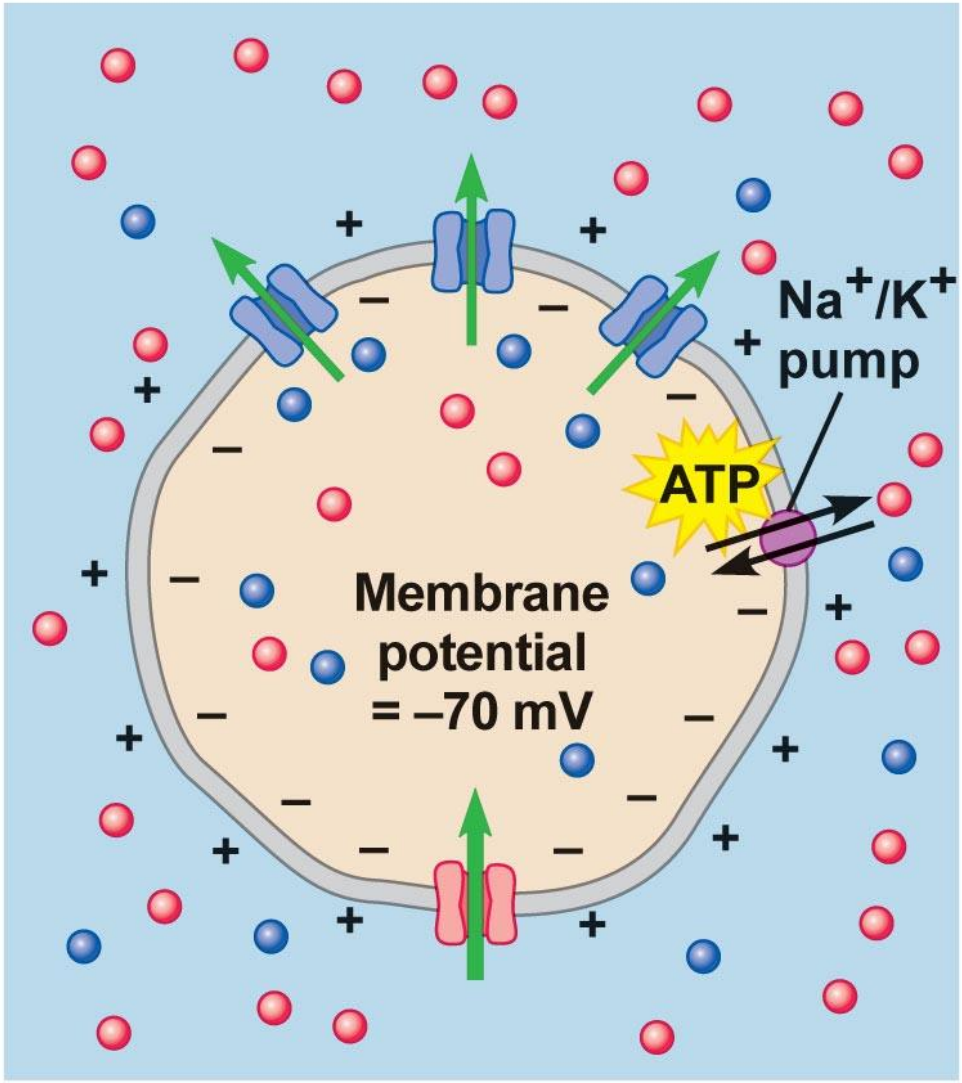
Chemical and electrical driving forces are

--Opposite in direction

--Equal in magnitude

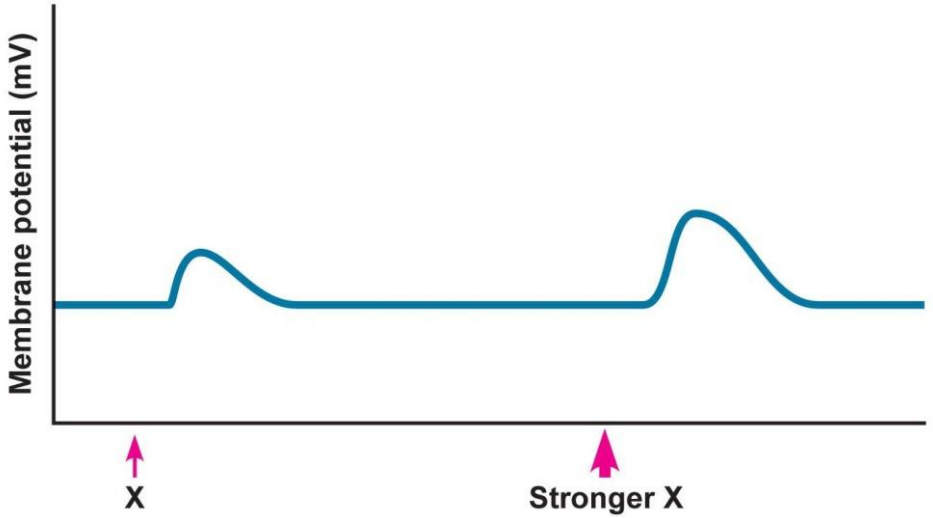
A Neuron at Rest

- Small Na^+ leak at rest (**high** force, **low** permeability)
- Large K^+ leak at rest (**low** force, **high** permeability)
- **Na^+/K^+ pump** returns Na^+ and K^+ to maintain gradients

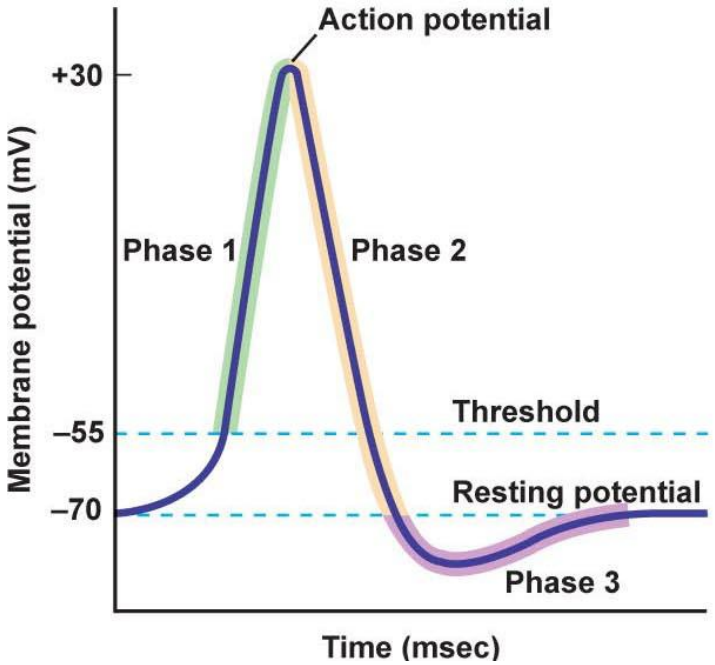


Types of Electrical Signals

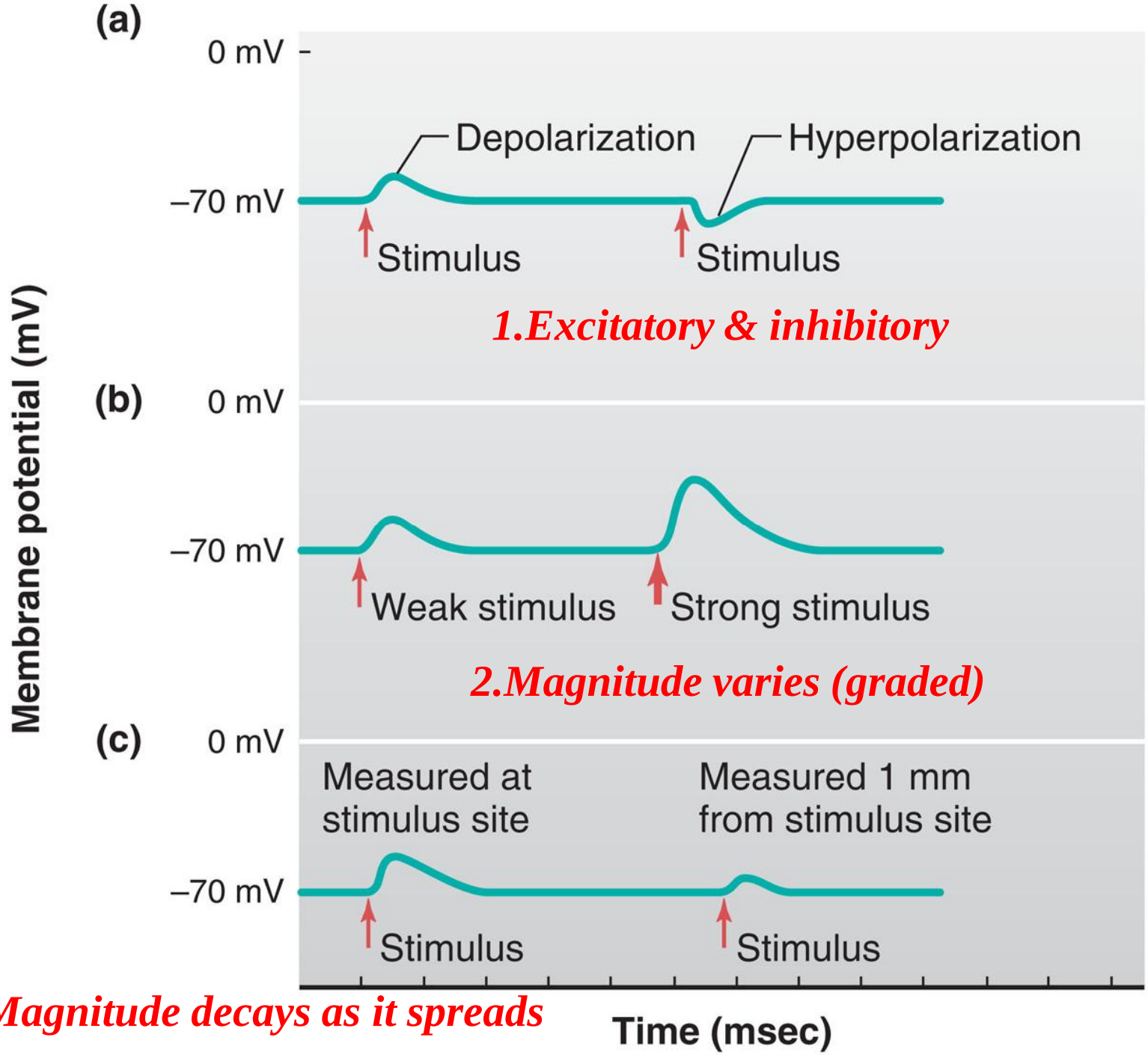
- **Graded potentials**
  - --Small (graded=local)
  - -- Occur most often in the dendrites and cell body of a neuron
  - --Communicate over short distances



- **Action potentials**
  - --Large
  - -- Occur most often in the axon hillock and axon of a neuron
  - --Communicate over long distances



Graded Potentials

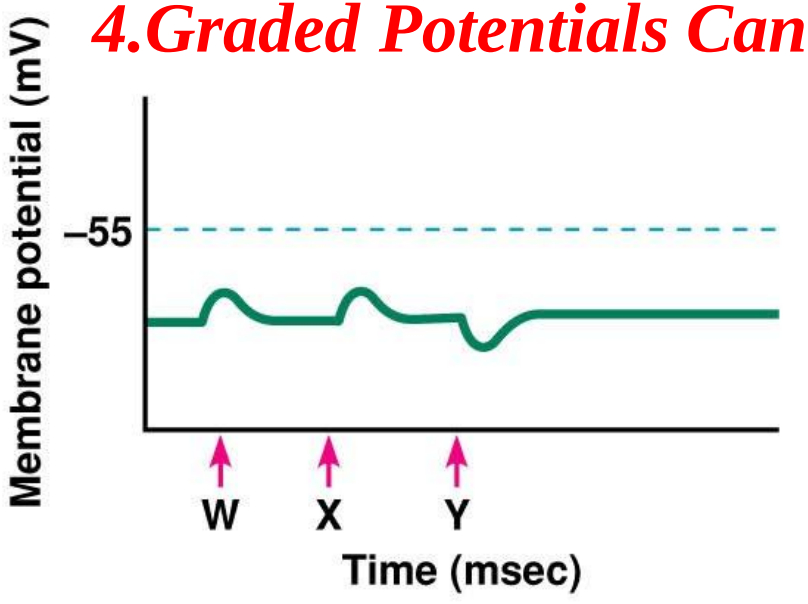


1.Excitatory & inhibitory

2.Magnitude varies (graded)

3.Magnitude decays as it spreads

4.Graded Potentials Can Sum



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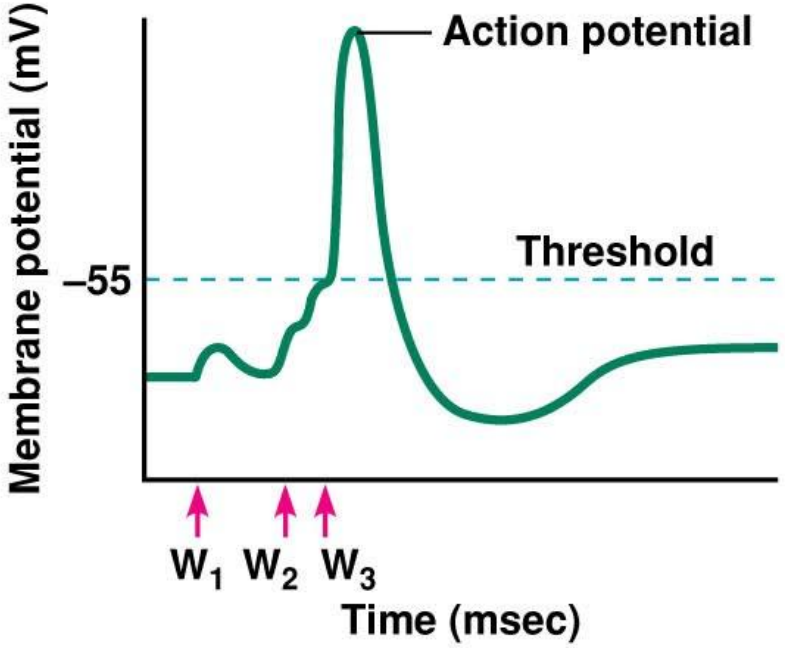
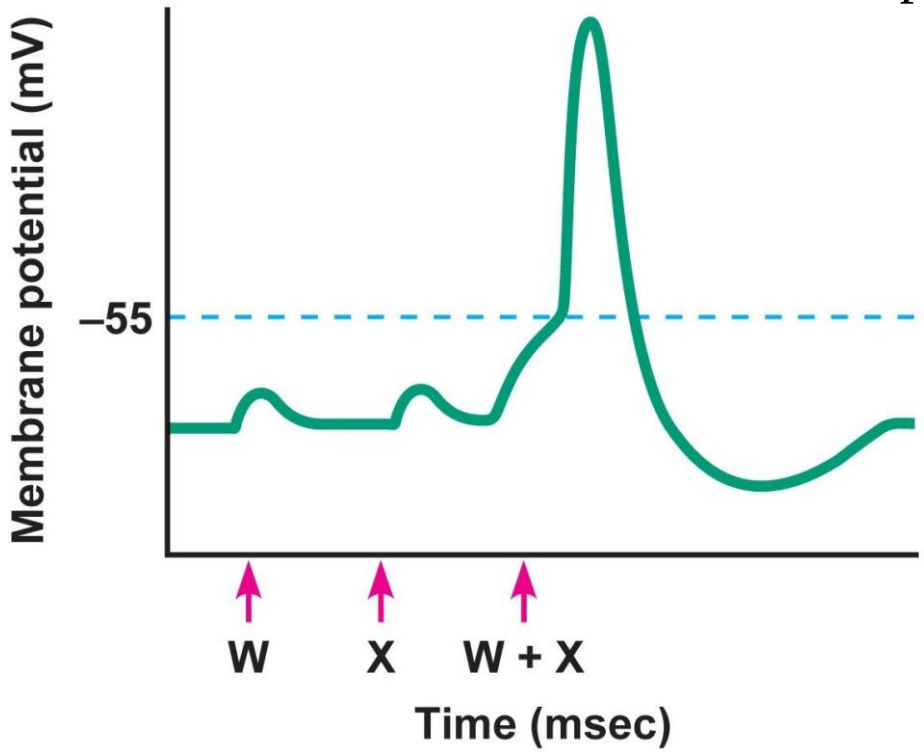


(b)

Temporal Summation

- Same stimulus
- Repeated close together in time



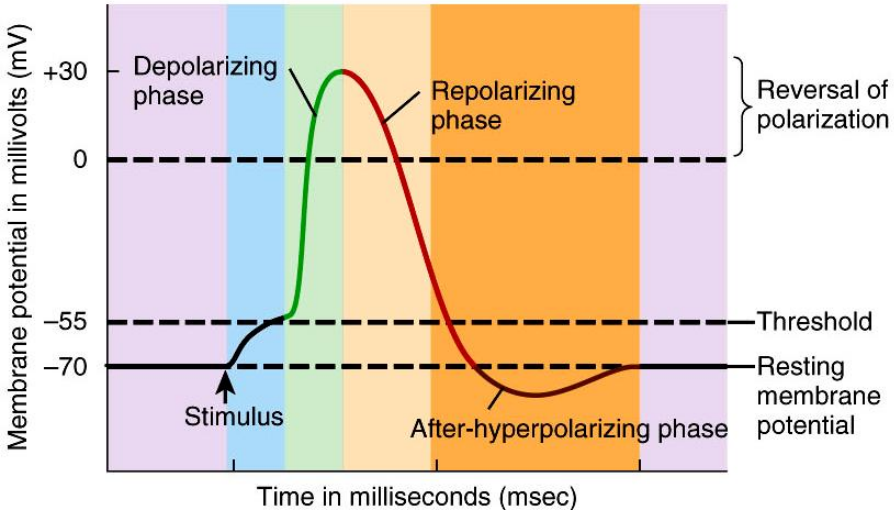
(c)

Spatial summation

- Different stimuli
- Overlap in time

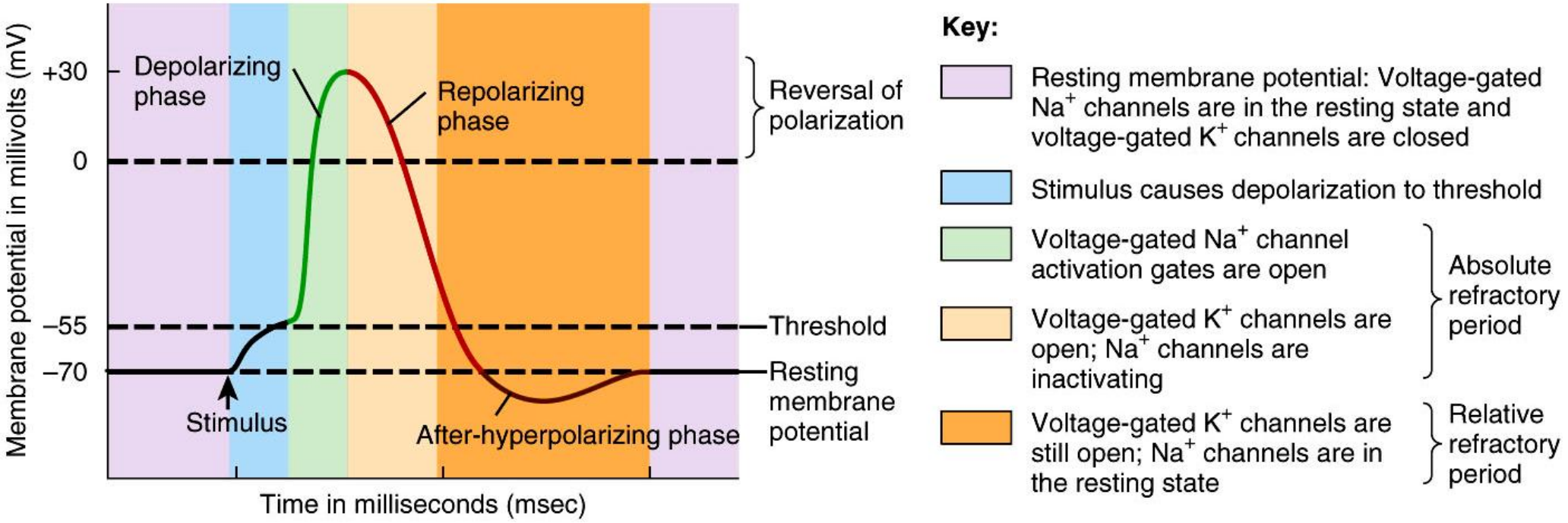
Action Potential (AP)= *Impulse*

- Excitable membranes have ability to generate action potentials
- Action potential
  - --Rapid large depolarization used for communication
- Phases of an action potential
  - --***Depolarization***
  - --***Repolarization***
  - --***After-hyperpolarization***



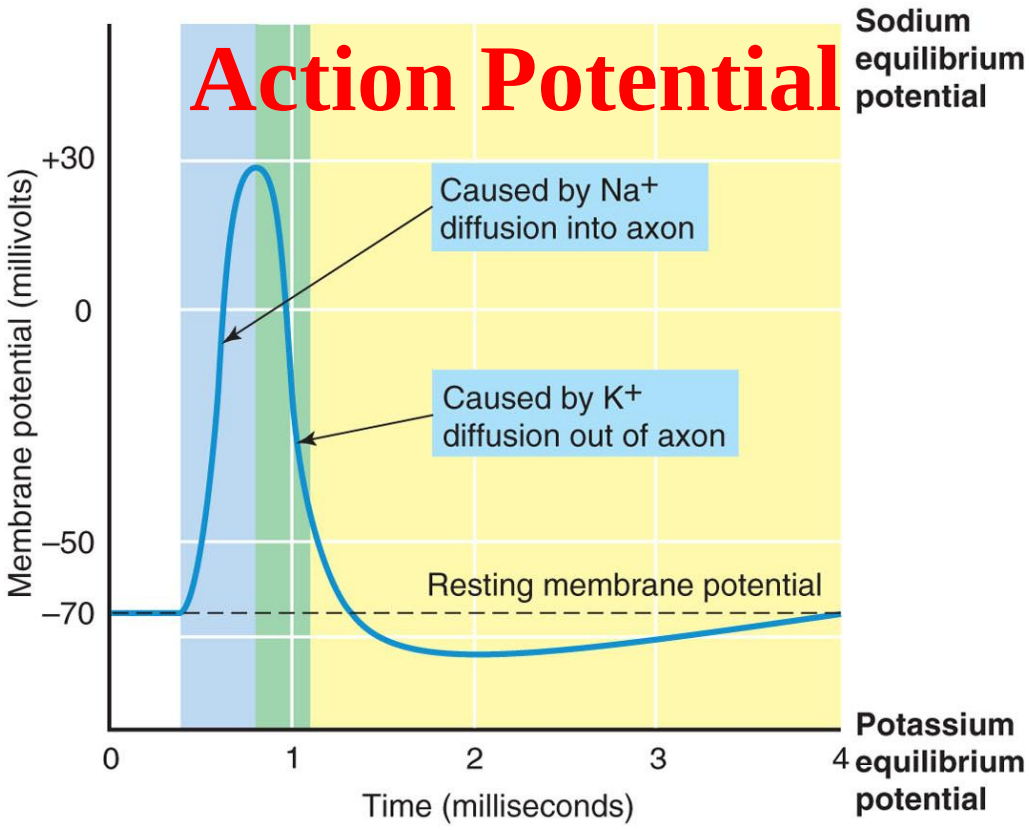
- In neurons
  - --Action potentials travel along axons from cell body to axon terminal (or if afferent neuron, from receptor to terminal)

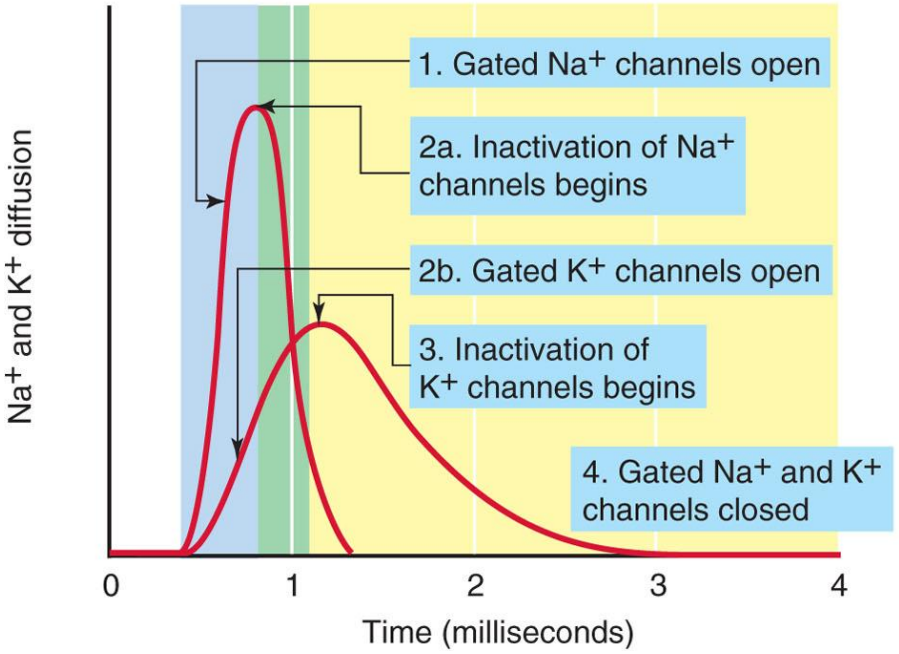
Action Potential (AP)



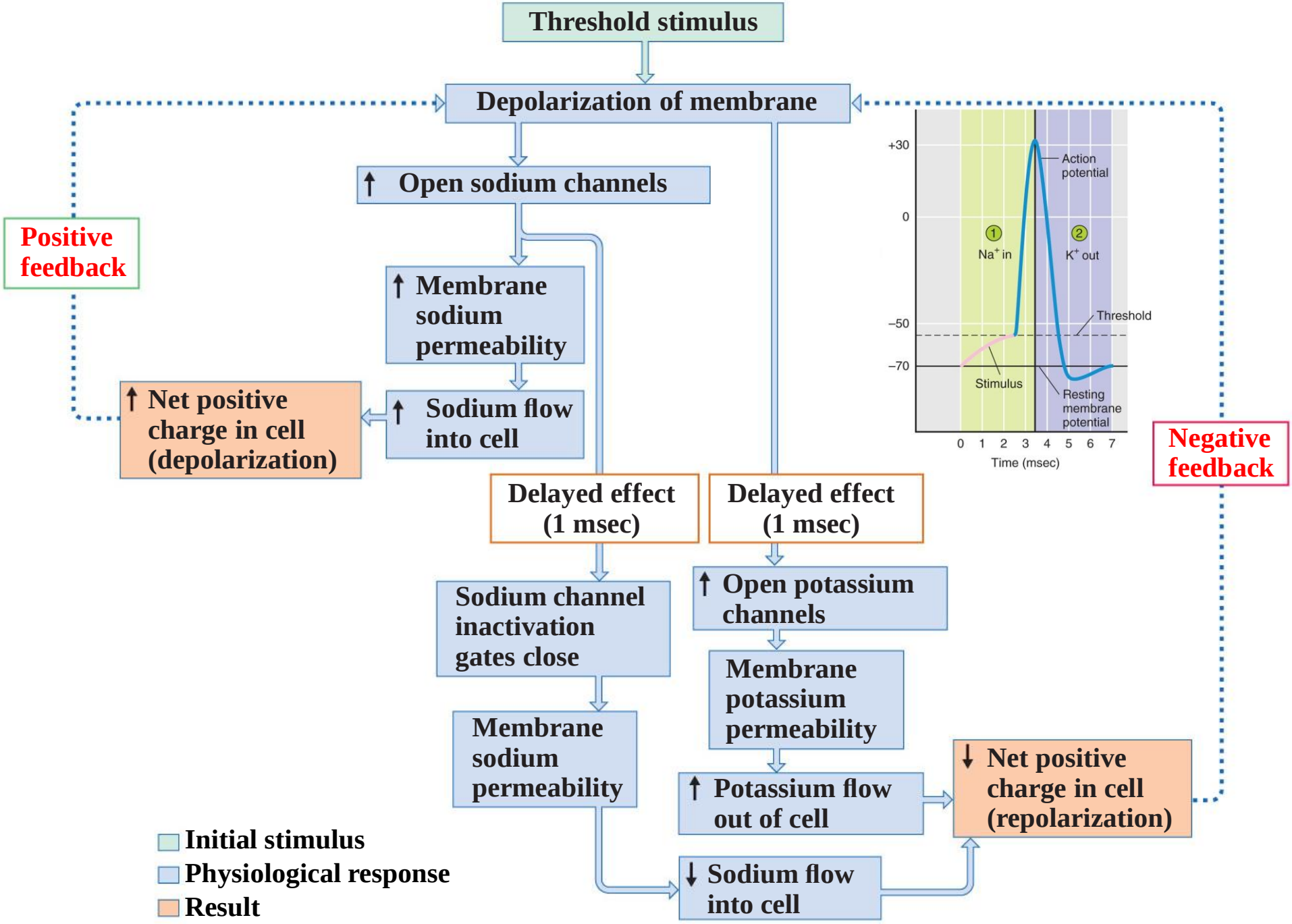
- Ion channels open, **Na+ rushes in** (depolarization), **K+ rushes out** (repolarization)
- **All-or-none** principal = with stimulation, either happens one specific way or not at all (lasts 1/1000 of a second)
- Travels (spreads) over surface of cell without dying out

Action Potential





Action Potential (AP)

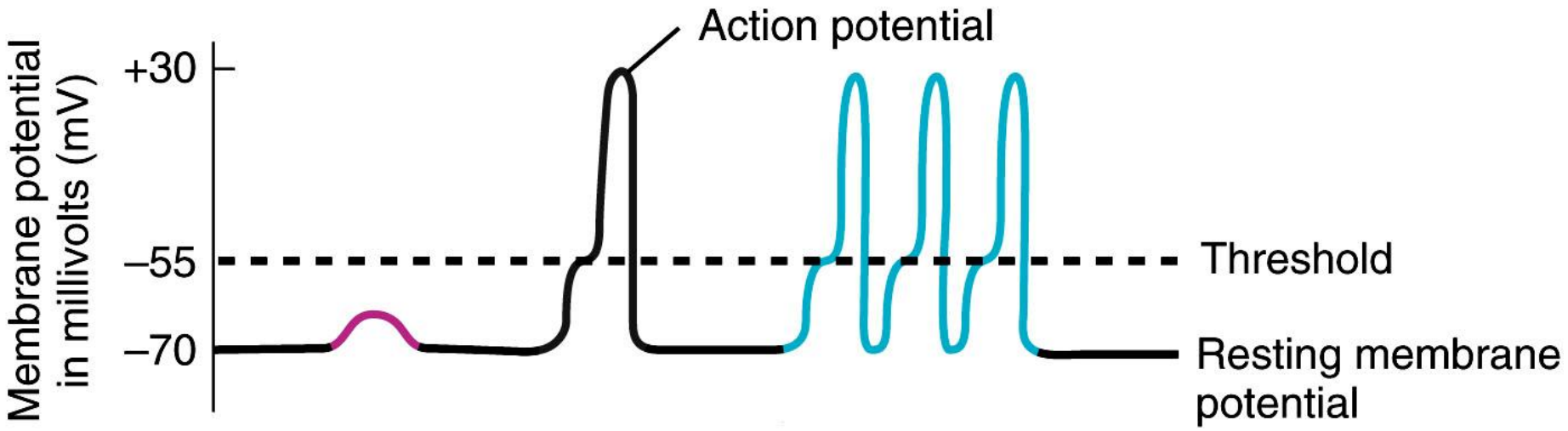


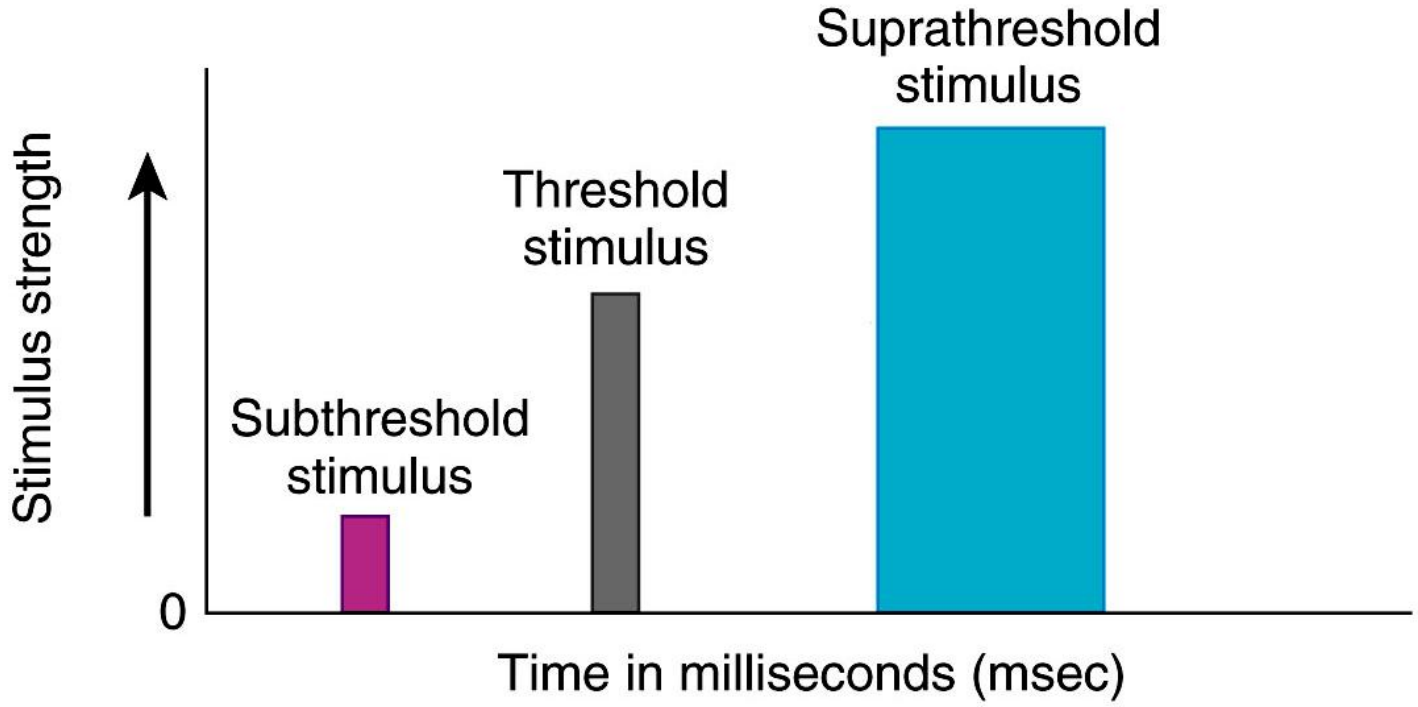
Characteristics of a Neuron at Rest and During 3 Phases of an Action Potential

	Resting	Depolarization	Repolarization	After-hyperpolarization
Membrane potential	−70 mV	−70 mV to +30 mV	+30 mV to −70 mV	−70 mV to −85 mV
Voltage-gated sodium channel	Closed	Open	Closed	Closed
Activation gate	Closed	Open	Open	Closed
Inactivation gate	Open	Open	Closed	Open
Sodium flow	Low inward, through leak channels	High inward, through voltage-gated channels*	Low inward, through leak channels	Low inward, through leak channels
Voltage-gated potassium channel	Closed	Closed	Open	Closing
Potassium flow	Low outward, through leak channels	Low outward, through leak channels	High outward, through voltage-gated channels*	High outward, through voltage-gated channels, but decreasing*

*Even though at any given time ions move through both voltage-gated channels and leak channels, the conductance through the leak channels is negligible compared to that through voltage-gated channels.

All-or-None Law (AP)

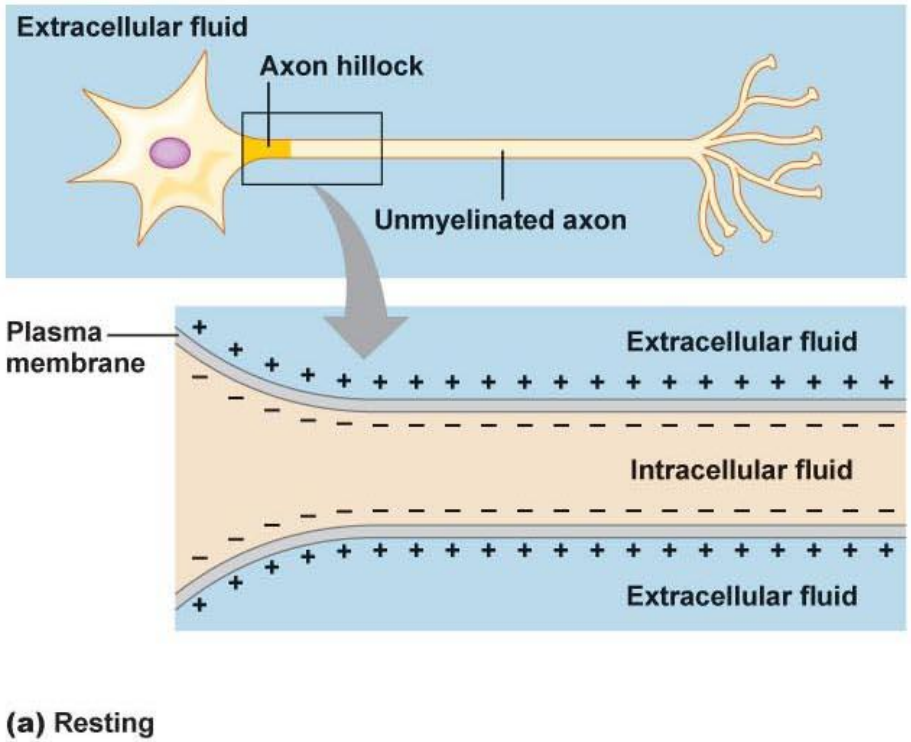




Graded Potentials & Action Potential

Property	Graded potential	Action potential
Location	Dendrites, cell body, sensory receptors	Axon
Strength	Relatively weak, proportional to strength of stimulus; dissipates with distance from stimulus	100 mV All-or-none
Direction of change in membrane potential	Can be depolarizing or hyperpolarizing depending on stimulus	Depolarizing
Summation	Spatial and temporal	None
Refractory periods	None	Absolute and relative
Channel types involved in producing change in potential	Ligand-gated, mechanically gated	Voltage-gated
Ions involved	Usually Na^+, Cl^-, or K^+	Na^+ and K^+
Duration	Few milliseconds to seconds	1–2 msec (after-hyperpolarization may last 15 msec)

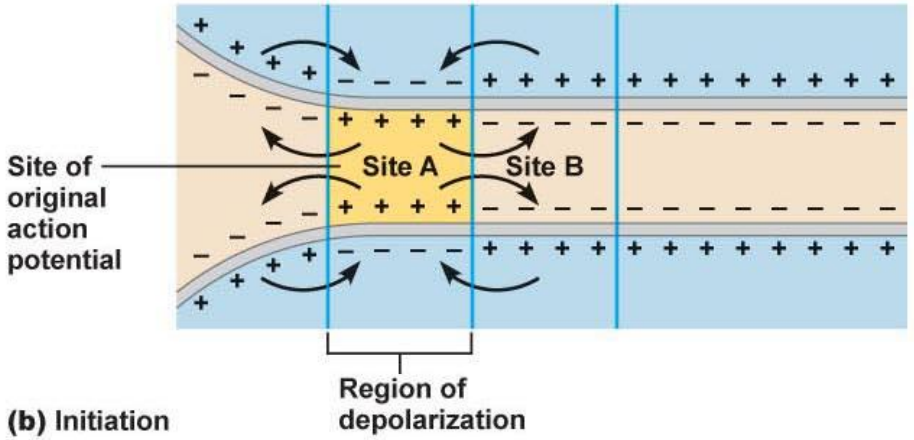
Propagation of AP= *Nerve Impulse*

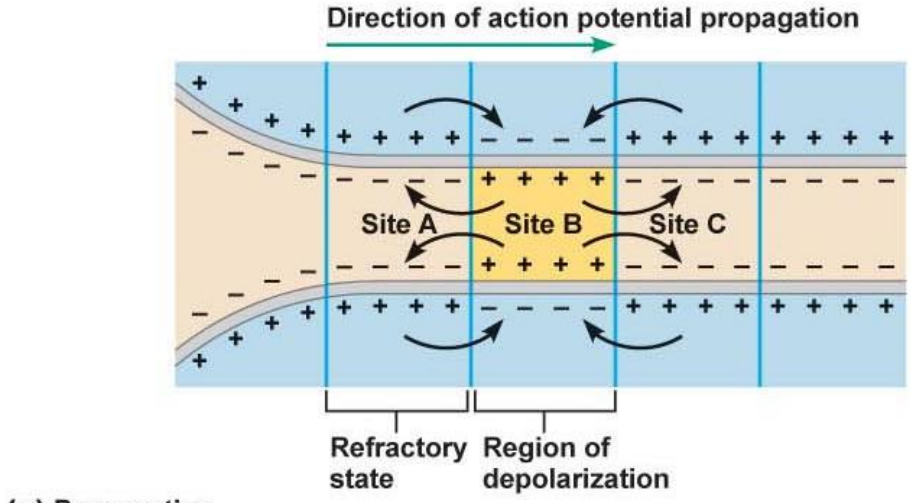


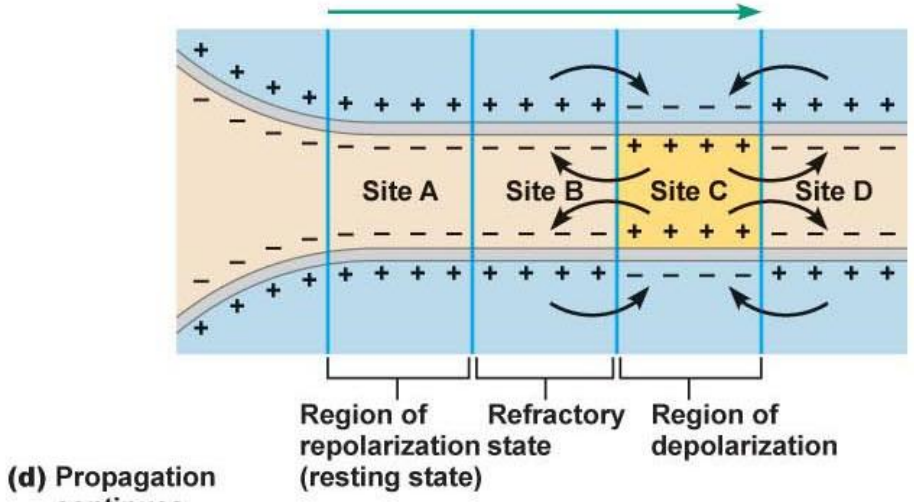
➢**Unmyelinated Neuron:**

--***Continuous conduction***

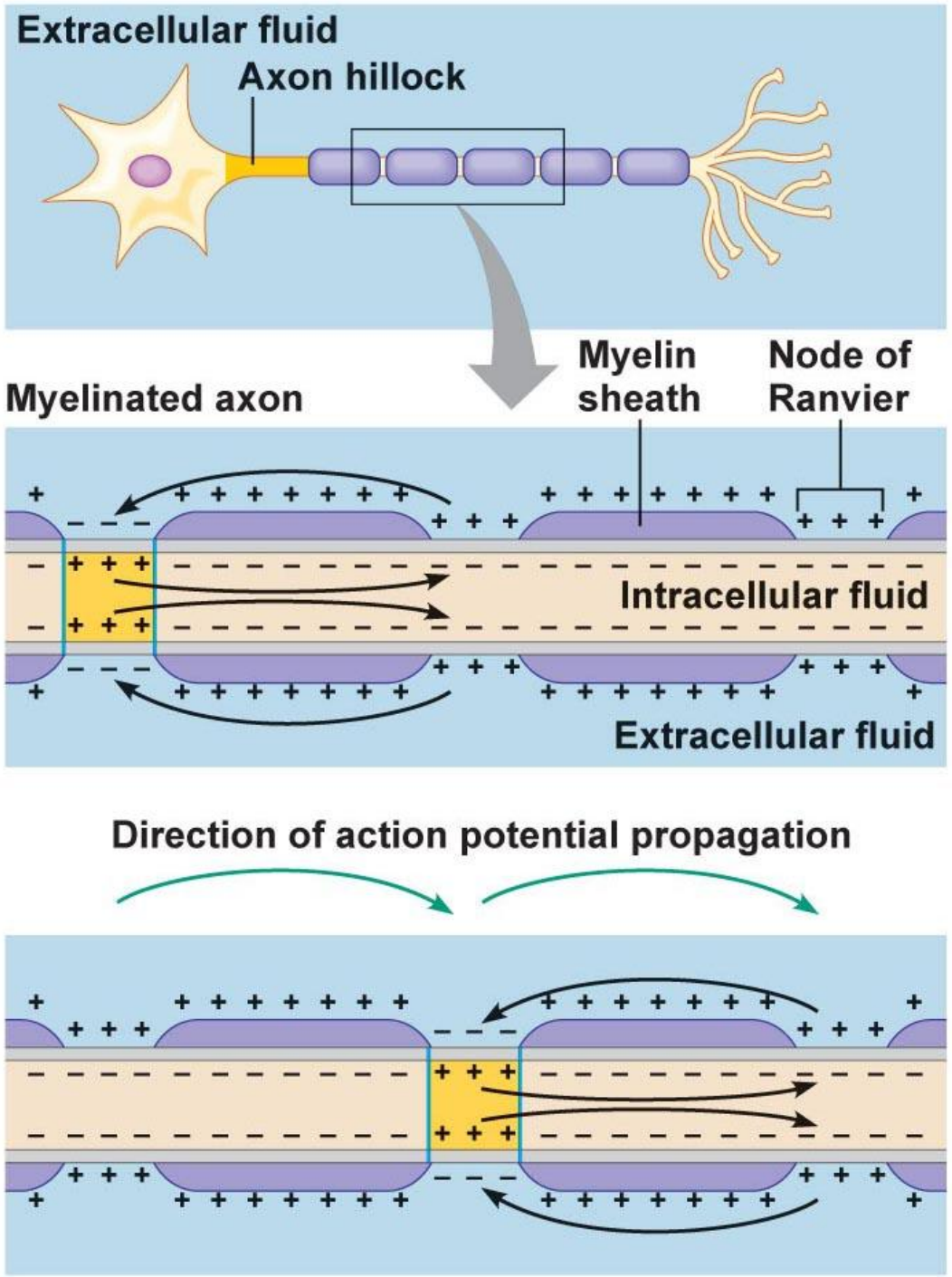
--*Step-by-step depolarization*







Propagation of AP= *Nerve Impulse*



- **Myelinated Neuron:**
  --***Saltatory conduction***
- Depolarization only at **nodes of Ranvier** where there is a high density of voltage-gated Na channels
- Current carried by ions flows through extracellular fluid from node to node

Factors Affecting Propagation

- **Refractory period**
  - --Unidirectional
- **Axon diameter**
  - --Larger (Less resistance, faster)
  - --Smaller (More resistance, slower)
- **Myelination**
  - --Saltatory conduction: Faster propagation
- **Temperature**
  - --High temperature: Faster propagation

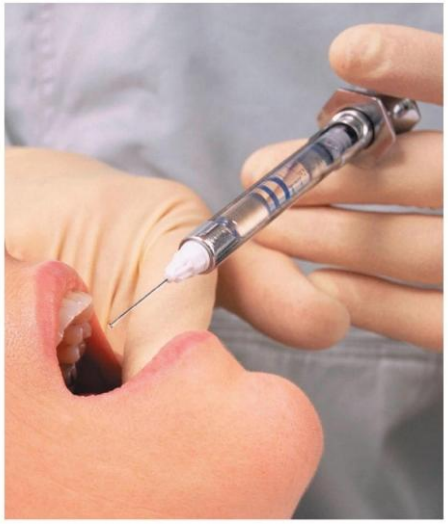
Conduction Velocity Comparisons

Fiber type	Myelin present?	Example of function	Fiber diameter (μm)	Conduction velocity (m/sec)
A alpha	Yes	Stimulation of skeletal muscle contraction	12–20	70–120
A beta	Yes	Touch, pressure sensation	5–12	30–70
A gamma	Yes	Stimulation of muscle spindle contractile fibers	3–6	15–30
A delta	Yes, but little	Pain, temperature sensation	2–5	12–30
B	Yes	Visceral afferents, autonomic preganglionics	1–3	3–15
C	No	Pain, temperature sensation, autonomic postganglionics	0.3–1.3	0.7–2.3

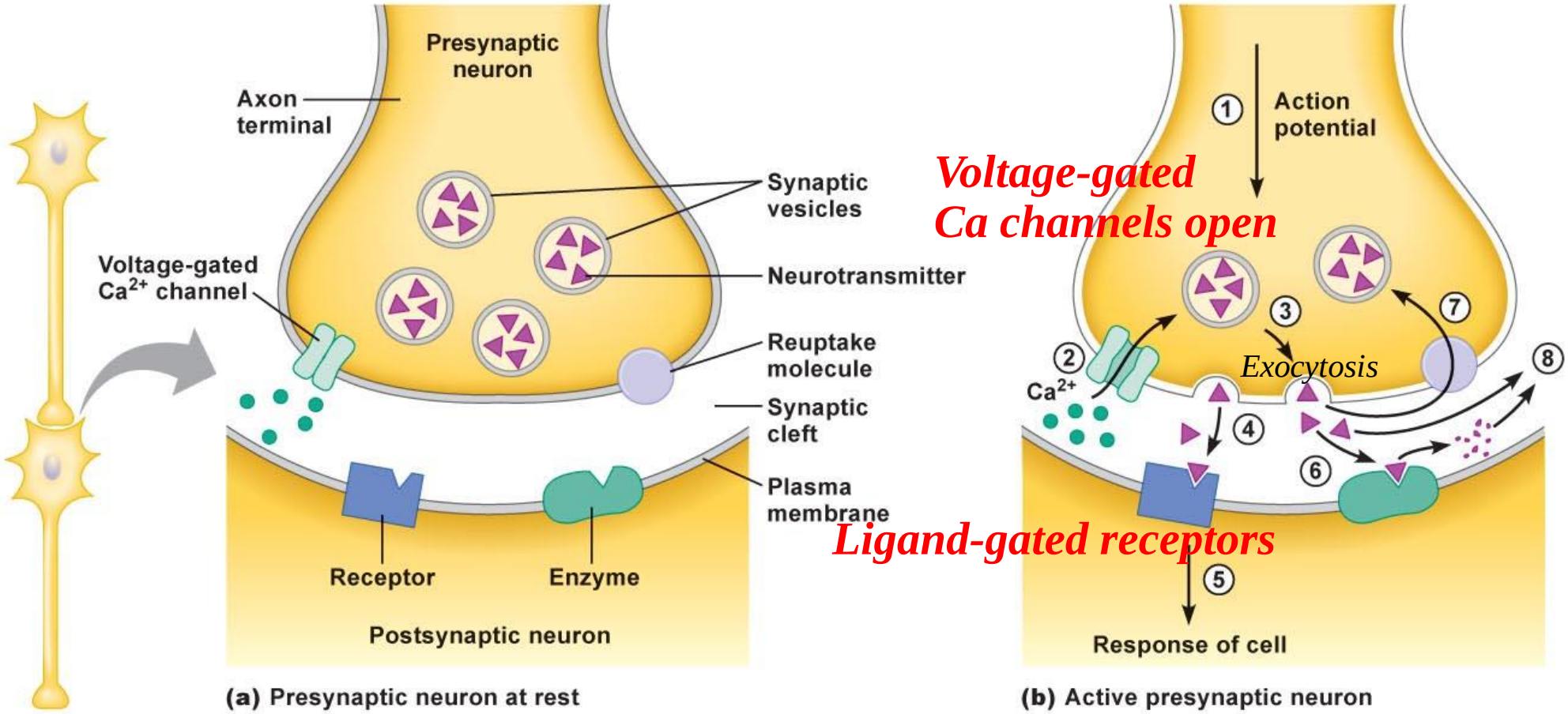
- **A fibers largest (2-20 microns & 130 m/sec)**
  --Myelinated somatic sensory & motor to skeletal muscle
- **B fibers medium (1-3 microns & 15 m/sec)**
  --Myelinated visceral sensory & autonomic preganglionic
- **C fibers smallest (0.3-1.3 microns & 2 m/sec)**
  --Unmyelinated sensory & autonomic postganglionic

Clinical Application: Local Anesthetics

- Local anesthetics and certain neurotoxins
  - --Prevent opening of **voltage-gated Na^+ channels**
  - --Nerve impulses cannot pass the anesthetized region
  - --**Procaine (Novocaine)** and **Lidocaine (Xylocaine)**

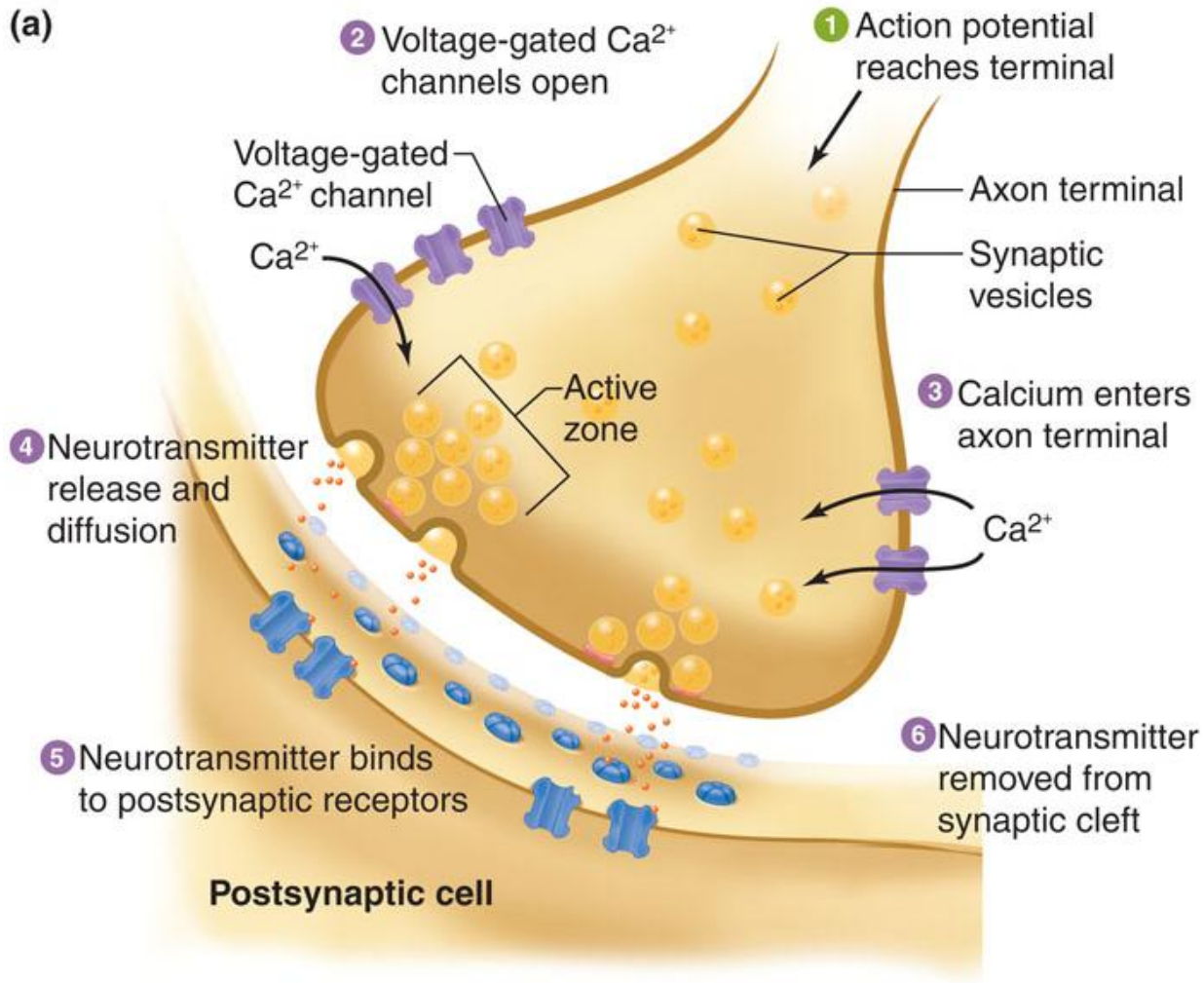


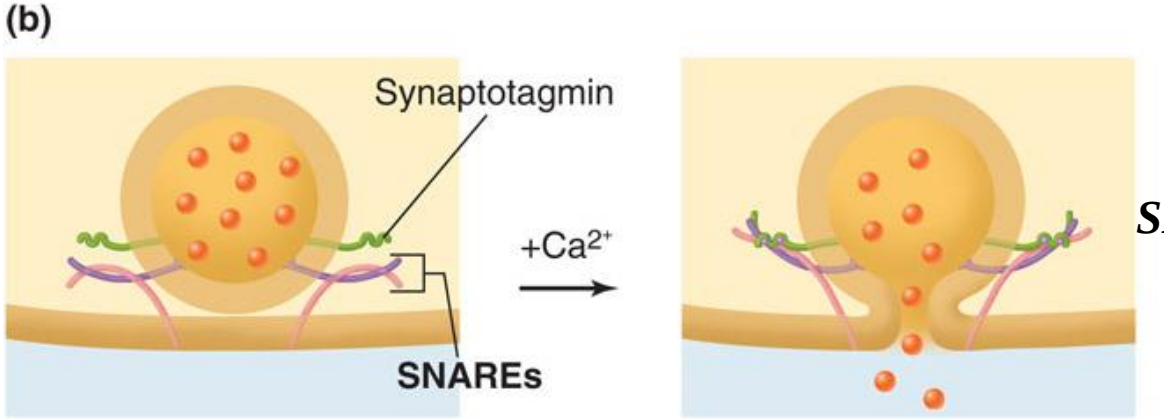
Anatomy of a Synapse
Neuron-Neuron



- ***Release of neurotransmitters: <u>Ca influx</u>***

6. ***Degradation***
7. ***Re-uptake***
8. ***Diffusion***





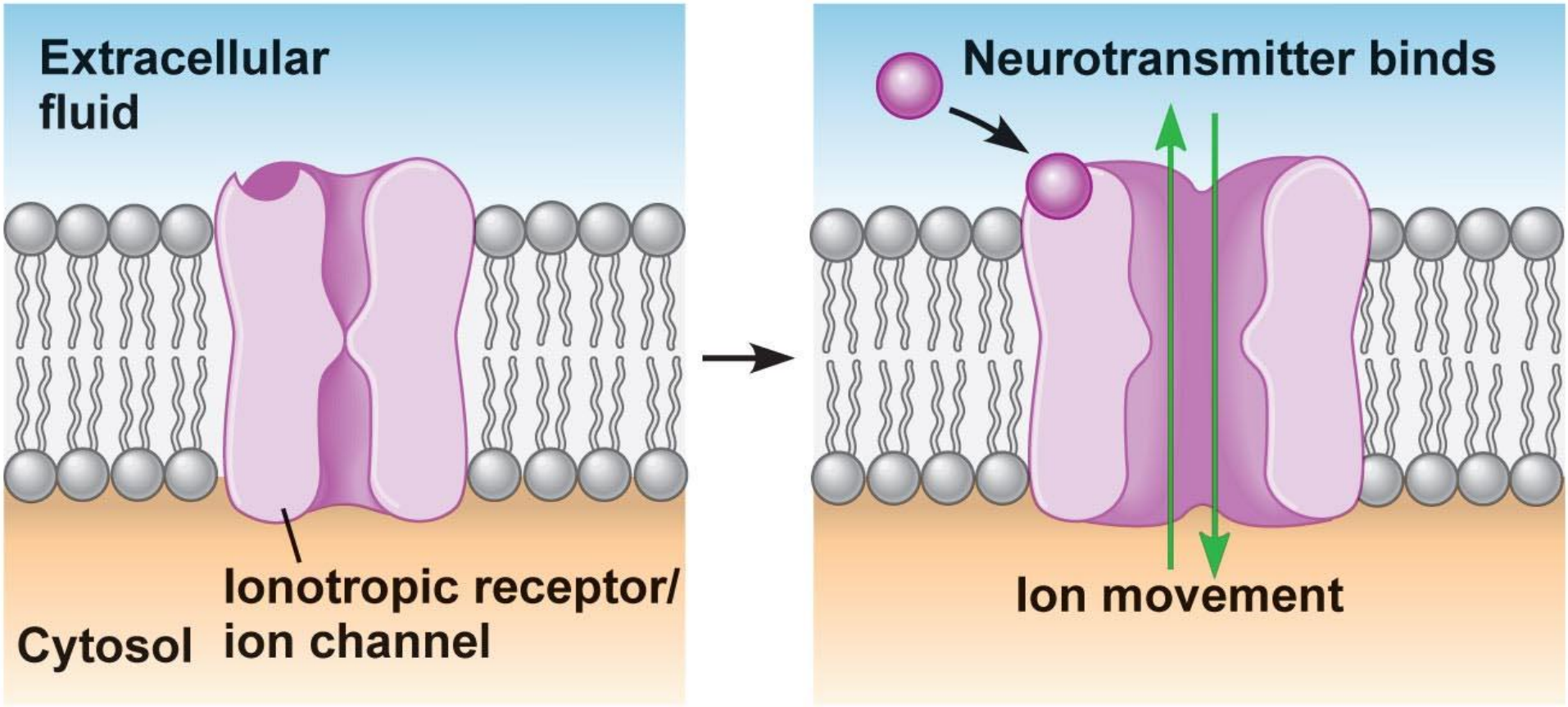
- When Ca^{2+} enters the cell, it binds to a protein called **synaptotagmin**
- Vesicles are docked at the plasma membrane by **SNARE** proteins
- The **Ca^{2+} synaptotagmin complex** displaces part of SNARE, and the vesicle fuses

SNARE=Soluble N-ethylmalemide–sensitive factor Attachment protein REceptor

Signal Transduction at Synapses

Channel-linked receptors = Ligand-gated receptors

= Ionotropic receptor

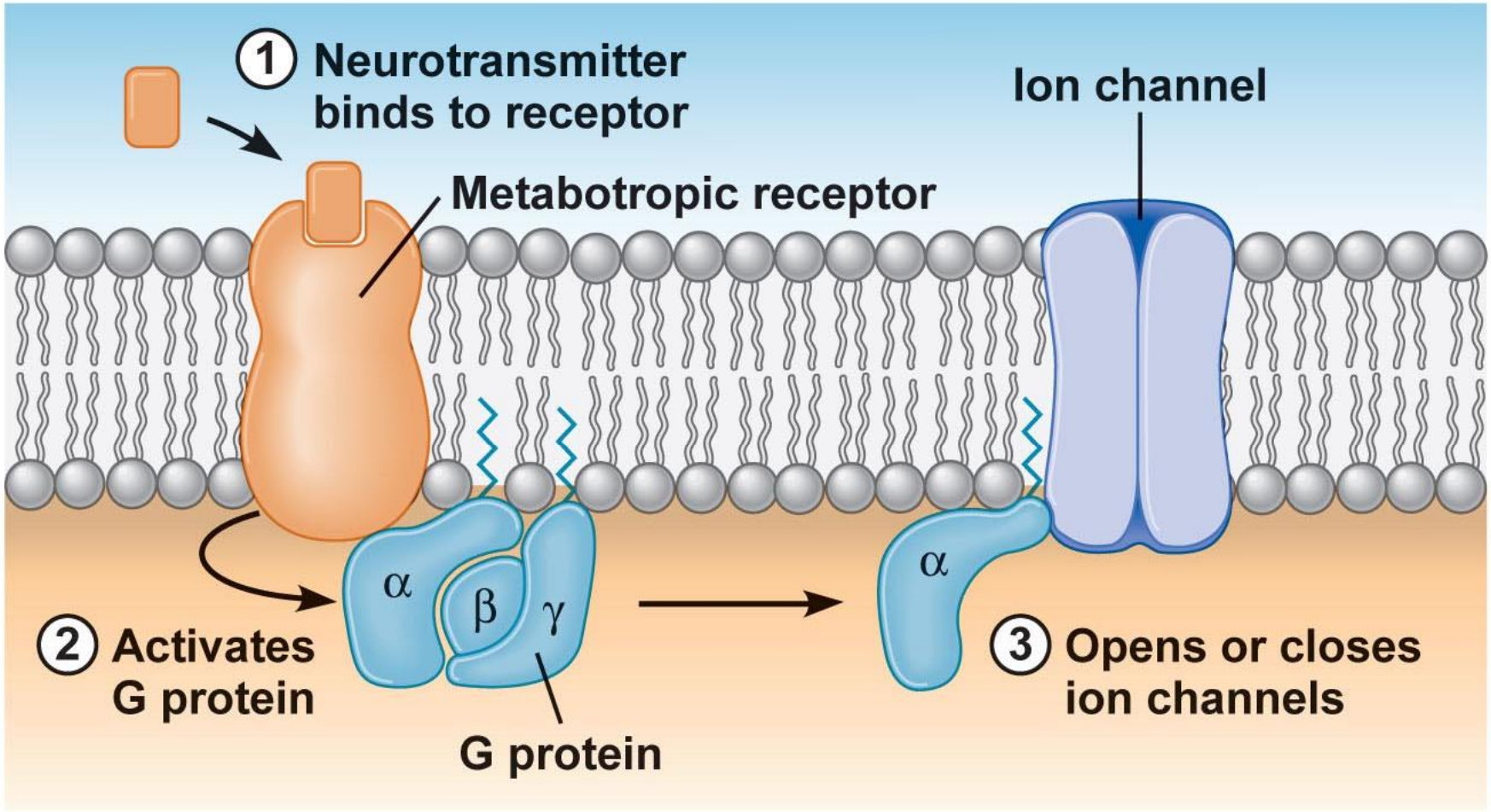


(a) Fast response **Direct-acting**

Signal Transduction at Synapses

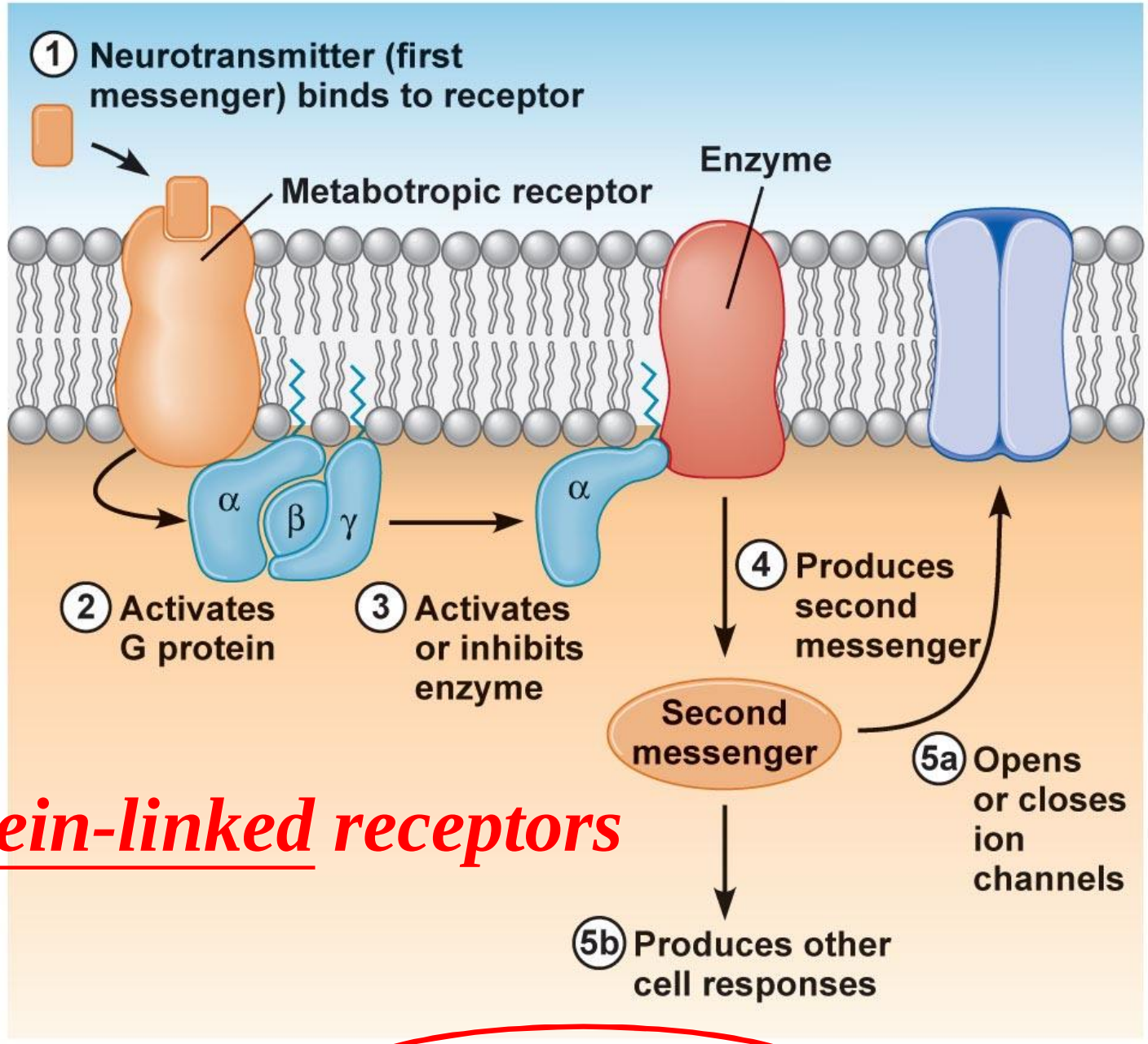
G protein-linked receptors* = *G protein-coupled receptors

= *Metabotropic receptors*



(b) Slow response, direct coupling ***to channel***

Signal Transduction at Synapses



G protein-linked receptors

(c) Slow response, second messenger system

Synaptic Potential

- The effect of a neurotransmitter can be either excitatory or inhibitory

--a depolarizing (*excitatory*) postsynaptic potential

= EPSP

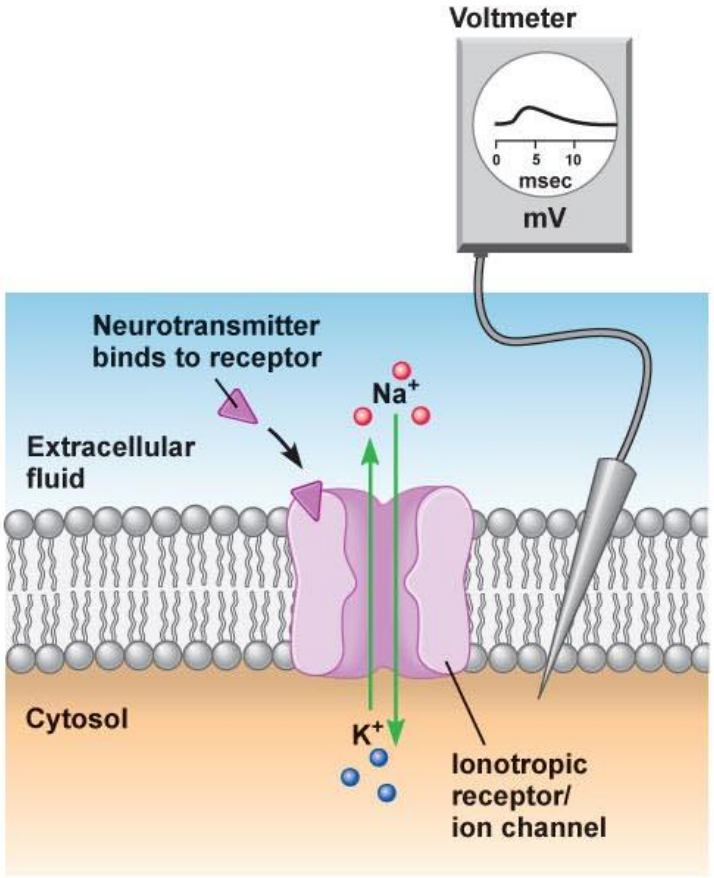
- it results from the opening of ligand-gated Na+ channels
- the postsynaptic cell is more likely to reach threshold

--a hyperpolarizing (*inhibitory*) postsynaptic potential

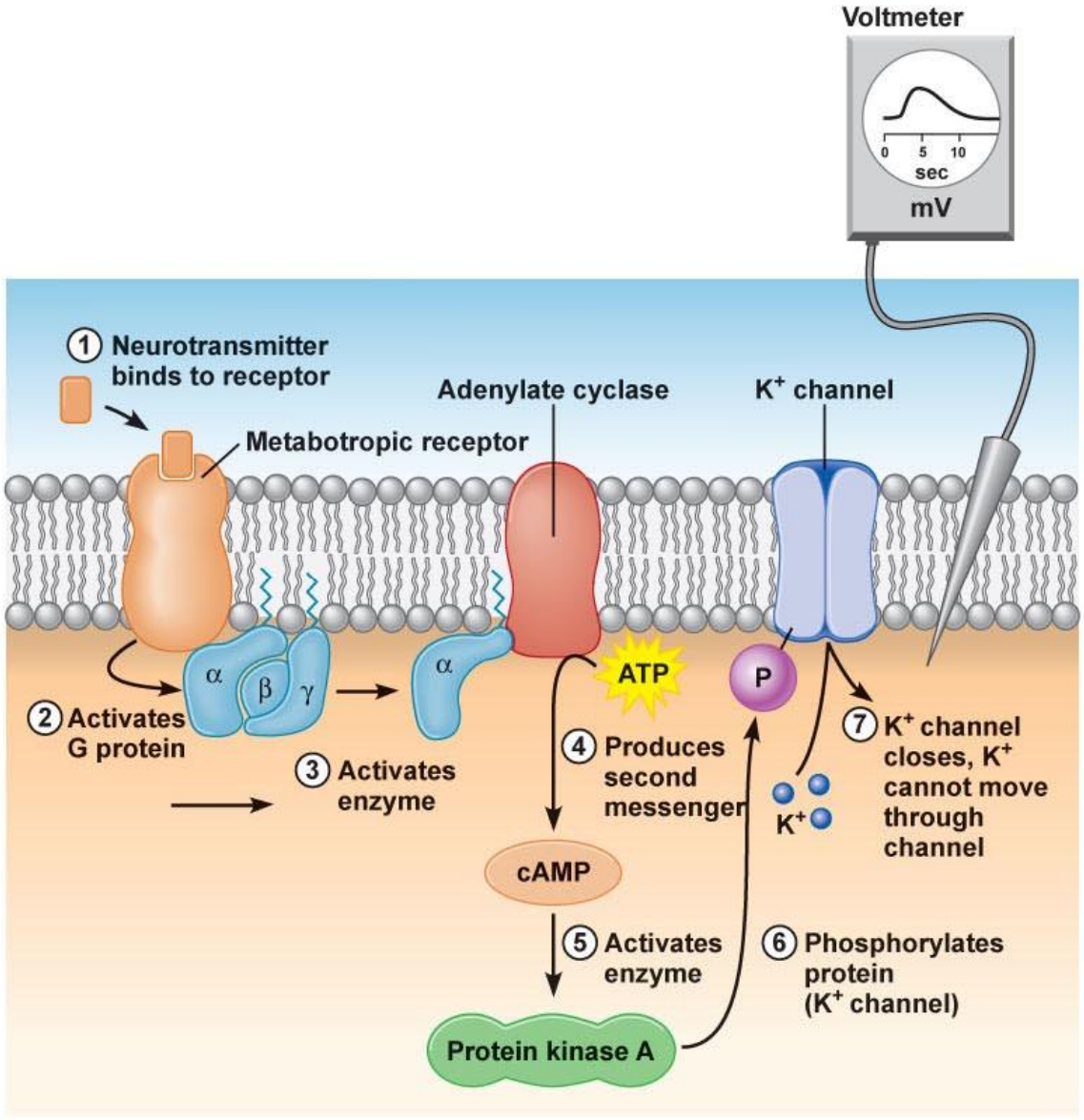
= IPSP

- it results from the opening of ligand-gated Cl- or K+ channels
- it causes the postsynaptic cell to become more negative or hyperpolarized
- the postsynaptic cell is less likely to reach threshold

Excitatory Synapses= EPSP

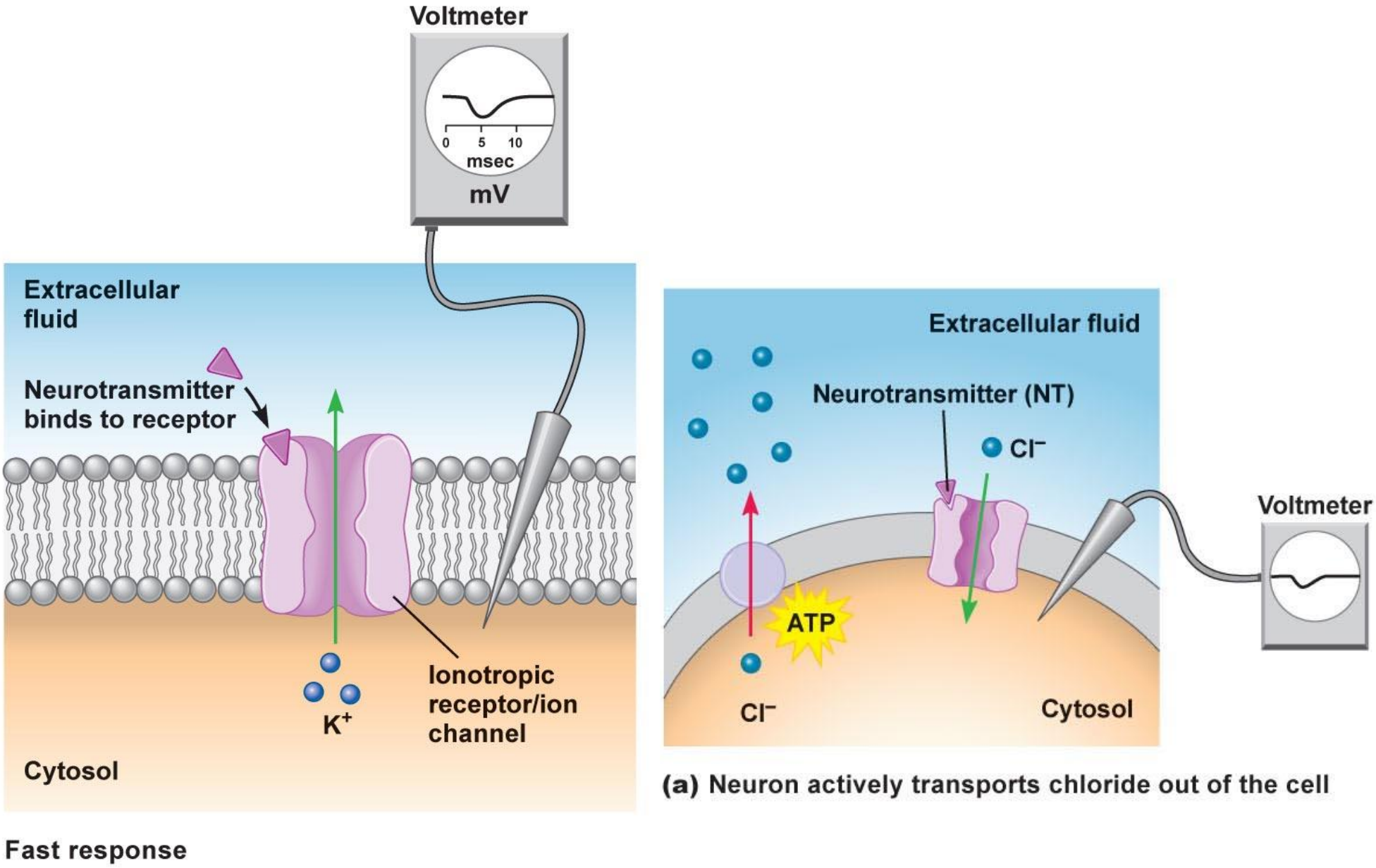


(a) Fast response



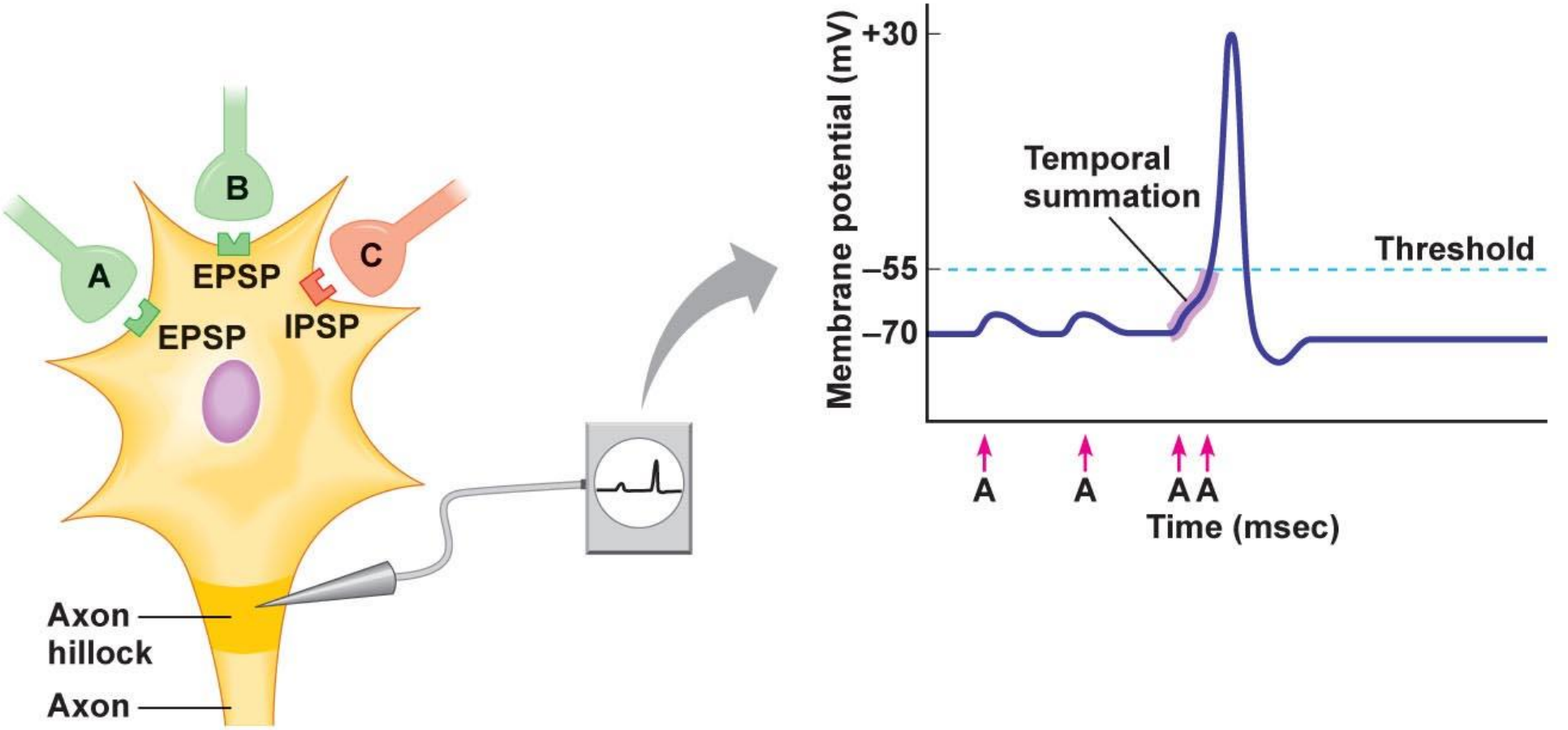
(b) Slow response

Inhibitory Synapses= IPSP



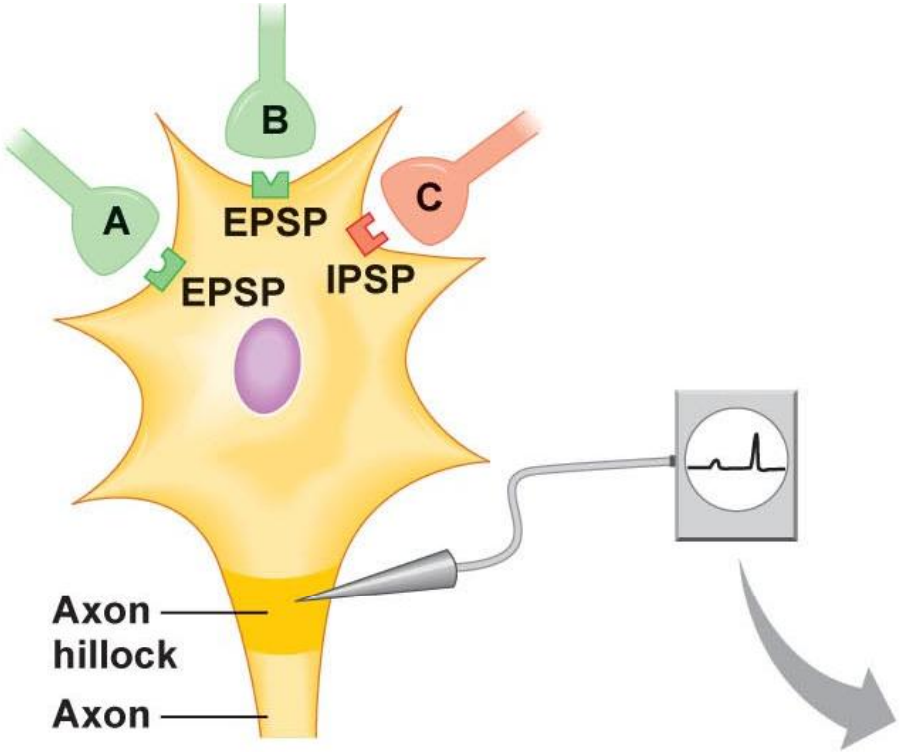
IPSPs and EPSPs= Graded Potentials

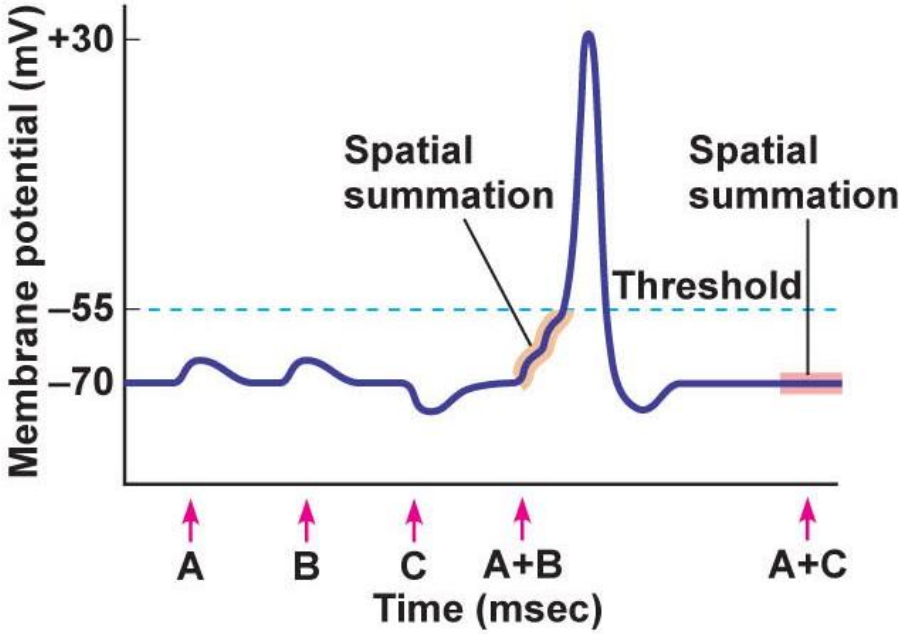
Temporal Summation



IPSPs and EPSPs= Graded Potentials

Spatial Summation



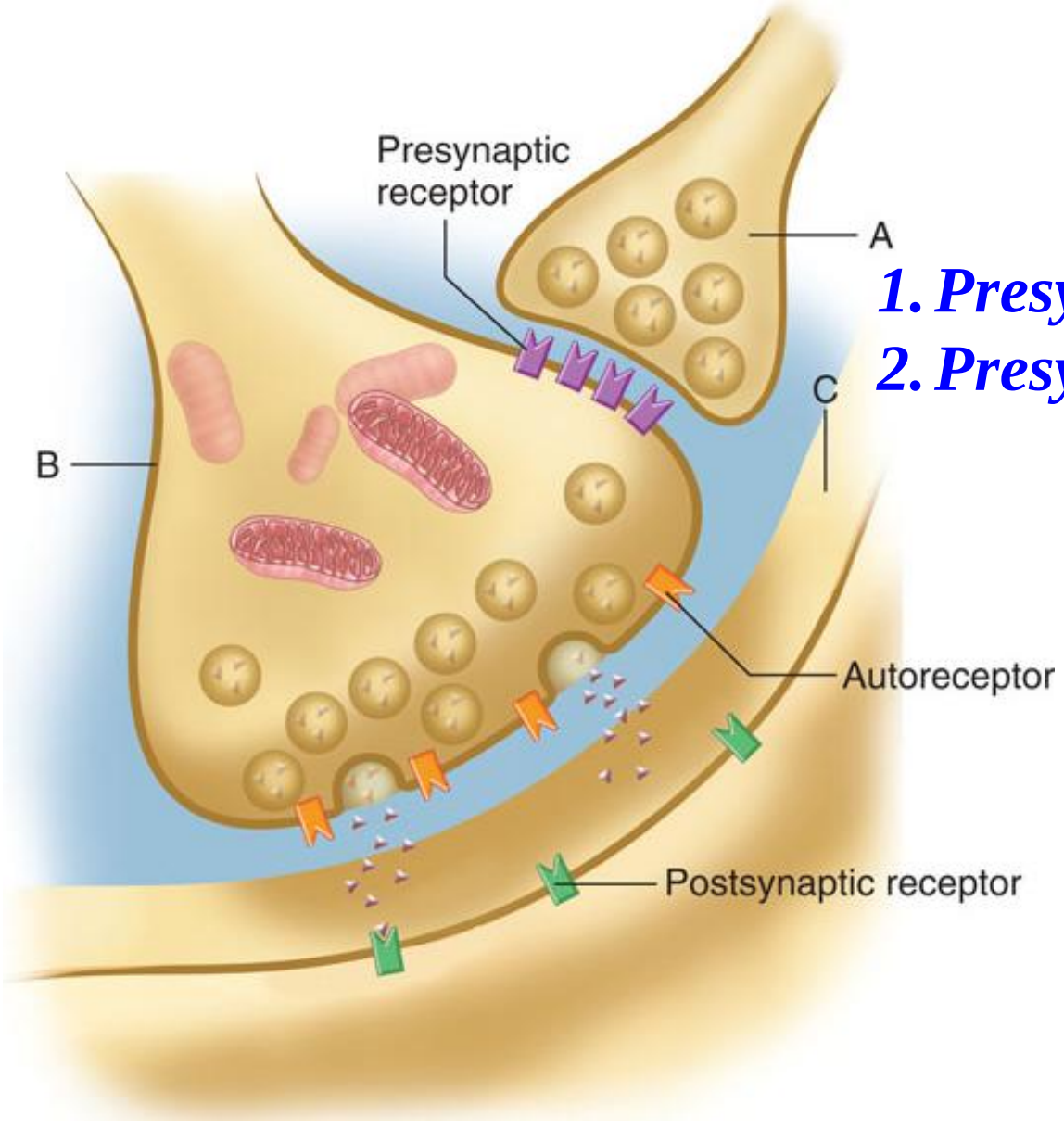


Comparison of Graded & Action Potentials

CHARACTERISTIC	GRADED POTENTIALS	ACTION POTENTIALS
Origin	Arise mainly in dendrites and cell body.	Arise at trigger zones and propagate along the axon.
Types of channels	Ligand-gated or mechanically gated ion channels.	Voltage-gated channels for Na^+ and K^+.
Conduction	Decremental (not propagated); permit communication over short distances.	Propagate and thus permit communication over longer distances.
Amplitude (size)	Depending on strength of stimulus, varies from less than 1 mV to more than 50 mV.	All-or-none; typically about 100 mV.
Duration	Typically longer, ranging from several msec to several min.	Shorter, ranging from 0.5 to 2 msec.
Polarity	May be hyperpolarizing (inhibitory to generation of an action potential) or depolarizing (excitatory to generation of an action potential).	Always consists of depolarizing phase followed by repolarizing phase and return to resting membrane potential.
Refractory period	Not present, thus summation can occur.	Present, thus summation cannot occur.

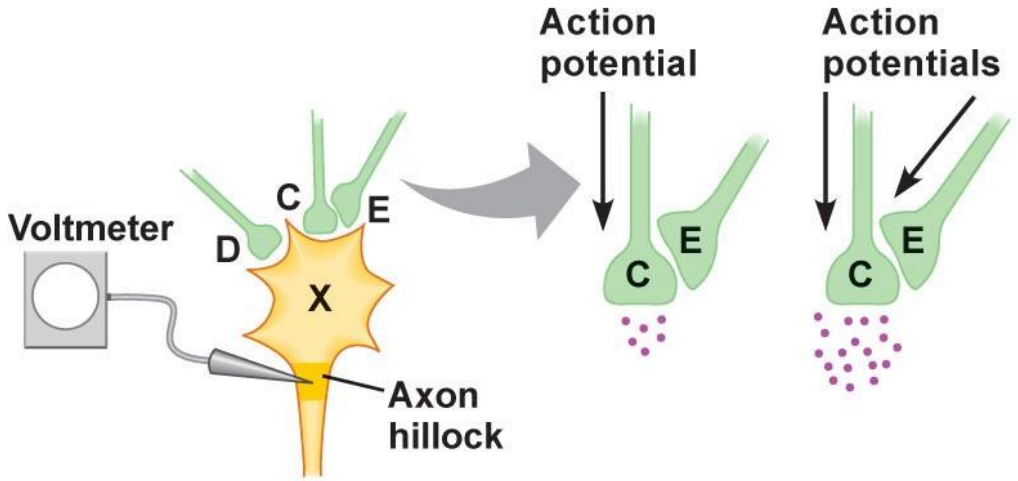
Presynaptic Modulation

Axo-axonal communication (between A & B) can modify classical synaptic communication (between B & C):

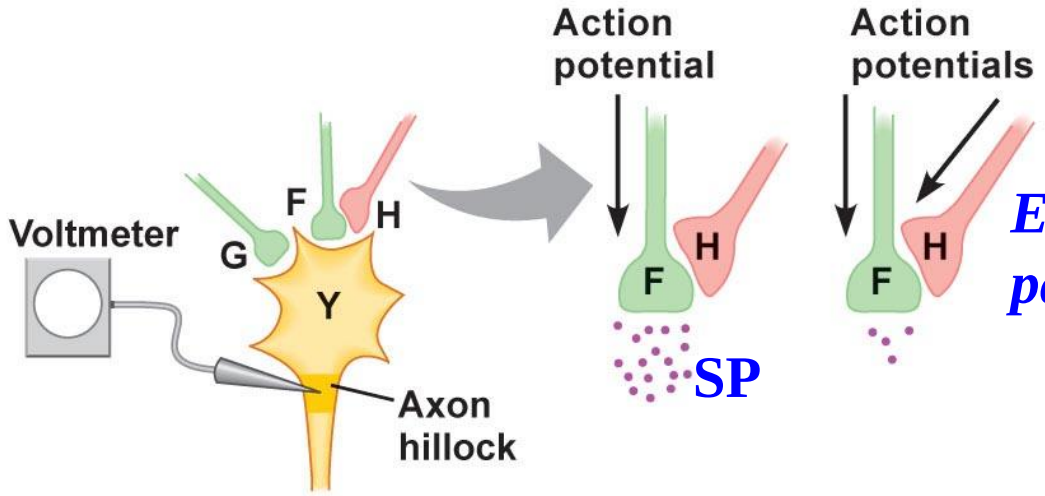


1. ***Presynaptic inhibition***
2. ***Presynaptic facilitation***

Presynaptic Modulation



Presynaptic Facilitation



Endogenous opioids in pain reduction

Presynaptic Inhibition

Neurotransmitters

Choline derivative	Biogenic amines	Amino acids	Purines	Neuropeptides	Unique molecules
Acetylcholine	Catecholamines	Glutamate	ATP	TRH	Nitric oxide
	Dopamine	Aspartate	ADP	Vasopressin	Endocannabinoids
	Epinephrine	Glycine	Adenosine	Oxytocin	
	Norepinephrine	GABA		Substance P	
	Serotonin			Endogenous opioids	
	Histamine			Enkephalins	
				Endorphins	
				Orexin	

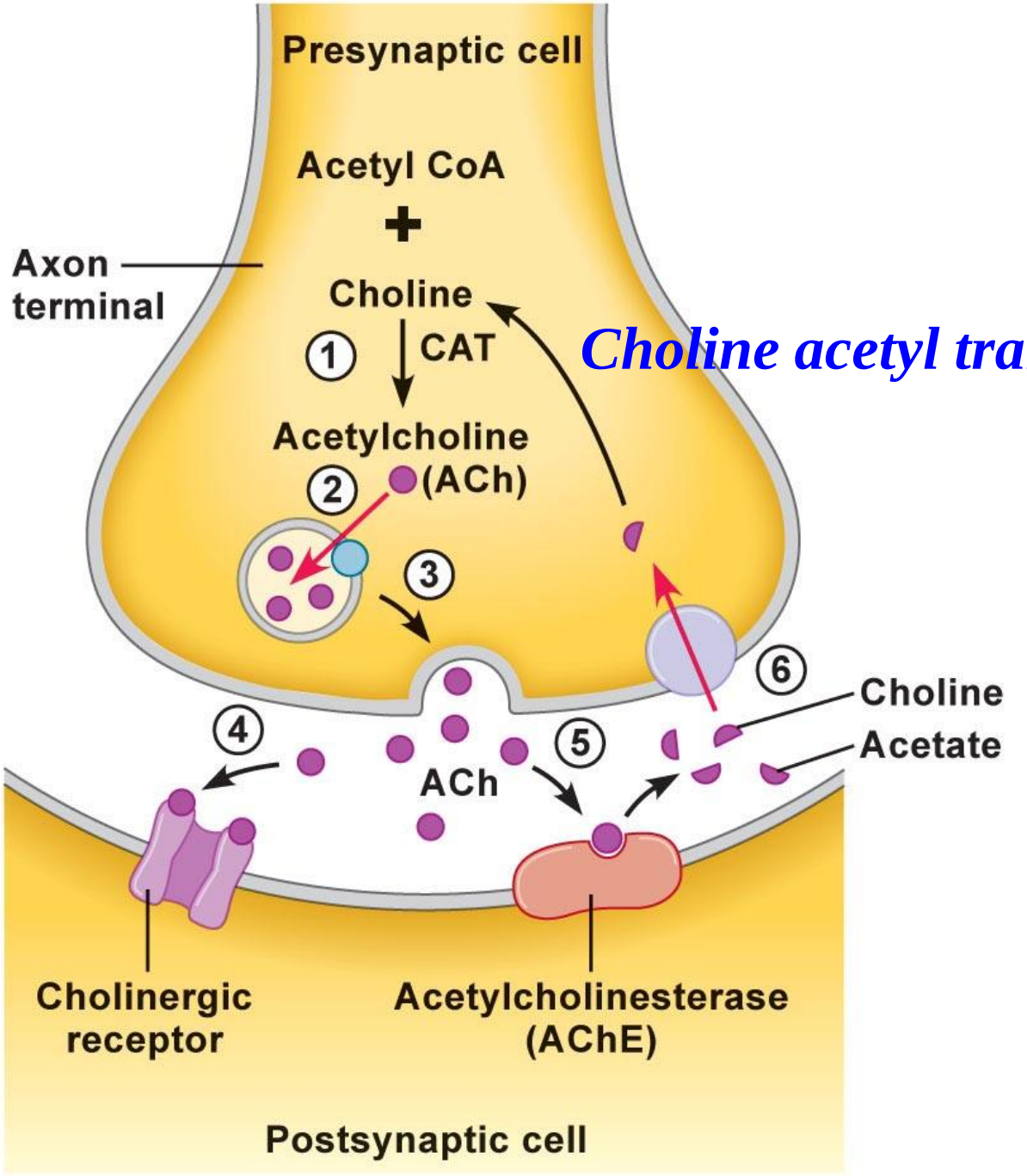
Acetylcholine

- 在周邊神經系統，以**乙醯膽鹼**(acetylcholine, ACh)為神經傳遞物質的神經纖維稱為**膽鹼性纖維**(**cholinergic fiber**)。
- 在中樞神經系統，以 ACh 為神經傳遞物質的神經元稱為**膽鹼性神經元**(**cholinergic neuron**)。
- 膽鹼(choline) 和乙醯輔酶A (acetyl coenzyme A)在膽鹼乙醯轉移酶(**choline acetyl transferase, CAT**)的催化下合成ACh。

- **有機磷農藥和神經毒氣**如沙林(sarin)、梭門(soman)、泰奔(tabun) 等是不可逆的乙醯膽鹼酯酶抑制劑(**AChE inhibitors**)，造成ACh 聚集在突觸裂隙，持續地作用在動作器細胞的膽鹼性接受器，可導致膽鹼性纖維所支配的神經中樞和周邊器官功能亢進，最終衰竭以至死亡。

AChE = acetylcholinesterase

Synthesis and Action of ACh



Choline acetyl transferase

Cholinergic Receptor

- 根據對不同生物鹼的反應，膽鹼性接受器分為兩大類:

1. 蕈毒鹼型接受器(**muscarinic** receptor)：

Metabotropic receptor = G protein-coupled receptor

--簡稱 M 接受器

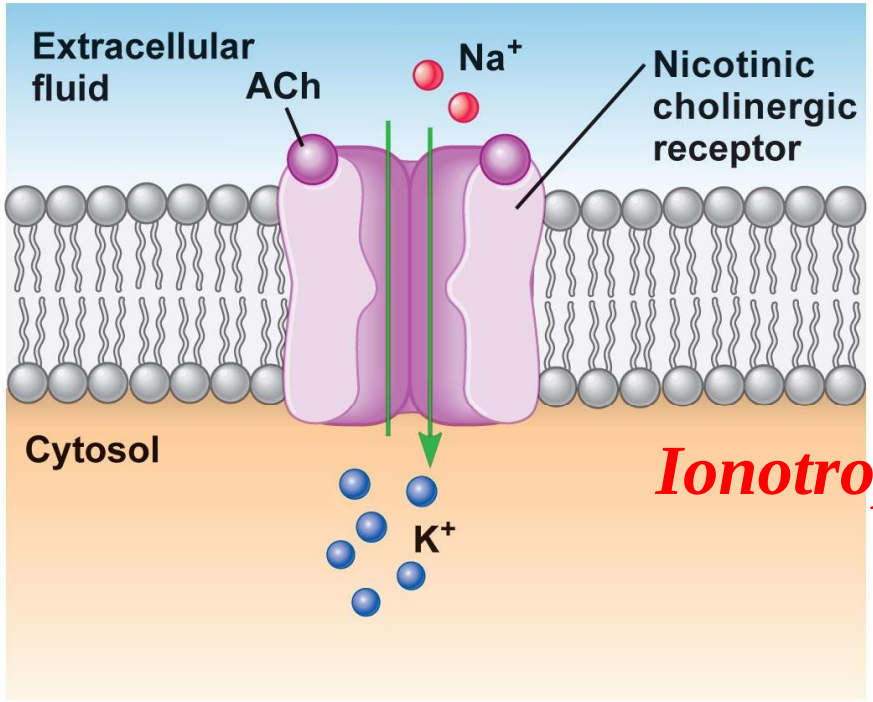
--除了乙醯膽鹼外，此型接受器亦可被蕈毒鹼(muscarine)啟動，而被阿托品(atropine) 阻斷。

2. 尼古丁型接受器(**nicotinic** receptor)：

Ionotropic receptor = ligand-gated channel

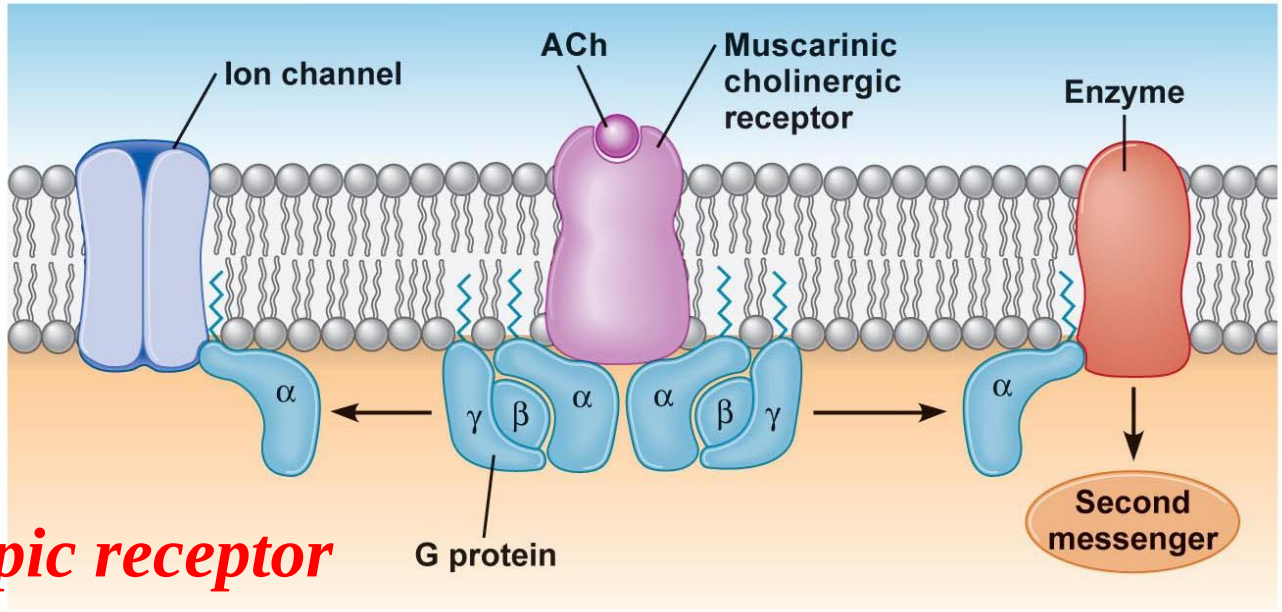
--又稱為菸鹼型接受器，或簡稱 N 接受器。

--除了乙醯膽鹼外，此型接受器亦可被尼古丁(nicotine) 啟動，而被箭毒(curare) 阻斷。



Ionotropic receptor

(a) Nicotinic cholinergic receptors



Metabotropic receptor

(b) Muscarinic cholinergic receptor

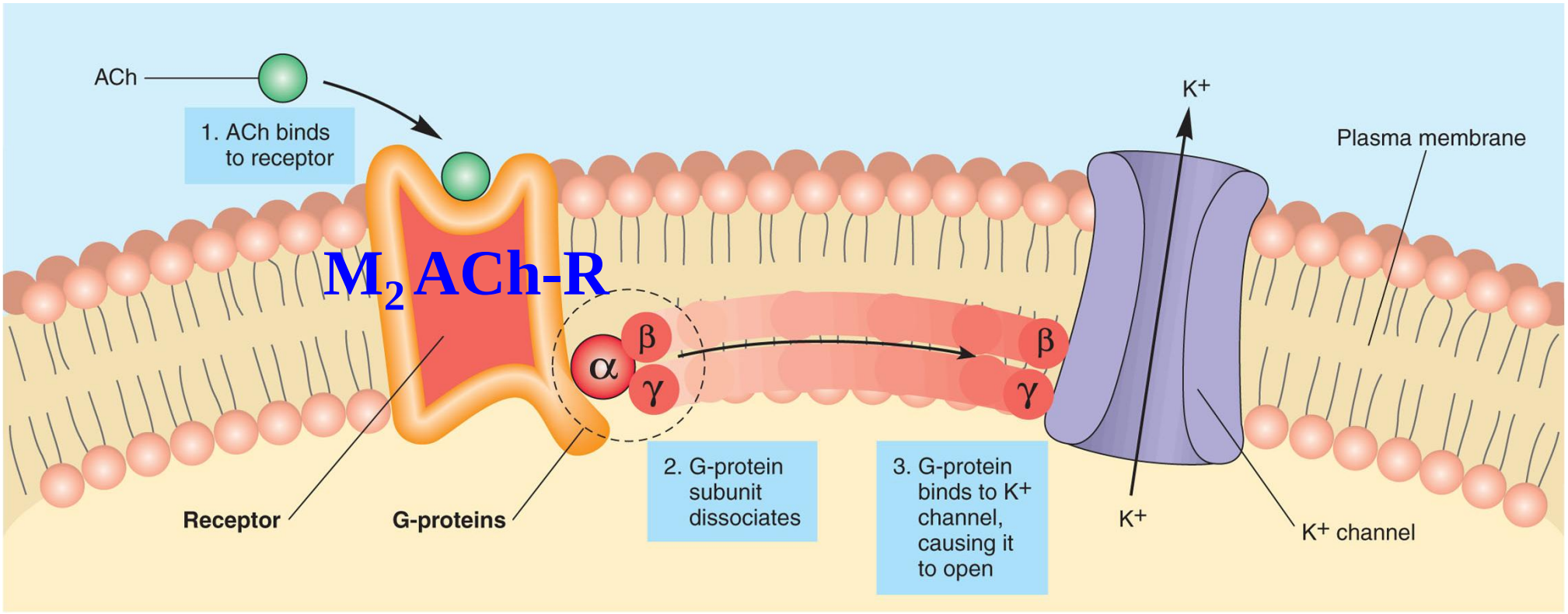
Muscarinic Receptor

G protein-coupled receptor

- 現已發現的蕈毒鹼型接受器有 5 種亞型
  - --**M_1、M_3、M_5** 透過 G 蛋白和第二傳訊物質發揮興奮性生理效應。
  - --**M_2、M_4** 與G蛋白結合後，分別使 Ca^{2+} 內流減少、K^+ 外流增加，產生過極化效應，並且降低第二傳訊物質 cAMP 的濃度，減少神經傳遞物質的釋放。
- M 接受器存在於大多數副交感神經節後纖維和少數交感神經節後纖維所支配的動作器細胞膜上如心肌或平滑肌等。

Muscarinic Receptor

IPSPs (hyperpolarization) ⟹ HR decrease/heart cell



K^+ channels close ⟹ EPSPs (depolarization)

⟹ Smooth muscles contraction /stomach

Muscarinic Receptor in CNS

- **M_1、M_3 和 M_4** 接受器主要位在大腦皮層和海馬回，可能媒介 ACh 在學習和記憶 (**Alzheimer's disease**)方面的作用。
- **M_1 和 M_4** 接受器可在紋狀體發現，可能媒介 ACh 對錐體外運動路徑的調節。
- **M_2** 接受器集中在基底前腦，它可能是突觸前接受器，調節基底前腦膽鹼性神經元 ACh 的合成和釋放。
- 腦中 **M_5** 接受器數量最少，其功能尚不清楚。

Nicotinic Receptor

Channel-linked receptor

- N 接受器本身即是離子通道(Na^+)，有兩種亞型
  - --N_1 接受器：主要存在於自主神經節神經元。
  - --N_2 接受器：位於骨骼肌運動終板(NMJ)。
- 在中樞神經系統，當 N 接受器興奮時，離子通道開放，Ca^{2+} 大量內流，產生興奮性作用，顯示這類接受器可能在促進突觸後興奮和學習記憶中具有重要作用。
- 膽鹼性接受器在周邊組織中的分布和效應(ANS)。

Clinical Application: Drugs Affect Neural Control of Skeletal Muscles

Drug	Origin	Effects
Botulinum toxin	Produced by *Clostridium botulinum* (bacteria)	Inhibits release of acetylcholine (ACh)
Curare	Resin from a South American tree	Prevents interaction of ACh with its nicotinic receptor proteins
α-Bungarotoxin	Venom of *Bungarus* snakes金環蛇毒 (BTX)	Binds to ACh receptor proteins and prevents ACh from binding (N-R blocker)
Saxitoxin	Red tide (*Gonyaulax*) algae	Blocks voltage-gated Na^+ channels 蛤蚌毒素(STX)
Tetrodotoxin	Pufferfish	Blocks voltage-gated Na^+ channels 河豚毒素(TTX)
Nerve gas	Artificial	Inhibits acetylcholinesterase in postsynaptic membrane
Neostigmine	Nigerian bean	Inhibits acetylcholinesterase in postsynaptic membrane
Strychnine	Seeds of an Asian tree	Prevents IPSPs in spinal cord that inhibit contraction of antagonistic muscles

- *Puffer fish (blowfish) contain a **neurotoxin (TTX)***
- *TTX is concentrated in **liver and gonads** and cannot be destroyed by cooking*
- *TTX is present in some kinds of salamanders, octopus and goby*

影響突觸傳訊的物質

自然界中許多生物會分泌毒液或毒素用以防禦或攻擊，其中有一些屬於神經毒素，可作用於人類或其他生物的神經系統，產生麻痺、癱瘓、痙攣等效應，嚴重時甚至可導致死亡。例如**肉毒桿菌毒素** (botulinum toxin) 是由肉毒桿菌所產生的毒素，為已知最毒的天然化合物。該化合物經由切割突觸小泡膜和突觸前膜上的結合蛋白，阻止突觸小泡與突觸前膜的融合，從而阻止 ACh 的釋放。肉毒桿菌毒素中毒可導致肌肉無力及麻痺，現今臨床上則廣泛用於治療肌肉痙攣及醫學美容之除皺等方面。

黑寡婦蜘蛛 (black widow spider) 所分泌的毒液中含有一種稱為 **latrotoxin** 的蛋白質，其可作用於突觸前膜的接受器，使離子通道持續打開，因而使 Ca^{2+} 大量進入，引起 ACh 的大量釋放，從而導致肌肉持續而強烈的痙攣。一旦突觸小泡被耗盡，該毒素阻止突觸小泡重新裝入乙醯膽鹼，並阻止突觸小泡向突觸前膜活化區移動。

破傷風毒素 (tetanus toxin) 是由破傷風桿菌所分泌，亦屬於神經毒素，是一種強毒性蛋白質，對腦幹神經和脊髓前角神經細胞有高度親和力。此毒素可阻斷脊髓的抑制性突觸，阻止突觸末梢釋放抑制性神經傳遞物質，致使上下神經元之間正常的抑制性作用受阻，導致興奮性增高。可造成肌肉痙攣，患者常出現牙關緊閉及角弓反張。

Clinical Application:
Drugs Affect Neural Control of Skeletal Muscles

- **Botulinum toxin** ⇨ ***inh. ACh release*** ⇨ ***Flaccid paralysis***
- **Curare** ⇨ ***ACh N-R blocker*** ⇨ ***Flaccid paralysis***
- **BTX** ⇨ ***ACh N-R blocker*** ⇨ ***Flaccid paralysis***
- **STX** ⇨ ***inh. V-gated Na*** ⇨ ***Flaccid paralysis***
- **TTX** ⇨ ***inh. V-gated Na*** ⇨ ***Flaccid paralysis***
- **Nerve gas** ⇨ ***inh. AChE*** ⇨ ***Spastic paralysis***
- **Neostigmine** ⇨ ***inh. AChE*** ⇨ ***Spastic paralysis***
- **Strychnine** ⇨ ***glycine-R blocker*** ⇨ ***Spastic paralysis***
- **Latrotoxin** ⇨ ***ACh release*** ⇨ ***Spastic paralysis***
- **Tetanus toxin** ⇨ ***blocks inhibitory synapses/CNS*** ⇨ ***Spastic paralysis***

Biological Amines

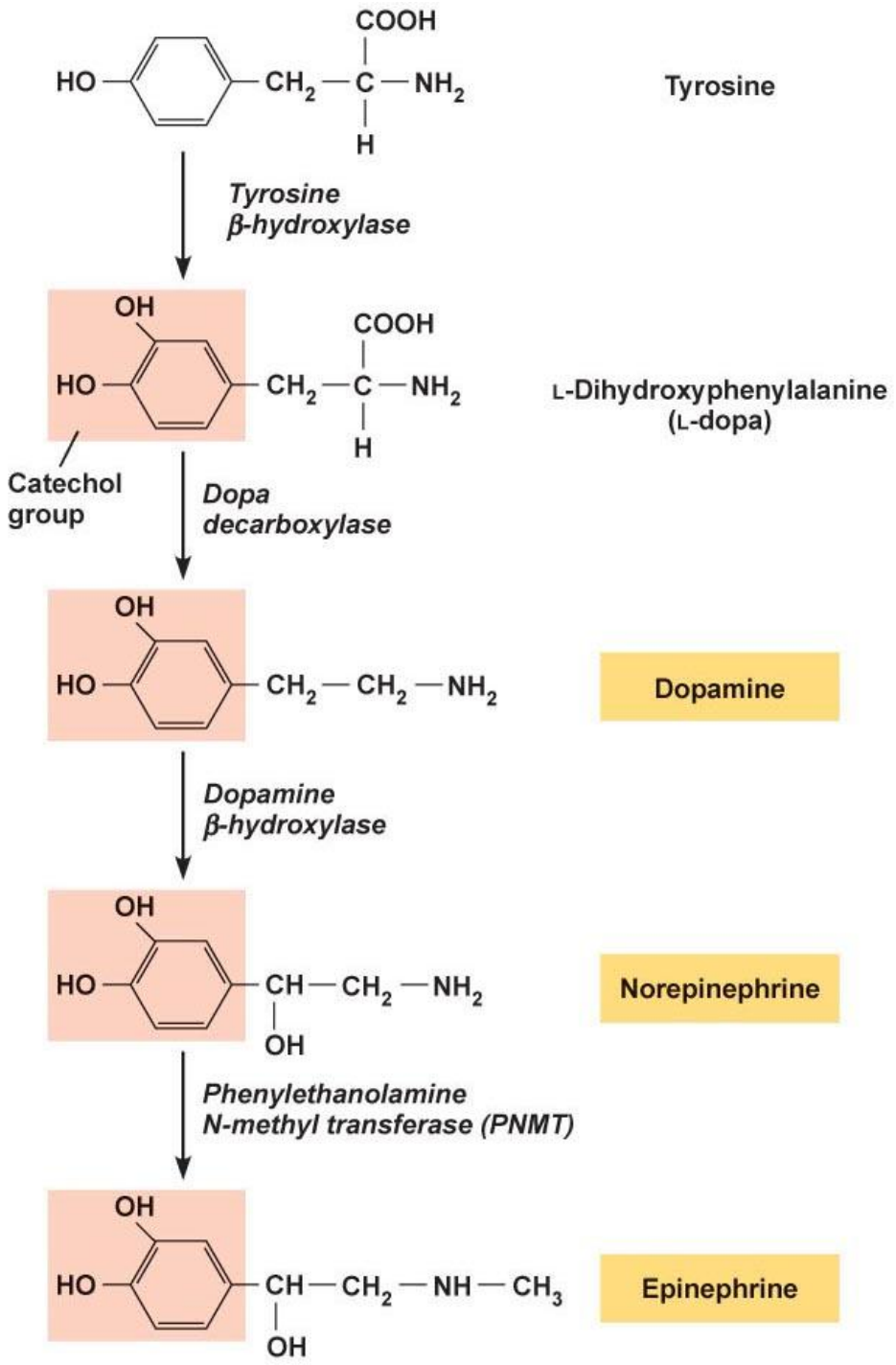
- Derived from **amino acids**
  - **--Catecholamines**—derived from **tyrosine**
    1. ***Dopamine (DA)***
    2. ***Norepinephrine (NE) = Noradrenaline***
    3. ***Epinephrine (Epi) = Adrenaline***
  - **--Serotonin**—derived from **tryptophan**
  - **--Histamine**—derived from **histidine**
- Like ACh, monoamines are made in the **presynaptic axon**, released via exocytosis, diffuse across the synapse, and bind to specific receptors
- Serotonin, dopamine, and norepinephrine are neurotransmitters

Biological Amines: Catecholamines

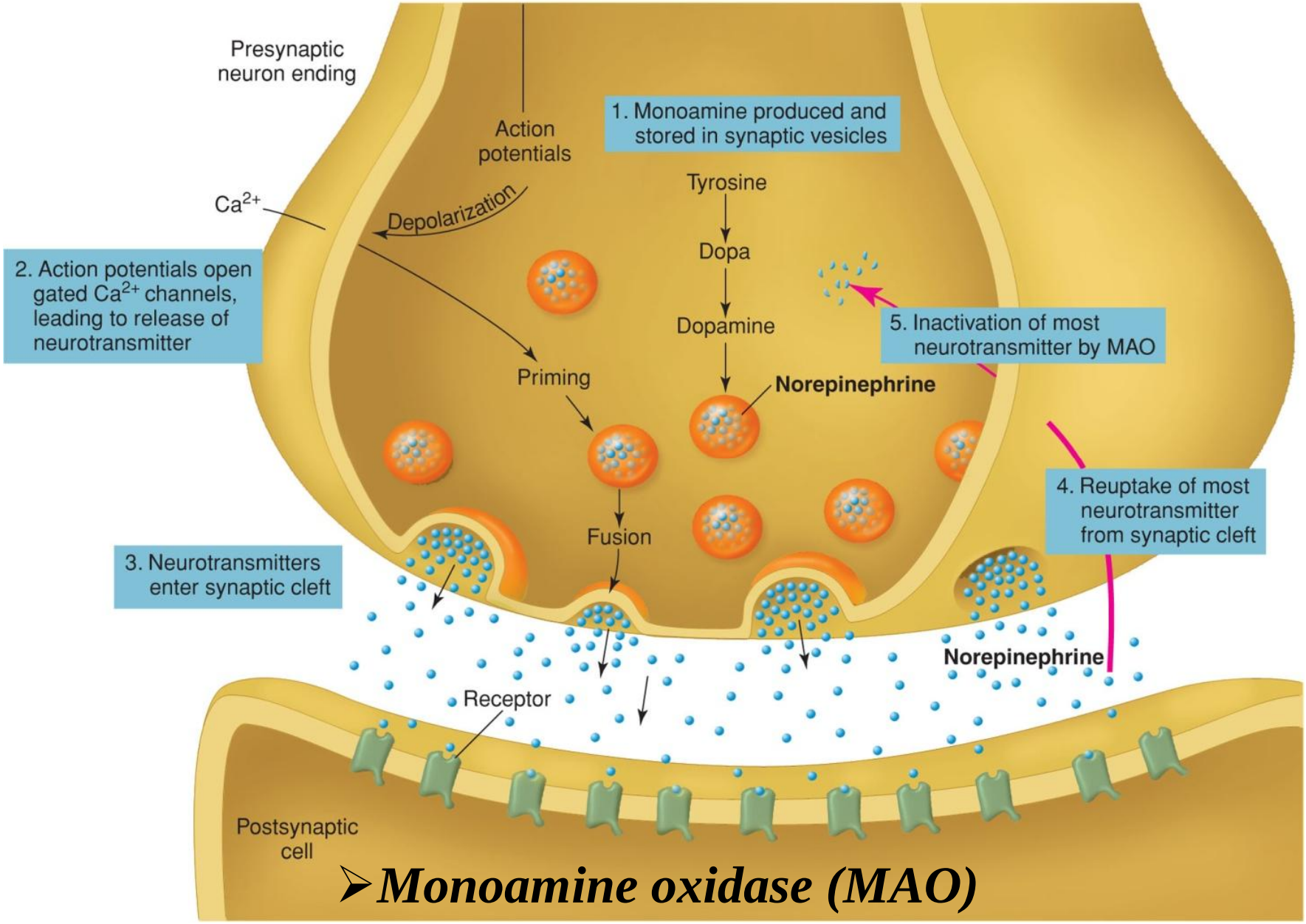
- 在周邊神經系統，多數交感神經節後纖維釋放的神經傳遞物質都是正腎上腺素(NE)，以 NE 為傳訊物質的纖維稱為腎上腺素性纖維(**adrenergic fiber**)。
- 在CNS (與情緒、動機、意識、警覺及食慾等有關)，存在有
  - --以 Epi 為傳訊物質的神經元，稱為**腎上腺素性神經元**：主要分布在延腦。
  - --以 NE 為傳訊物質的神經元，稱為**正腎上腺素性神經元**：主要集中在低位腦幹。
- 多巴胺性神經元的細胞體主要位於中腦和間腦，中腦的DA過多可能造成精神分裂症。
- 中腦的黑質是腦內生成多巴胺的主要部位，與運動協調有關，對紋狀體神經元主要具有抑制作用，損毀黑質的多巴胺性神經元(DA太少)可引起巴金森氏病(**Parkinson disease**)。
- DA與情緒、報償及成癮行為如酒精成癮有關。

Catecholamines Synthesis

1. Tyrosine經**tyrosine hydroxylase**催化dopa，再經多巴脫羧酶(dopa decarboxylase) 作用轉化為DA，並運輸入突觸小泡。
2. 在小泡內，dopa-β-hydroxylase催化後生成NE。
3. 由於dopa-β-hydroxylase完全存在於突觸小泡內，因此，NE合成的最後一步是在突觸小泡內完成。
4. 在腎上腺髓質嗜鉻細胞和腎上腺素性神經元，NE 可經由細胞質中的PNMT作用，使NE甲基化而生成Epi，再將腎上腺素運輸入嗜鉻細胞的嗜鉻顆粒或腎上腺素性神經元的突觸小泡中儲存。



Release & Inactivation of NE



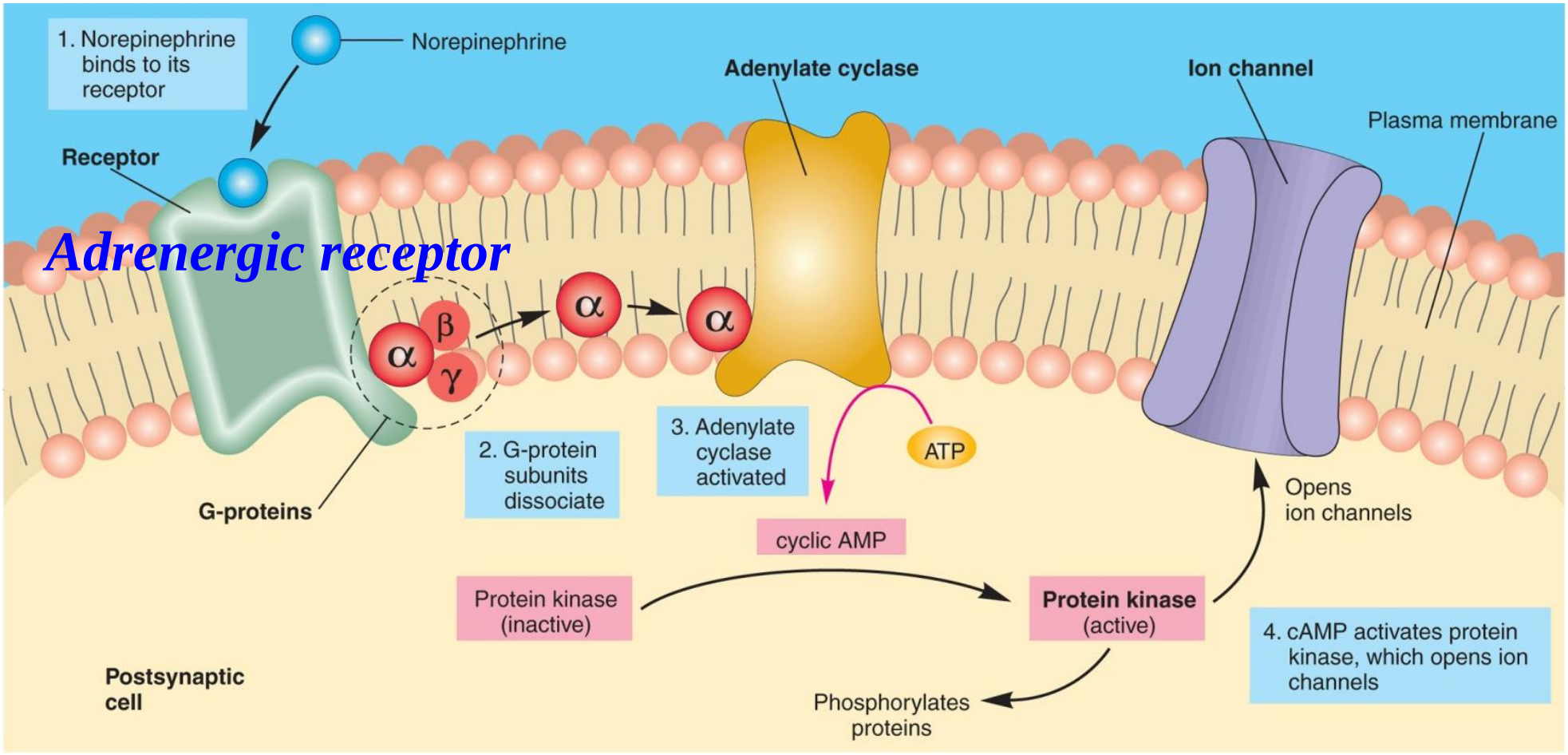
- ***Monoamine oxidase (MAO)***
- ***Catechol-o-methyltransferase (COMT)***

Adrenergic Receptor

- 能與腎上腺素和正腎上腺素結合的接受器，稱為腎上腺素性接受器(**adrenergic receptor**)。
- 主要分為
  - --**α型**(α-接受器)：有**α_1**和**α_2**兩種亞型
  - --**β型**(β-接受器)：有**β_1**、**β_2**、**β_3**三種亞型
- 所有的兒茶酚胺接受器都屬於**G protein-coupled receptor** (通常與**second messengers**形成有關)。
- 腎上腺素性接受器在周邊組織中分布極為廣泛，不僅能對交感神經末梢釋放的NE起反應，也能對血液中的Epi、NE和某些藥物起反應。
- 腎上腺素性接受器啟動後產生的效應較複雜，有興奮性及抑制性(ANS)。

Effect of Monoamines (NE)

G protein-coupled receptor



➢ ***All use a second messenger system***

--Cyclic adenosine monophosphate (**cAMP**) is the most common second messenger for catecholamines

Biological Amines: Serotonin

- **血清胺(serotonin) =5-羥色胺(5- hydroxytryptamine, 5-HT)**，在化學上屬於吲哚胺化合物。
- 由於它是從人的血清中發現，並具有使血管收縮的作用，因此亦被稱為血清胺。
- 血清胺廣泛分布於植物及動物的各種組織中。
- 人體約有90% 的血清胺存在於消化道黏膜，8% 在血小板，1% 存在中樞神經系統(特別是brainstem)中，另一小部分位於各種組織的肥大細胞中。
- 血腦障壁(BBB)的存在，血液中的血清胺很難進入中樞神經系統。
- 在CNS中，血清胺性神經元細胞體主要集中在中腦下部、橋腦上部和延腦的中縫核(raphe nuclei)，調節睡眠、食慾、腦血流(偏頭痛)、行為與情緒。

Synthesis, Release and Inactivation of 5-HT

- 血清胺生物合成的前體為**色胺酸(tryptophan)**。
- 由於色胺酸是人體必需胺基酸，人體內不能自行合成，只能從食物蛋白中攝取，經肝臟水解而獲得。
- 腦內血清胺的合成首先取決於色胺酸的有效利用率。
- 血中的色胺酸進入血清胺性神經元後，先經色胺酸羥化酶(**tryptophan hydroxylase**)催化形成 5- 羥色胺酸(5-hydrotryptophan)，然後再脫羧成5-HT。
- 色胺酸羥化酶專一性高，只存在於血清胺性神經元中，且含量較少也較低。因此成為血清胺合成過程中的主要限速酶。

Synthesis, Release and Inactivation of 5-HT

- 合成的血清胺和兒茶酚胺等神經傳遞物質一樣，儲存於血清胺性神經末梢的突觸小泡中。
- 釋放入突觸間隙的血清胺與接受器結合，又迅速解離，這些血清胺大部分被**突觸前末梢回收(reuptake)**。
- 回收入神經末梢的血清胺
  --一部分進入突觸小泡儲存和再利用，
  --一部分被突觸間隙、膠細胞或神經末梢之粒線體表面的**單胺氧化酶(MAO)** 所催化形成 5- 羥吲哚乙醛(5-hydroxyindole acetaldehyde)，而後迅速被醛去氫酶(aldehyde dehydrogenase) 催化生成 5- 羥吲哚乙酸(5-hydroxyindoleacetic acid, 5-HIAA)，這是CNS中 5-HT 代謝的最主要途徑。

Serotonic Receptor

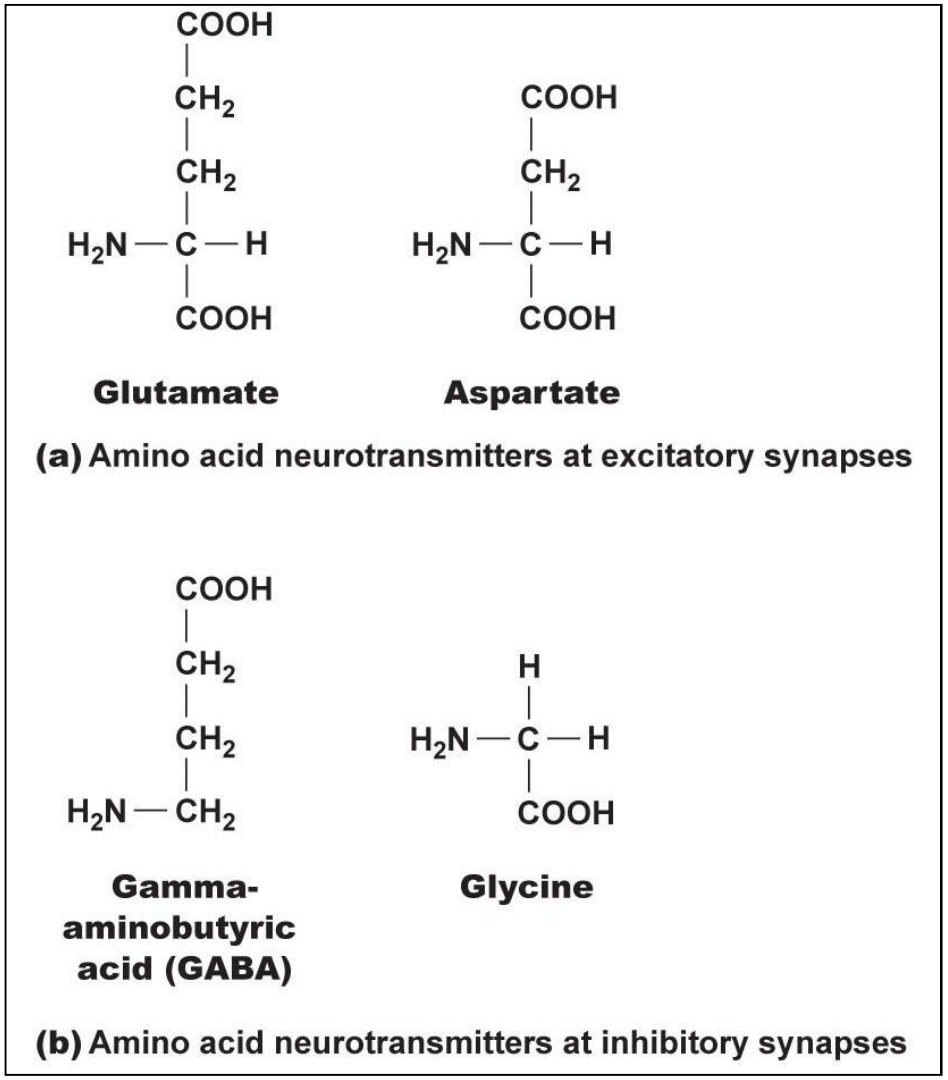
- 血清胺接受器(**serotonic receptors**) 有超過12種亞型，依據其對配體的親和力和功能藥理學特徵加以區分，主要可分為兩大類：
  - --***G protein-coupled receptor (Metabotropic receptor)***
  - --***Channel-linked receptor (Ionotropic receptor)***
- 血清胺接受器在睡眠機制中有重要作用，抑制血清胺可以引起嚴重的失眠，提高血清胺的濃度可以促進睡眠。
- 參與攝食、體溫調節、情緒、痛覺之調節作用。例如：腦內血清胺升高會抑制攝食。
- Serotonin specific reuptake inhibitors (**SSRIs**)用於治療治療憂鬱症如**Prozac**；治療肥胖的藥物如**fenfluramine**，因可促進血清胺釋放及抑制其回收進而降低食慾。
- **LSD** (d-lysergic acid diethylamide)因結構相似於血清胺，為最強效能改變情緒的化學物質(迷幻藥)。它是由麥角菌株上所發現的麥角酸製造出來的，麥角是一種生長在黑麥及其他穀類上的黴菌。

Biological Amines: Histamine

- 組織胺性神經元(histaminergic neuron)位於**下視丘(hypothalamus)**後部的結節乳頭體核中，發出纖維到達中樞內幾乎所有部分，但其纖維末梢很少與鄰近的神經元形成突觸聯繫。
- 主要是依靠非突觸性化學傳遞的方式調節神經元的功能。
- 腦內組織胺接受器分為 **H_1**、**H_2** 和 **H_3**三型。
- 組織胺與 **H_1 接受器**/平滑肌結合能啟動磷脂酶C (PLC) 。
- 與 **H_2 接受器**/胃或心肌結合能提高細胞內cAMP濃度。
- 大多數 **H_3 接受器**是突觸前接受器(**autoreceptor**)，可抑制組織胺和其他神經傳遞物質的釋放。

Amino Acid Neurotransmitters

- **Amino acid neurotransmitters at excitatory synapses (EAA)**
  - ***--Aspartate (Asp)***
  - ***--Glutamate (Glu)***
- **Amino acid neurotransmitters at inhibitory synapses (IAA)**
  - ***--Glycine (Gly)***
  - ***--GABA (γ-aminobutyric acid)***



Amino Acid: Glutamate

- 麩胺酸(glutamate)是哺乳動物腦內最重要的**興奮性**神經傳遞物質。
- 在CNS中麩胺酸分布極為廣泛，以**大腦皮層**含量最高，其次為小腦、紋狀體、延腦和橋腦。
- 脊髓中麩胺酸含量雖明顯低於腦內，但有特異分布，背根和背角灰質含量比腹根和前角灰質高。
- 過量的麩胺酸也具有某些神經毒性作用。
- 在神經退行性病變、學習記憶、神經發育、癲癇發作、腦缺血引起的腦損傷等疾病的發生和發展過程中，麩胺酸可能具有重要作用。

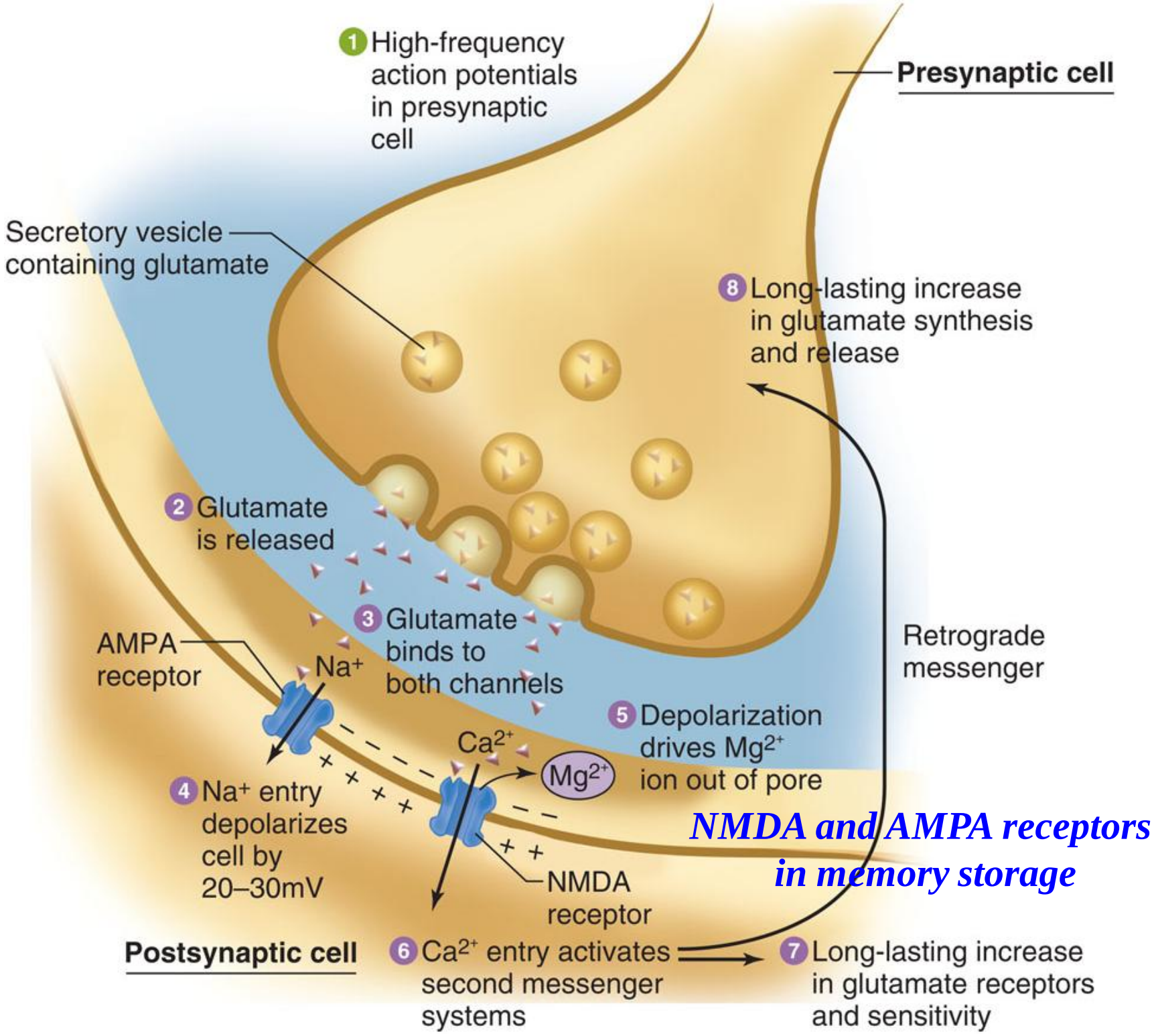
Glutamate Receptor

- 麩胺酸接受器可分為兩大類：
  - --促離子型接受器(**ionotropic receptor**)
  - --促代謝型接受器(**metabotropic receptor**)
- 根據其選擇性致效劑和拮抗劑的不同，

  促離子型接受器包括三個類型：
  1. ***KA*** *(kainic acid) receptor*
  2. ***AMPA*** *(α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) receptor*
  3. ***NMDA****(N-methyl-D-aspartate) receptor*

Glutamate Receptor

- 通常將 KA 接受器和 AMPA 接受器又統稱為**非 NMDA 接受器**(**non-NMDA receptor**)。非 NMDA 接受器啟動時，離子通道開放，允許大量的 **Na^+** 內流和少量的 K^+ 外流，使細胞膜去極化，產生 **EPSP**。
- NMDA 接受器(**NMDA receptor**)啟動後，接受器上的陽離子通道迅速開放，除允許 Na^+ 內流和 K^+ 外流外，主要是引起大量的 **Ca^{2+}** 內流，使突觸後膜去極化，產生慢**EPSP**。
- NMDA 接受器在**海馬回**的密度較高(**學習和記憶**)。
- **促代謝型接受器**主要是透過G 蛋白媒介，啟動PLC，該酶水解PIP_2， 使細胞內IP_3及DAG含量增高。
- IP_3 快速動員內質網中的 Ca^{2+}，使細胞內 Ca^{2+} 濃度升高而產生一系列效應。



NMDA and AMPA receptors in memory storage

Amino Acid: GABA

- γ- 胺基丁酸(GABA) 是哺乳動物中樞神經系統中最重要的**抑制性**神經傳遞物質。
- 腦內(特別是大腦皮質和小腦皮質)大部分抑制性中間神經元及投射神經元都是以 GABA為神經傳遞物質。
- 精神疾病如癲癇、亨丁頓氏症、睡眠障礙等，與 GABA 性神經元數量減少或 GABA功能降低有關。

知識小補帖 Knowledge Supplements

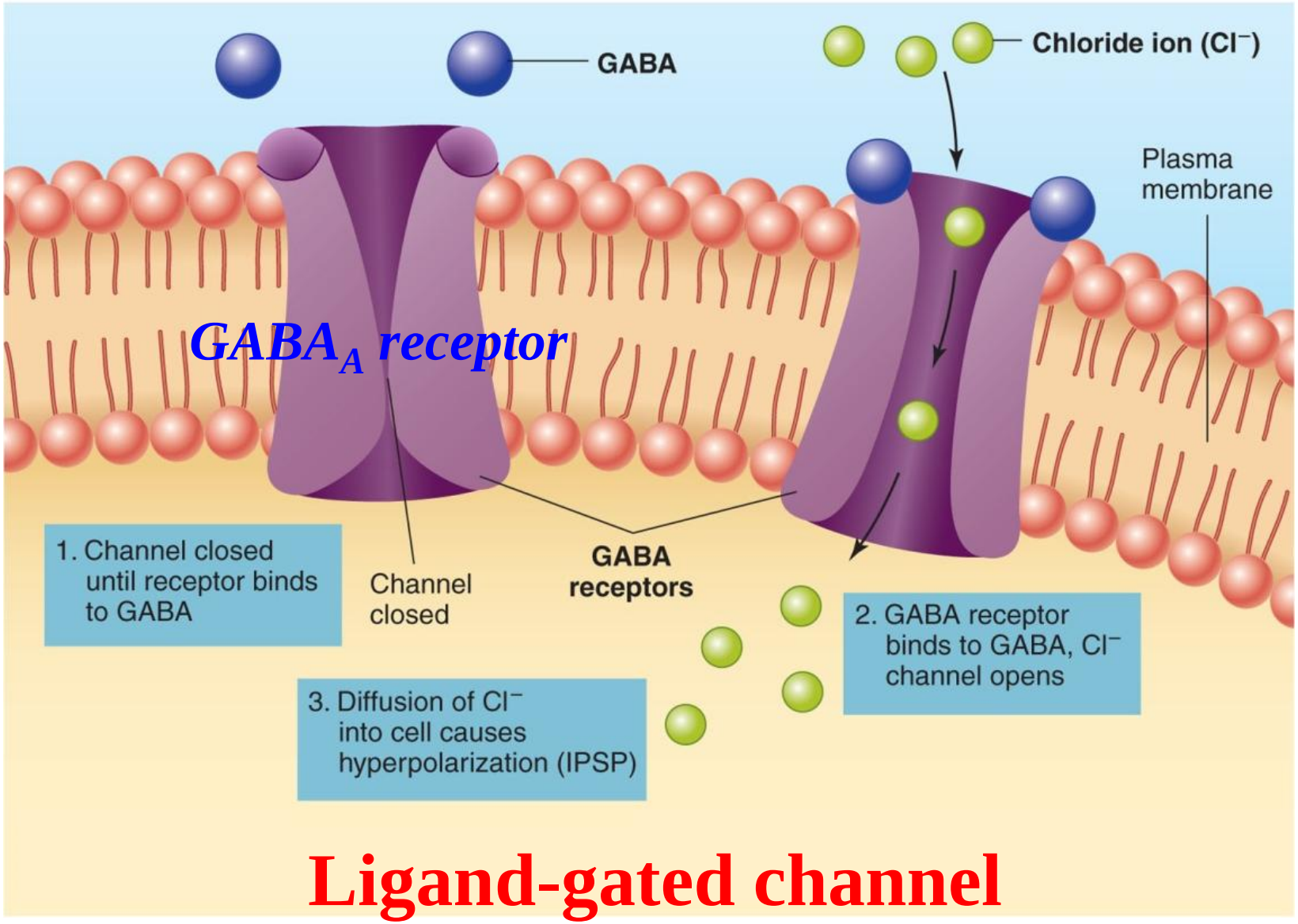
亨丁頓氏症 (Huntington's disease) 又稱為亨丁頓氏舞蹈症 (Huntington's chorea)。此病是顯性遺傳疾病，由第 4 對染色體上稱為 huntingtin 的基因缺損所導致。目前認為，亨丁頓氏症的產生是由於基底核紋狀體中可產生 GABA 及腦啡肽 (enkephalin) 的神經元發生病變、數量減少，導致抑制作用減弱，興奮性傳出活動增加，從而產生不自主運動。患者通常於 30~50 歲時出現症狀，主要表現為頭部和上肢不自主的晃動，動作協調能力變差，並伴有肌張力降低等。隨著病程進展，可能併發認知能力下降、失智及精神方面的症狀。

GABA Receptor

- **GABA接受器主要分為兩型**
  - --**$GABA_A$** receptor：
    - 屬促離子型接受器，本身為Cl^- channel
    - 主要分布在突觸後膜，媒介突觸後抑制(IPSP)。
  - --**$GABA_B$** receptor ：
    - 屬促代謝型接受器。
    - 主要分布在突觸前神經末梢。

$GABA_A$ Receptor

Channel-linked receptor = Ionotropic receptor



Ligand-gated channel

GABA Receptor

- 位於興奮性突觸前末梢上的 $GABA_B$ 接受器被啟動後，經由G 蛋白媒介，使突觸前末梢的 K^+ 通道開放和 Ca^{2+} 通道關閉，而使突觸前末梢釋放的興奮性神經傳遞物質減少， 產生突觸前抑制效應(presynaptic inhibition)。
- 位於 GABA 性纖維神經末梢上的 $GABA_B$ 接受器作為 **Autoreceptor**， 抑制 GABA 的釋放。
- $GABA_B$ 接受器也存在於突觸後膜。
- 啟動突觸後膜的 $GABA_B$ 接受器，透過G 蛋白媒介使 K^+ 通道開放，K^+ 外流，產生慢IPSP 和較弱的突觸後抑制效應(postsynaptic inhibition)。
- 中樞神經系統還存一種新的GABA 接受器—$GABA_C$ 接受器如視網膜參與視覺訊號調節，其功能尚未清楚。

Amino Acid: Glycine

- 甘胺酸(Gly) 是主要存在於**脊髓**的抑制性神經傳遞物質，調節骨骼肌運動。
- 呼吸時，甘胺酸在橫膈膜放鬆也拌演重要角色。
- 甘胺酸接受器也屬於促離子型接受器家族(**ionotropic receptor**)，本身為**Cl^- channel (IPSP)**。
- 馬錢子素(**Strychnine**) 是glycine receptor antagonist ，易造成呼吸肌麻痺致死 。

Neuropeptides

- Short chains of amino acids (< 50 aa)
- Most are co-located with other neurotransmitters
- Modulate response caused by other neurotransmitter
- Many chemicals used as hormones or paracrine signals are also found in the brain acting as neurotransmitters
  - **Examples:** ***Endogenous opioids,Vasopressin (ADH), Oxytocin, Neuropeptide Y and Substance P etc.***

Neuropeptide: Opioid Peptide

- 腦內具有類似嗎啡活性的胜肽類物質，稱為類鴉片胜肽(**opioid peptide= endogenous opioids**)。
- 分為β- 內啡肽(**β-endorphin**)、腦啡肽(**enkephalin**) 和強啡肽(**dynorphin**) 三類。
- 類鴉片胜肽在CNS中作用廣泛，參與心血管活動、呼吸運動、體溫、攝食和飲水行為的調節，並影響精神活動、內分泌和免疫功能，但最顯著的作用是在**痛覺**調節中的作用。
- 三種類鴉片胜肽在CNS中的分布不同，但都是在與處理和調節痛覺訊息有關的腦區

Opioid Receptor

- 類鴉片胜肽接受器: **μ、κ** 和 **δ** receptor 都屬於 **G protein-coupled receptor** 。
  - **--μ 接受器**的主要自然ligand是**β-endorphin**
  - **--κ 接受器**的自然ligand是**dynorphin**
  - **--δ 接受器**的自然ligand是**enkephalin**
- 類鴉片胜肽與接受器結合的專一性不強，如enkephalin除可與δ 接受器結合外，也可與其他兩種接受器結合。
- 啟動μ 接受器可增加 K^+ 電位傳導，引起神經元和初級傳入纖維的過極化(IPSP)。
- 啟動κ 和δ 接受器則引起 Ca^{2+} 通道關閉。

Location and Responses of Opioid Receptors

Receptor	CNS location	Response on activation
μ	Brain (laminae III and IV of the cortex, thalamus, periaqueductal gray), spinal cord (substantia gelatinosa)	μ_1: supraspinal analgesia, physical dependence; μ_2: respiratory depression, miosis, euphoria, reduced gastrointestinal motility, physical dependence
κ	Brain (hypothalamus, periaqueductal gray, claustrum), spinal cord (substantia gelatinosa)	Spinal analgesia, sedation, miosis, inhibition of antidiuretic hormone release
δ	Brain (pontine nucleus, amygdala, olfactory bulbs, deep cortex)	Analgesia, euphoria, physical dependence

Neuropeptide: Brain-Gut Peptide

- 在胃腸道和中樞神經系統雙重分布的胜肽類物質稱為腦－ 胃腸胜肽(**brain-gut peptide**)。
- 膽囊收縮素(**cholecystokinin, CCK**)、血管活性腸胜肽(**vasoactive intestinal peptide, VIP**)、胃泌素(**gastrin**) 等。
- 在中樞神經系統中，CCK 具有抑制攝食行為(飽食感)、調節腦下腺激素釋放、鎮痛和調節腦血流等功能。
- VIP 有興奮大腦皮質和海馬回中間神經元及促進內分泌激素釋放的作用。
- 胃泌素有增加胃黏膜壁細胞分泌胃酸

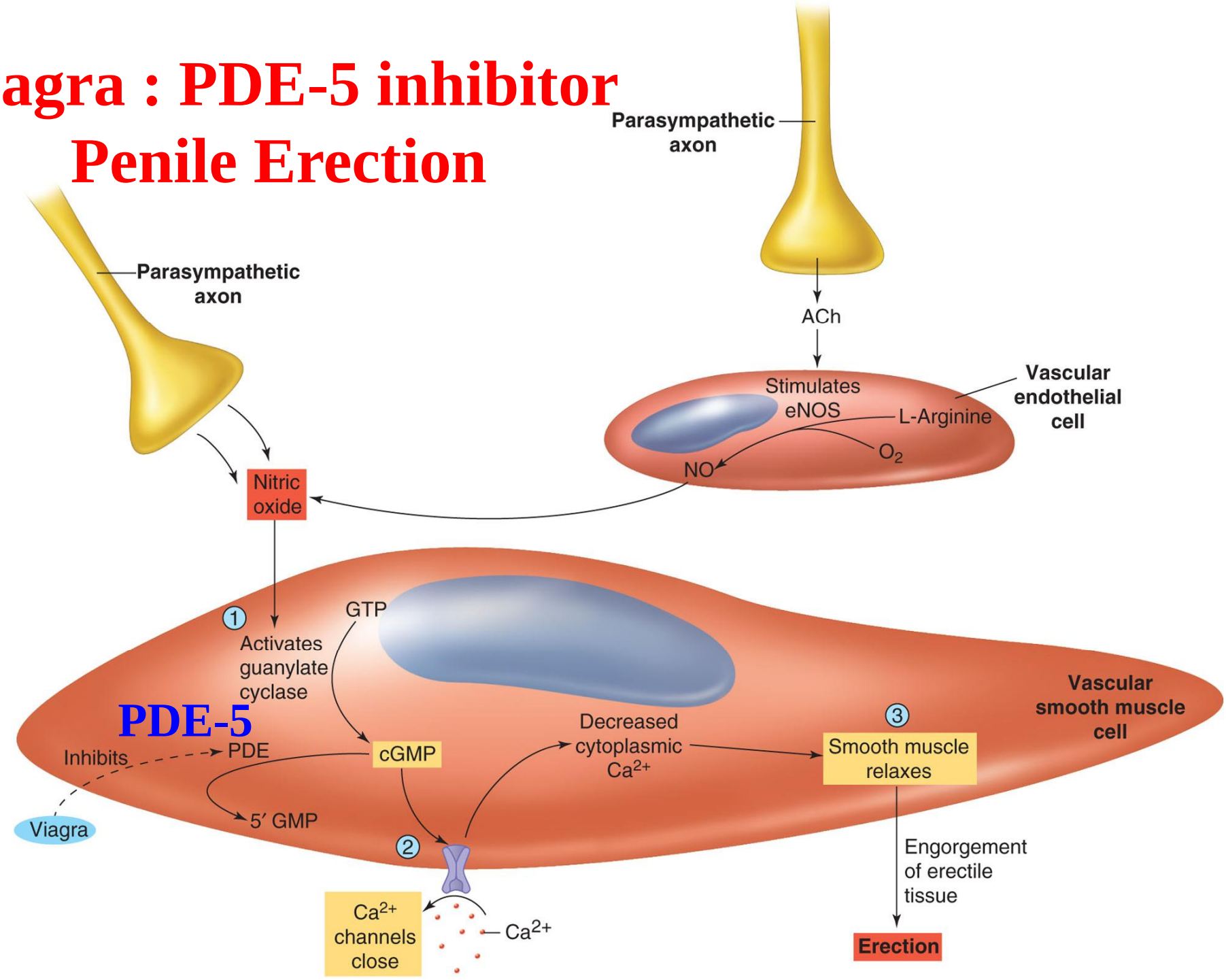
Neuropeptide: Neuropeptide Y

- 神經胜肽Y (**neuropeptide Y**) 是大腦皮質內最豐富的神經胜肽。
- 神經胜肽Y 也存在於脊髓背角及下視丘。
- 神經胜肽Y 接受器在腦內分布有明顯的區域特異性(regional specificity)。
- 杏仁核和皮質的接受器有抗焦慮作用，下視丘的接受器能**促進食慾和攝食行為**。
- 與壓力反應、日夜週期(circadian rhythms)及心血管功能調控有關。

Gas: Nitric Oxide

- CNS中有些神經元含有NO synthase (NOS, **nNOS**)，可促使精胺酸(**arginine**)生成 NO。
- PNS中有些自主神經可在消化道、呼吸道及陰莖處釋放NO 。
- 與傳統的傳訊物質不同，NO 是一種氣體分子，生成後不儲存於突觸小泡內，不能直接由去極化導致胞吐作用而釋放，也沒有相應的細胞膜接受器。
- NO 以**擴散**到達標的細胞，直接啟動細胞內的鳥苷酸環化酶(**guanylye cyclase**)，使細胞內**cGMP** 增加而發揮其生理效應如血管擴張、免疫及學習記憶等。
- NO 還可作為逆行性傳訊物質(retrograde messenger)，促進突觸前末梢傳訊物質的合成和釋放，並影響突觸的可塑性。

Viagra : PDE-5 inhibitor
Penile Erection



Gas: Carbon Monoxide

- 一氧化碳(CO) 是另一種可能作為神經傳遞物質的氣體分子。
- CO 的產生是血紅素在血紅素加氧酶的催化下氧化分解而成。
- 其作用方式與 NO 相似，也是透過啟動標的細胞的鳥苷酸環化酶(**guanylye cyclase**)，使細胞內 cGMP 濃度增加而發揮其生理效應。

Lipids: Endocannibinoids

- Neurotransmitters that bind to the same receptors that bind to the active ingredient in **marijuana** (**tetrahydrocannabinol, THC**)

  --Short fatty acids produced in the dendrites and cell bodies and released directly from the plasma membrane (no vesicle)

  --**Retrograde neurotransmitters** released from the postsynaptic neuron; inhibit further neurotransmitter release from the presynaptic axon

Lipids: Endocannibinoids

- Endocannibinoids can **inhibit** IPSP-producing NTs from one neuron, so EPSP-producing NTs from another neuron can have a greater effect
- Endocannibinoids may enhance **learning and memory** and have been shown to **induce appetite**
- **Marijuana** (central psychoactive drug) use impairs learning and memory because the action of tetrahydrocannabinol (**THC**) is widespread and not controlled

Purines: ATP & Adenosine

- 嘌呤類傳訊物質主要是指**腺苷(adenosine)** 和**腺苷三磷酸(ATP)**。
- ATP 常與典型神經傳遞物質共存於同一神經末梢、甚至同一突觸小泡內，ATP 的釋放是一個 Ca^{2+} 依賴的胞吐過程。
- 腺苷是以非突觸小泡形式釋放， 它通過雙向運輸的核苷酸運輸體(nucleotide transporter) 運輸出細胞外。
- 釋放的 ATP 可迅速分解成為腺苷，因此釋放出來的 **ATP** 是細胞外腺苷的一個重要來源。
- 嘌呤類物質(主要是腺苷和ATP)在中樞和周邊神經系統中主要作為**抑制性神經傳遞物質**。
- CNS中的腺苷具有抑制神經元過度興奮和擴張腦血管的作用。
- PNS中的嘌呤性神經纖維對腸道活動有抑制作用。

Purinergic Receptor

- 嘌呤接受器主要分為兩類
  - --**P_1** receptor (**adenosine receptor**)：
    - 對adenosine的親和力高，也稱為腺苷接受器
    - 屬於 **G protein-coupled receptor**
  - --**P_2** receptor ：
    - 主要與ATP or ADP 結合，分為
      - P_2X ：屬於**Ionotropic receptor**
      - P_2Y ：屬於**G protein-coupled receptor**

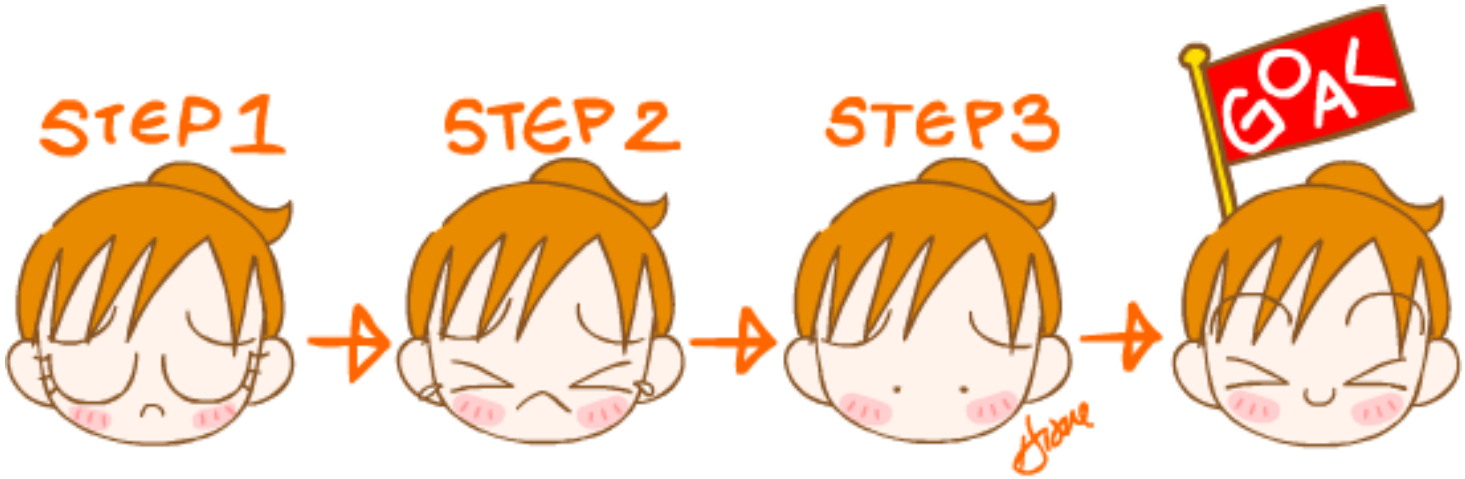
Condition	Symptoms	Imbalance of Neurotransmitter in brain
Alzheimer's disease	Memory loss, depression , disorientation, dementia, hallucinations, death	Deficient ACh
Clinical depression	Debilitating, inexplicable sadness	Deficient NE and/or 5-HT
Epilepsy	Seizures, loss of consciousness	Deficient GABA leads to excess glutamate, NE and DA
Huntington disease	Personality changes, loss of coordination, uncontrollable dancelike movements, death	Deficient GABA
Hypersomnia	Excessive sleeping	Excess 5-HT
Insomnia	Inability to sleep	Deficient 5-HT
Mania	Elation, irritability, overtalkativeness, increased movements	Excess NE (CAs)
Myasthenia gravis	Progressive muscular weakness	Deficient ACh receptors at neuromuscular junctions
Parkinson's disease	Tremors of hands, slowed movements, muscle rigidity	Deficient DA & Excess ACh
Schizophrenia	Inappropriate emotional responses, hallucinations	Deficient GABA leads to excess DA
Sudden infant death syndrome ("'crib death")	Baby stops breathing , dies if unassisted	Excess DA
Tardive dyskinesia	Uncontrollable movements of facial muscles	Deficient DA

Drug	Neurotransmitter	Affected Mechanism of Action	Effect
Tryptophan	Serotonin	stimulates neurotransmitter synthesis	Sleepiness
Reserpine	Norepinephrine	Decrease packaging neurotransmitter into vesicles	Decreases blood pressure
Curare	Acetylcholine	Decreases neurotransmitter in synaptic cleft	Muscle paralysis
Botulinus toxin	Acetylcholine	decrease neurotransmitter release	Muscular weakness
Tertodotoxin	Acetylcholine….	Block Na channels	Muscle paralysis
Nerve gas	Acetylcholine	Blocks enzymatic degradation of neurotransmitter in postsynaptic cell (AChE)	Spastic paralysis
Neostigmine	Acetylcholine	Blocks enzymatic degradation of neurotransmitter in postsynaptic cell (AChE)	Muscle contraction
Nicotine	Acetylcholine	Stimulates synthesis of enzyme that degrades neurotransmitter	Increases alertness

Drug	Neurotransmitter	Affected Mechanism of Action	Effect
Valium (Benzodiazepines)	GABA	Enhances receptor binding ($GABA_A$-R= BZ-R)	Decrease anxiety; status epilepticus
Cocaine	Norepinephrine	Blocks reuptake	Euphoria
Amphetamines	Norepinephrine	Enhances release	CNS stimulant
Tricyclic antidepressants (TCA)	Norepinephrine; 5-HT	Blocks reuptake	Mood elevation (antidepressants)
Monoamine oxidase inhibitors (MAOI)	Norepinephrine; 5-HT; DA	Blocks enzymatic degradation of neurotransmitter in presynaptic cell	Mood elevation (antidepressants)
Prozac and SSRIs	Serotonin	Blocks reuptake	Mood elevation (antidepressants)

➢ ***MAOI + tyramine: Hypertensive crisis***

快樂才是終點



不快樂。傷心。難过　是過程

快樂　才是終点，