Al-Mustaqbal University
College of Pharmacy
4th stage
Pharmacology II
Lecture: 1

# Introduction to CNS Pharmacology

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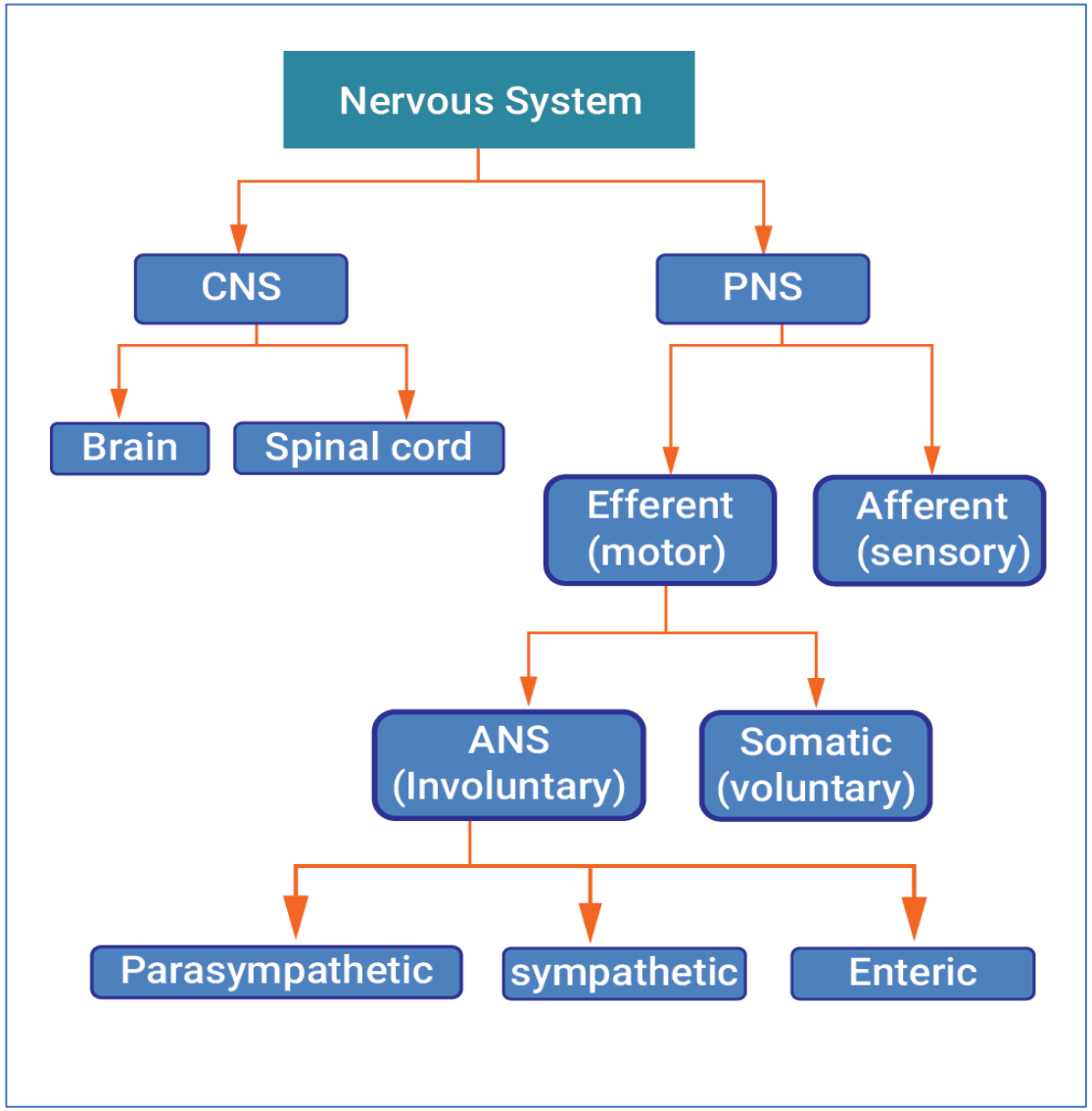
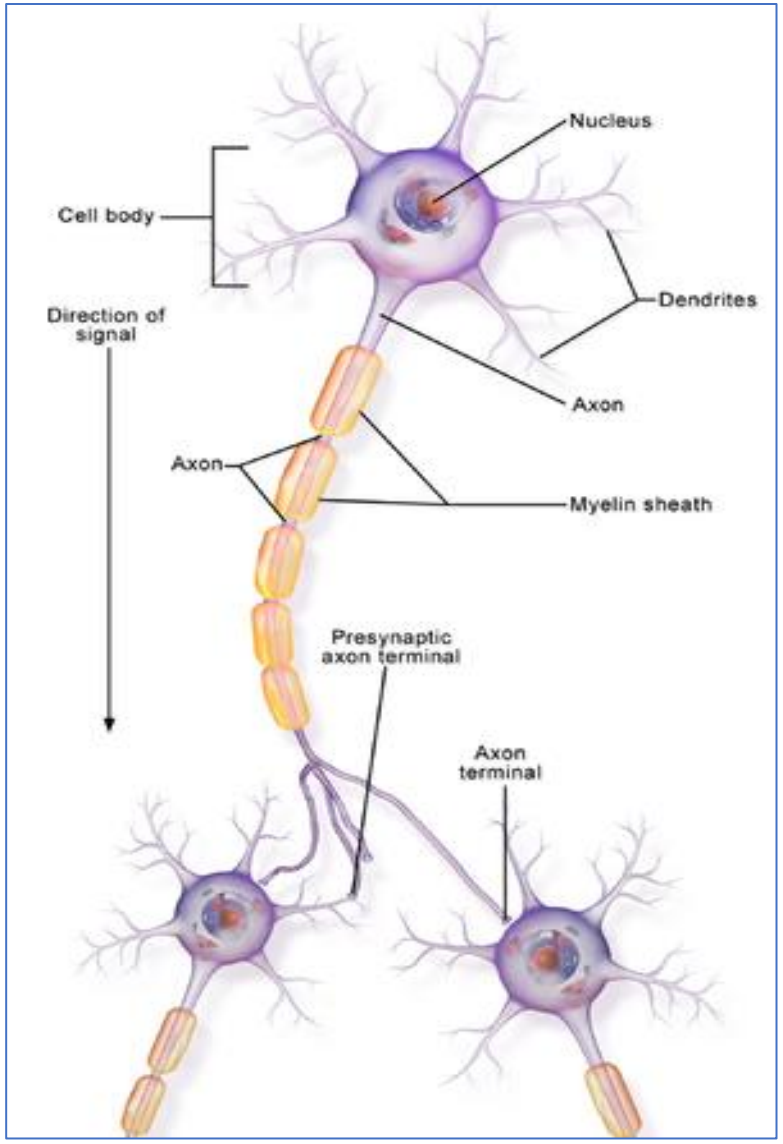
# Overview

- The nervous system **transmits** signals between the **brain** and the rest of the **body.**



# Overview

- 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**.



# TARGETS OF CNS DRUG ACTION

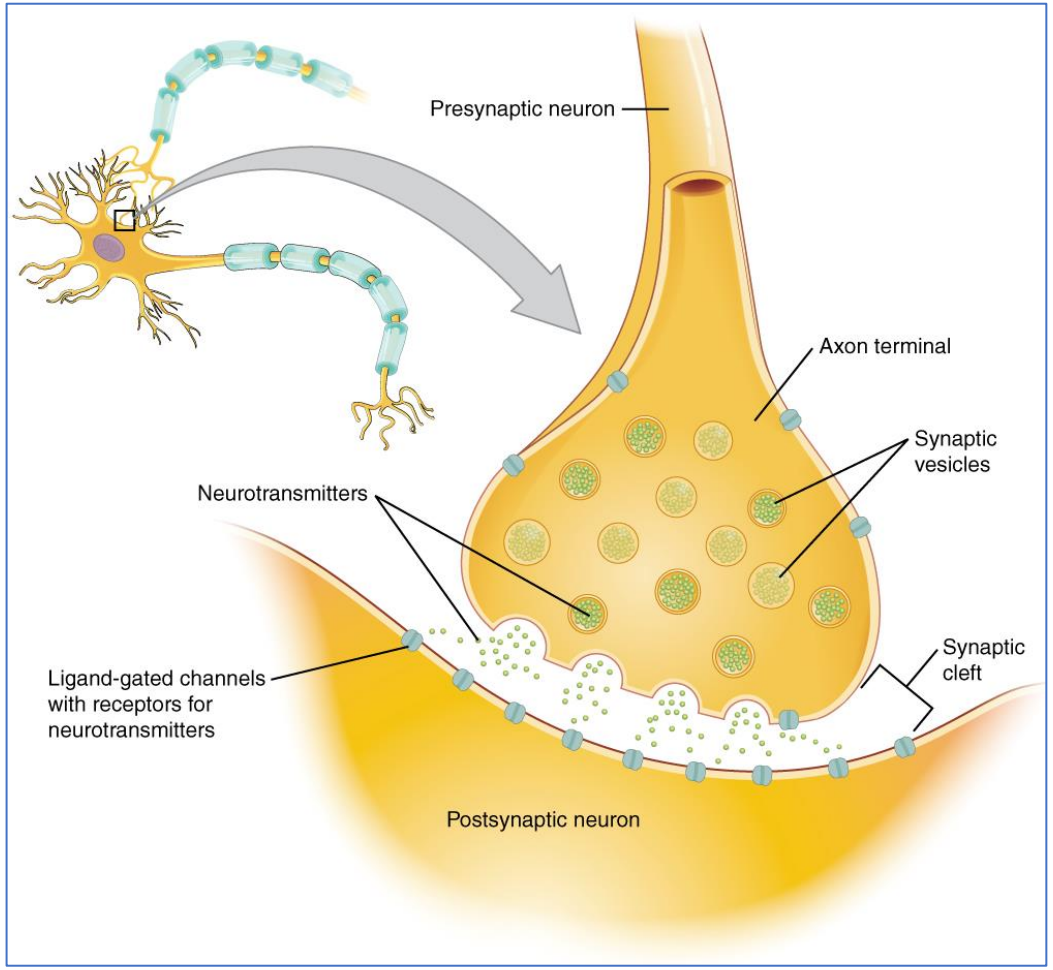
- Most drugs that act on the central nervous system (CNS) appear to do so **by changing ion flow** through transmembrane channels of nerve cells.

- CNS Drug Action depend on :

A. Types of **Ion Channels**

B. Types of **Receptor-Channel Coupling**

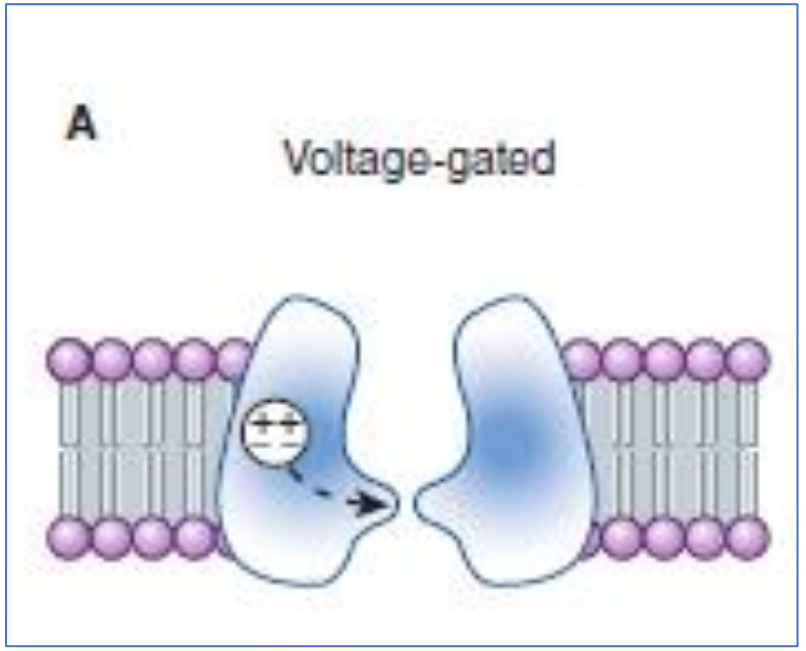
C. Role of the **Ion Current** Carried by the Channel



# A. Types of Ion Channels

**1. Voltage-gated ion channels:**

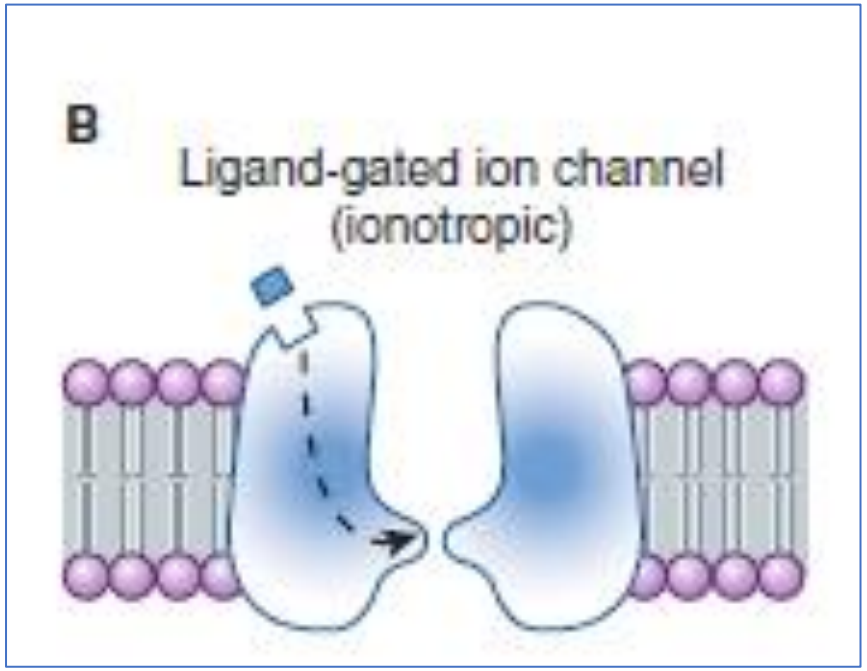
- These channels respond to **changes** in membrane **potential**.
- They are **concentrated** on the **axons** of nerve cells and include the **sodium channels** responsible for action potential propagation.
- **Cell bodies** and dendrites also have voltage-sensitive ion channels for **potassium and calcium**.



# A. Types of Ion Channels

## 2. Ligand-gated ion channels:

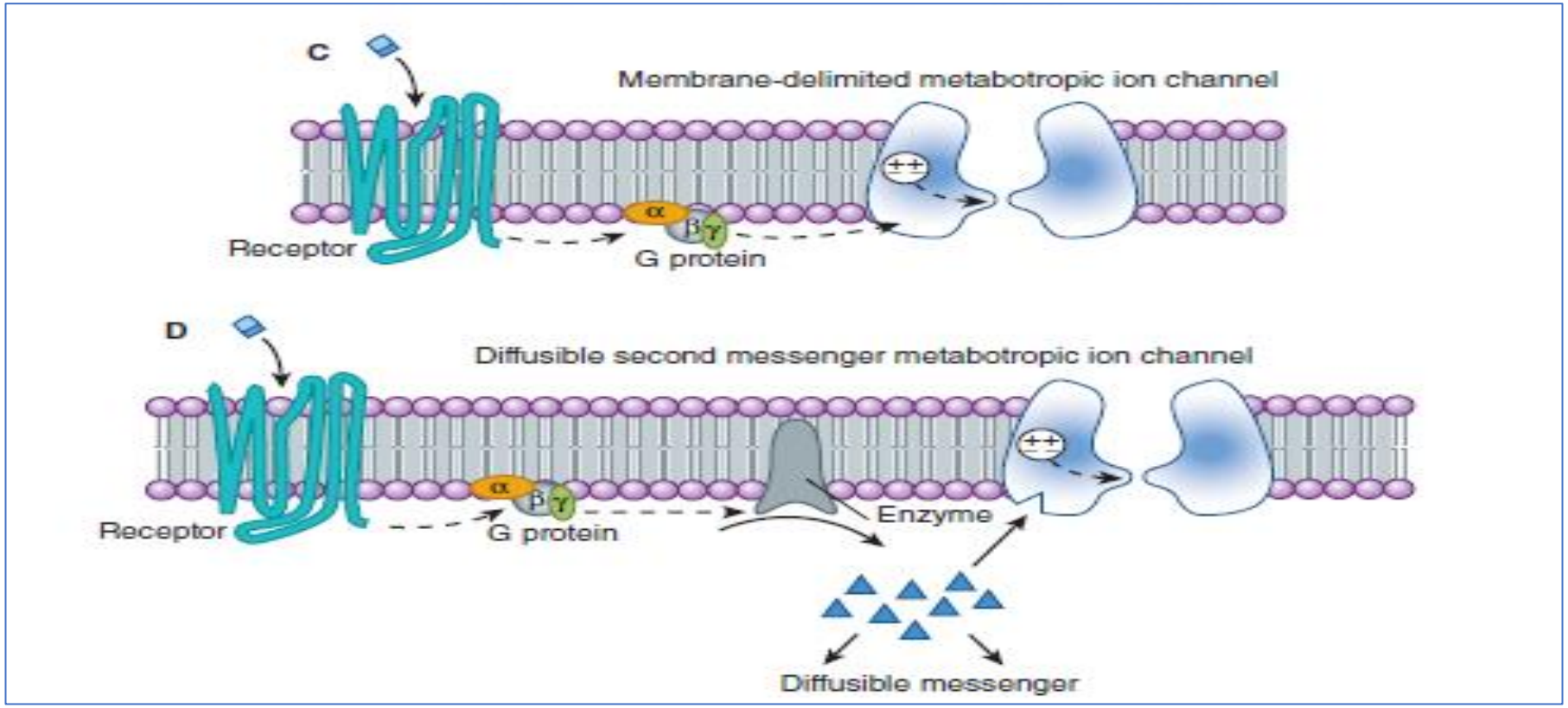
- also called **ionotropic** receptors, respond to chemical **neurotransmitters** that bind to **receptor** subunits present in their macromolecular structure.
- Neurotransmitter-coupled ion channels are found on **cell bodies** and on both the **presynaptic** and **postsynaptic** sides of synapses.



# A. Types of Ion Channels

## 2. Ligand-gated ion channels:

- Neurotransmitters also bind to **G protein-coupled** receptors (**metabotropic** receptors) that can **modulate** voltage-gated ion channels.

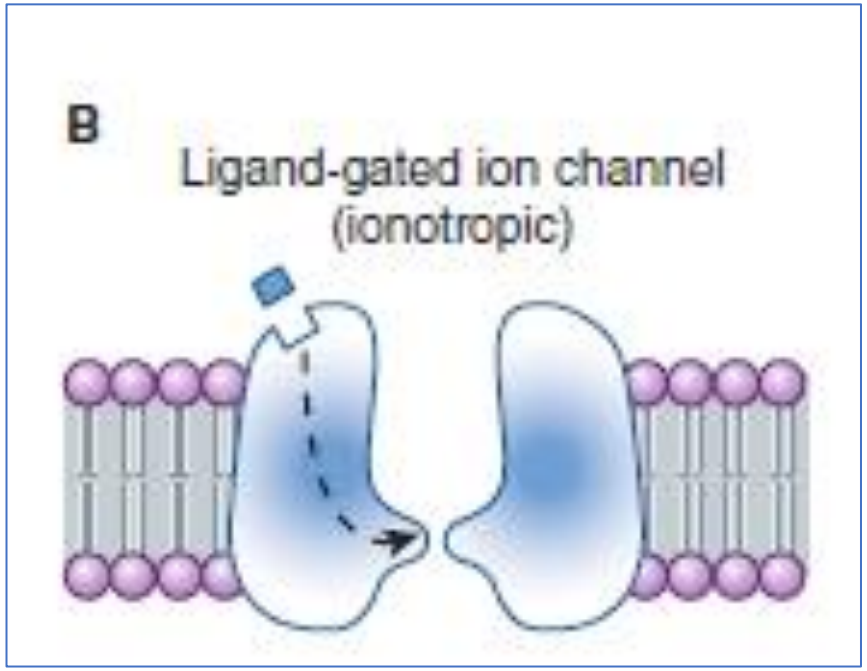


# B. Types of Receptor-Channel Coupling:

- In the case of ligand-gated ion channels, activation (or inactivation) is initiated by the interaction between chemical neurotransmitters and their receptors.

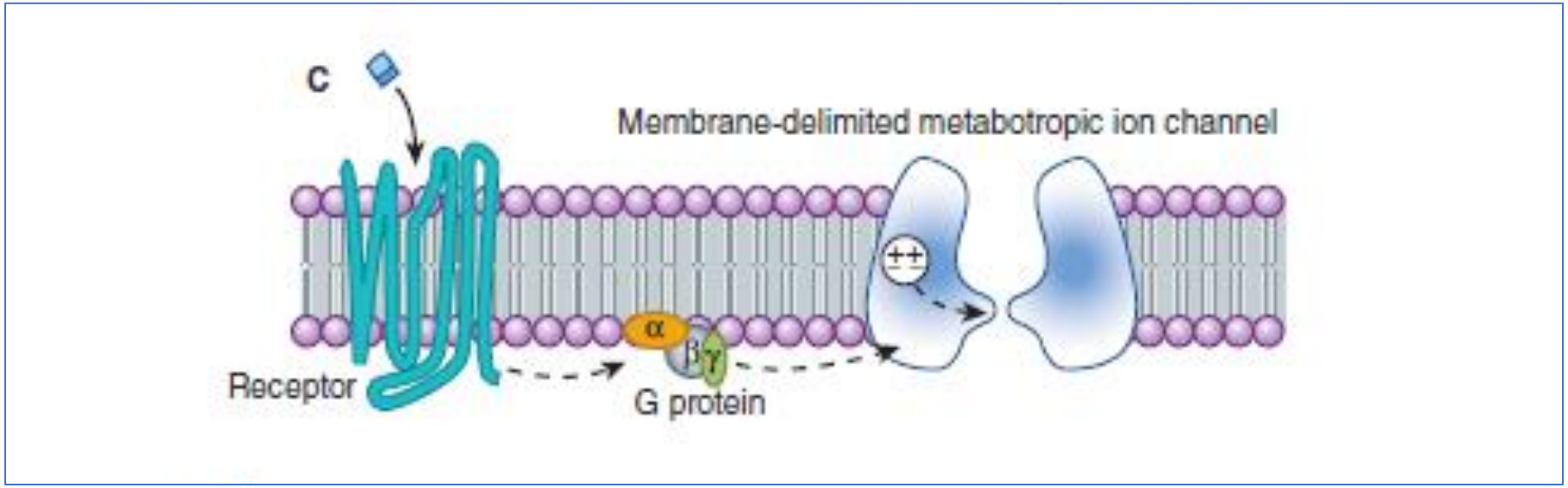
- **Coupling may be through a receptor :**

1. That acts **directly** on the channel protein (B)



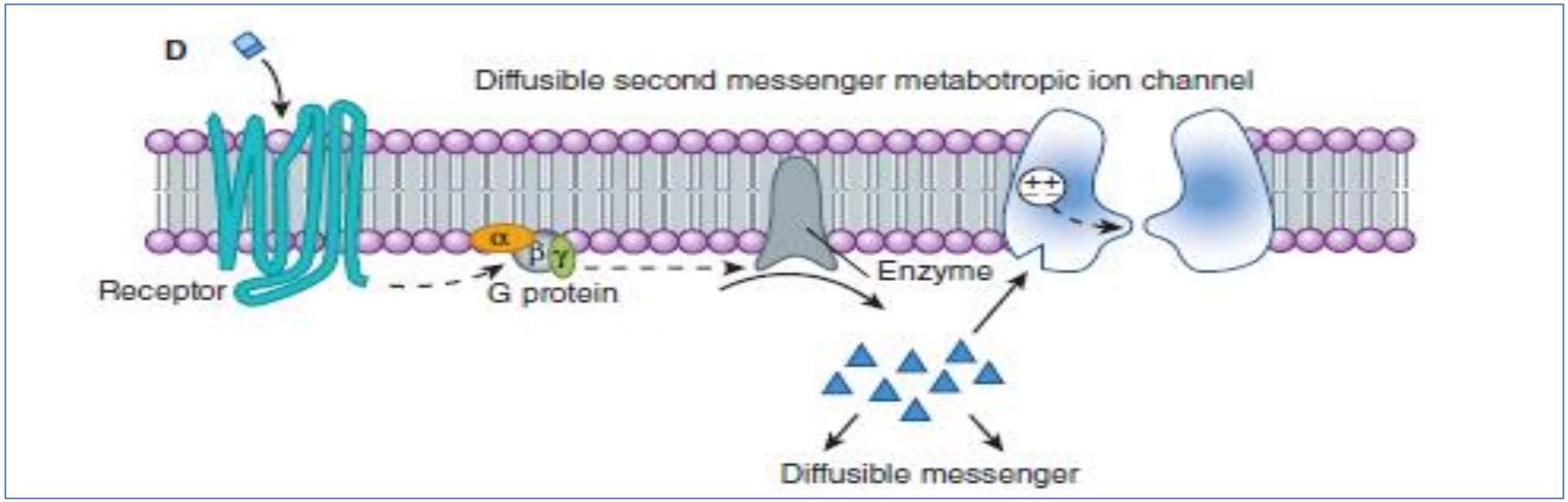
# B. Types of Receptor-Channel Coupling:

2. That is coupled to the ion channel through a **G protein** (C)



# B. Types of Receptor-Channel Coupling:

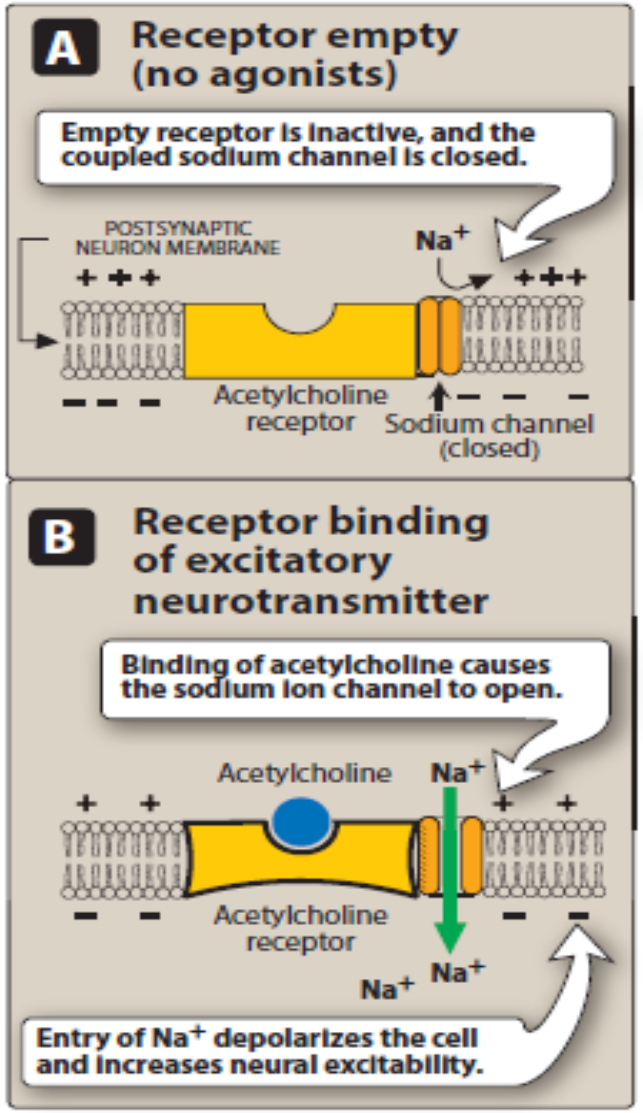
**3.** Coupled to a G protein that modulates the formation of **diffusible second messengers**, including cyclic adenosine monophosphate (cAMP), inositol trisphosphate (IP3), and diacylglycerol (DAG), which secondarily modulate ion channels (D)



# C. Role of the Ion Current Carried by the Channel

## 1. Excitatory postsynaptic potentials (EPSPs):

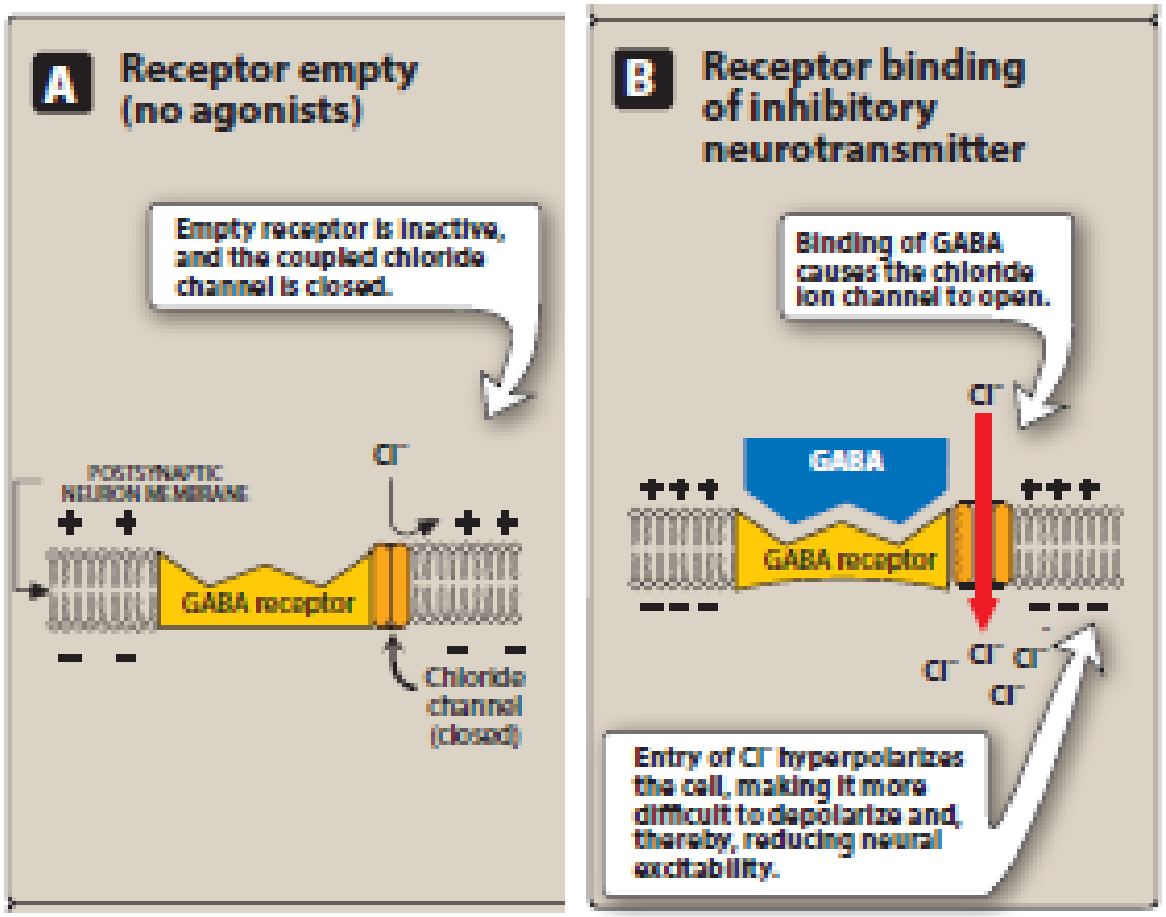
- These potentials are usually generated by the **opening** of **sodium** or **calcium** channels.
- In some synapses, similar depolarizing potentials result from the **closing** of **potassium** channels.



# C. Role of the Ion Current Carried by the Channel

**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.



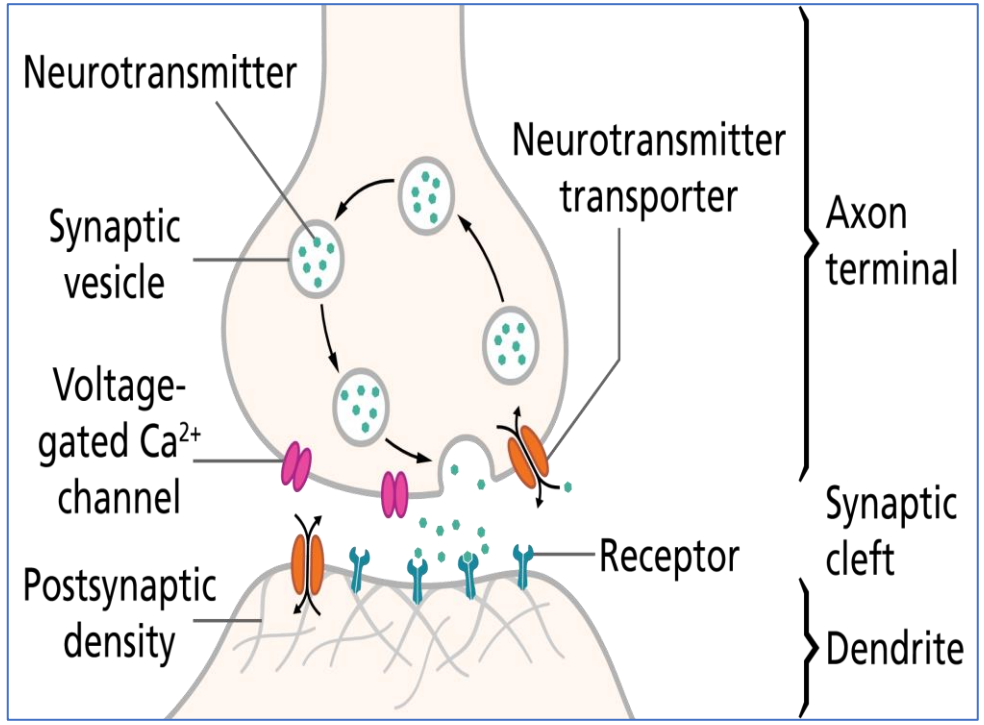
# SITES & MECHANISMS OF DRUG ACTION

- 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.

# SITES & MECHANISMS OF DRUG ACTION

- Other drugs can **activate** or **block** both **pre- and postsynaptic receptors** for **specific transmitters** or can interfere with the actions of **second messengers**.

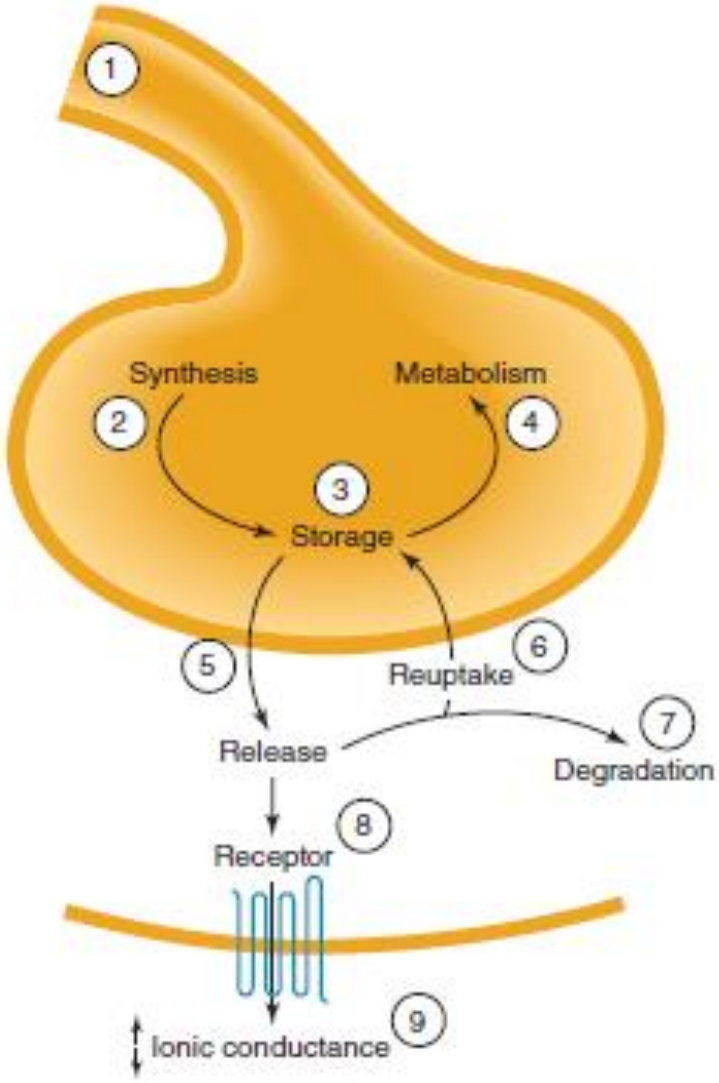
- The **selectivity** of CNS drug action is largely based on the fact that **different** groups of **neurons** use **different neurotransmitters** and that they are segregated into **networks** that subserve different CNS functions.



# SITES & MECHANISMS OF DRUG ACTION

**Sites of CNS drug action:** Drugs may alter:

1. The action potential in the presynaptic fibre
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.

# ROLE OF CNS ORGANIZATION

## 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:**

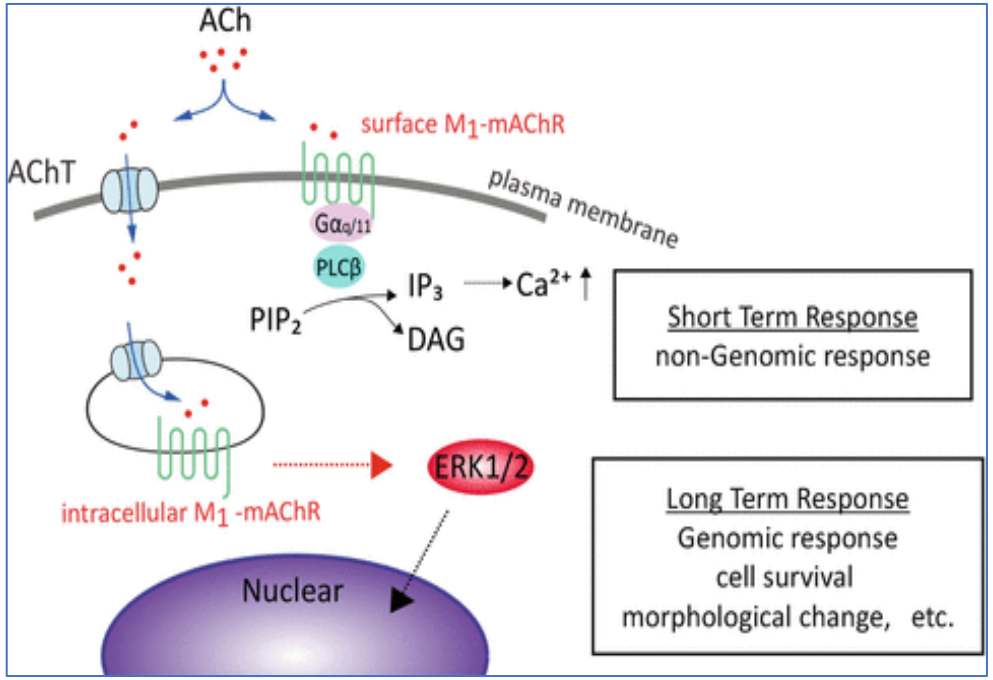
- To be **accepted** as a neurotransmitter, a candidate chemical **must**:

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**).

# TRANSMITTERS AT CENTRAL SYNAPSES

**Acetylcholine:**

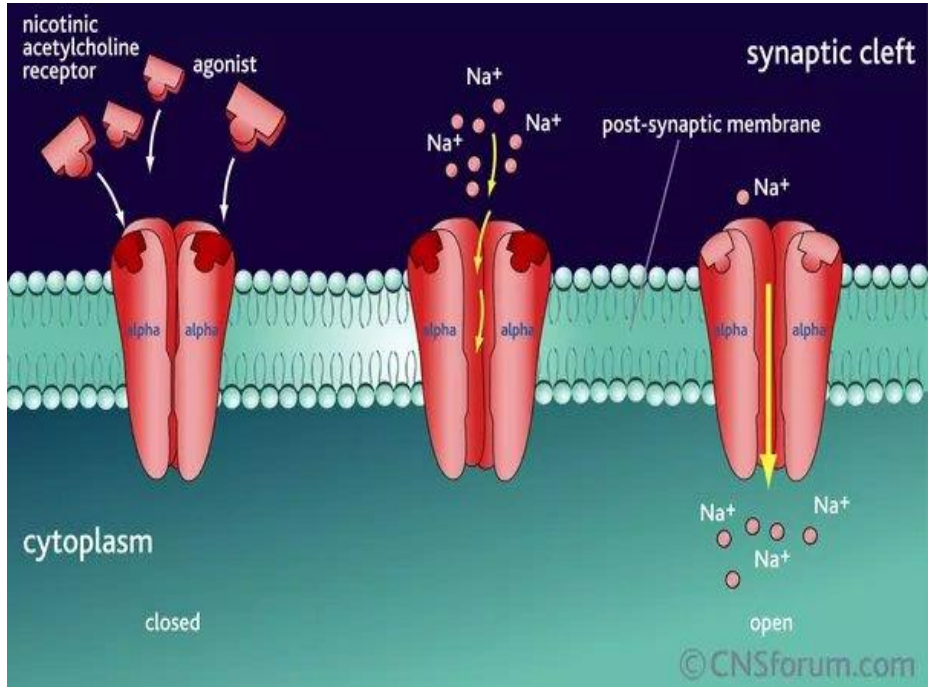
- Approximately **5%** of brain neurons have receptors for acetylcholine (ACh).
- Most CNS responses to ACh are mediated by a large family **of G protein-coupled muscarinic M1 receptors** that lead to slow **excitation** when activated.
- The ionic mechanism of slow excitation involves a **decrease in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



# TRANSMITTERS AT CENTRAL SYNAPSES

**Acetylcholine:**

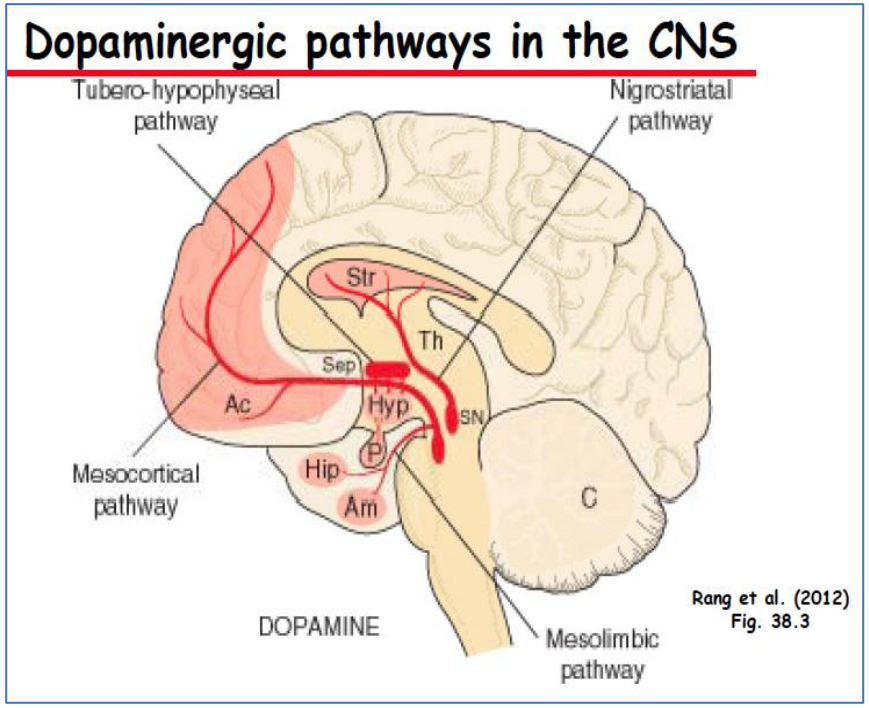
- Of the **nicotinic** receptors present in the CNS are **less common** than muscarinic receptors.
- **Drugs** affecting the activity of cholinergic systems in the brain include the **acetylcholinesterase inhibitors** used in Alzheimer's disease (eg, tacrine) and the **muscarinic blocking agents** used in parkinsonism (eg, benztropine).



# TRANSMITTERS AT CENTRAL SYNAPSES

**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 **tuberoinfundibular** tracts.



# TRANSMITTERS AT CENTRAL SYNAPSES

**Dopamine:**

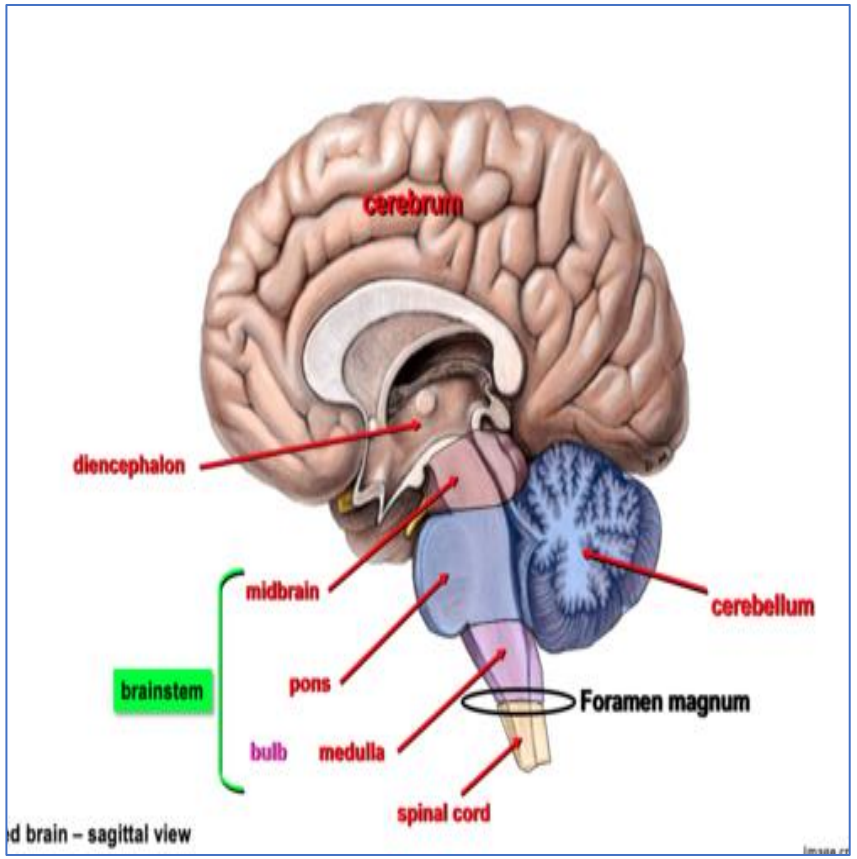
- **Drugs** that **block** the activity of dopaminergic pathways include older **antipsychotics** (eg, chlorpromazine, haloperidol), which may cause **parkinsonian** symptoms.


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

# TRANSMITTERS AT CENTRAL SYNAPSES

**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.

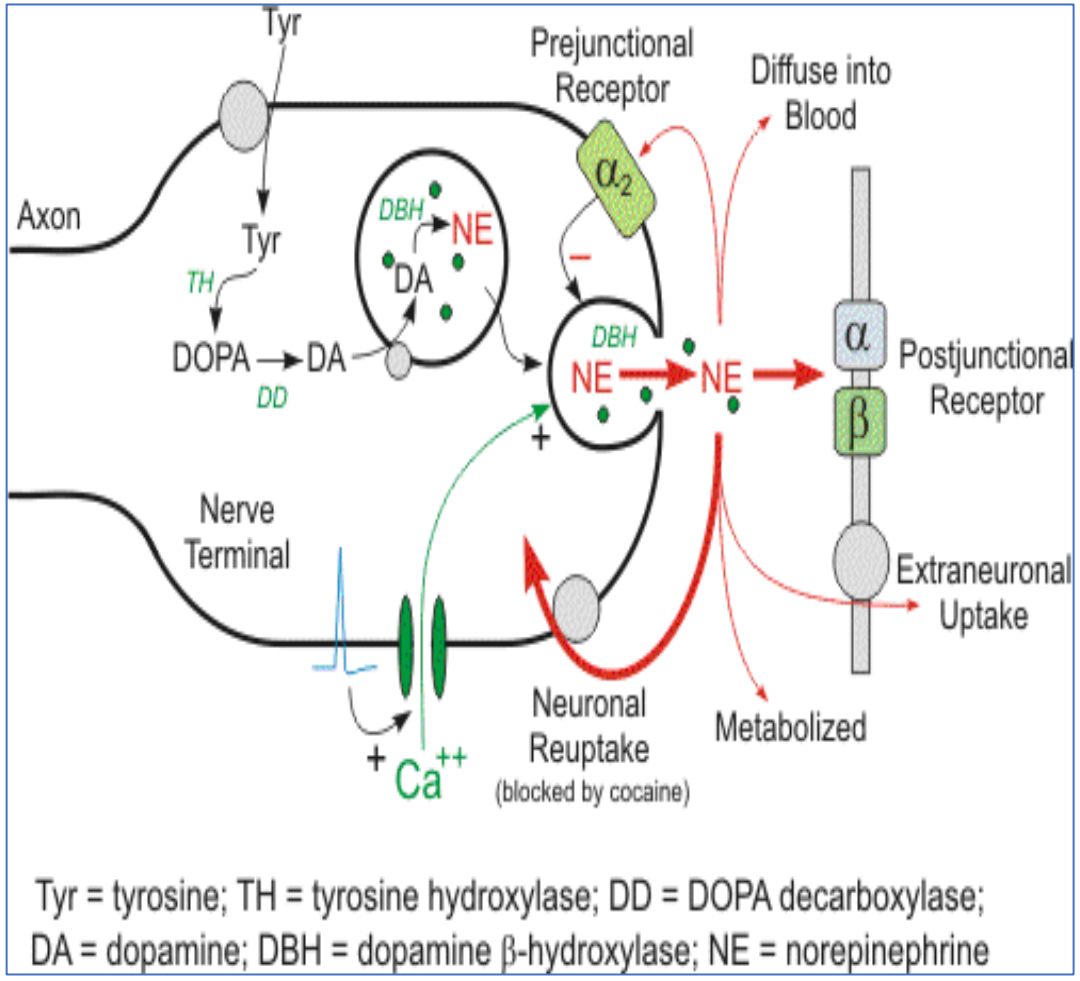


# TRANSMITTERS AT CENTRAL SYNAPSES

**Norepinephrine:**

- Drugs that **enhance** the activity of noradrenergic pathways like:

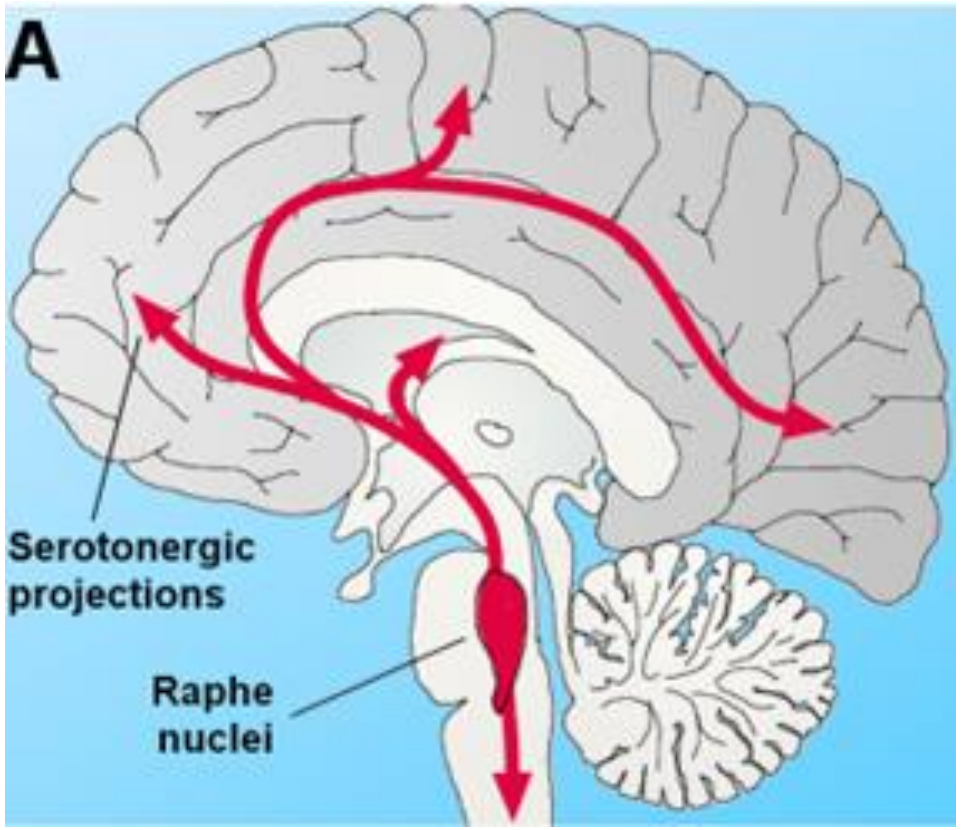
1. **CNS stimulants** such as amphetamines & cocaine.
2. **Monoamine oxidase inhibitors** like phenelzine.
3. **Tricyclic antidepressants** like amitriptyline



# TRANSMITTERS AT CENTRAL SYNAPSES

**Serotonin:**

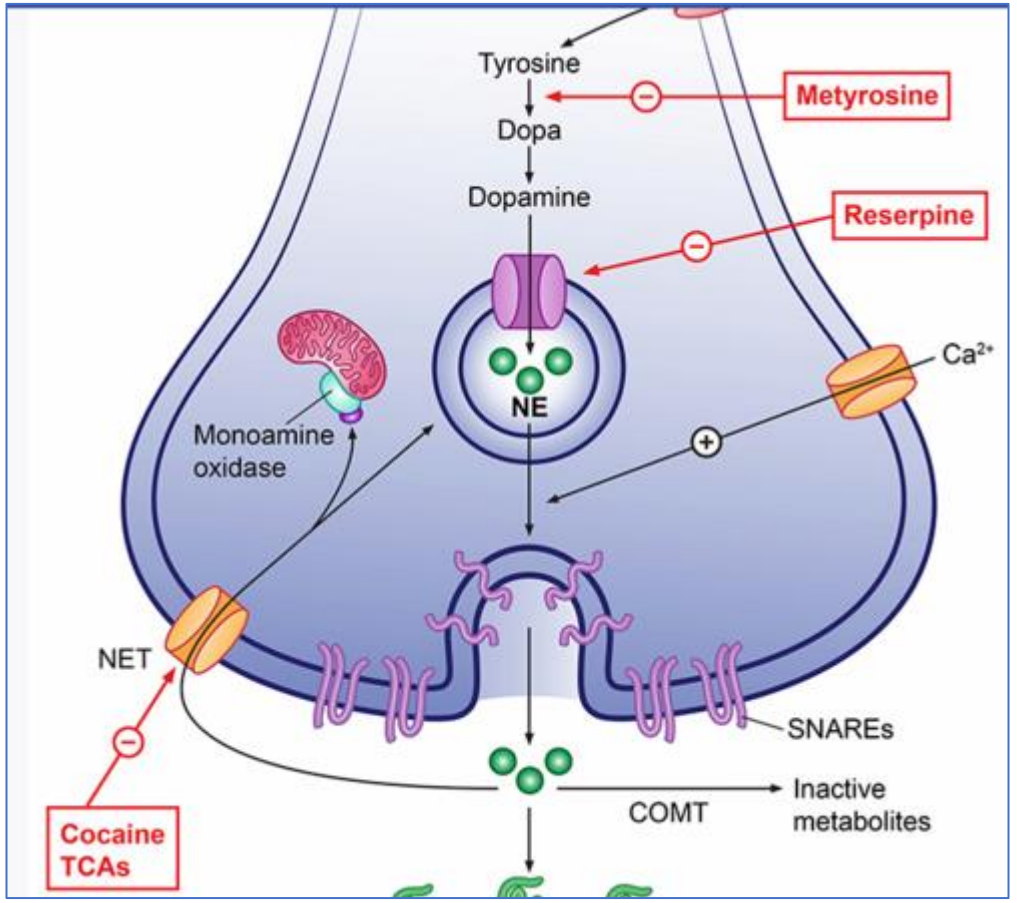
- Most serotonin (5-HT) pathways originate from cell bodies in the **raphe or midline regions** of the **pons** and **upper brain stem**; these pathways innervate most regions of the CNS.
- **Multiple** 5-HT receptor subtypes have been identified and, with the **exception of the 5-HT3** subtype, all 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.



# TRANSMITTERS AT CENTRAL SYNAPSES

**Serotonin:**

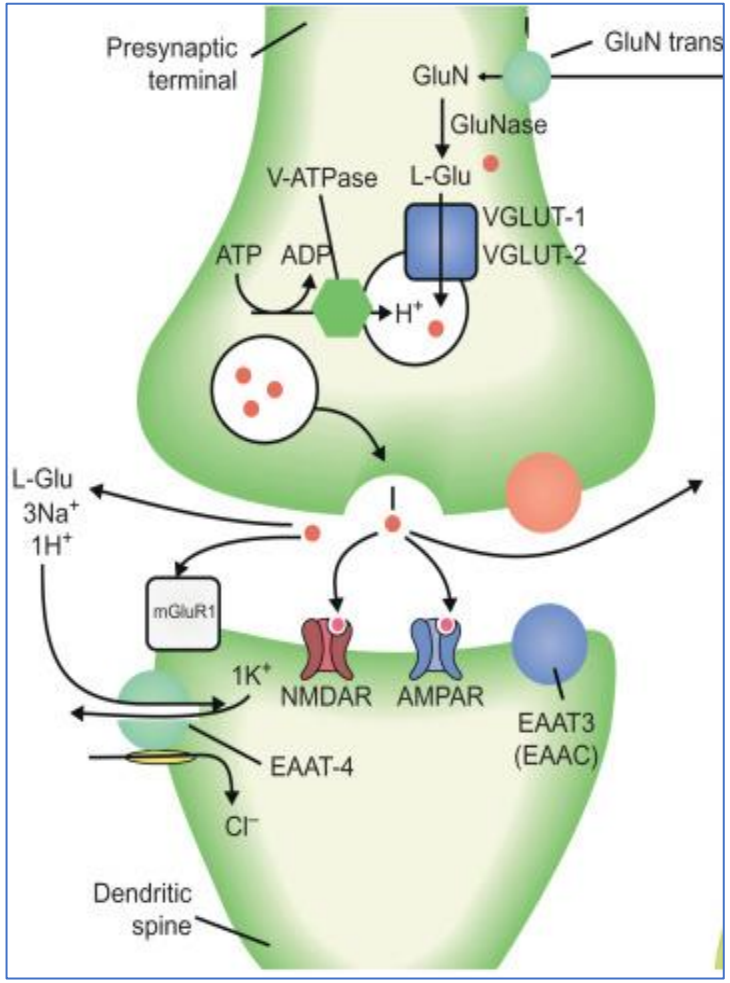
- Most of the agents used in the treatment of **major depressive disorders** affect serotonergic pathways (eg, tricyclic antidepressants, selective serotonin reuptake inhibitors).
- The actions of some **CNS stimulants** and **newer antipsychotic** drugs (eg, olanzapine) also appear to be mediated via effects on **serotonergic** transmission.
- **Reserpine**, which may cause **severe depression** of mood, depletes vesicular **stores** of both serotonin and norepinephrine in CNS neurons.



# TRANSMITTERS AT CENTRAL SYNAPSES

## Glutamic Acid:

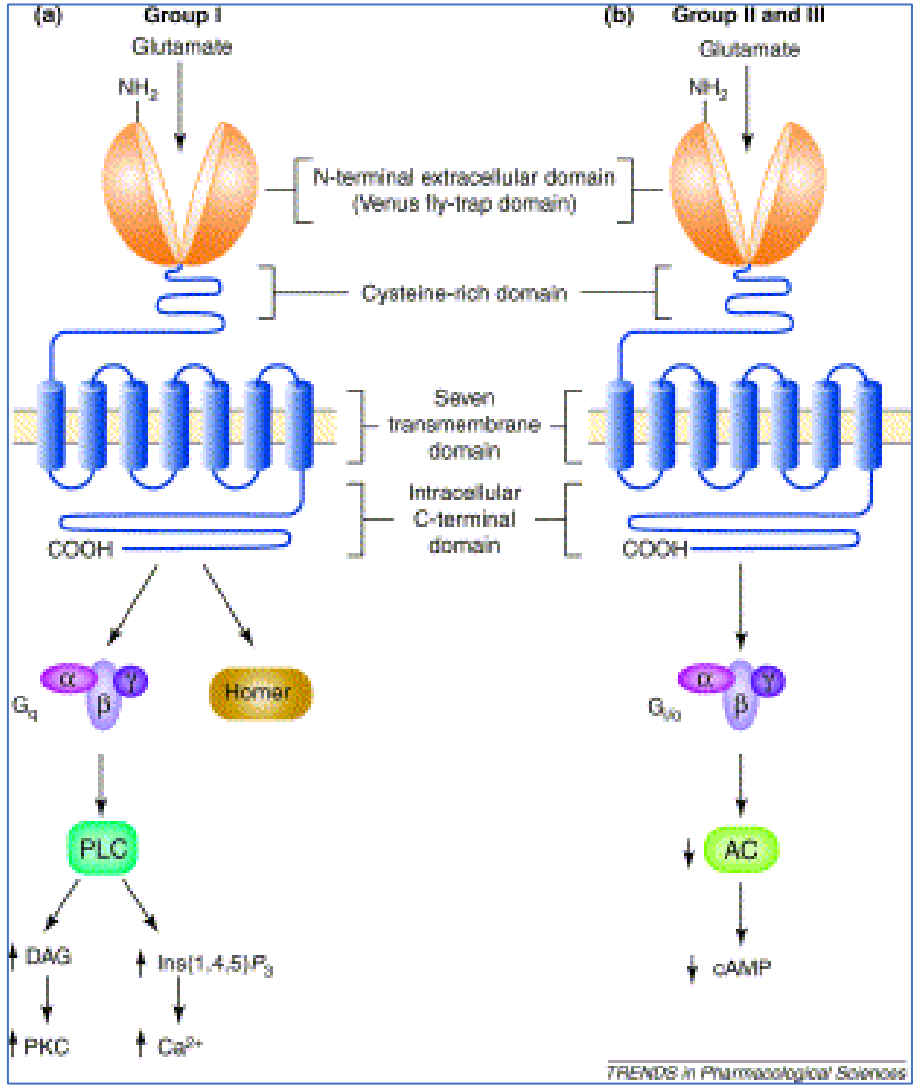
- Most neurons in the brain are **excited by glutamic acid**.
- **High** concentrations of glutamic acid in synaptic vesicles is achieved by the vesicular glutamate transporter (**VGLUT**).
- Both **ionotropic** and **metabotropic** receptors have been characterized.
- Subtypes of glutamate receptors 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**.



# TRANSMITTERS AT CENTRAL SYNAPSES

## Glutamic Acid:

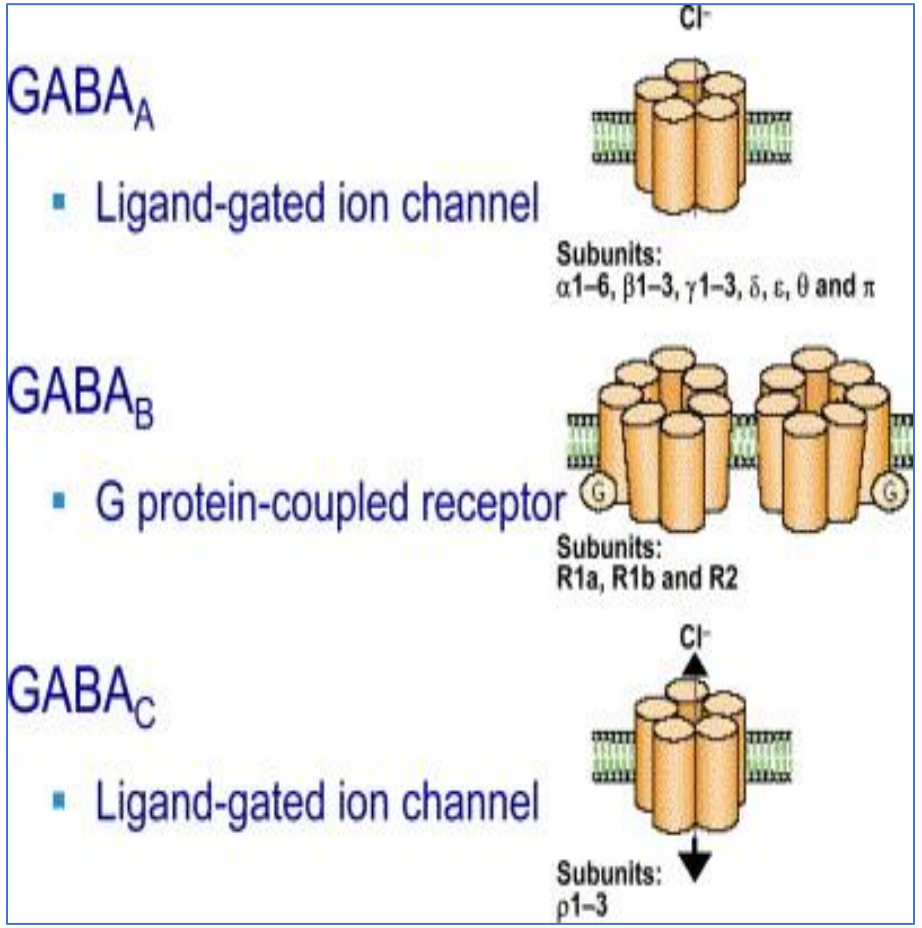
- **Memantine** is an **NMDA antagonist** introduced for treatment of **Alzheimer's dementia**.
- **Excessive activation of NMDA** receptors after neuronal injury may be responsible for **cell death**.
- Glutamate metabotropic receptor activation can result in G protein-coupled **activation** of **phospholipase C** or **inhibition** of **adenylyl cyclase.**



# TRANSMITTERS AT CENTRAL SYNAPSES

## GABA and Glycine:

- **GABA** is the primary neurotransmitter mediating **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.

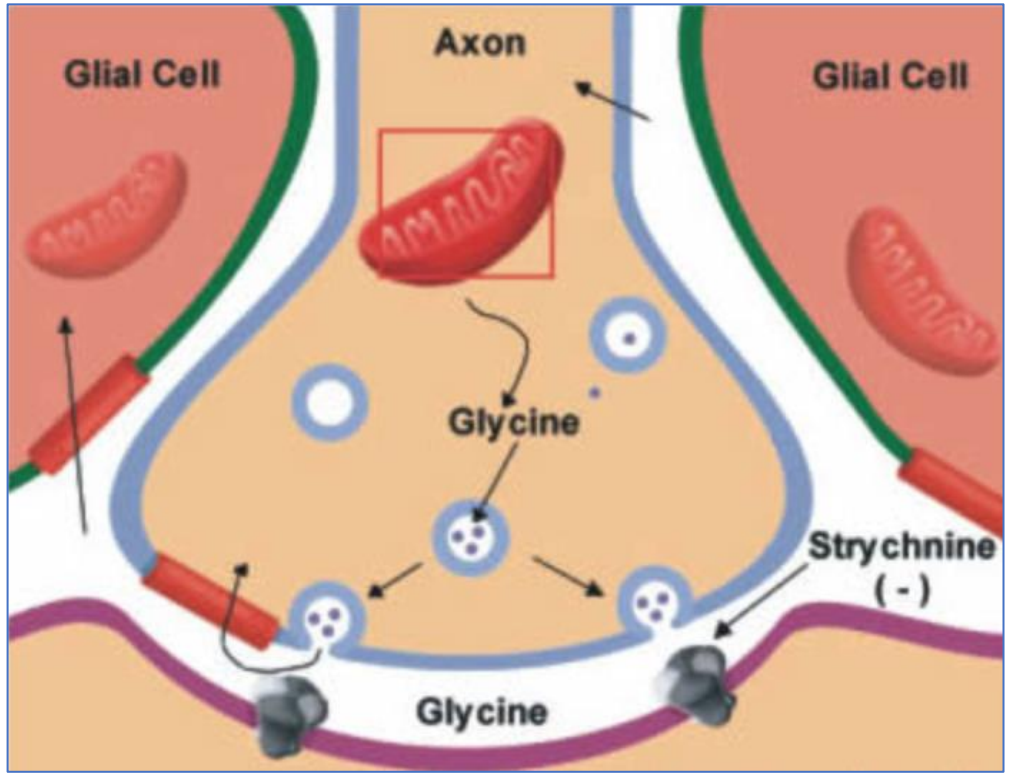


# TRANSMITTERS AT CENTRAL SYNAPSES

## 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.



# TRANSMITTERS AT CENTRAL SYNAPSES

**Peptide Transmitters:**

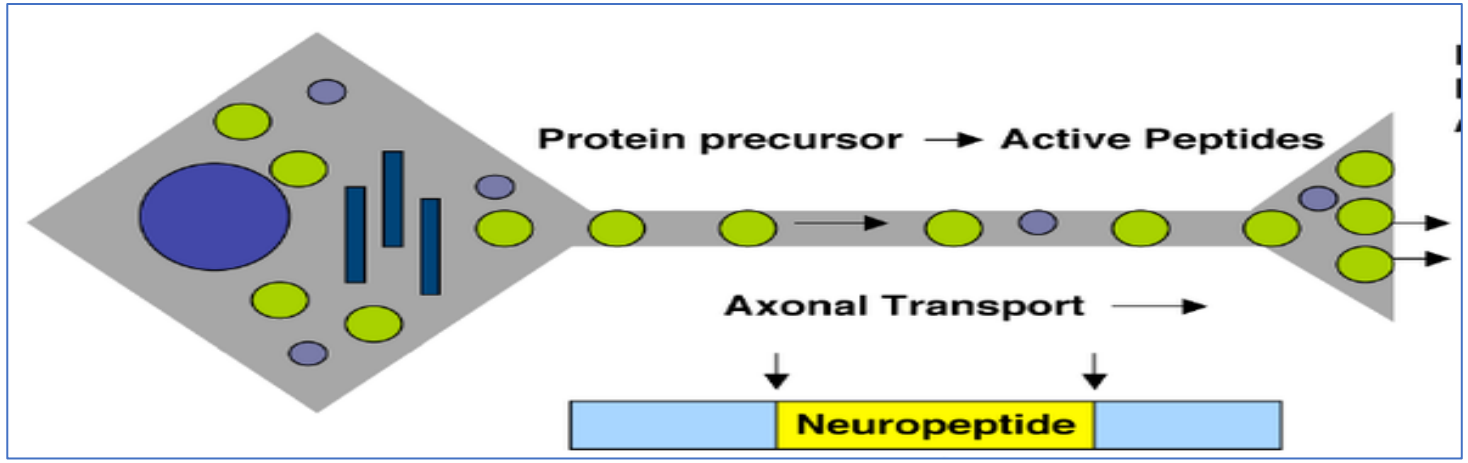
- The best-defined peptides are the **opioid peptides** (**beta-endorphin**, **met- and leu-enkephalin**, and **dynorphin)**
- Some of the important therapeutic actions of **opioid analgesics** (eg, morphine) are mediated via the **activation** of receptors for these endogenous peptides.
- Another peptide **substance P** is a mediator of **slow EPSPs** in neurons involved in **nociceptive sensory pathways** in the spinal cord and brain stem.

# TRANSMITTERS AT CENTRAL SYNAPSES

**Peptide Transmitters:**

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

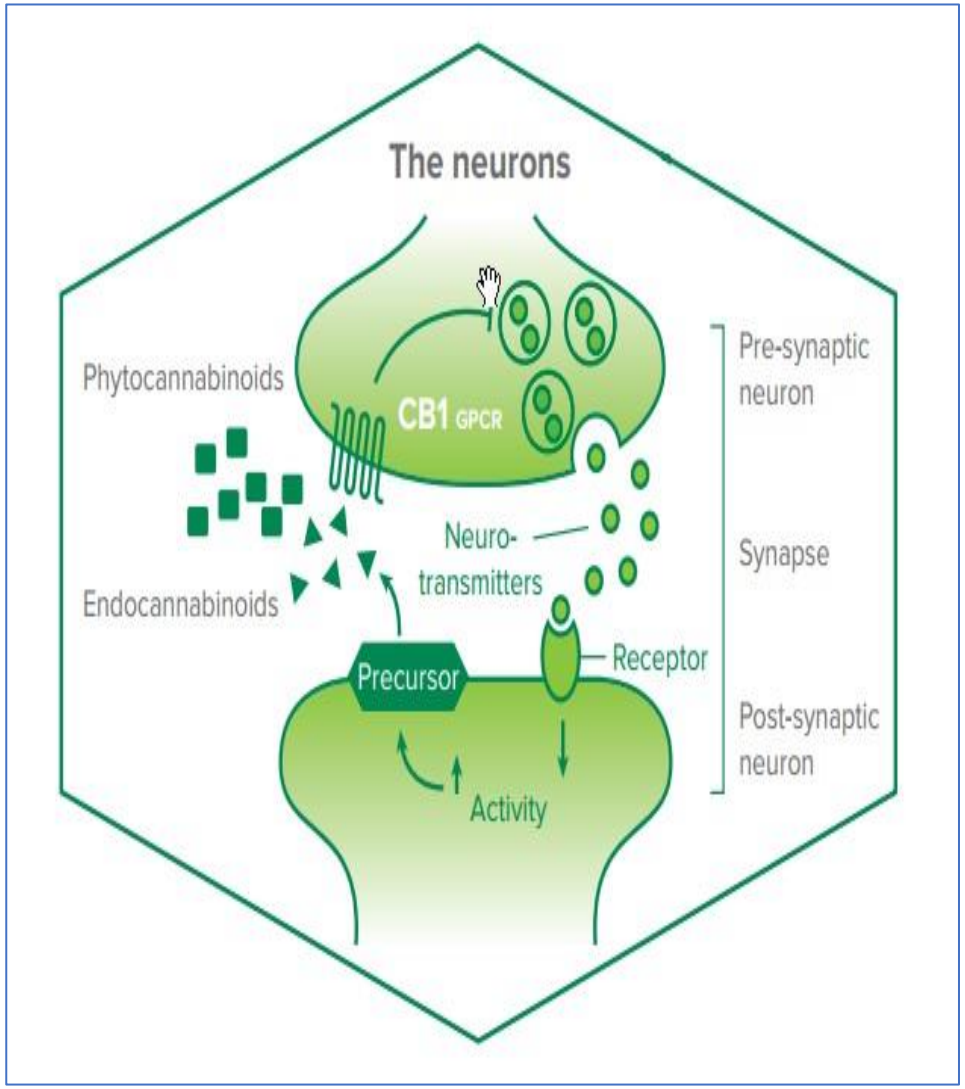
1. They are **synthesized** in the cell body and **transported** to the nerve ending via **axonal transport**
2. **No reuptake** or **specific enzyme** mechanisms have been identified for terminating their actions.



# TRANSMITTERS AT CENTRAL SYNAPSES

**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 **postsynaptically** after membrane **depolarization** but travel **backward** acting presynaptically (retrograde) to **decrease transmitter release**, via their interaction with a specific cannabinoid receptor **CB1**



# THANK YOU FOR YOUR ATTENTION