Neuron types and Neurotransmitters

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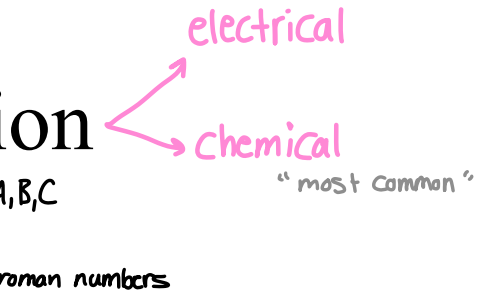
Objectives

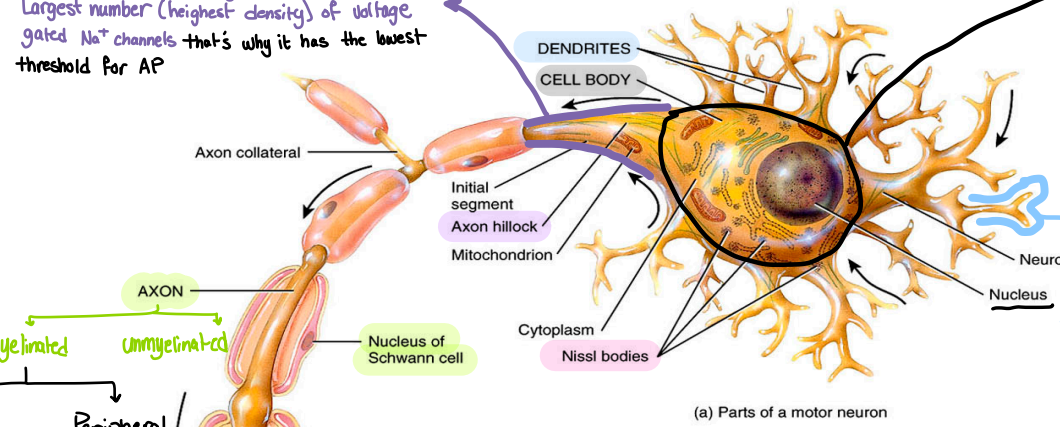
- Understand synaptic transmission
- List types of sensory neurons
- Classify neurotransmitters
- Explain the mechanism of neurotransmission
- Judge the types of receptors for the neurotrasmitters



Functional Unit (Neuron)

Axon Hillock
(unmyelenated) it has the Largest number (heighest density) of voltage gated Na^+ channels that's why it has the lowest threshold for AP

Soma = cell body → contains All the organisms of any cells
↳ nucleus, ER
+ mitochondria
+ Nissl granules
↓
Similar to ribosomes of any cell, sites where Proteins are formed in cells.



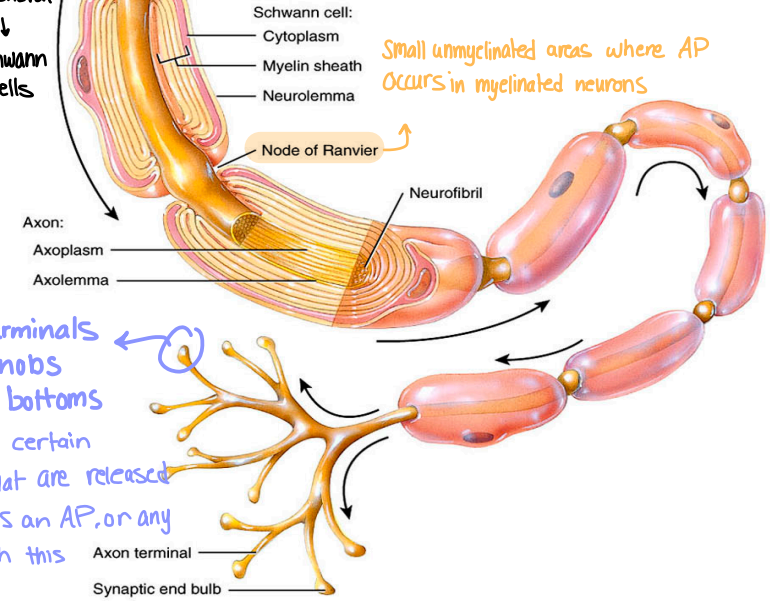
(a) Parts of a motor neuron

dendrites "trees"
they Lack voltage gated Na^+ channels so threshold is very high. (we can rarely see AP in them) but they are imp Because they collect the information from larger Area

(rounding of cell mem.) myelinated / unmyelinated

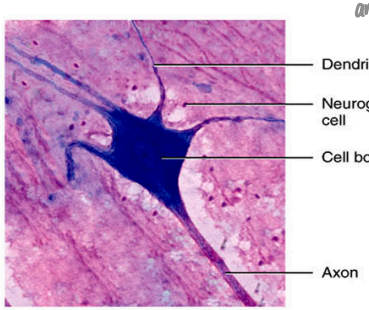
Central → oligodendrocytes

Peripheral → Schwann cells



Small unmyelinated areas where AP occurs in myelinated neurons

Axon terminals
" nobs
" bottoms
they contain certain chemicals that are released once there is an AP, or any impulse reach this area
↓
chemicals act as mediators between AP that occures in Pre/Post synaptic nuerons.



(b) Motor neuron

Figure 12.02 Tortora - PAP 12/e

* The Organism that is deficient or Lacking → Centrioles? Because neurons don't divide or regenerate once the cell die or get damaged and that's the problem of nervous system. That's why the CNS (Brain + Spinal cord) are enclosed with a very hard connective tissue which is the Bone
Brain → Skull
Spinal cord → vertebral column

Transmission of Receptor Information to the Brain

- The larger the nerve fiber diameter the faster the rate of transmission of the signal
- Velocity of transmission can be as fast as 120 m/sec or as slow as 0.5 m/sec
- Nerve fiber classification
  - type A - myelinated fibers of varying sizes, generally fast transmission speed
    - subdivided into α, β, γ, δ → According to their Diameter
  - type B- partially myelinated neurons (3-14m/sec speed) → found in ANS
  - type C - unmyelinated fibers, small with slow transmission speed (Sympathetic + Parasympathetic)

Types of Nerve Fiber

-Myelinated fibers –

Type A (types I, II and III)

- A α → Largest
- A β
- A γ
- A δ → Smallest

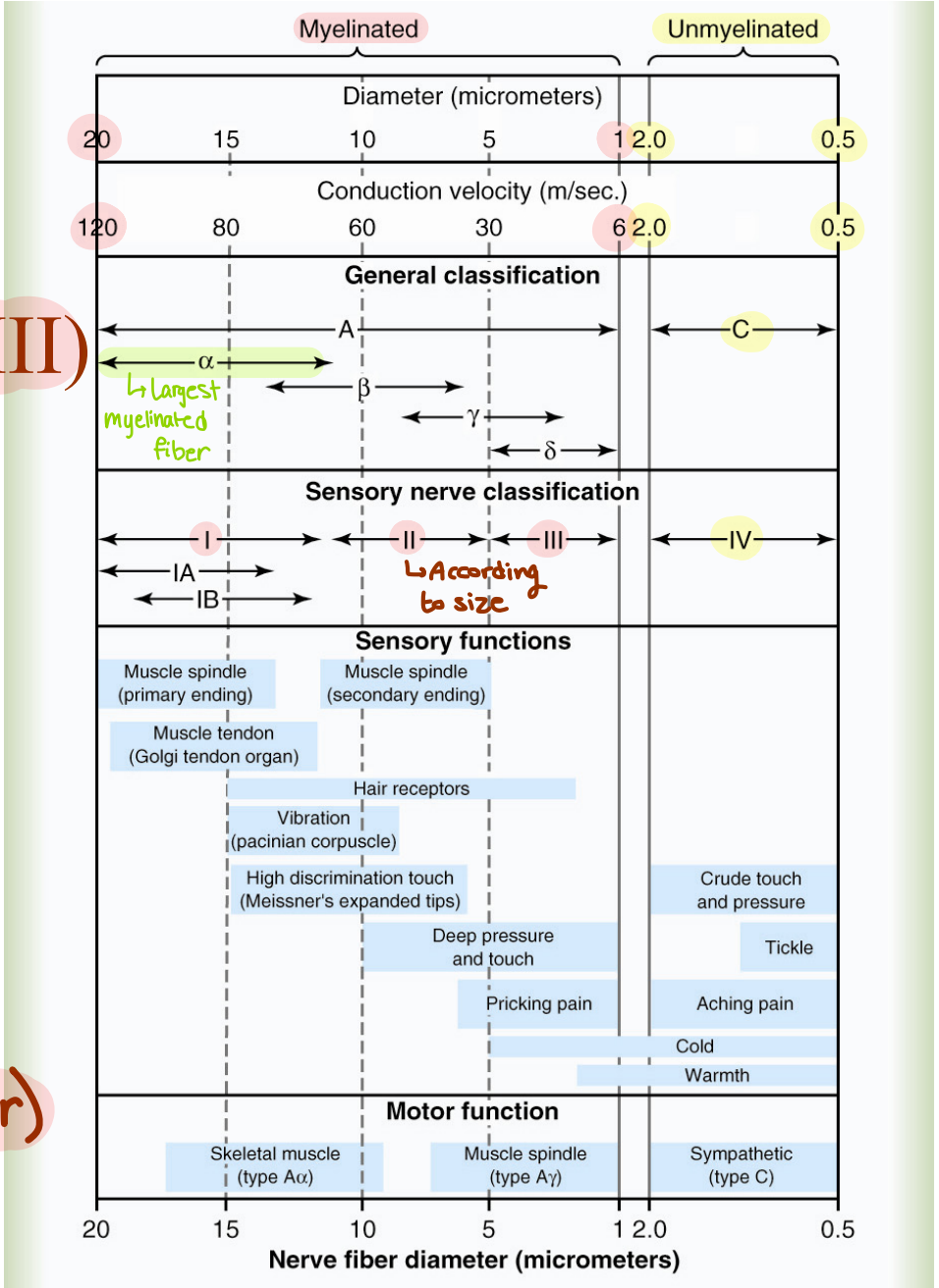
-Umyelinated Fibers-

Type C (type IV)

→ According to the Size (diameter)

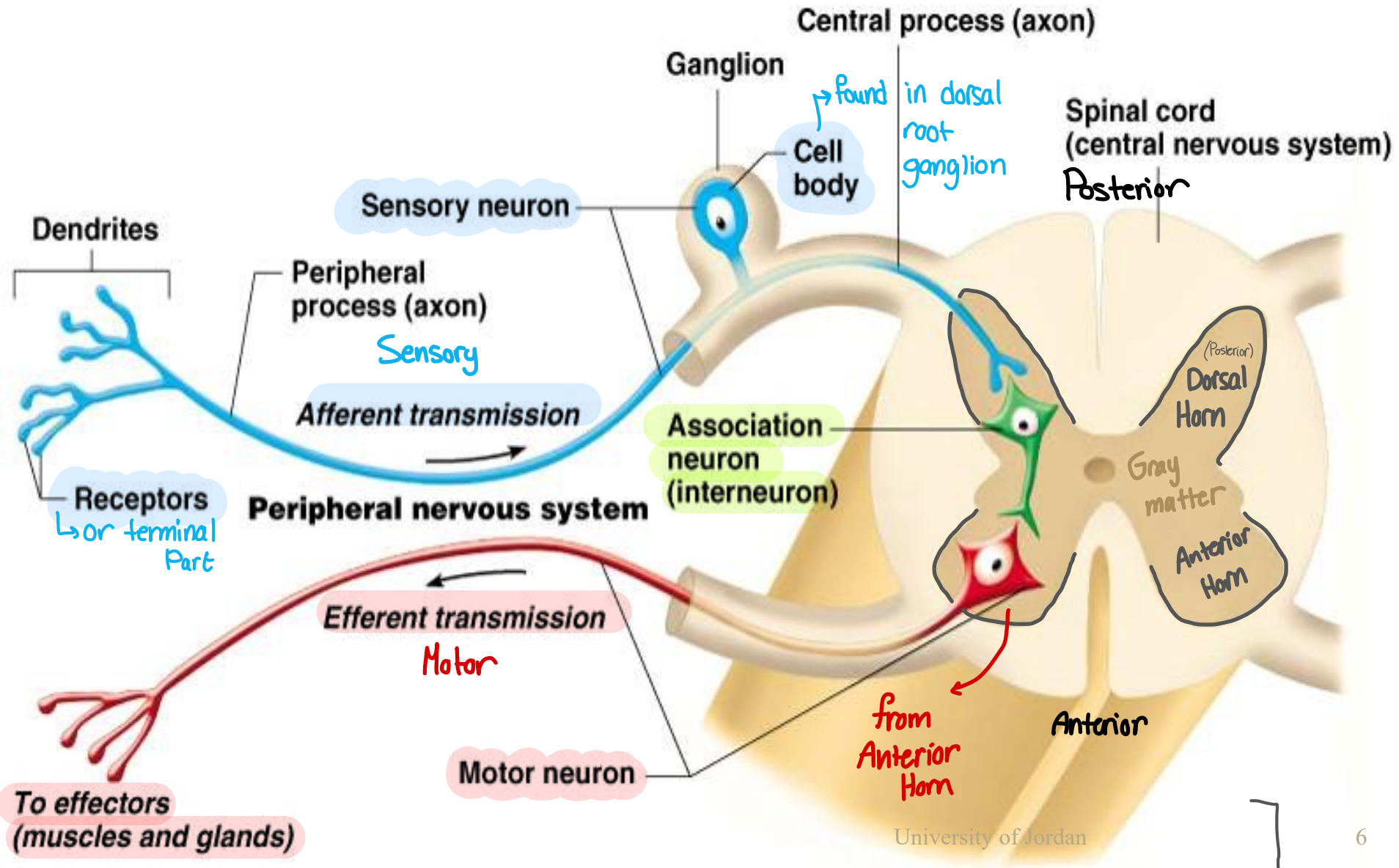
→ I / II / III → myelinated

→ IV → unmyelinated



Neuron Classification

Sensory (Afferent)
Motor (Efferent)
Association.



According to Function

Afferent (Sensory)

→ Collects info. from our body and carry it to CNS.

→ Collects info. by receptors.

→ Cell body is found in dorsal root ganglion.

→ They enter the dorsal Horn and synapse with Interneuron (Association : it associates Afferent with efferent) that connects with Efferent neuron.

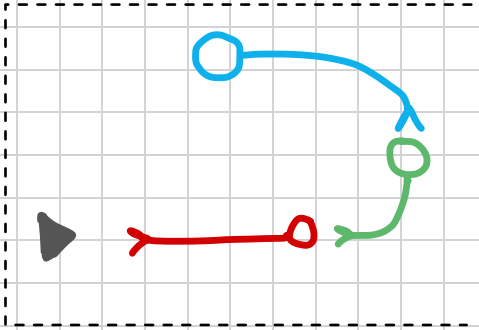
Association Interneuron

↓

Connects sensory with motor

Efferent (Motor)

→ it goes from Anterior horn of spinal cord and supplies the effectors (Glands / Muscles)



- Connection of cell bodies + dendrites in peripheral nervous system. ⟹ Ganglion
- Connection of cell body + dendrites in CNS ⟹ Nucleus

Structural Classification of Neurons

↳ Anatomically

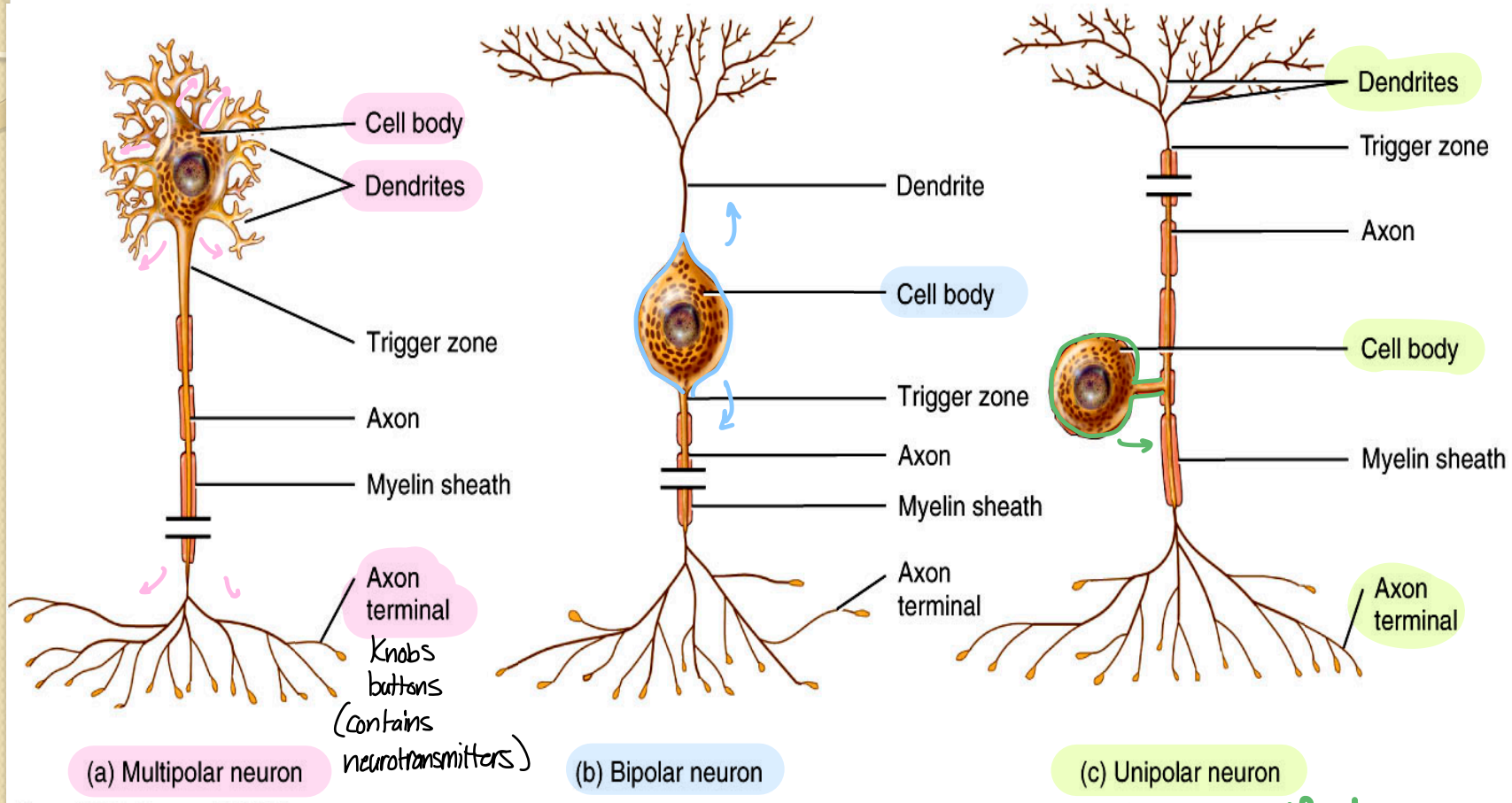


Figure 12.03 Tortora - PAP 12/e

→ divided into 2 Parts (up/down)

→ found in Visual system (Optic)

→ found in olfactory system (smell)

Neurotransmitters →

Chemicals act as a mediators between AP in 1st neuron & 2nd neuron around a synapse.

- Chemical substances that function as synaptic transmitters
  1. Small molecules which act as rapidly acting transmitters
     - acetylcholine, norepinephrine, dopamine, serotonin, GABA, glycine, glutamate, NO, CO → Gases
  2. Neuropeptides (Neuromodulators) → they modulate the action of type 1
     - more potent than small molecule transmitters, cause more prolonged actions
     - (endorphins, enkephalins) VIP, ect.
       - Endogenous Opioids → they function like Opioid → derivative from Opioid tree (Morphine) — شجرة الخشخاش
       - VIP → Vasoactive Intestinal peptide.
     - hypothalamic releasing hormones → Anything that comes from Hypothalamus might act as neurotransmitters.
     - TRH, LHRH, ect. + GnRH
       - TRH → Thyrotropin Releasing Hormone (3 aminoacids)
       - LHRH → Luteinizing Hormone-Releasing Hormone
       - GnRH → Gonadotropin-Releasing Hormone (10 aminoacids)
     - pituitary peptides
     - ACTH, prolactin, vasopressin, ect.
       - ACTH → Adrenocorticotropic Hormone (39 aminoacids) Acts on Adrenal cortex
       - prolactin → "milk Hormone" Stimulates milk formation in the breast
       - vasopressin (ADH) → Antidiuretic Hormone (8 amino acids) "octapeptide"

All of them are peptides.

Neurotransmitters

don't memorise ↓

Table 45–1

Small-Molecule, Rapidly Acting Transmitters

- Class I
  - Acetylcholine
- Class II: The Amines → derived from Tyrosine amino acids.
  - Norepinephrine
  - Epinephrine → difference = methyl group (CH_3) in EPI
  - Dopamine
  - Serotonin
  - Histamine
- Class III: Amino Acids
  - Gamma-aminobutyric acid (GABA) ⇒ inhibitory
  - Glycine ⇒ inhibitory
  - Glutamate ⇒ excitatory
  - Aspartate ⇒ excitatory
- Class IV
  - Nitric oxide (NO) + CO

- released in larger amounts
- their action is short.
- Rapidly broken down by enzymes that doesn't let them stay longer in the synapse.

Table 45–2

Neuropeptide, Slowly Acting Transmitters or Growth Factors

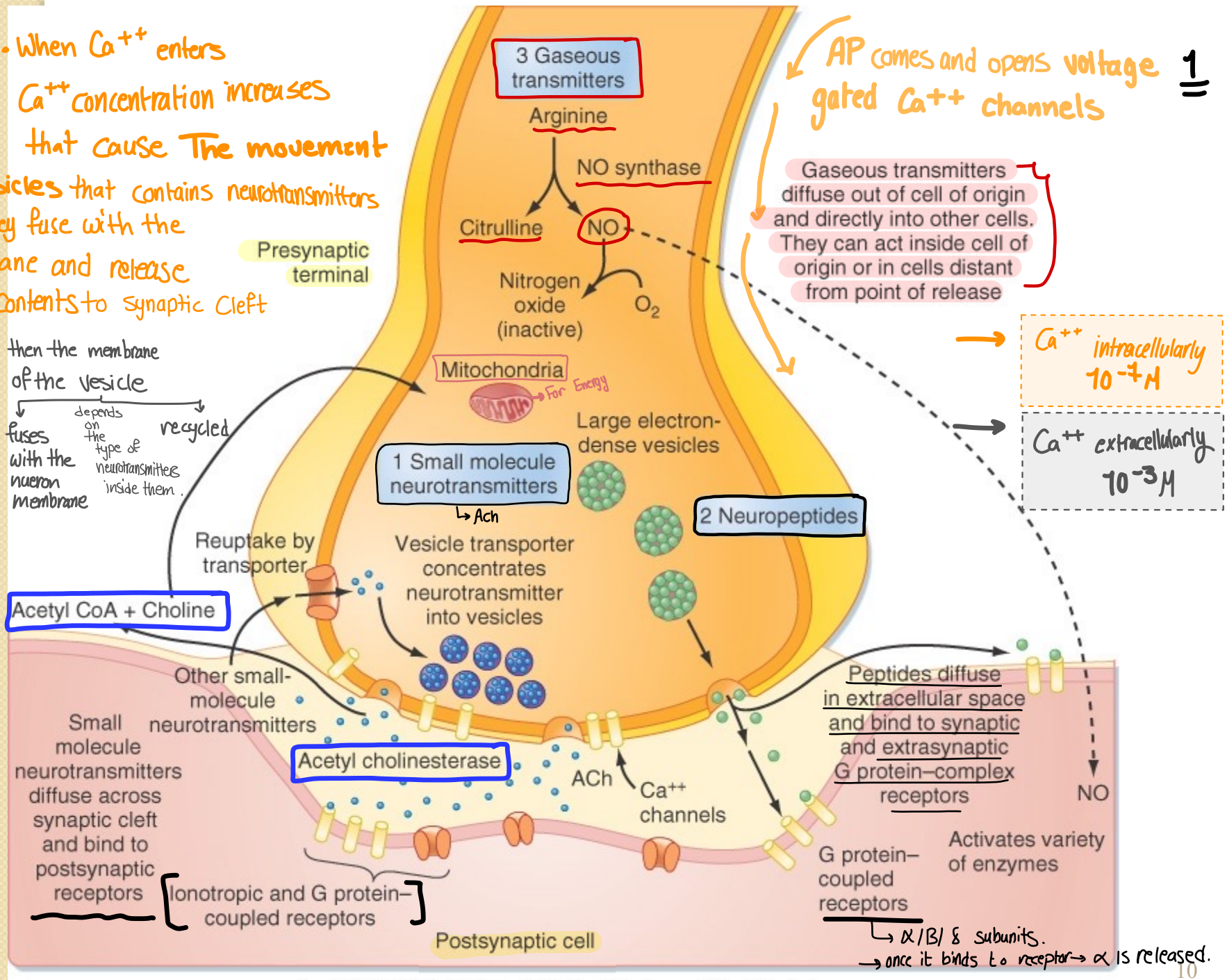
neuromodulators → All are peptides / proteins that comes from the brain

- Hypothalamic-releasing hormones → comes from Hypothalamus
  - Thyrotropin-releasing hormone
  - Luteinizing hormone–releasing hormone
  - Somatostatin (growth hormone inhibitory factor) 40 aa
- Pituitary peptides
  - Adrenocorticotropic hormone (ACTH)
  - β-Endorphin (endogenous Opioid)
  - α-Melanocyte-stimulating hormone MSH
  - Prolactin
  - Luteinizing hormone
  - Thyrotropin TSH (Thyroid stimulating H)
  - Growth hormone
  - Vasopressin
  - Oxytocin
- Peptides that act on gut and brain
  - Leucine enkephalin } (endogenous Opioid) → similar to morphine in actions but it is formed in our body.
  - Methionine enkephalin } (endogenous Opioid) → similar to morphine in actions but it is formed in our body.
  - Substance P → for pain
  - Gastrin → Stomach
  - Cholecystokinin → released from duodenum
  - Vasoactive intestinal polypeptide (VIP)
  - Nerve growth factor
  - Brain-derived neurotropic factor
  - Neurotensin
  - Insulin
  - Glucagon
- From other tissues (they might be found in the brain and act as neurotransmitters.)
  - Angiotensin II
  - Bradykinin
  - Carnosine
  - Sleep peptides
  - Calcitonin

2

- When Ca^{++} enters Ca^{++} concentration increases that cause The movement of vesicles that contains neurotransmitters and they fuse with the membrane and release their contents to synaptic Cleft

AP comes and opens voltage gated Ca^{++} channels 1



Gaseous transmitters diffuse out of cell of origin and directly into other cells. They can act inside cell of origin or in cells distant from point of release

Ca^{++} intracellularly 10^{-7} M

Ca^{++} extracellularly 10^{-3} M

then the membrane of the vesicle
↓ depends on the type of neurotransmitters inside them.
fuses with the nueron membrane — recycled

G protein–coupled receptors
↳ α/β/δ subunits.
→ once it binds to receptor → α is released.

3 once Ach diffuses it goes to the postsynaptic membrane and it Binds to it's receptor there → then it usually opens ligand / chemical gated Na^+ channels.

4 membrane becomes depolarized → if it reaches the threshold → Action Potential.

(Small molecules rapidly acting)

- On the postsynaptic membrane there's enzymes that breaks Ach called **Acetyl cholinesterase** into acetyl CoA + Choline and then choline can be reuptaken through a transporter that is usually coupled to Na^+ this called **Active reuptake**

once they are reuptaken → enter a vesicle again

- peptides are broken down by **Proteases / Peptiase**

- once Ach is reuptaken → it enters a vesicle again after it being reformed

1. Ach vesicle is pushed inside the presynaptic terminal, it's not going to diffuse in the membrane (recycled)
2. Neuropeptides vesicle → diffuses in the membrane. → ?!? why

→ because neuropeptides are proteins → found in the Soma (cell body) - since there is no Nissl granules in the terminals so they are only formed in the Soma -

→ once they are formed in the Soma (Nissl granule) → Golgi apparatus for post-translational modification + packaging → vesicles are punched of the golgi apparatus

→ they reach the terminal by axonal transport which is very slow (1-2 mm / day).

→ since these proteins are not going to be reformed in axonal terminals → they will be hydrolyzed (Broken down) by proteases or peptiases → not reused or reuptaken.

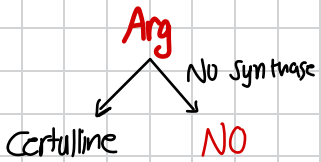
So there's no need for their vesicle

↓

so it diffuses with the membrane of presynaptic neuron.

3. Gaseous transmitters → NO → formed from Arginine by NO synthase

↳ gas = High lipid soluble



so it goes from pre → post synaptic terminals without having receptors on post-synaptic neuron It has receptors inside post-synaptic cell → it acts through GMP second messenger

- they can act → inside cell of origin
  → distant from point of release.

Comparison between Small Molecules and Neuropeptides Neurotramsmitters (NT)

- Small molecules NT are rapidly acting as compared to slowly acting neuropepides
- Neuron has only one NT but may have one or more NP
- Small molecules NT are have short lived action compared to prolonged time of action for neuropeptides
- Small molecules NT are excreted in larger amounts compared to smaller quantities of neuropeptide → Why? because they have a very long journey to come from the soma where they are formed to terminals
- Small molecules NT vesicles are recycled but neuropeptide ones are not
- Neuropeptides are co-secreted with small molecules NT
- Neuropeptides are synthesized at the soma while small molecules could be formed at the presynaptic terminals

Removal of Neurotransmitter

- Diffusion
  - move down concentration gradient
- Enzymatic degradation
  - Acetylcholinesterase for (Ach), peptidases for neuropeptides → EPI/NE ⇒ by Monoaminoxidases (MAO) or (COMT)

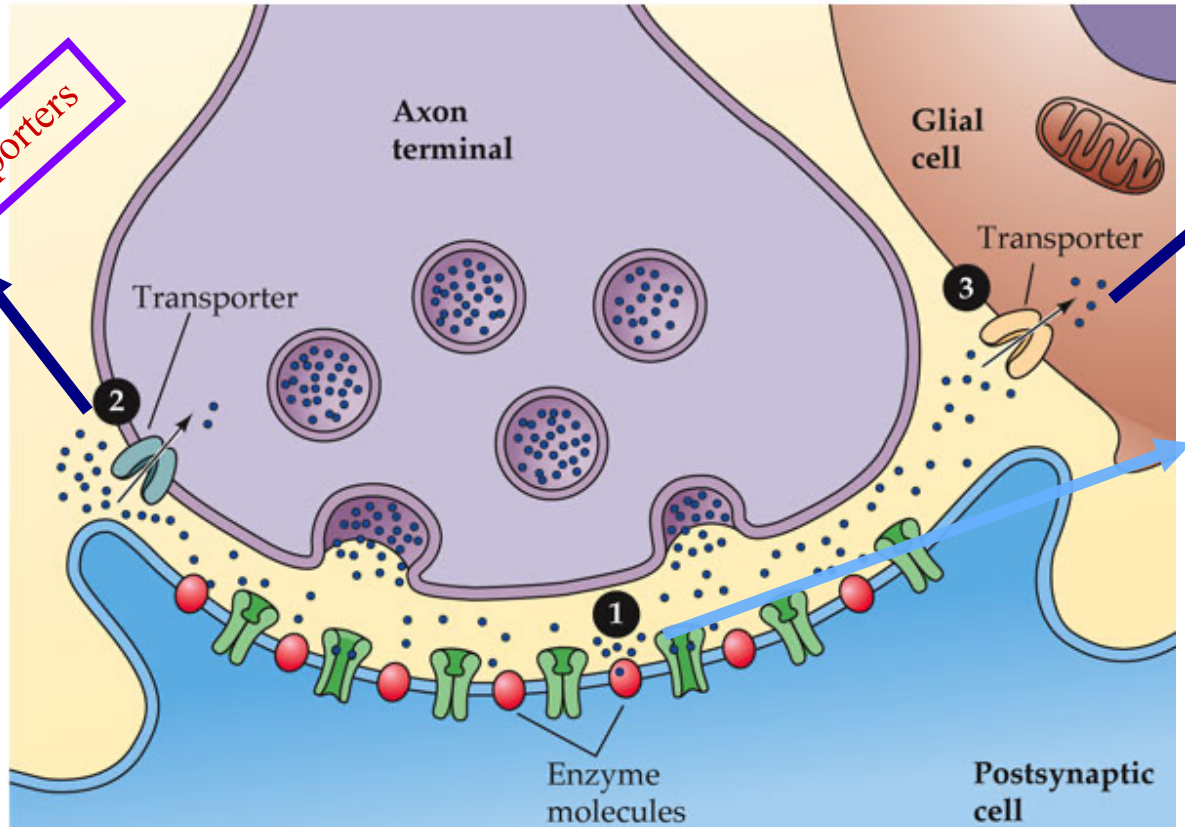
catecholamines ⇕ epi / nor epi.

- Uptake by neurons or glia cells
  - neurotransmitter transporters (usually active like Na^+–Ach Co transport)
  - Prozac = serotonin reuptake inhibitor

↳ drug → for depression

↳ it prolongs the action of Serotonin

- **Transmitter Inactivation: reuptake and enzymatic breakdown**



Neurotransmitter can be recycled in presynaptic terminal or can be broken down by enzymes within the cell

II Neurotransmitters and receptors

Basic Concepts of NT and receptor

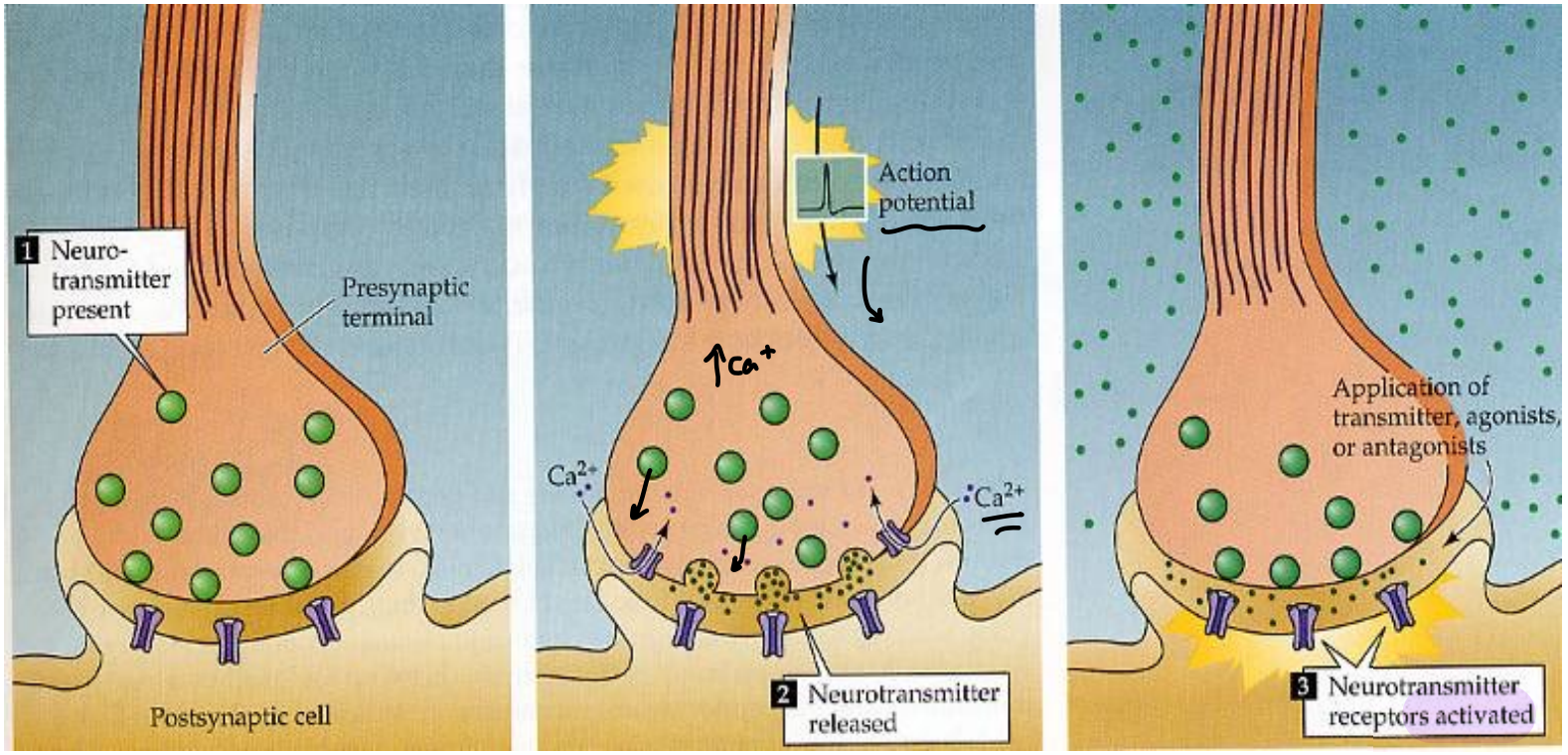
Neurotransmitter: Endogenous signaling molecules that alter the behaviour of neurons or effector cells.

Neuroreceptor: Proteins on the cell membrane or in the cytoplasm that could bind with specific neurotransmitters and alter the behavior of neurons of effector cells

- Vast array of molecules serve as neurotransmitters → NP → small molecules, Rapidly acting
- The properties of the transmitter do not determine its effects on the postsynaptic cells
- The properties of the **receptor** determine whether a transmitter is excitatory or inhibitory → Ach → Heart → inhibitory (decreases the ♡ rate)
  → GI → excitatory (Increases movement, secretion...)
  depending on the receptor → ♡ → coupled to K^+ ions
  → GI → coupled to Na^+ ions

A neurotransmitter must (classical definition)

- Be synthesized and released from neurons
- Be found at the presynaptic terminal
- Have same effect on target cell when applied externally
- Be blocked by same drugs that block synaptic transmission
- Be removed in a specific way



Agonist

A substance that mimics a specific neurotransmitter,

↳ simulate - have same effect

is able to attach to that neurotransmitter's receptor

and thereby produces the same action that the neurotransmitter usually produces.

Drugs are often designed as receptor agonists to treat a variety of diseases and disorders when the original chemical substance is missing or depleted.

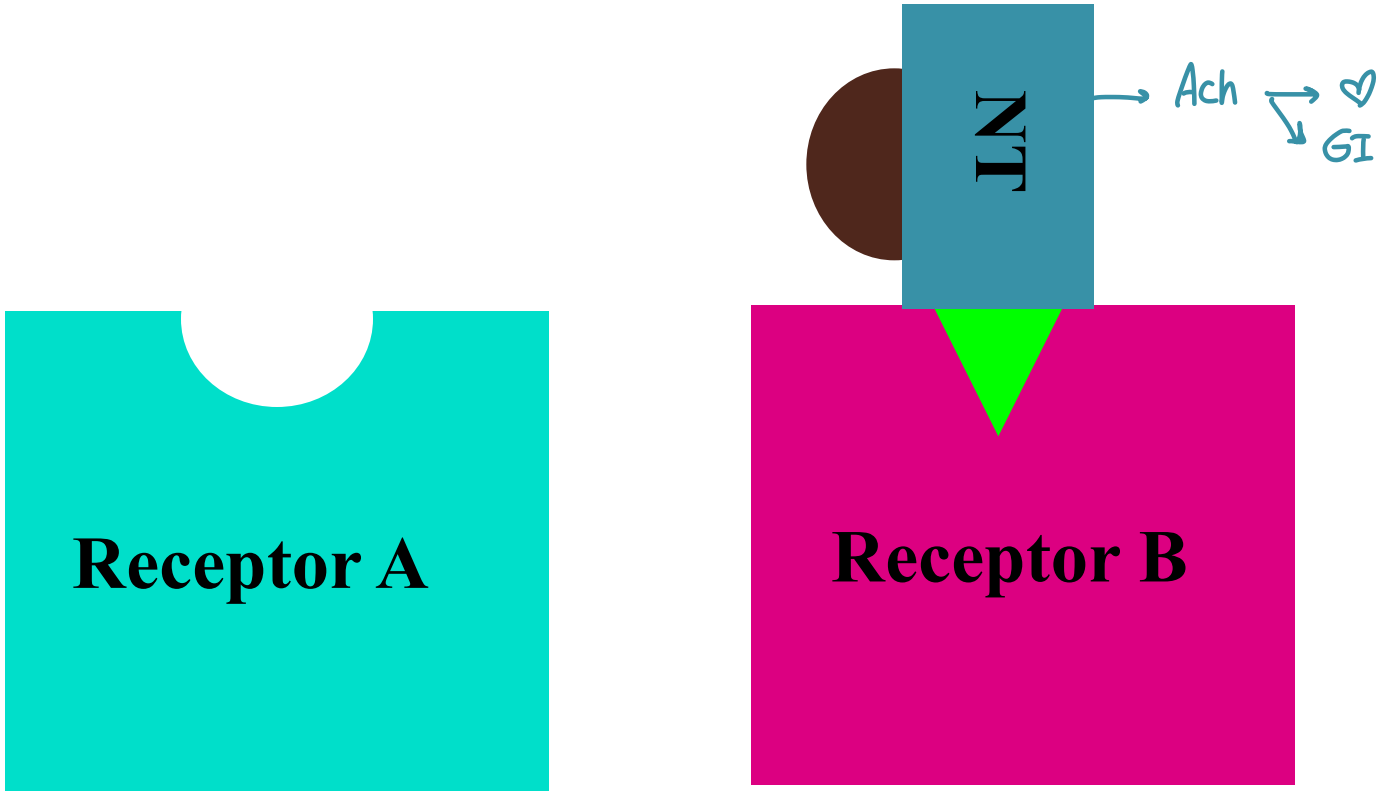
Antagonist

Drugs that bind to but do not activate neuroreceptors,

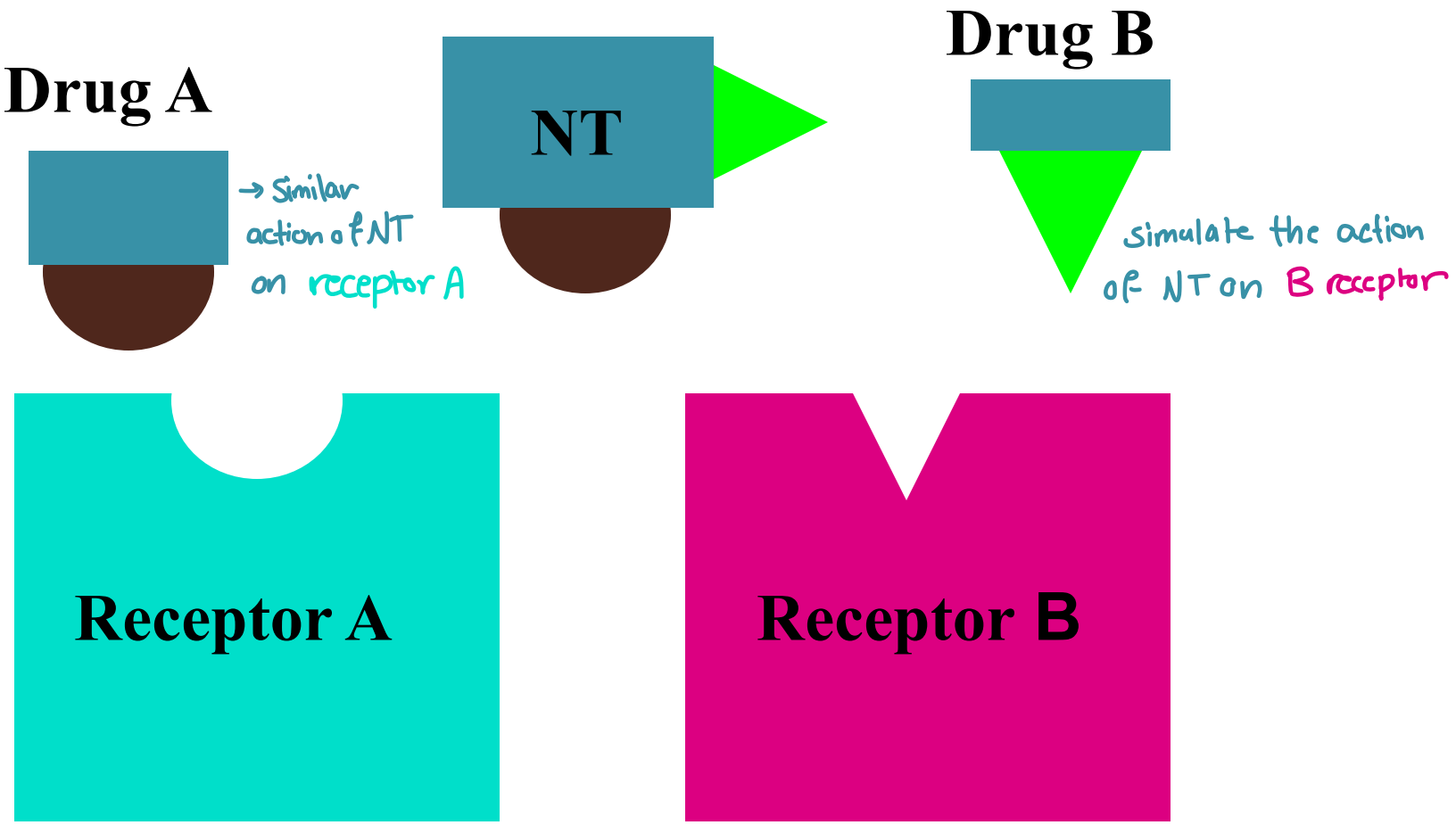
thereby blocking the actions of neurotransmitters or the neuroreceptor agonists.

→ Beta receptor Blocker / Alpha receptor Blocker → To treat certain diseases.

- Same NT can bind to different -R (two types of receptors)
- different part of NT ~

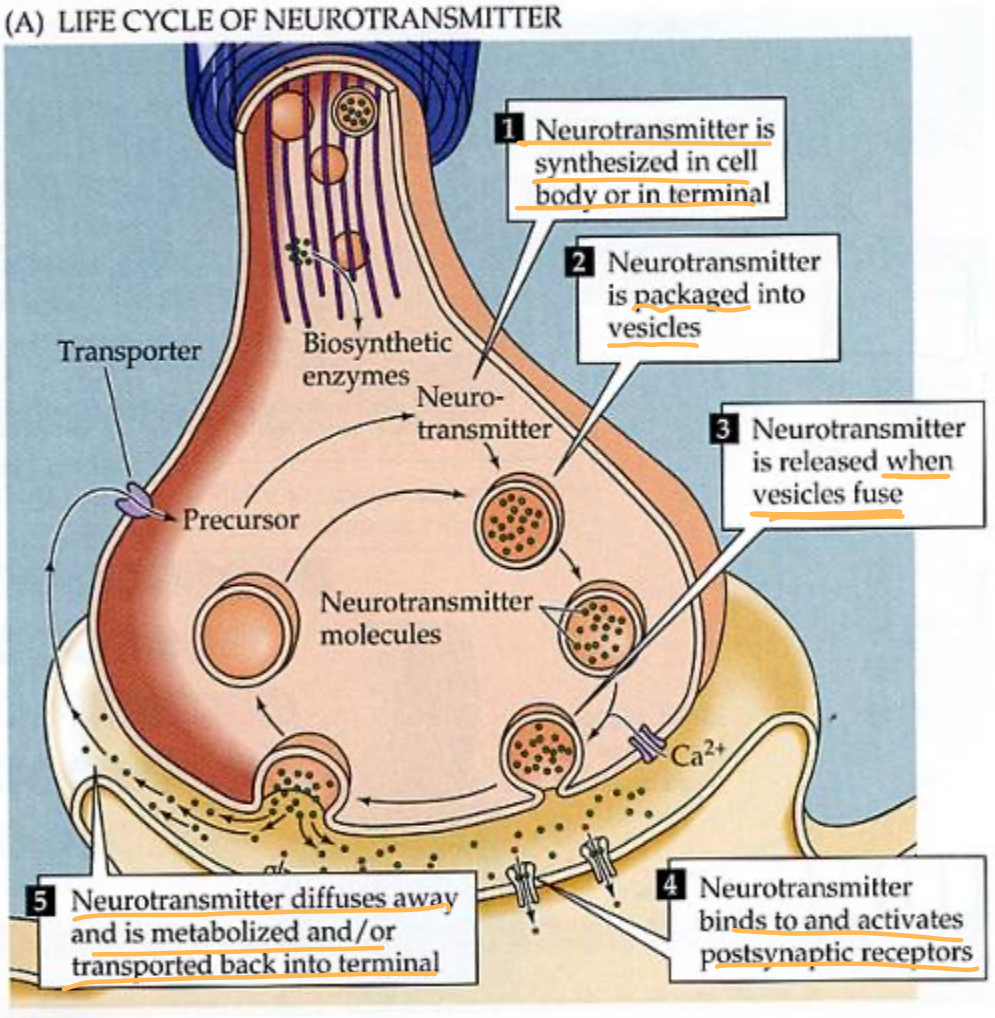


Specificity of drugs



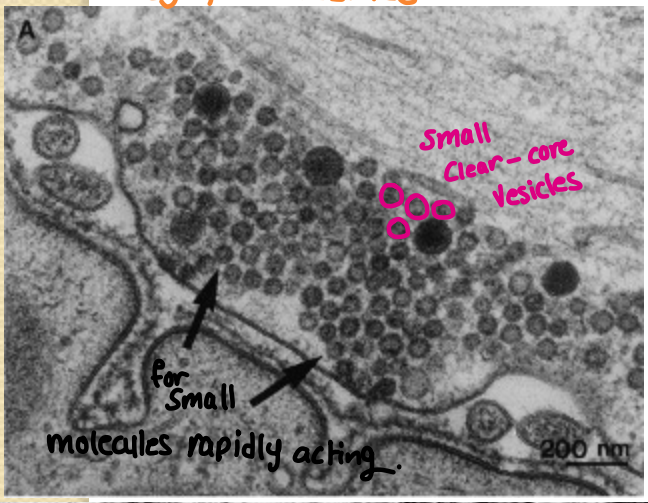
Five key steps in neurotransmission

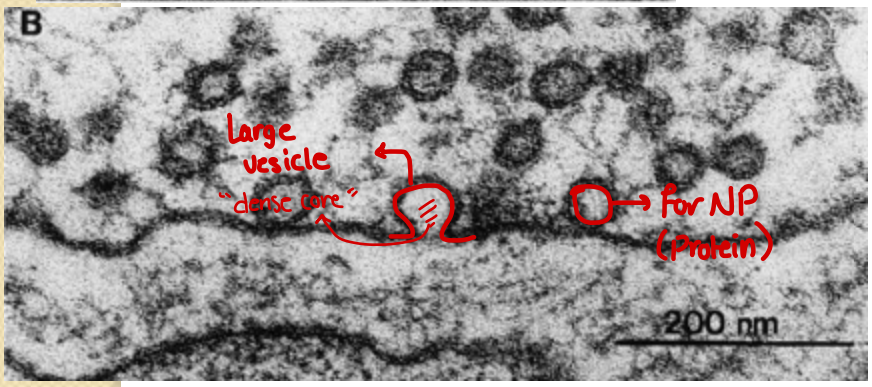
- Synthesis → In presynaptic terminal
- Storage → inside vesicle in Presynaptic terminal
- Release
- Receptor Binding
- Inactivation



Synaptic vesicles

Electromicroscopy for Synaptic Vesicles





- Concentrate and protect transmitter
- Can be docked at active zone
- Differ for classical transmitters (small, clear-core) vs. neuropeptides (large, dense-core)

Neurotransmitter Co-existence (Dale principle)

Some neurons in both the PNS and CNS produce both a classical neurotransmitter (ACh or a catecholamine) and a polypeptide neurotransmitter.

They are contained in different synaptic vesicles that can be distinguished using the electron microscope.

The neuron can thus release either the classical neurotransmitter or the polypeptide neurotransmitter under different conditions.

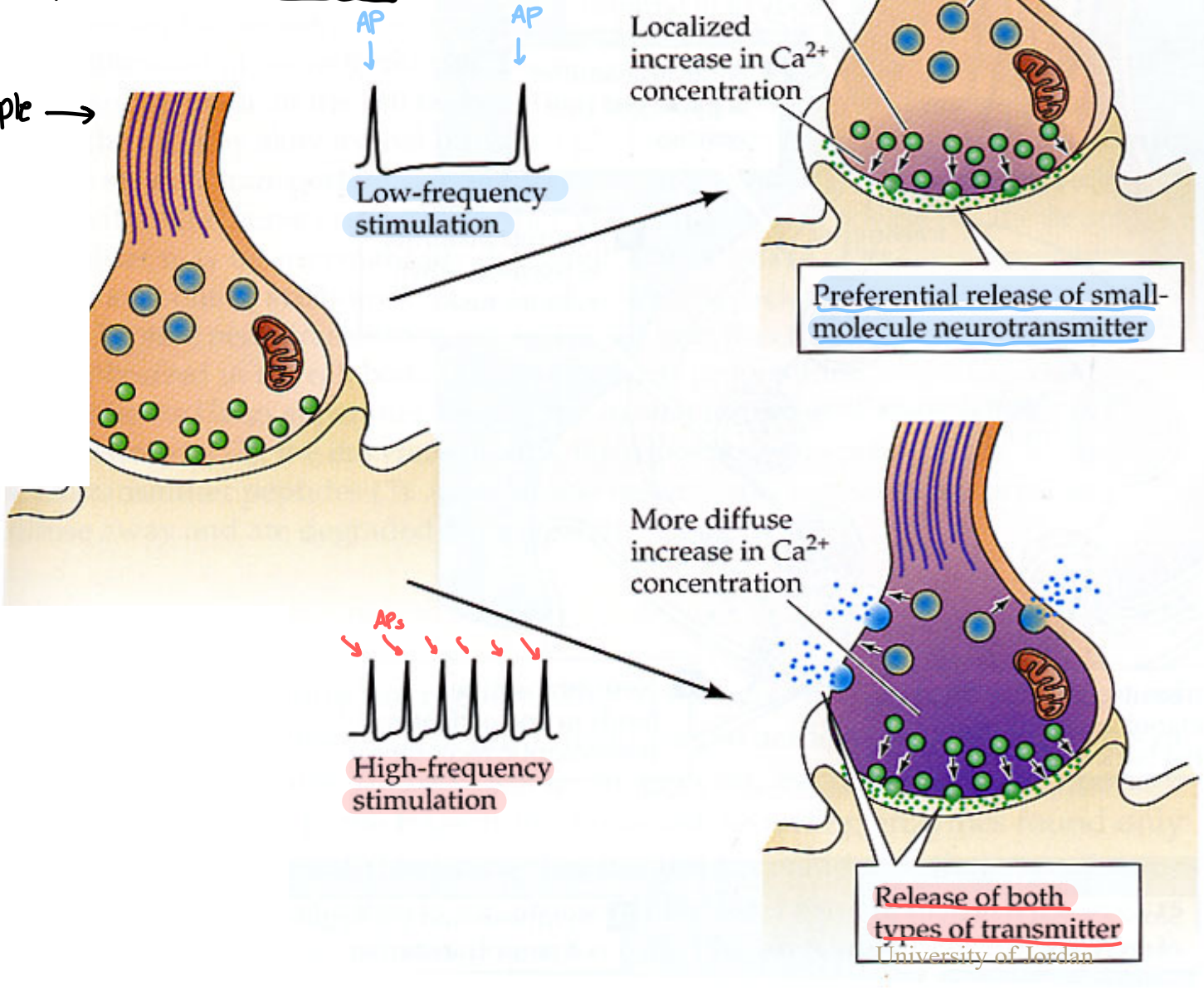
•Sometimes in other neurons

Low frequency → Both

Hig = → small molecule -NT

it depends on the neuron.

Example →



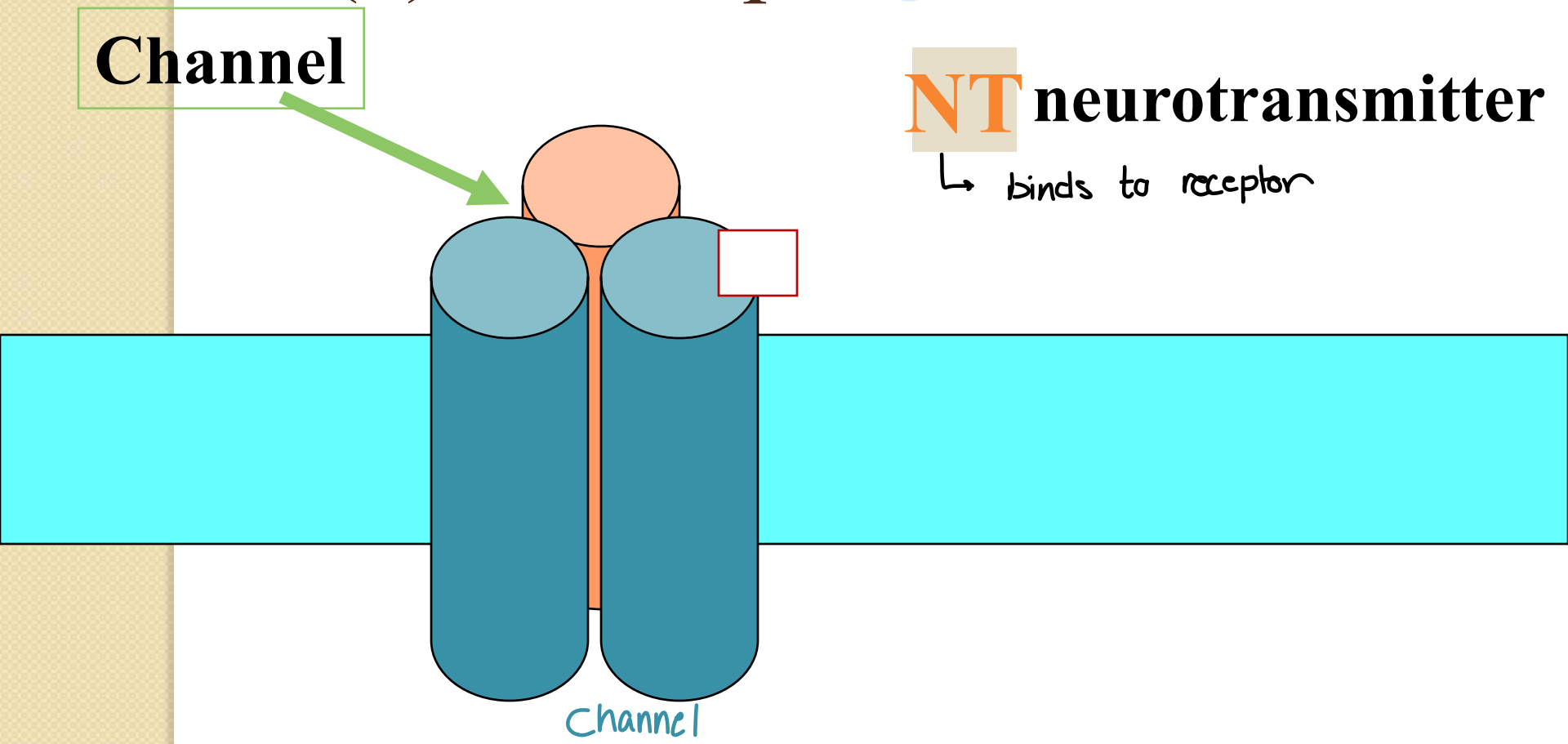
Receptors determine whether:

- Synapse is excitatory or inhibitory
  - NE is excitatory at some synapses, inhibitory at others
- Transmitter binding activates ion channel directly or indirectly.
  - Directly → The receptor itself is an ion channel (ionophores)
    - ionotropic receptors
    - fast
  - Indirectly
    - metabotropic receptors
    - G-protein coupled → Activated → Alpha subunit dissociate → α subunit and opens a channel does other actions like 2nd messenger actions.
    - slow

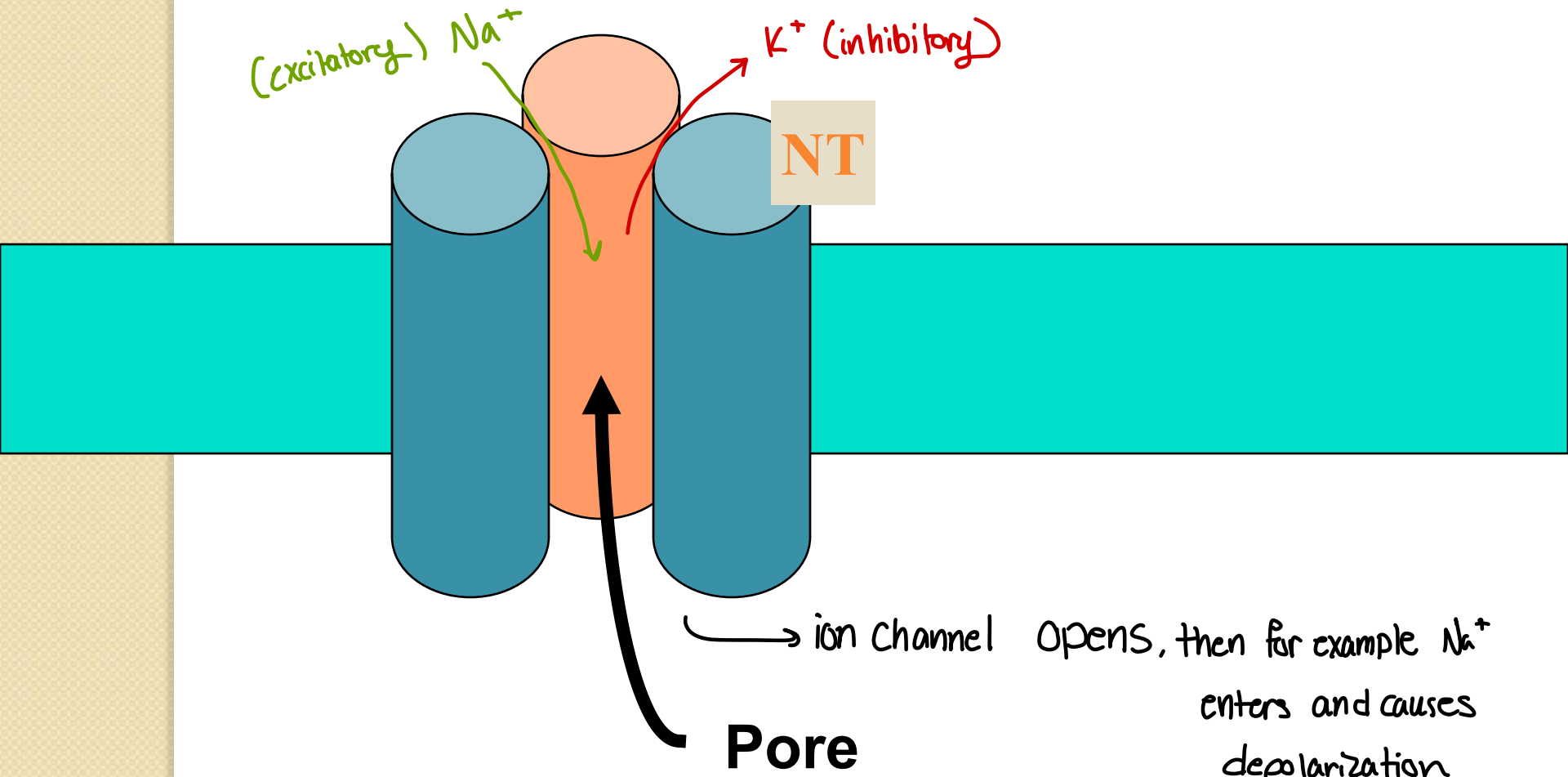
Receptor Activation

- Ionotropic channel
  - directly controls channel
  - fast
- Metabotropic channel
  - second messenger systems
  - receptor indirectly controls channel ~

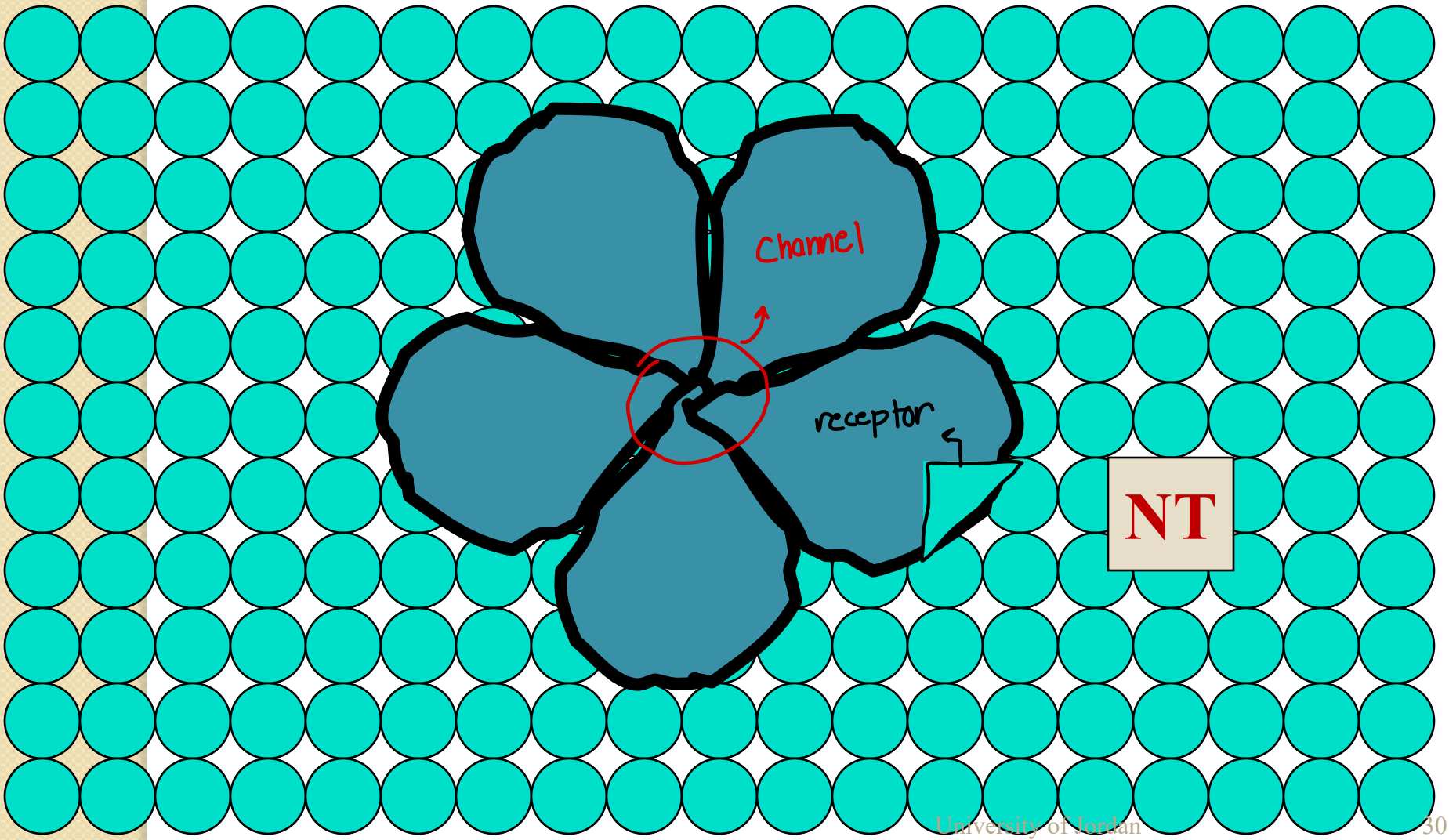
(1) Ionotropic Channels



Ionotropic Channels

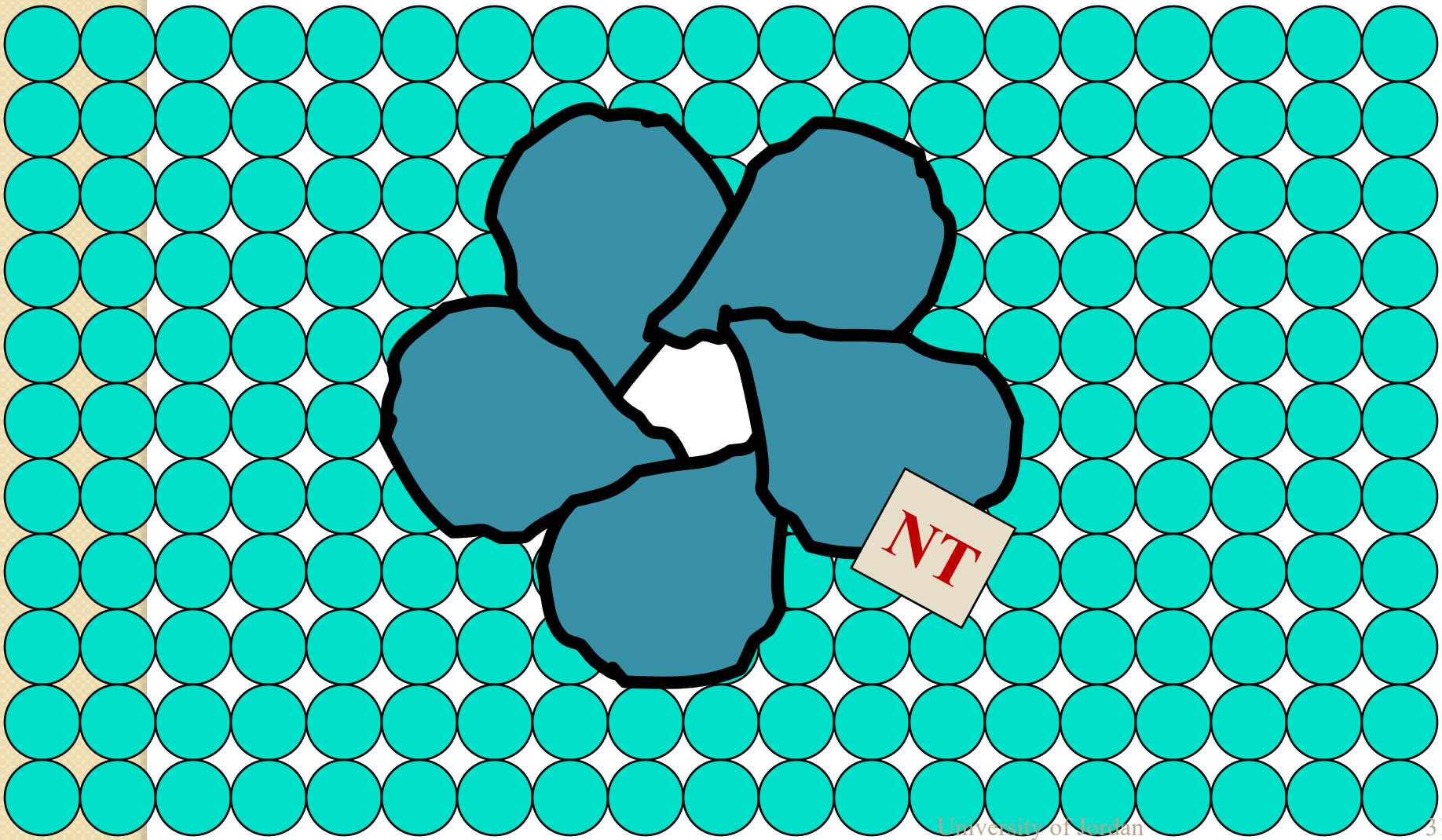


Ionotropic Channels



Ionotropic Channels

NT Binds to receptor → opens channel.



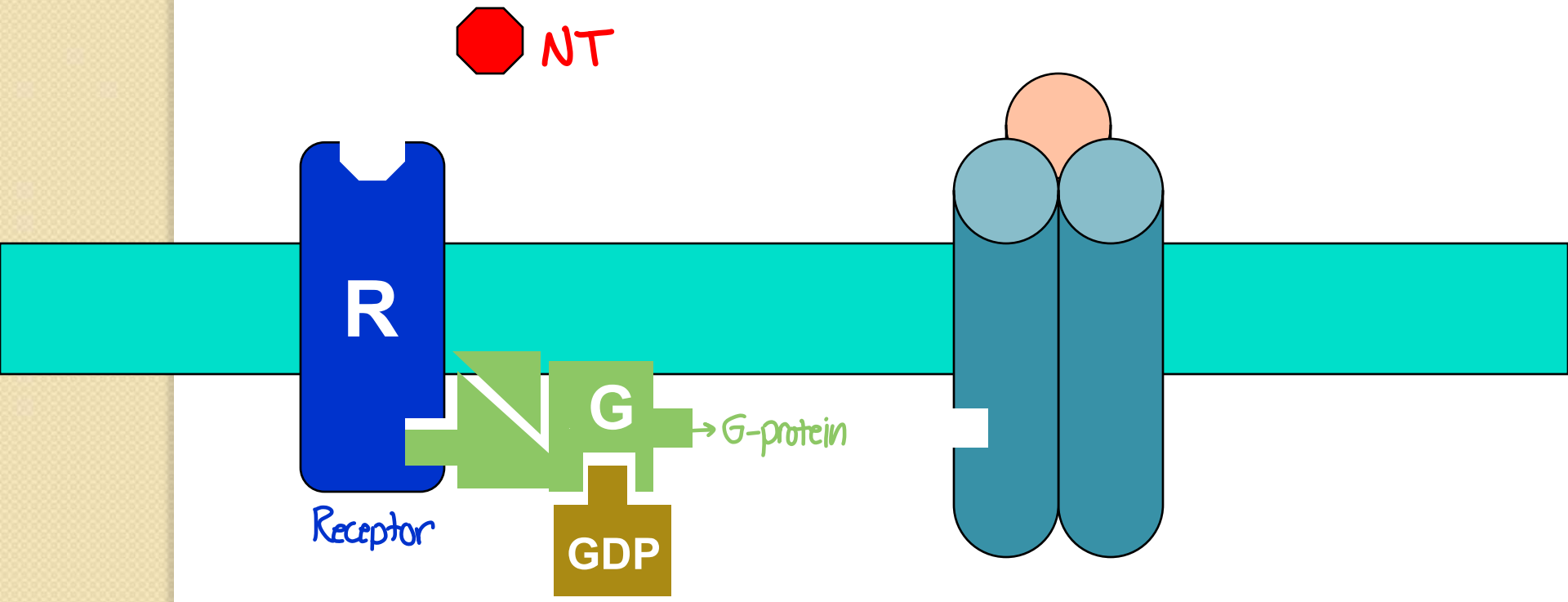
Metabotropic Channels

- Receptor separate from channel
- G proteins → Subunits : α /β/ δ
  - α → DNA → Alter gene / receptor properties.
  - when α subunit dissociates → might stimulate Adenylate cyclase : converts ATP → C-Amp (second messenger)
- 2nd messenger system
  - cAMP
  - other types
- Effects
  - Control channel
  - Alter properties of receptors
  - regulation of gene expression ~

G protein: direct control

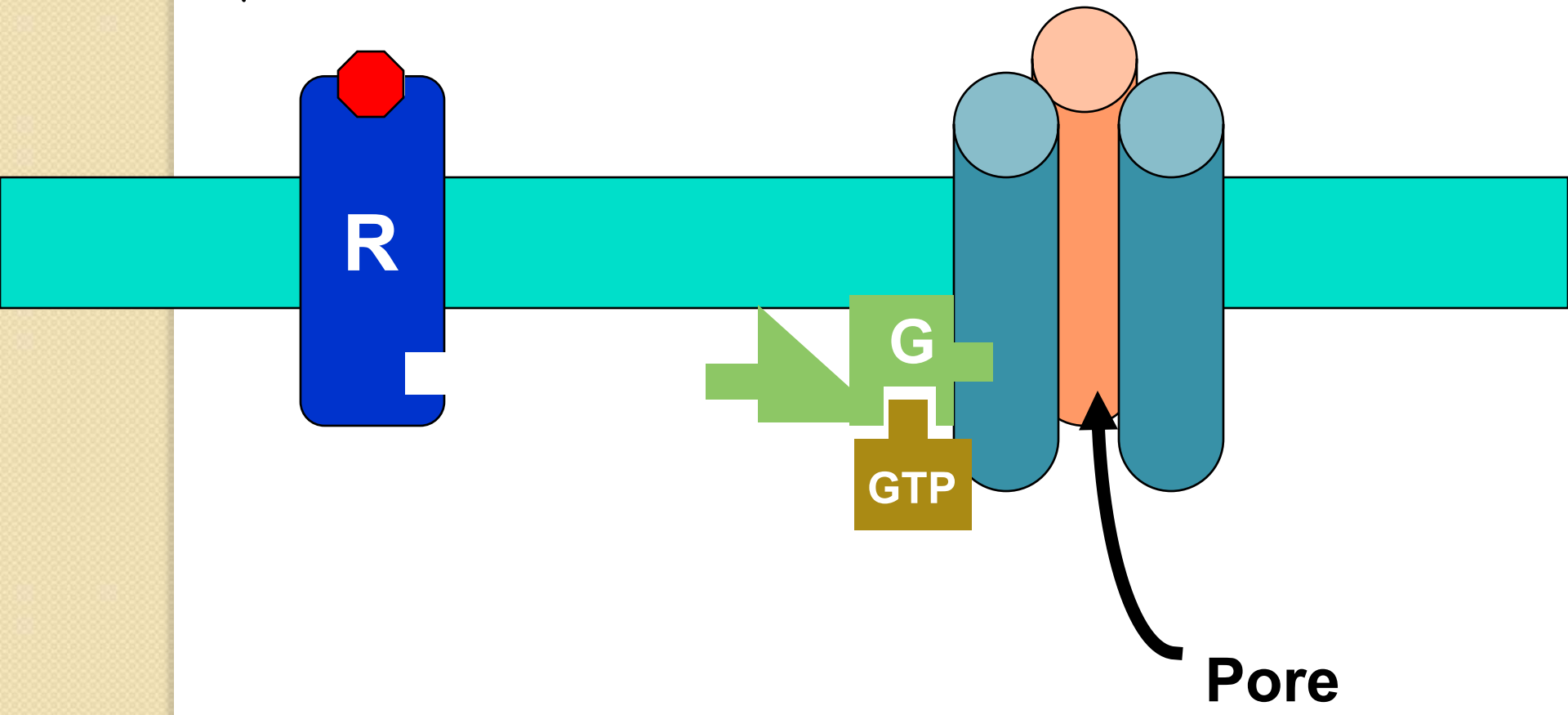
- NT is 1st messenger
- G protein binds to channel
  - opens or closes
  - relatively fast ~ (ionotropic is faster)

G protein: direct control

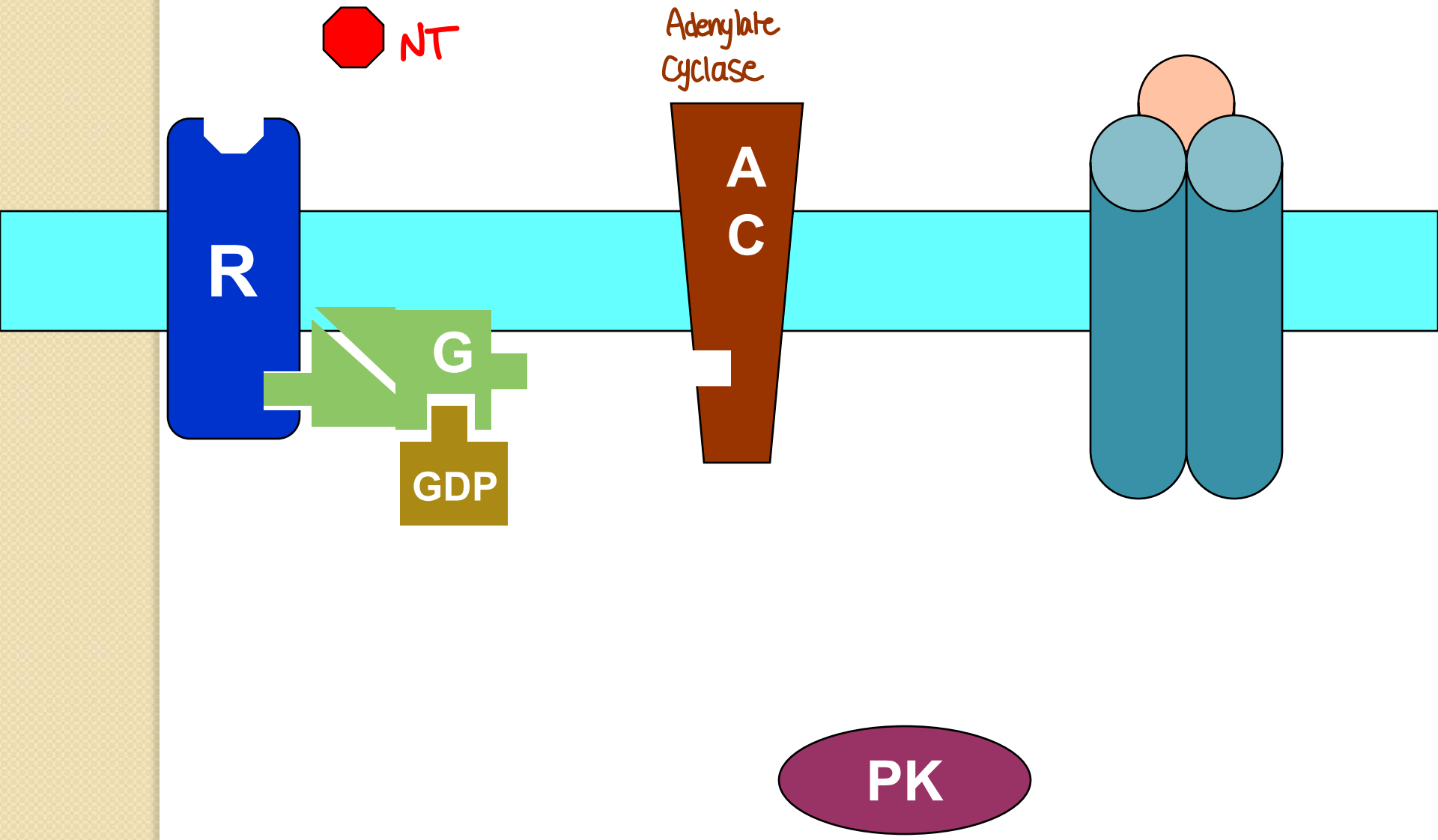


G protein: direct control

Once NT binds to receptor → α subunit of Gprotein dissociate and opens a channel.



G protein: Protein Phosphorylation



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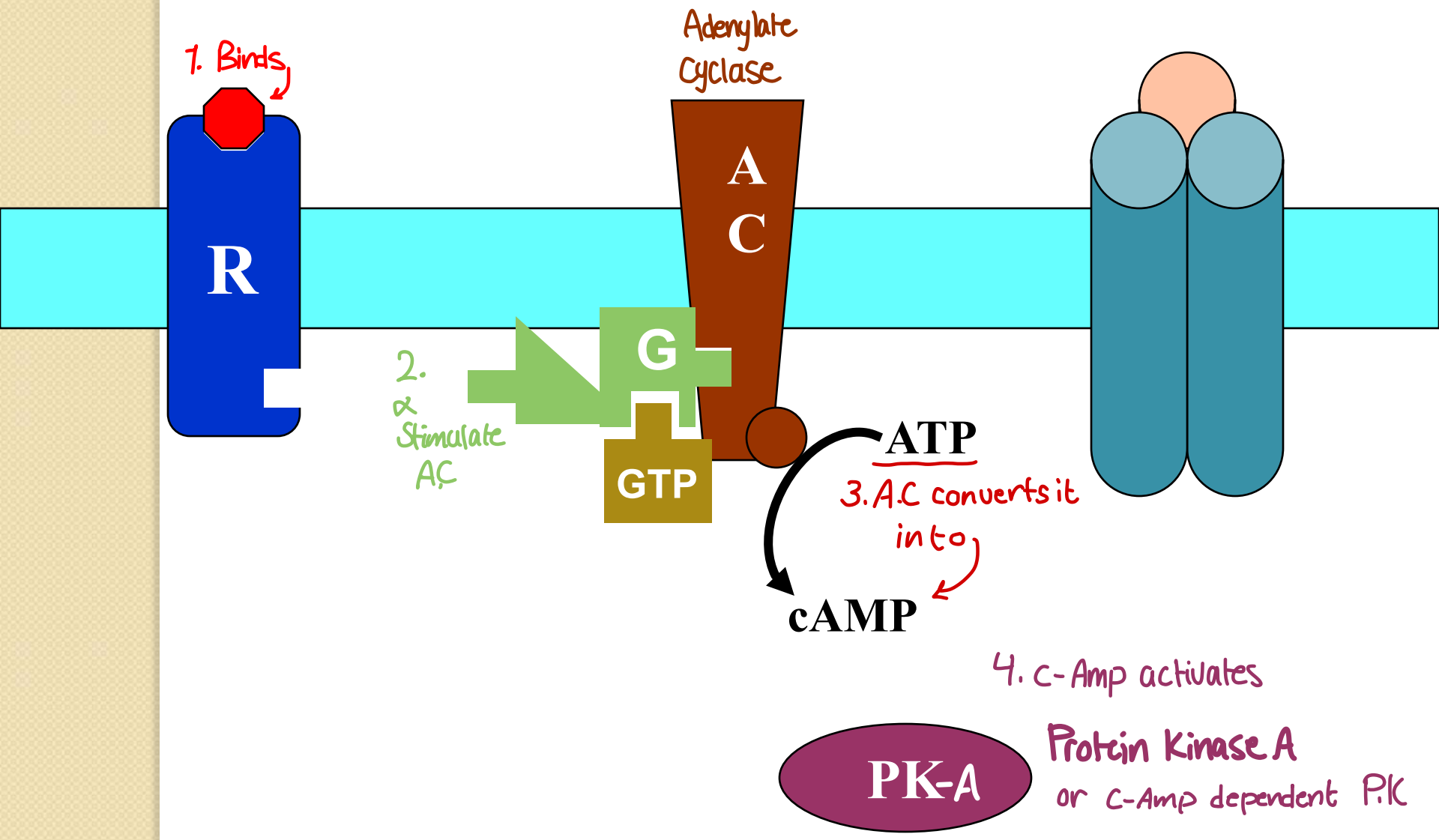

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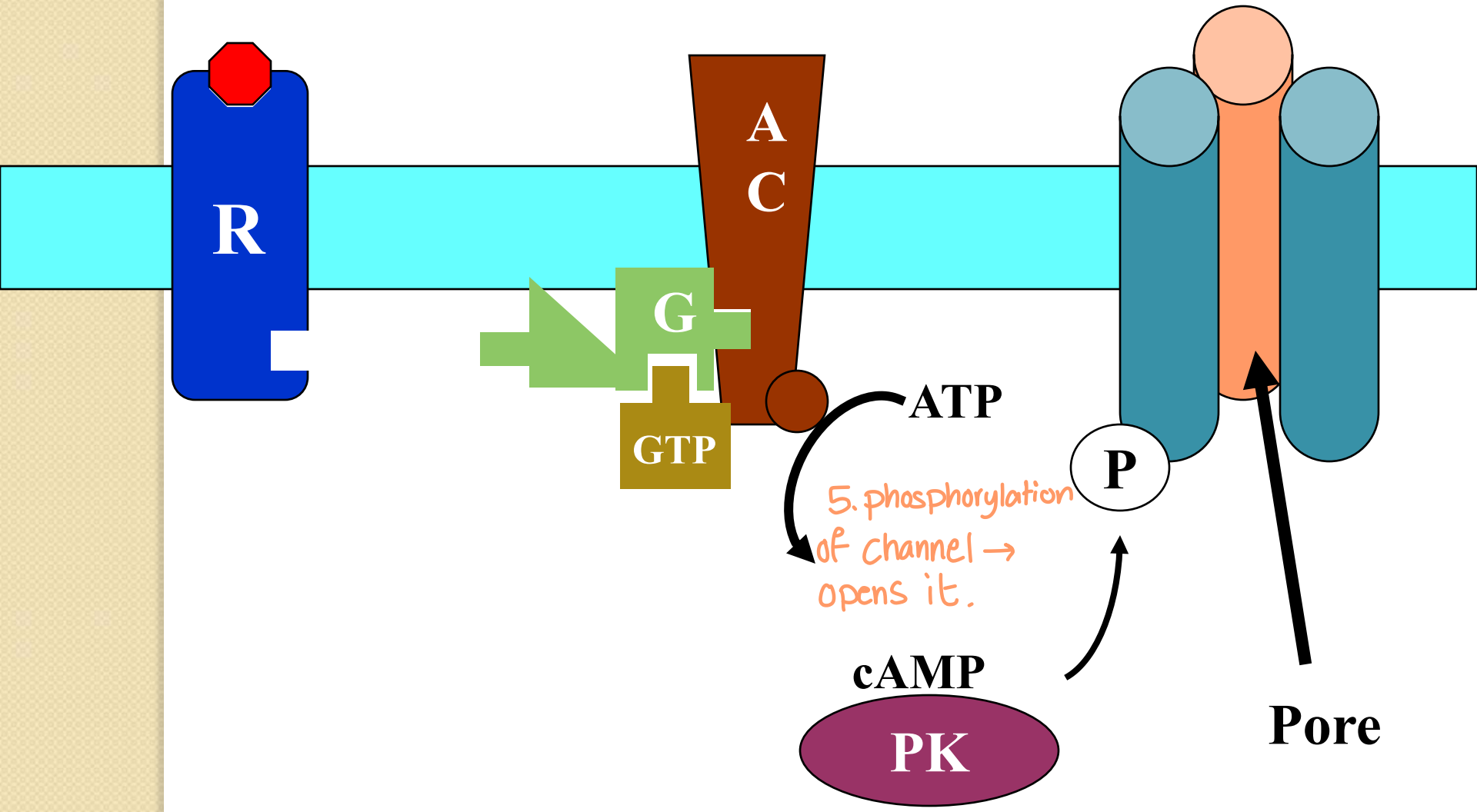


Protein Kinases types

generally phosphorylates proteins

- **Protein Kinase A** → Activated by c-AMP

or C-Amp dependent PK

- **Protein Kinase B**

or Ca^{+2} Calmodulin dependent PK → Calmodulin: intracellular protein that binds Ca^{++} to be active, each can bind 4 Ca^{+2} ions

↳ then it activates **PK-B**

- **Protein Kinase C** → Activated by Ca^{+2} and phospholipid (DAG)

or Ca^{+2}-phospholipid dependent PK

DAG = comes from breaking down phospholipids (PIP_2)

IP_3 DAG

Transmitter Inactivation

- Reuptake by presynaptic terminal
- Uptake by glial cells
- Enzymatic degradation → Ex: Acetylcholinesterase
- Presynaptic receptor ← might be deactivated
- Diffusion
- Combination of above

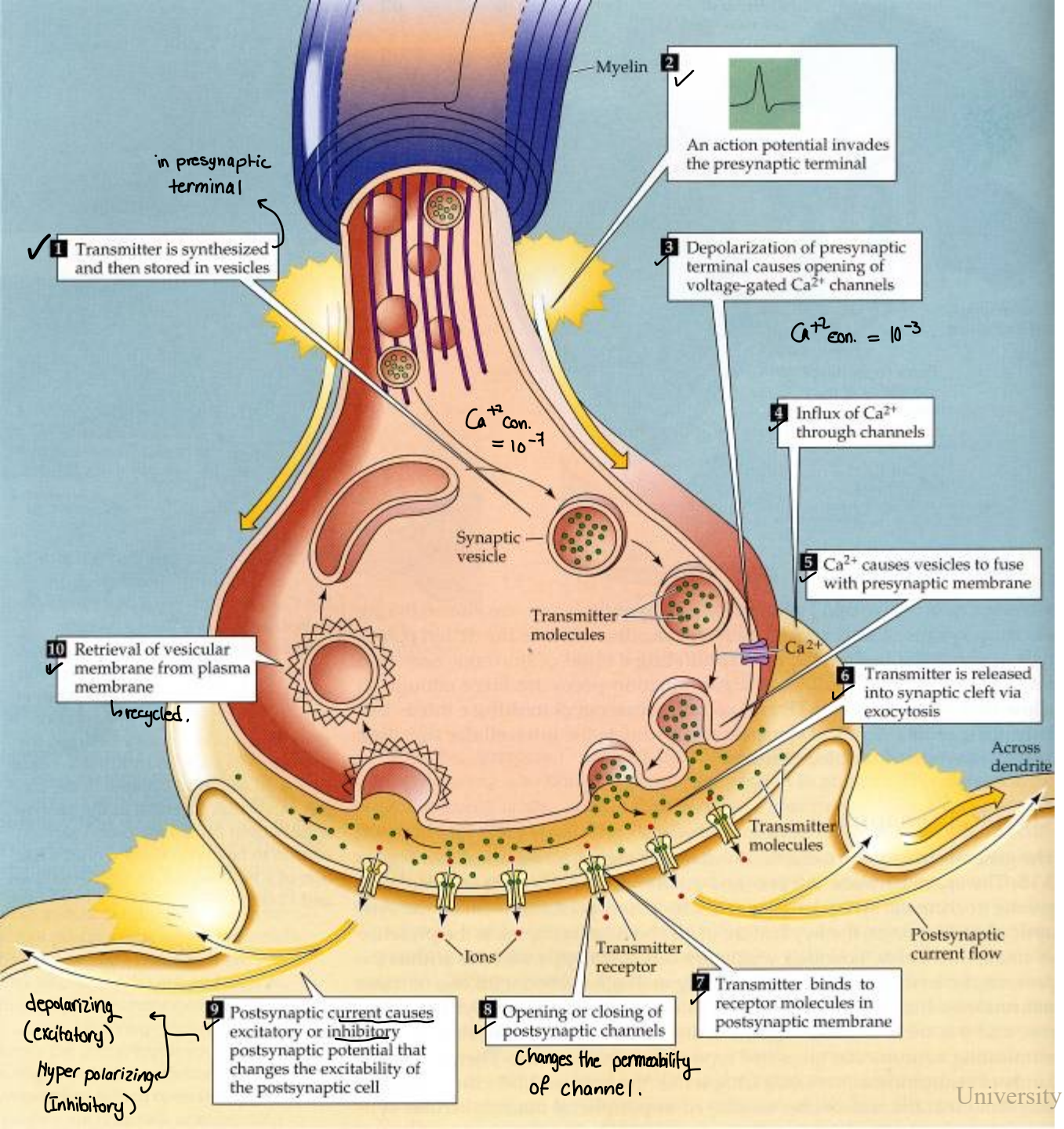
↓

We can have drugs than inhibits it → prolongs the action of Ach

or there might be an agonist that breaks down Ach very fast.

- Myasthenia Gravis : autoimmune disease where there's deficiency in Ach receptors → to prolong the action of Ach you give Acetylcholinesterase inhibitor

Summary of Synaptic Transmission



Purves,2001

اللهم نستودعك أهالي غزّة وفلسطين
فانصرهم واحفظهم بعينك التي لا
تنام، واربط على قلوبهم وأمدهم
بجُندك وأنزل عليهم سكينتك وسخر
لهم الأرض ومن عليها.

Duaa_blessings_

Best of Luck ☺