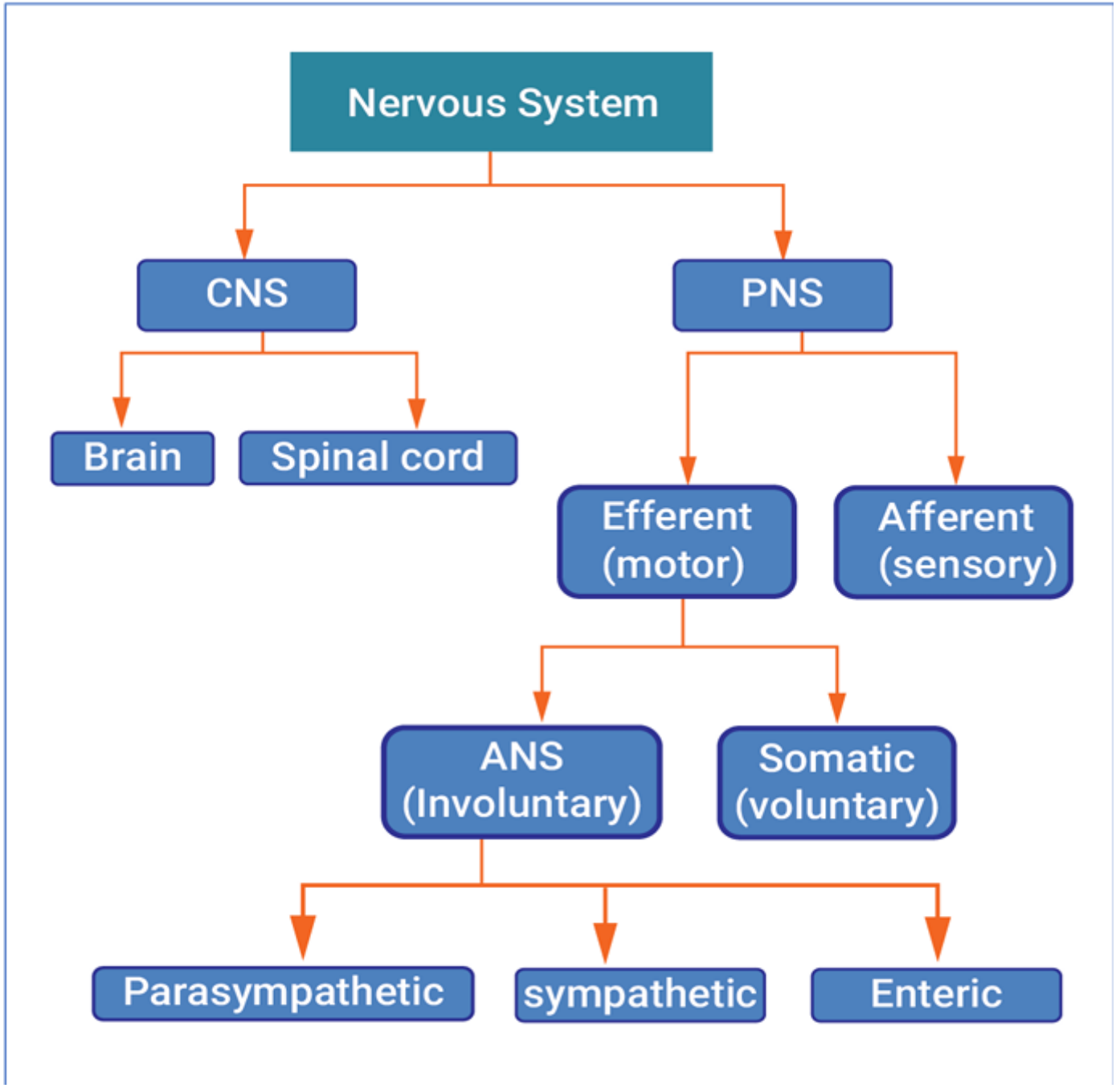
Lec 1 Introduction of CNS

Prof. Dr. Maysaa Ali Abdul Khaleq

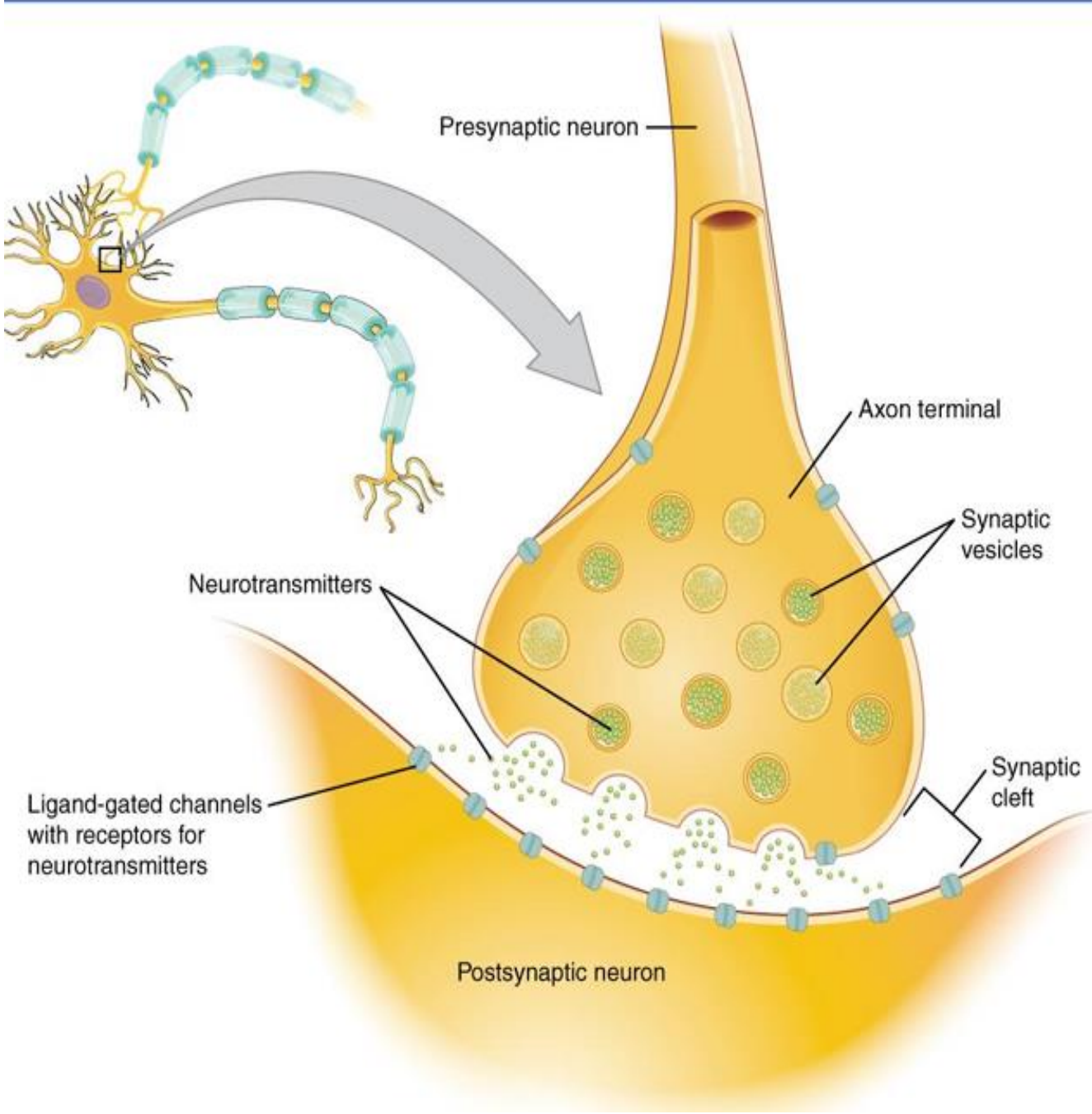
4th stage/ 1st course

- TARGETS OF CNS DRUG ACTION
- Drugs that act on the central nervous system (CNS) are the most commonly prescribed drugs in current use.
- Most of these drugs act by changing ion flow through transmembrane channels of nerve cells.
- Transmitter reuptake transporters constitute a second class of drug targets, especially for antidepressant agents.
- Inhibition of acetylcholine metabolism is the major action of the drugs currently approved for use in Alzheimer disease and y-aminobutyric acid (GABA) metabolism is inhibited by an anticonvulsant agent.
- Finally, a few drugs appear to act by altering the function of neuroglia. These satellite cells have been shown to modulate transmitter synthesis and disposition and support neurons metabolically.
- Microglia have also been shown to "prune" neuronal networks in the normal development of the CNS and possible in Alzheimer disease and schizophrenia.

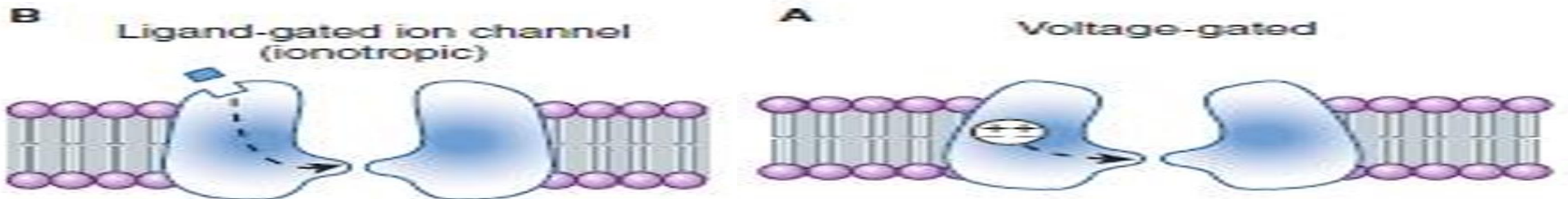
- The nervous system transmits signals between the brain and the rest of the body.
- The basic unit of the nervous system is a nerve cell or neuron.
  - The human brain contains about 100 billion neurons.
- A neuron has a **cell body**, which includes the **cell nucleus**, and special extensions called **axons and dendrites.**
- Axons and dendrites allow neurons to communicate.



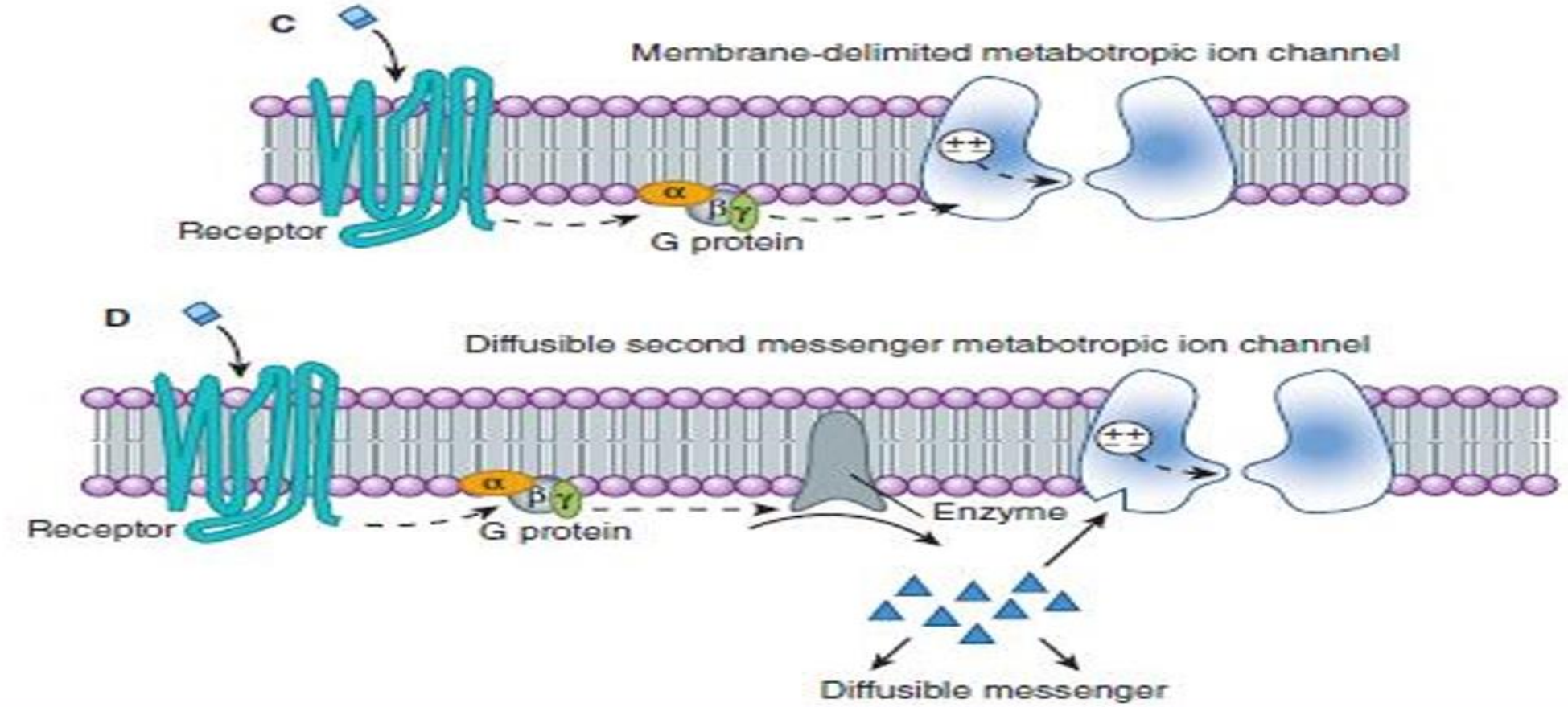
- • Most drugs that act on the central nervous system (CNS) appear to do so by changing ion flow through transmembrane channels of nerve cells.
- • **CNS Drug Action depend on :**
- A. Types of Ion Channels
- B. Types of Receptor-Channel Coupling
- C. Role of the Ion Current Carried by the Channel



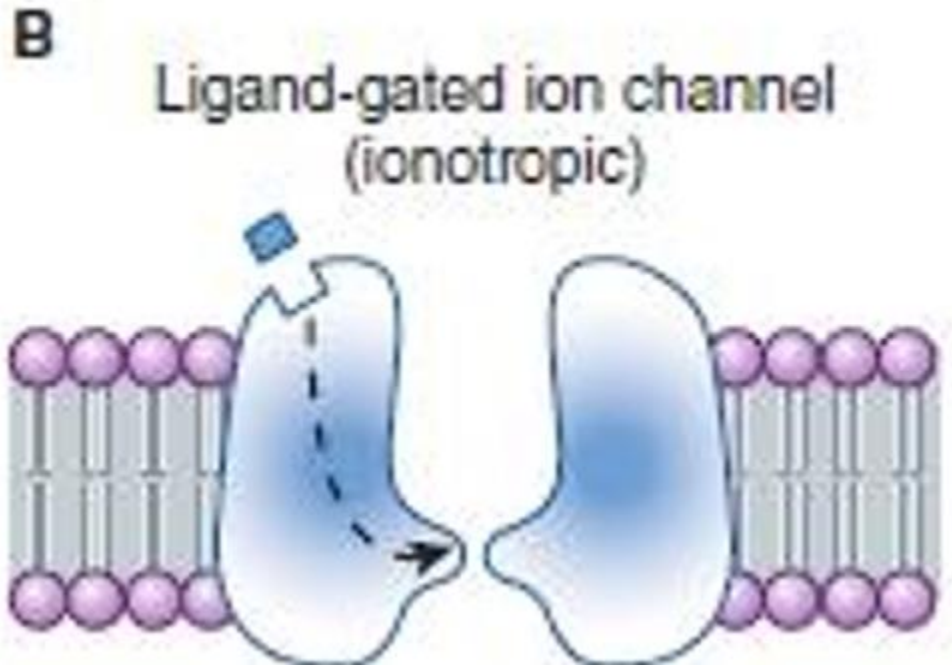
- **A. Types of Ion channels of neuronal membranes are of two major types:**
- **1. voltage gated and ligand gated** .
- Voltage-gated ion channels respond to changes in membrane potential.
- They are found in high concentration on the axons of nerve cells and include the sodium channels responsible for action potential propagation.
- Cell bodies, axon terminals, and dendrites have voltage-sensitive ion channels for sodium, potassium, and calcium.
- **2. Ligand-gated ion channels,** also called ionotropic receptors, respond to chemical neurotransmitters that bind to receptor subunits present in their macromolecular structure.

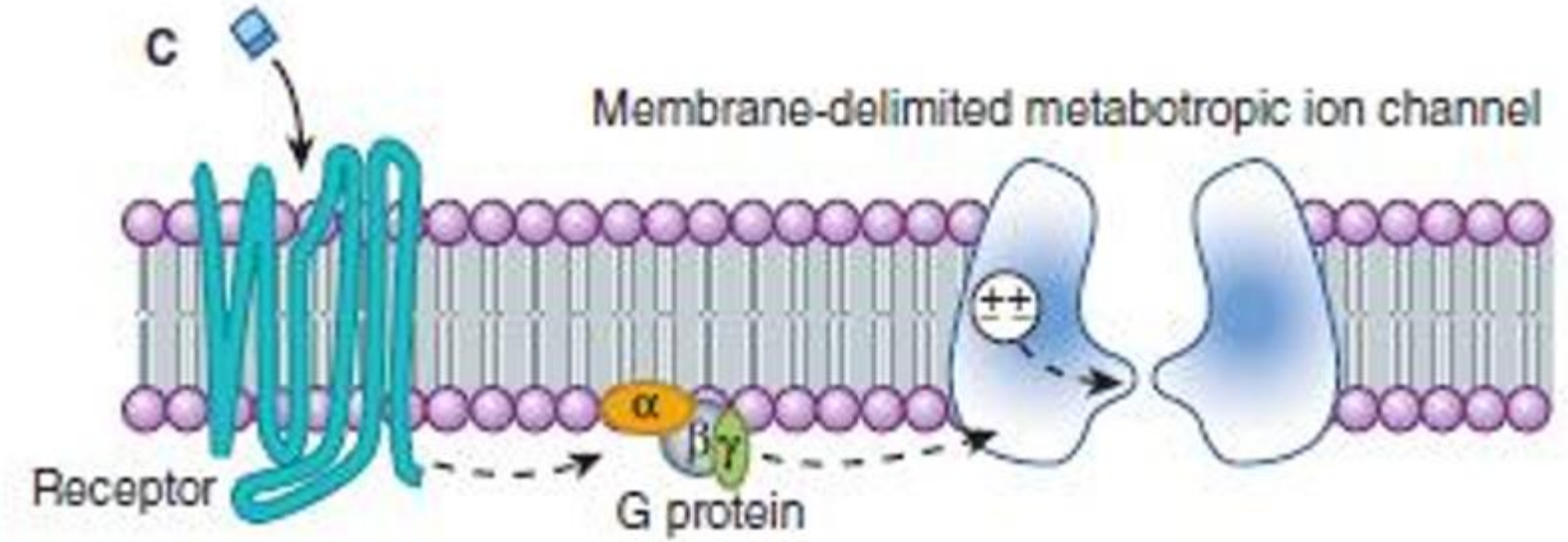


- Other Ligand-gated ion channels include Neurotransmitters bind to G-protein-coupled receptors (metabotropic receptors) that can **modulate** voltage gated ion channels.
- Neurotransmitter-coupled ion channels are found on cell bodies and on both the presynaptic and postsynaptic sides of synapses.

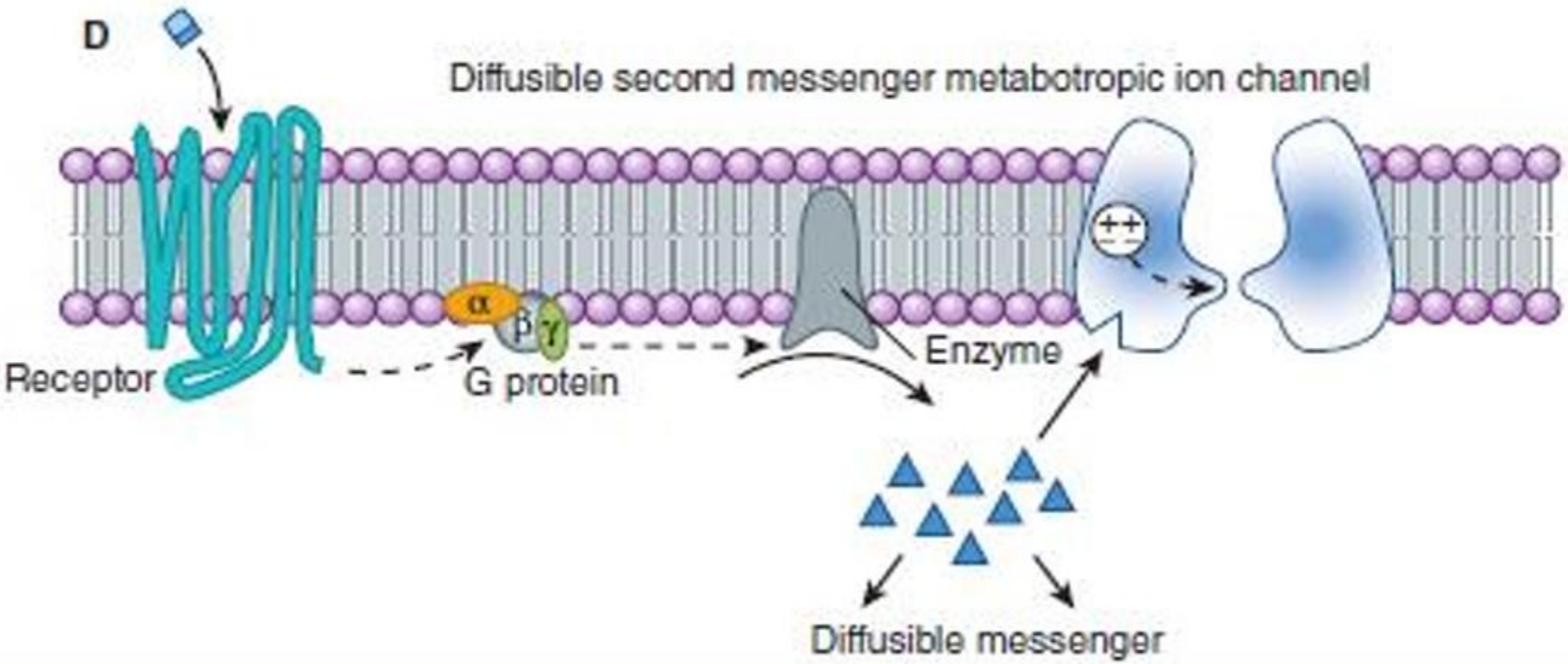


- **B. Types of Receptor-Channel Coupling**
- In the case of ligand-gated ion channels, activation (or inactivation) is initiated by the interaction between chemical neurotransmitters and their receptors.
  - **Coupling may be through a receptor :**
- 1. That acts directly on the channel protein (B)
- 2. That is coupled to the ion channel through a G protein (C)





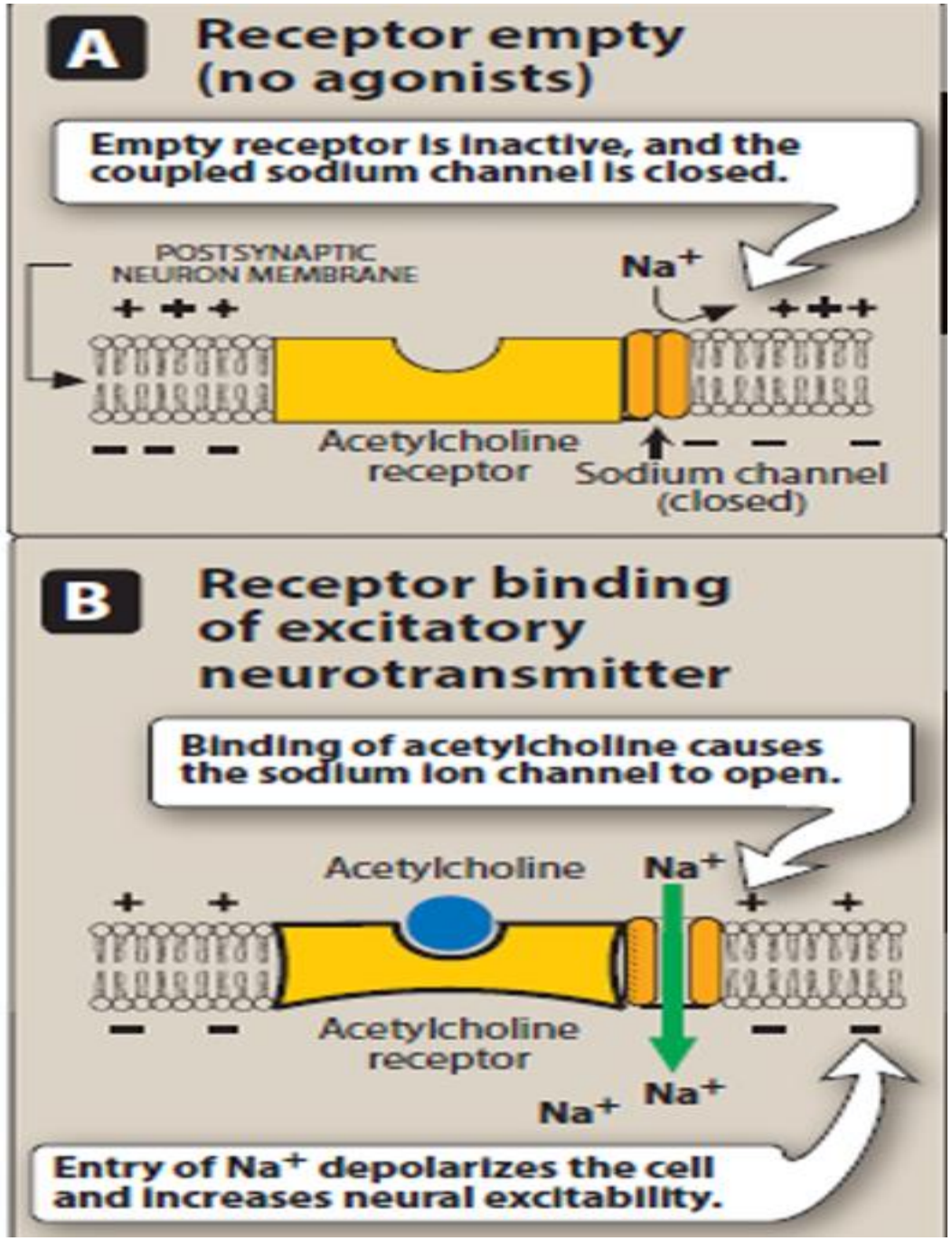
- 3. Coupled to a G protein that modulates the formation of diffusible second messengers, including cyclic adenosine monophosphate (cAMP), inositol trisphosphate (IP3), and diacylglycerol (DAG), which secondarily modulate ion channels (D)



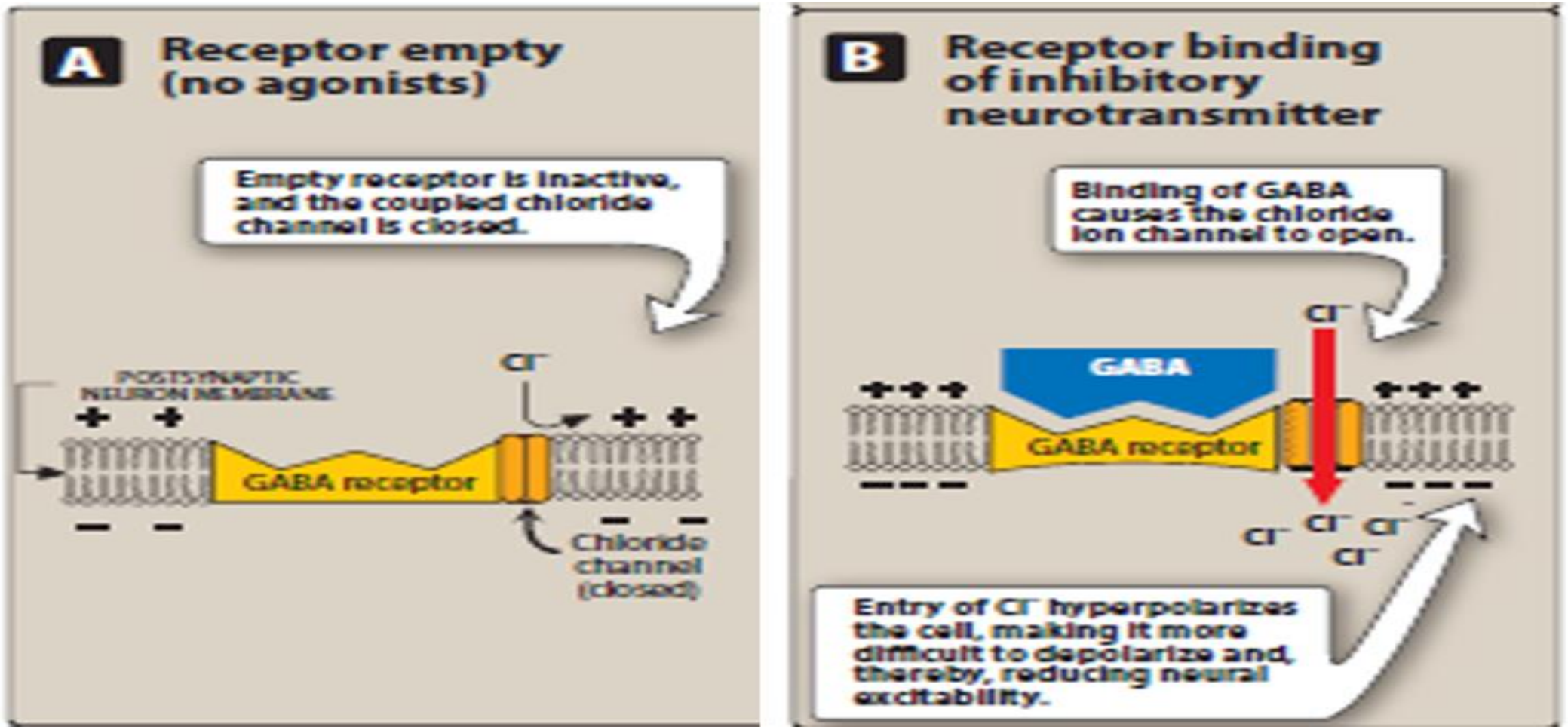
- **C. Role of the Ion Current Carried by the Channel**
- **1. Excitatory postsynaptic potentials (EPSPs):**

• These potentials are usually generated by the **opening of sodium or calcium** channels.

• In some synapses, similar depolarizing potentials result from the **closing of potassium channels.**



- **2. Inhibitory postsynaptic potentials (IPSPs):**
- These potentials are usually generated by the **opening** of potassium or chloride channels.
- For example, **activation of postsynaptic metabotropic receptors** increases the efflux of potassium.
- **Presynaptic inhibition** can occur via a **decrease in calcium influx** elicited by activation of metabotropic receptors.

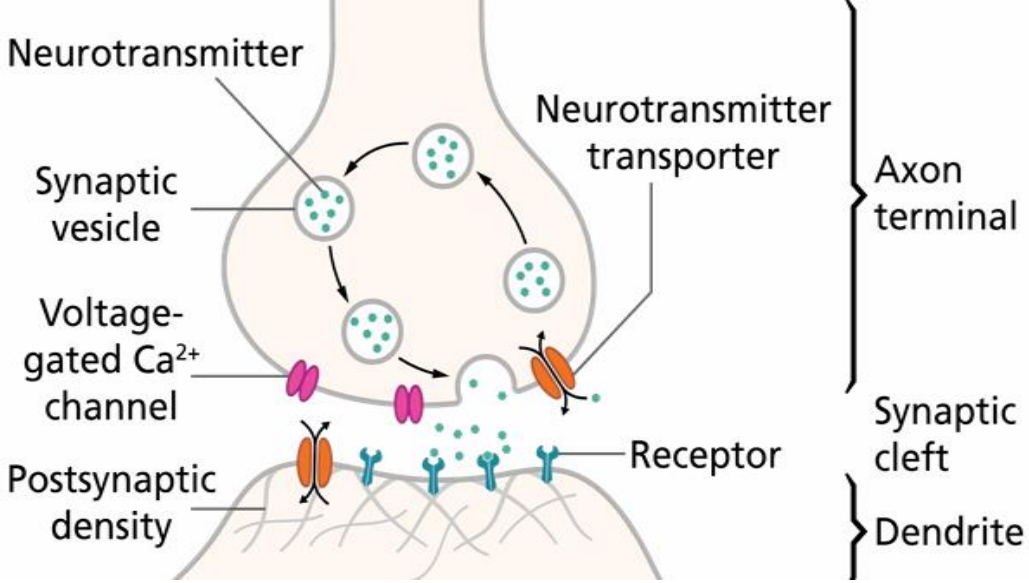


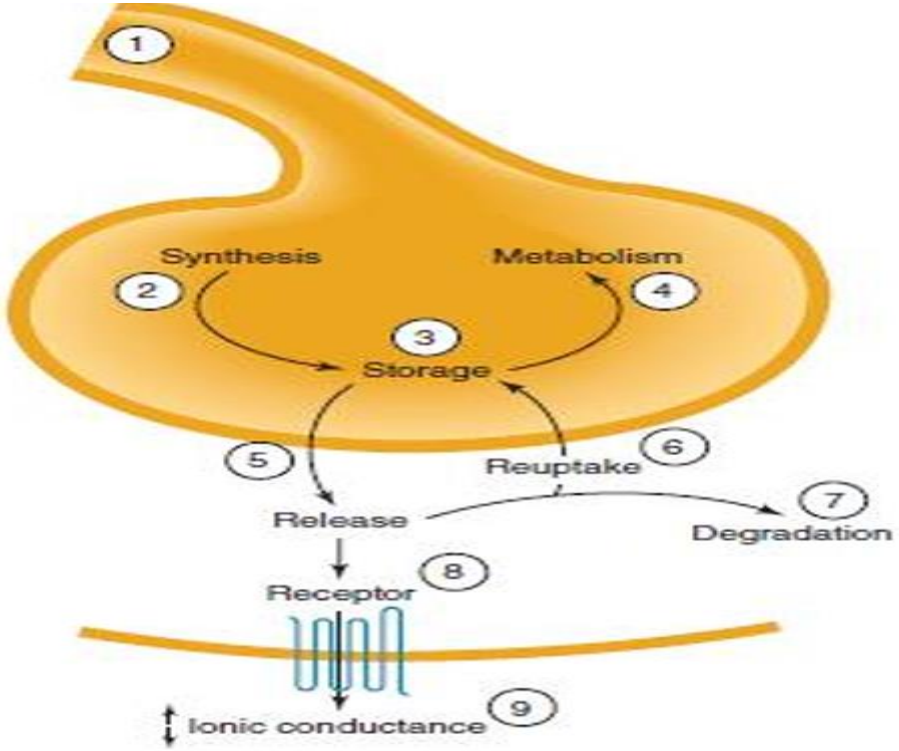
- **SITES & MECHANISMS OF DRUG ACTION**

A small number of neurotransmitters exert their effects through direct interactions with molecular components of ion channels on **axons**.

- Examples include certain anticonvulsants (eg, carbamazepine, phenytoin), local anesthetics, and some drugs used in general anesthesia.
- However, the effects of most therapeutically important CNS drugs are exerted mainly at synapses.
- Drugs may act **presynaptically** to alter the synthesis, storage, release, reuptake, or metabolism of transmitter chemicals.
  - Other drugs can **activate or block** both **pre and postsynaptic** receptors for specific **transmitters** or can **interfere with the actions of second messengers**.

- The selectivity of CNS drug action is largely based on the fact that **different groups of neurons use different neurotransmitters** and that they are segregated into networks that subserve different CNS functions
- **Sites of CNS drug action: Drugs may alter:**
- 1. The action potential in the presynaptic fiber
- 2. Synthesis of the transmitter
- 3. Storage
- 4. Metabolism
- 5. Release
- 6. Reuptake
- 7. Degradation
- 8. Receptors for the transmitter
- 9. Receptor-induced decrease or increase in ionic conduction





- **ROLE OF CNS ORGANIZATION**
- The CNS contains 2 types of neuronal systems: hierarchical and diffuse.
- **A. Hierarchical Systems**

➢• These systems are delimited in their anatomic distribution and generally contain large myelinated, rapidly conducting fibers.

➢• Hierarchical systems **control** major sensory and motor functions.

➢• The major **excitatory transmitters** in these systems are aspartate and glutamate.

➢• These systems also include numerous **small inhibitory interneurons**, which use γ-aminobutyric acid (GABA) or glycine as transmitters.

➢• **Drugs** that affect hierarchical systems often have profound effects on the overall excitability of the CNS.

- **B. Diffuse Systems**

➢• Diffuse or nonspecific systems are broadly distributed, with single cells frequently sending processes to many different areas.

➢• The axons are fine and branch repeatedly to form synapses with many cells.

➢• Axons commonly have periodic enlargements (**varicosities**) that contain transmitter vesicles.

➢• The transmitters in diffuse systems are often amines (norepinephrine, dopamine, serotonin) or peptides that commonly exert actions on metabotropic receptors.

➢• **Drugs** that affect these systems often have marked effects on such CNS functions as attention, appetite, and emotional states.

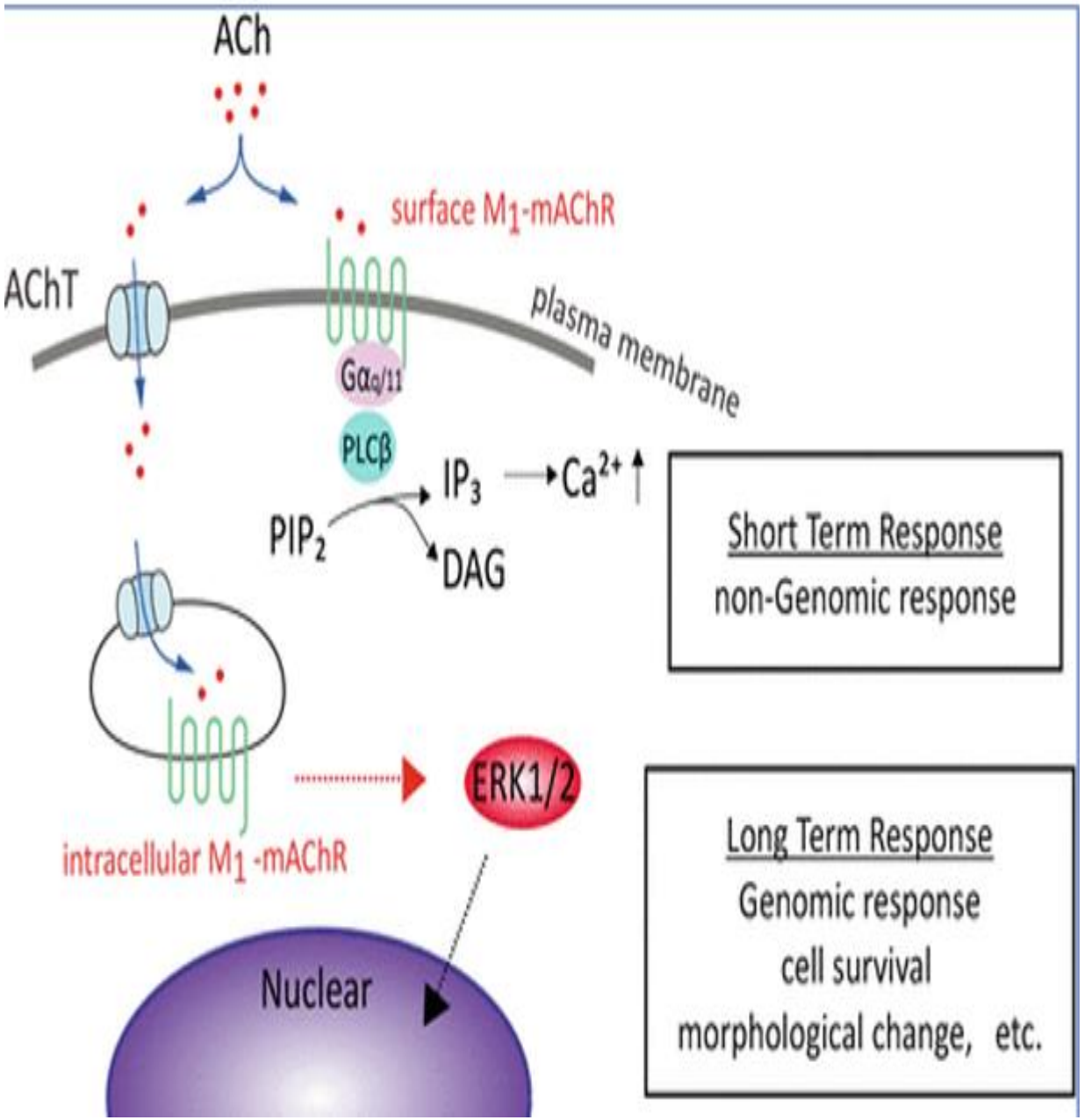
- **TRANSMITTERS AT CENTRAL SYNAPSES**
- **Criteria for Transmitter Status:**
- To be accepted as a neurotransmitter, a candidate chemical must:

❖1. be present in higher concentration in the **synaptic area** than in other areas (ie, must be localized in appropriate areas).

❖2. be released by electrical or chemical stimulation via a **calcium**-dependent mechanism.

❖3. produce the same sort of postsynaptic response that is seen with physiologic activation of the synapse (ie, must exhibit synaptic mimicry).

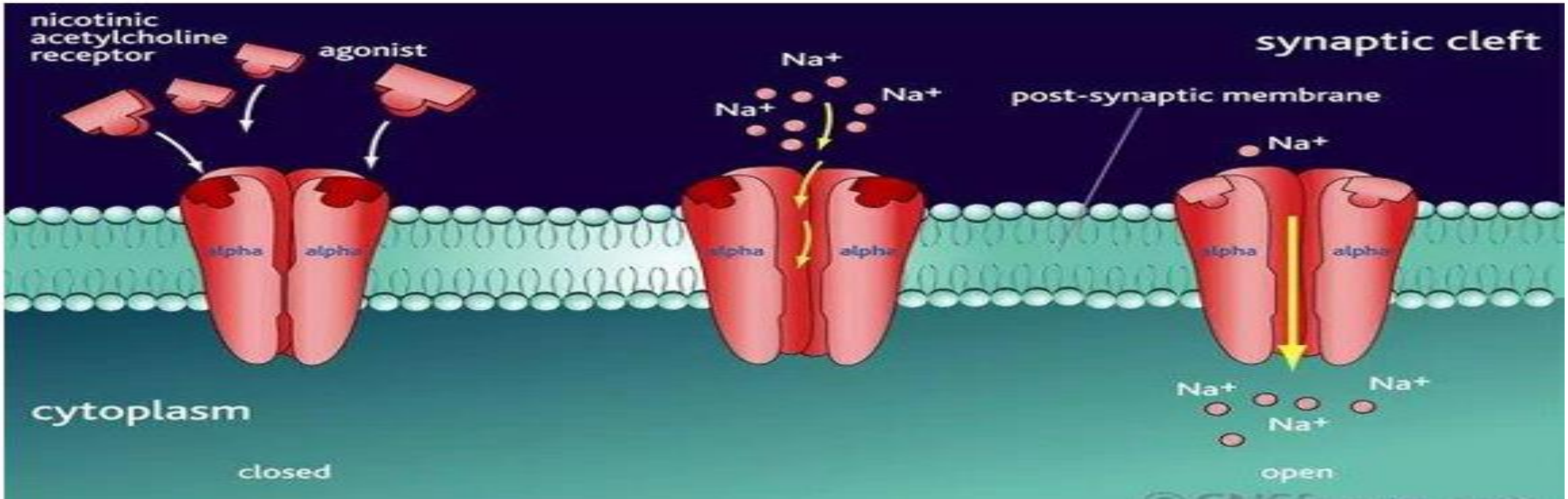
- **Acetylcholine:**
- Approximately 5% of brain neurons have receptors for acetylcholine (ACh).
- Most CNS responses to ACh are mediated by a large family of **G protein-coupled muscarinic M1** receptors that lead to slow excitation when **activated**.
- The ionic mechanism of slow excitation involves a decrease in membrane permeability to potassium.



- **Acetylcholine:**

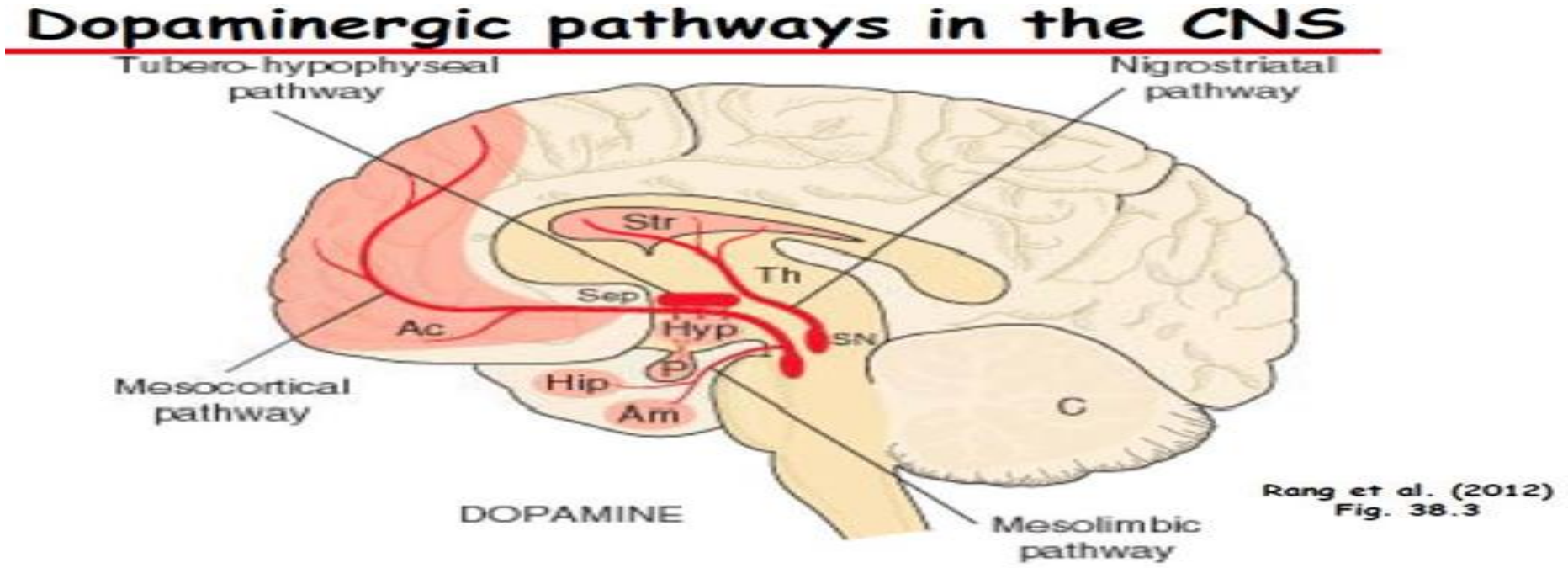
- Of the **nicotinic receptors** present in the CNS are less common than **muscarinic receptors**.

- Drugs affecting the activity of cholinergic systems in the acetylcholinesterase brain include **inhibitors** the used in Alzheimer's disease (eg, tacrine) and the muscarinic blocking agents parkinsonism (eg, benztropine).



- **Dopamine:**

- Dopamine exerts **slow inhibitory actions** commonly via G protein-coupled activation of **potassium channels** (postsynaptic) or inactivation of **calcium channels** (presynaptic).
- The D2 receptor is the main dopamine subtype in basal ganglia neurons.
- Dopaminergic pathways include the **nigrostriatal, mesolimbic, and tubero infundibular tracts.**



- **Dopamine:**

- Drugs that block the activity of dopaminergic pathways include **older antipsychotics** (eg, chlorpromazine, haloperidol), which may cause parkinsonian symptoms.

- Drugs that increase brain dopaminergic activity include **CNS stimulants** (eg, amphetamine), and commonly used **anti parkinsonism drugs** (eg, levodopa)

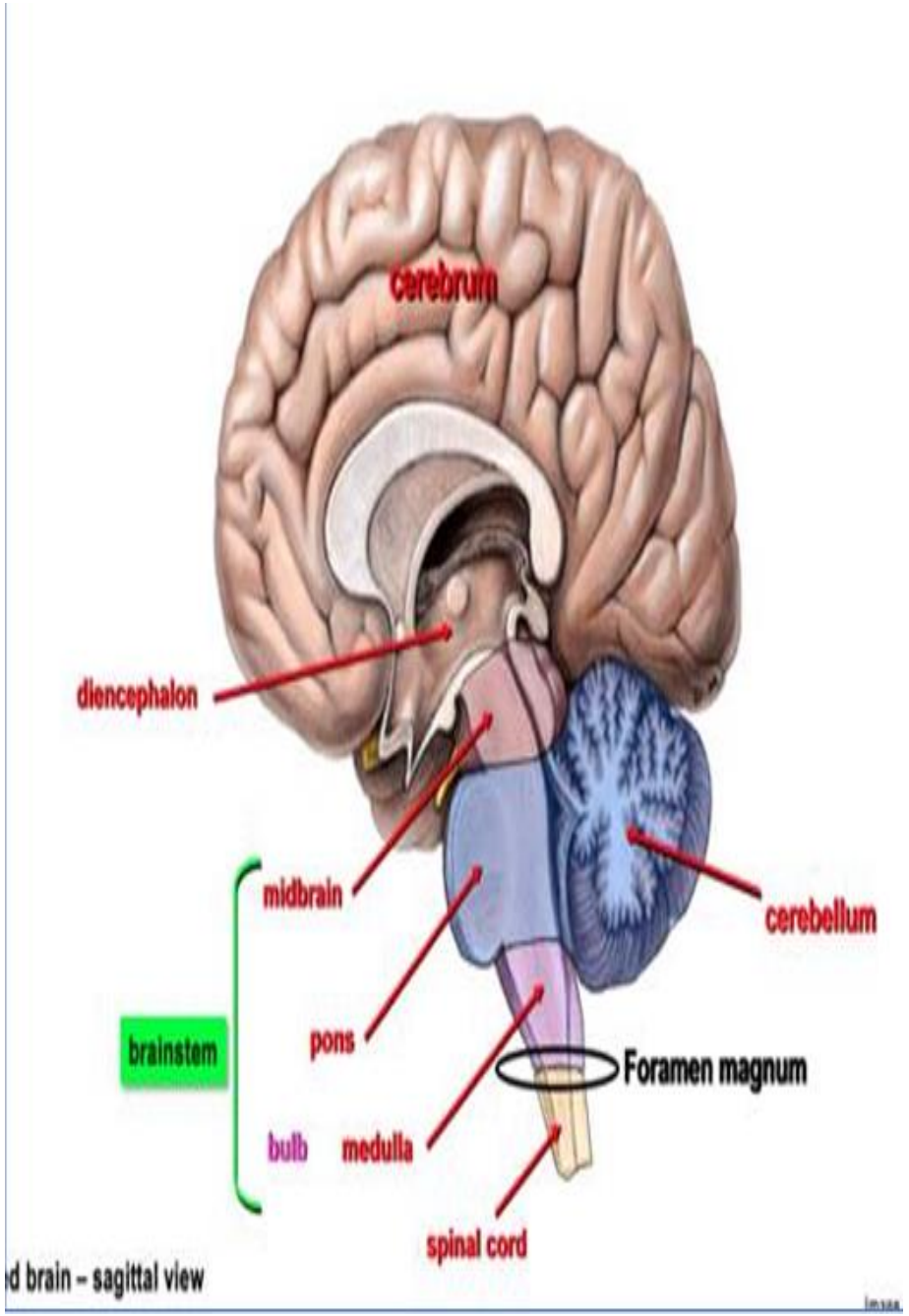
- **Norepinephrine:**

- Noradrenergic neuron cell bodies are mainly located in the **brain stem and the lateral tegmental area of the pons**.

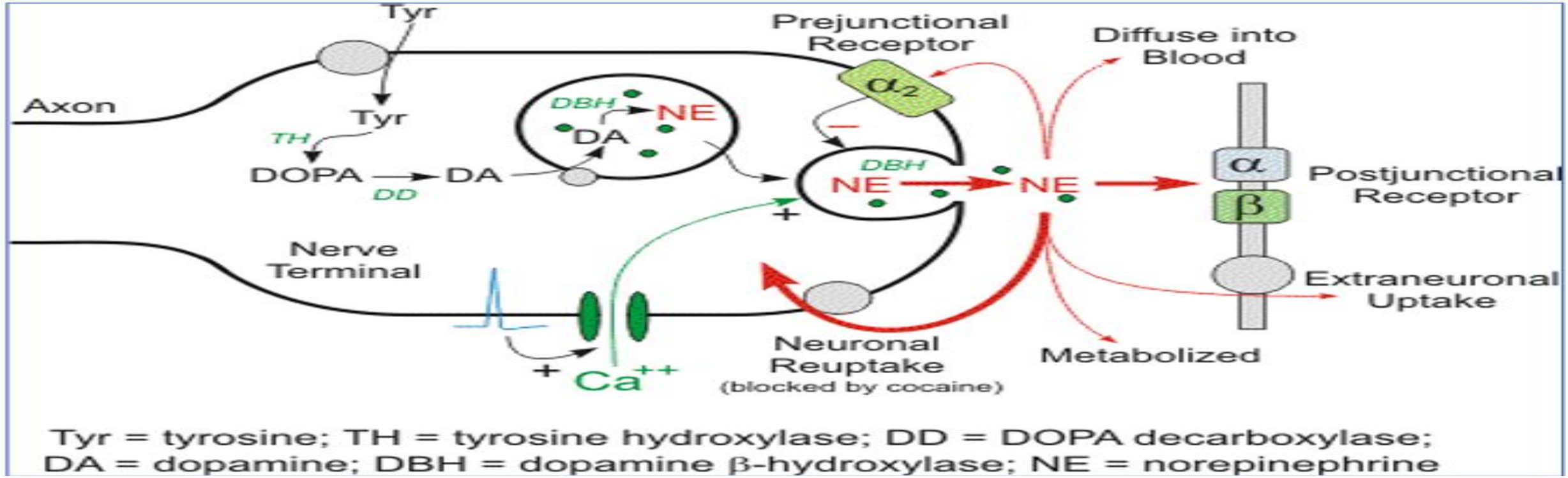
- These neurons fan out broadly to provide most regions of the CNS with diffuse noradrenergic input.

- **Excitatory effects** are produced by the activation of α1 and β1 receptors.

- **Inhibitory effects** are caused by activation of α2 and β2 receptors.



- **Norepinephrine:**
- • Drugs that **enhance** the activity of noradrenergic pathways like:
- 1. CNS stimulants such as amphetamines & cocaine.
- 2. Monoamine oxidase inhibitors MOI like phenelzine.
- 3. Tricyclic antidepressants TCA like amitriptyline



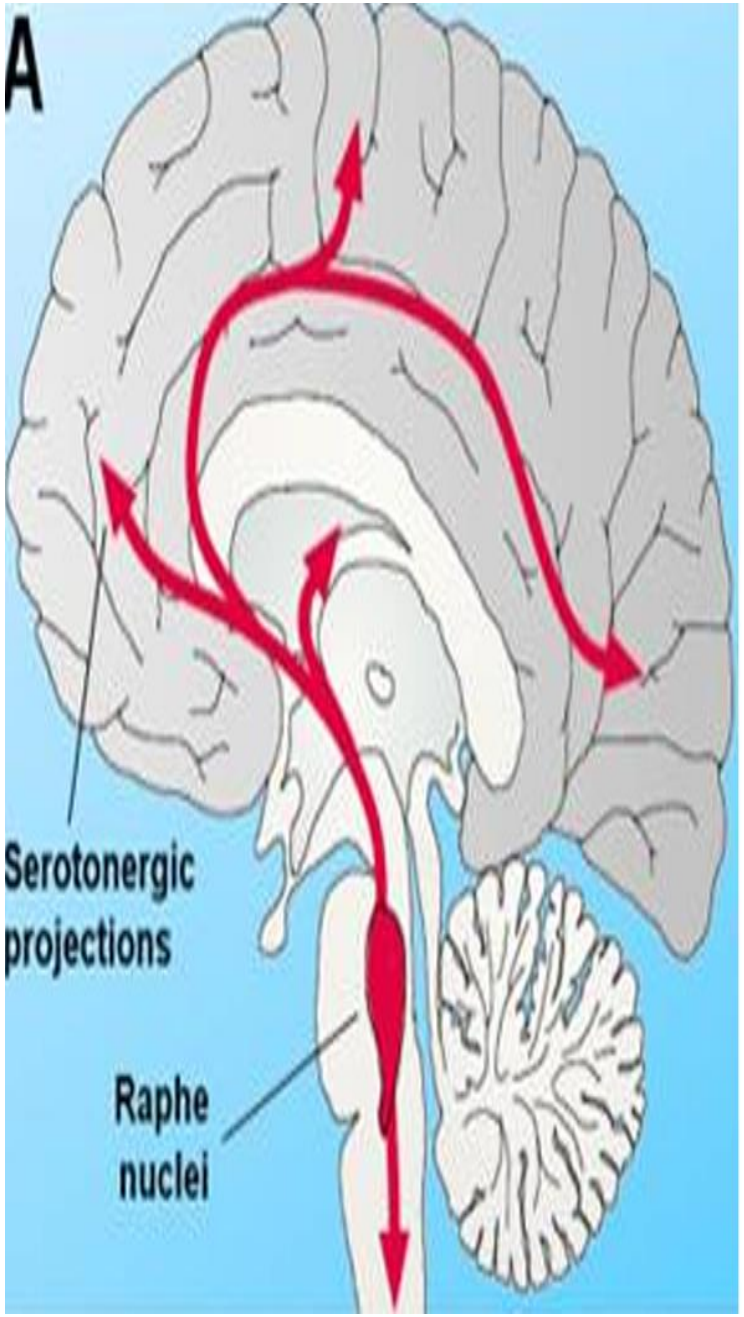
Serotonin:

- Most serotonin (5- Hydroxytryptamine 5-HT) pathways originate from cell bodies in the raphe or midline regions of the pons and upper brain stem; these pathways innervate most regions of the CNS.

- Multiple 5-HT receptor subtypes have been identified and, with the exception of the **5 HT3** subtype, all are **metabotropic**.

- **5-HT1A** receptors and **GABAB** receptors share the same potassium channel.

- Serotonin can cause **excitation or inhibition** of CNS neurons depending on the receptor subtype activated.

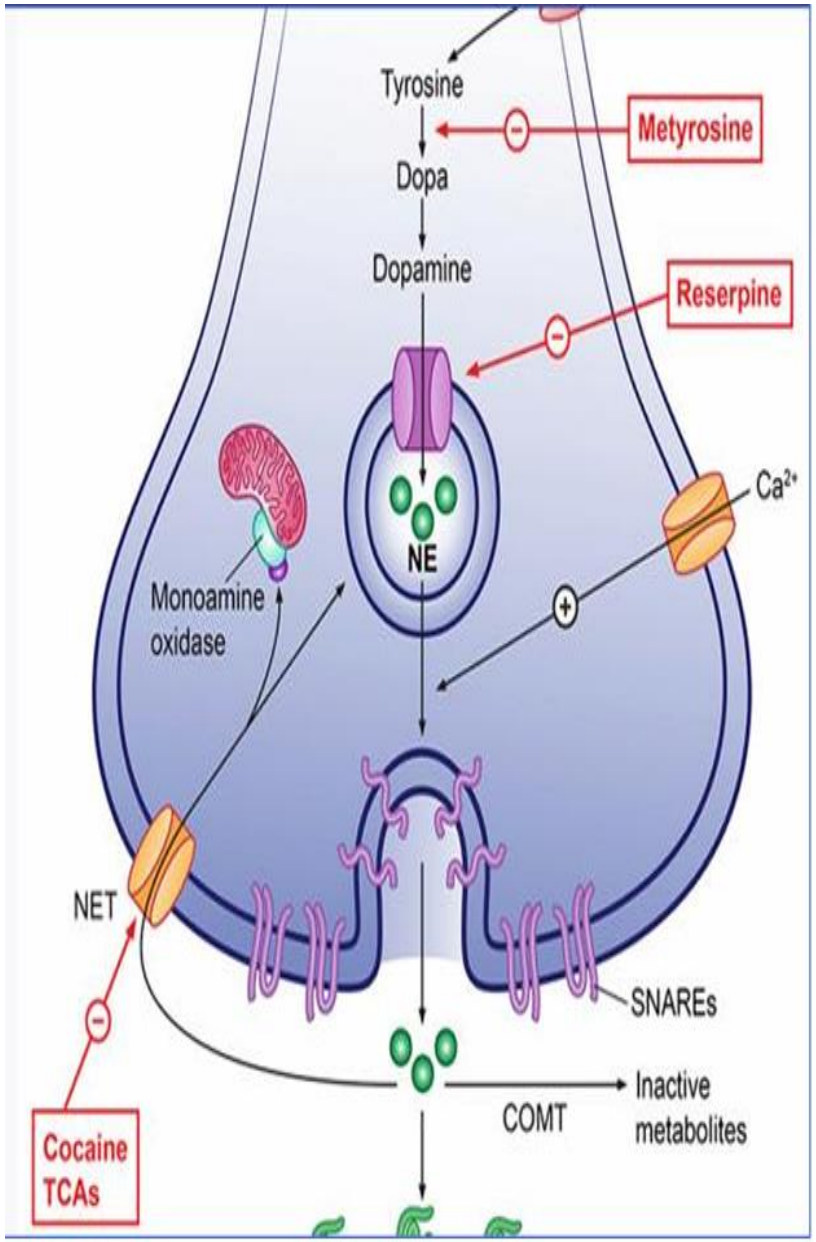


- **Serotonin:**

- Most of the agents used in the treatment of **major depressive disorders** affect serotonergic pathways (eg, tricyclic antidepressants, selective serotonin reuptake inhibitors).

- The actions of some CNS stimulants and newer antipsychotic drugs (eg, **olanzapine**) also appear to be mediated via effects on serotonergic transmission.

- **Reserpine**, which may cause severe depression of mood, depletes vesicular stores of both serotonin, norepinephrine in CNS neurons.



- **Glutamic Acid:**

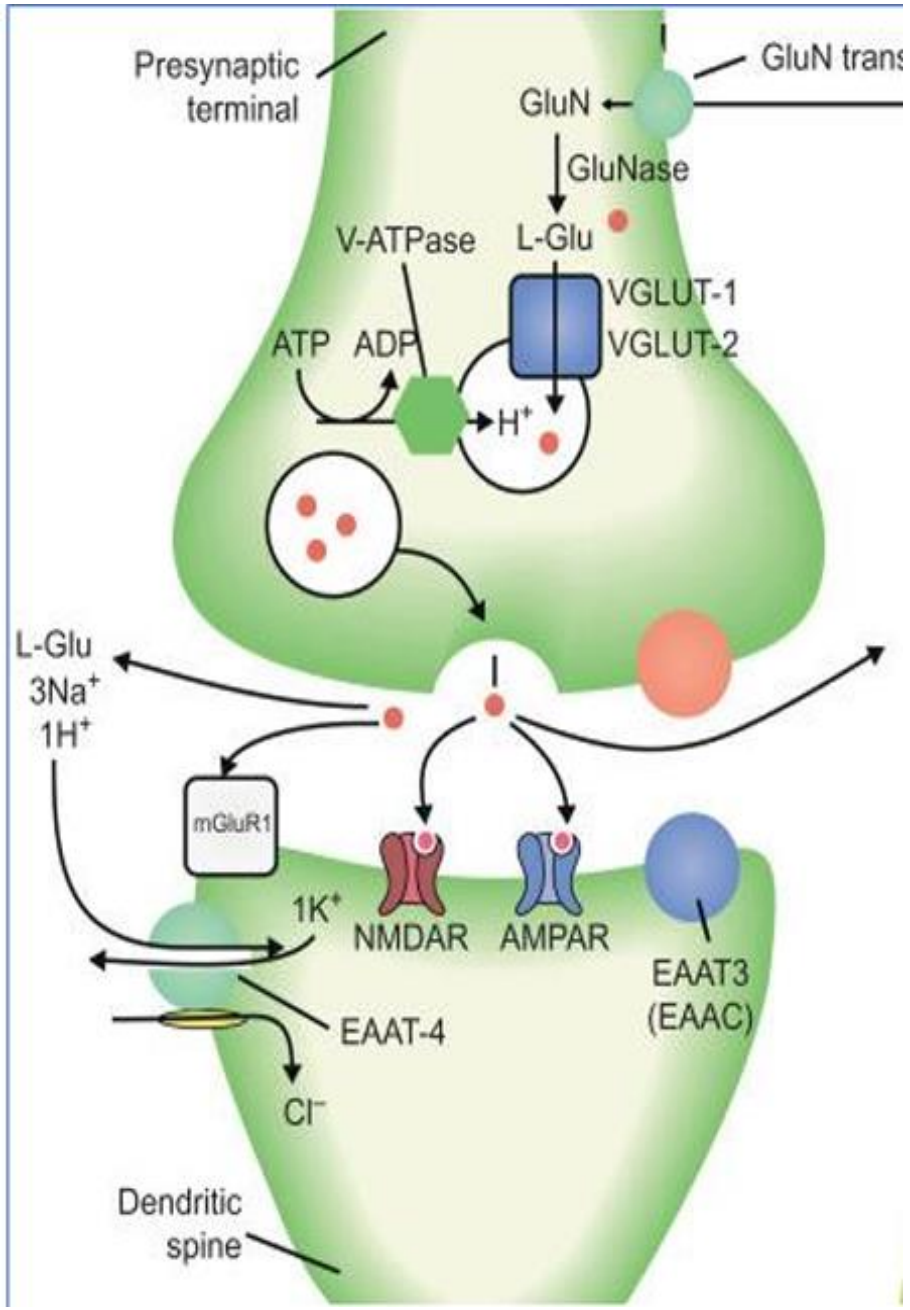
- Most neurons in the brain are **excited** by glutamic acid.

- High concentrations of glutamic acid in synaptic vesicles is achieved by the vesicular glutamate transporter (VGLUT).

- Both **ionotropic** and **metabotropic** receptors have been characterized.

- Subtypes of glutamate receptors include the **N methyl-D-aspartate (NMDA)** receptor, which is blocked by **phencyclidine (PCP)** and **ketamine**.

- **NMDA receptors** appear to play a role in synaptic plasticity related to **learning** and **memory**.

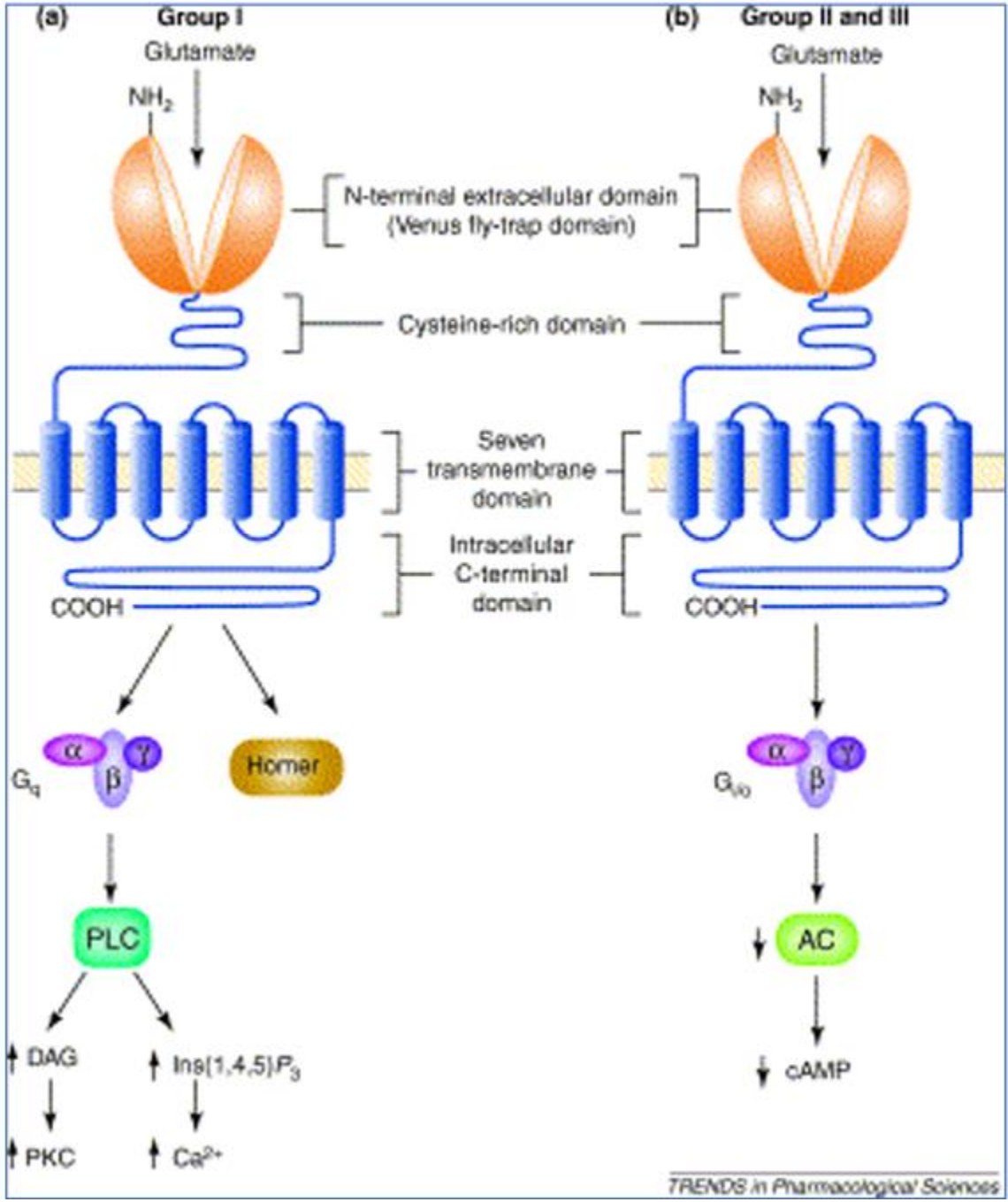


- **Glutamic Acid:**

- **Memantine** is an **NMDA antagonist** introduced for treatment of Alzheimer's dementia.

- Excessive activation of NMDA receptors after neuronal injury may be responsible for **cell death**.

- Glutamate **metabotropic** receptor activation can result in G protein-coupled **activation of phospholipase C** or **inhibition of adenylyl cyclase**.



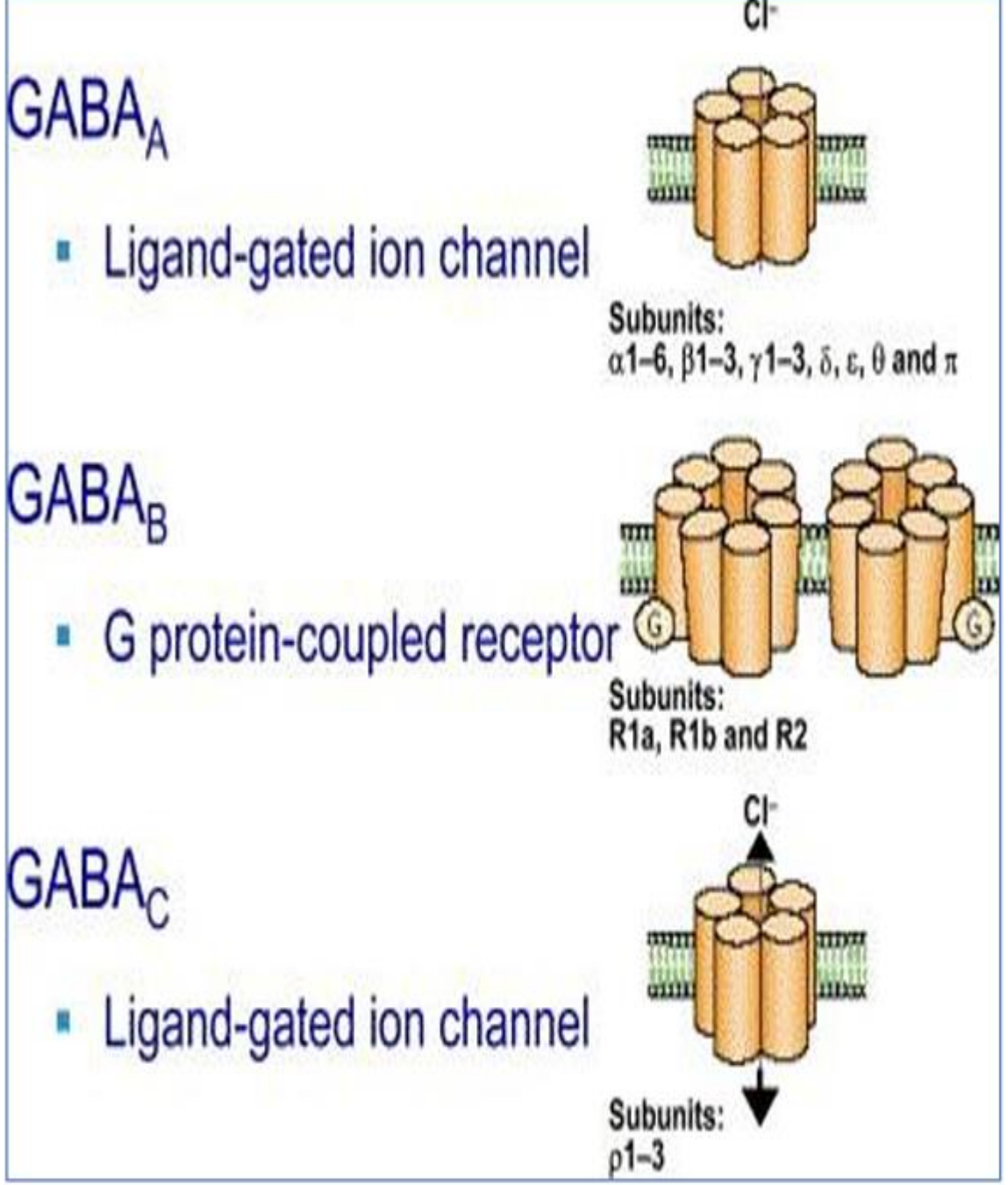
- **GABA and Glycine:**

- GABA is the primary neurotransmitter mediating **Inhibitory post synaptic potentials (IPSPs)** in neurons within CNS.

- **GABA-A** receptor activation **opens** chloride ion channels.

- **GABA-B** receptors (activated by baclofen, a centrally acting muscle relaxant) are coupled to G proteins that either open potassium channels or close calcium channels.

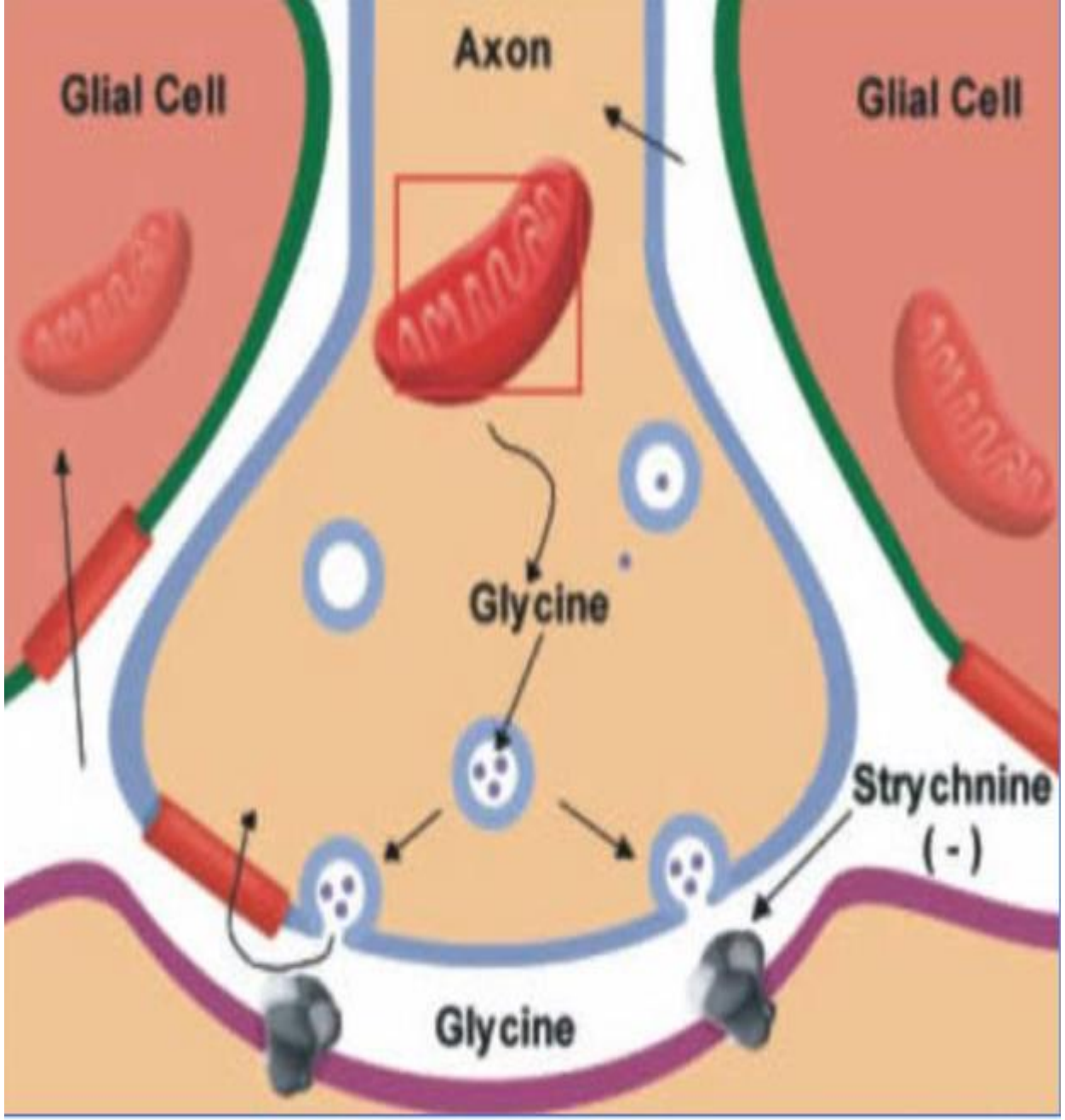
- **Fast IPSPs** are blocked by GABA-A receptor antagonists, and **slow IPSPs** are blocked by GABA-B receptor antagonists.



- **GABA and Glycine:**

- Drugs that influence GABA-A receptor systems include **sedative-hypnotics** (eg, barbiturates, benzodiazepines, zolpidem) and some **anticonvulsants** (eg,gabapentin, tiagabine, vigabatrin).

- **Glycine** receptors, which are more numerous in the cord than in the brain, are blocked by **strychnine**, a spinal convulsant



- **Peptide Transmitters:**

- The best-defined peptides are the **opioid peptides** (beta endorphin, met- and leu-enkephalin, and dynorphin)

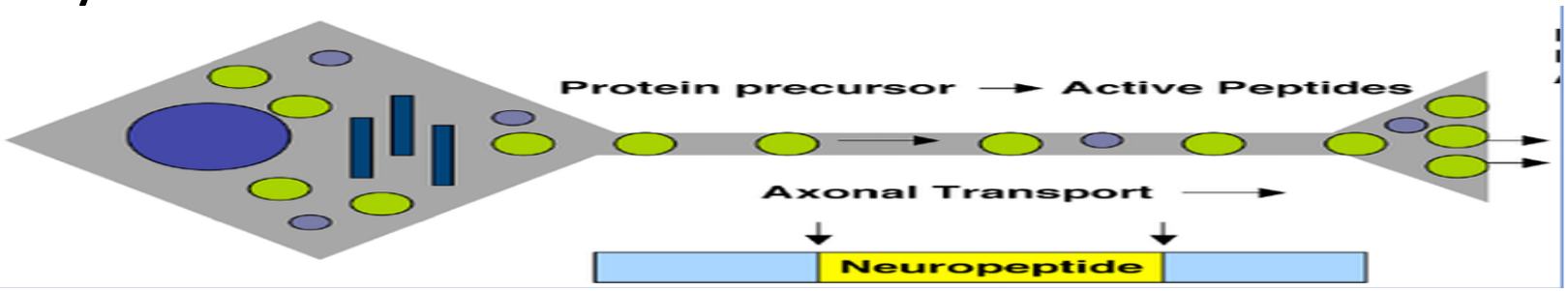
- Some of the important therapeutic actions of opioid analgesics (eg, **morphine**) are mediated via the activation of receptors for these endogenous peptides.

- Another peptide **substance P** is a mediator of slow Excitatory post synaptic potential (EPSPs) in neurons involved in nociceptive sensory pathways in the spinal cord and brain stem.

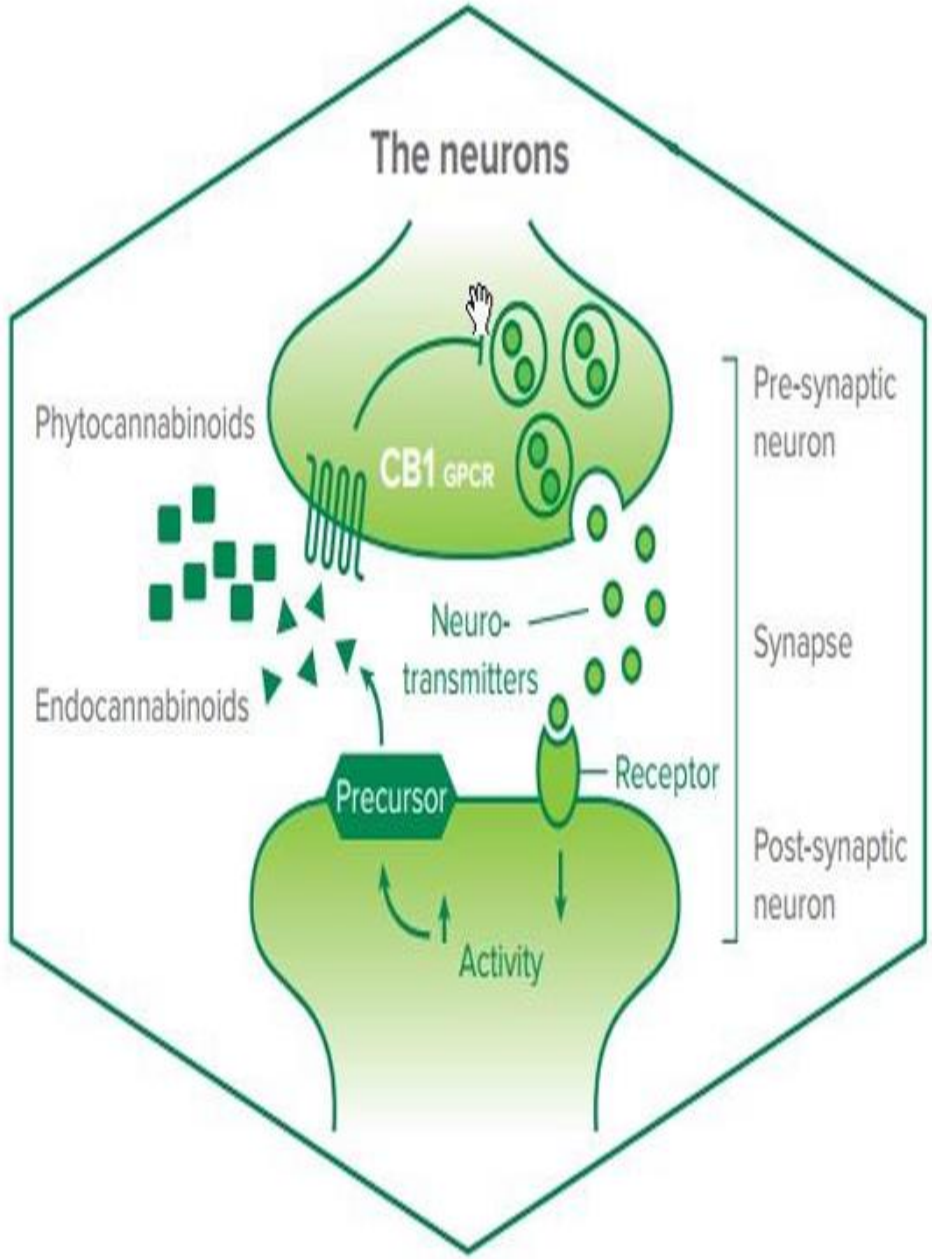
- **Peptide transmitters differ from nonpeptide transmitters in that**

➢1. They are synthesized in the cell body and transported to the nerve ending via axonal transport

➢2. No reuptake or specific enzyme mechanisms have been identified for terminating their actions.



- **Endocannabinoids:**
- •These are widely distributed brain lipid derivatives (eg, 2- arachidonyl glycerol) that bind to receptors for cannabinoids found in marijuana.
- •They are **synthesized and released** post synaptically after membrane depolarization but travel backward acting pre synaptically (**retrograde**) to decrease transmitter release, via their interaction with a specific **cannabinoid receptor CB1**



- **Peptide Transmitters**

- Many peptides have been identified in the CNS, and some meet most or all of the criteria for acceptance as neurotransmitters.

➢ The best-defined peptides are the **opioid peptides** (B-endorpbin, met- and leu-enkephalin, and dynorphin), which are distributed at all levels of the neuraxis.

➢ Some of the important therapeutic actions of opioid analgesics (eg, **morphine**) are mediated via activation of receptors for these endogenous peptides.

- Another peptide, **substance P,** is a mediator of slow EPSPs in neurons involved in nociceptive sensory pathways in the spinal cord and brain stem.
- **Orexins** are peptides associated with the sleep-wake cycle and promote wakefulness.
- Peptide transmitters differ from nonpeptide transmitters in that

➢ (1) the peptides are synthesized in the cell body and transported to the nerve ending via axonal transport, and

➢(2) no reuptake or specific enzyme mechanisms have been identified for terminating their actions.

- Other Transmitters **Histamine receptors** are widely distributed in the brain and appear to modulate **arousal, appetite, and memory**.
- Centrally acting antihistamines have significant **sedative** and **anti motion sickness** effects