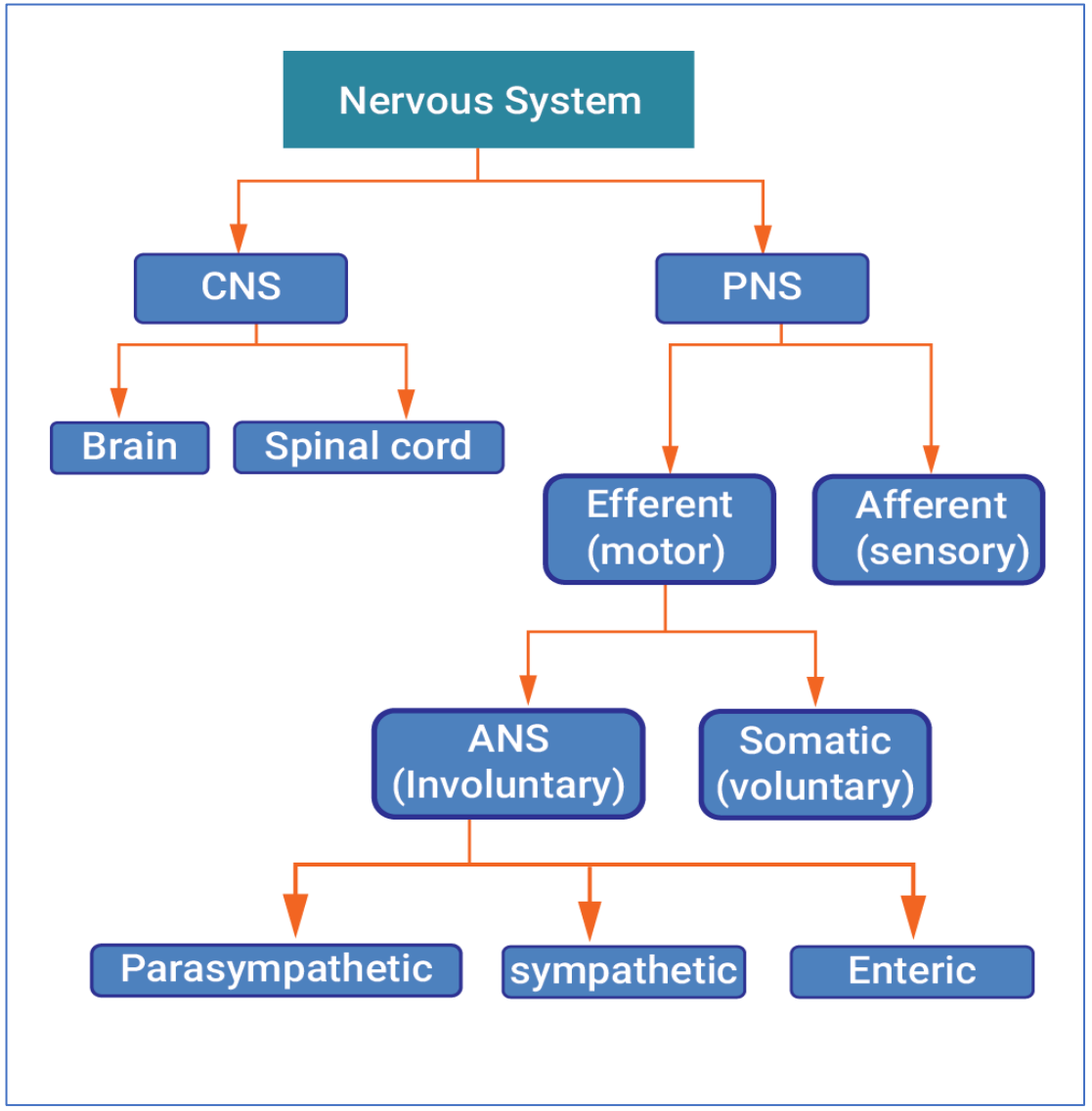
Al-Mustaqbal University College
Department of Pharmacy
4th stage
Pharmacology II
Lecture: 1

Introduction to CNS Pharmacology

Dr Qassim A zigam

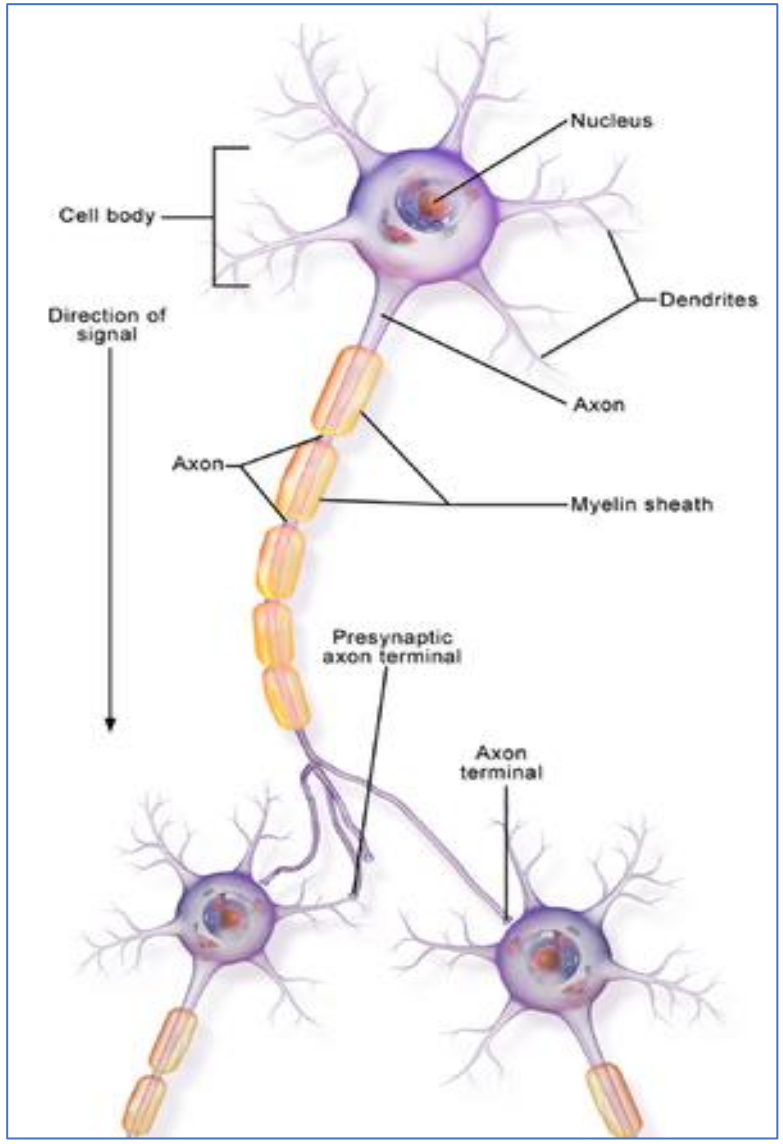
Overview

- 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

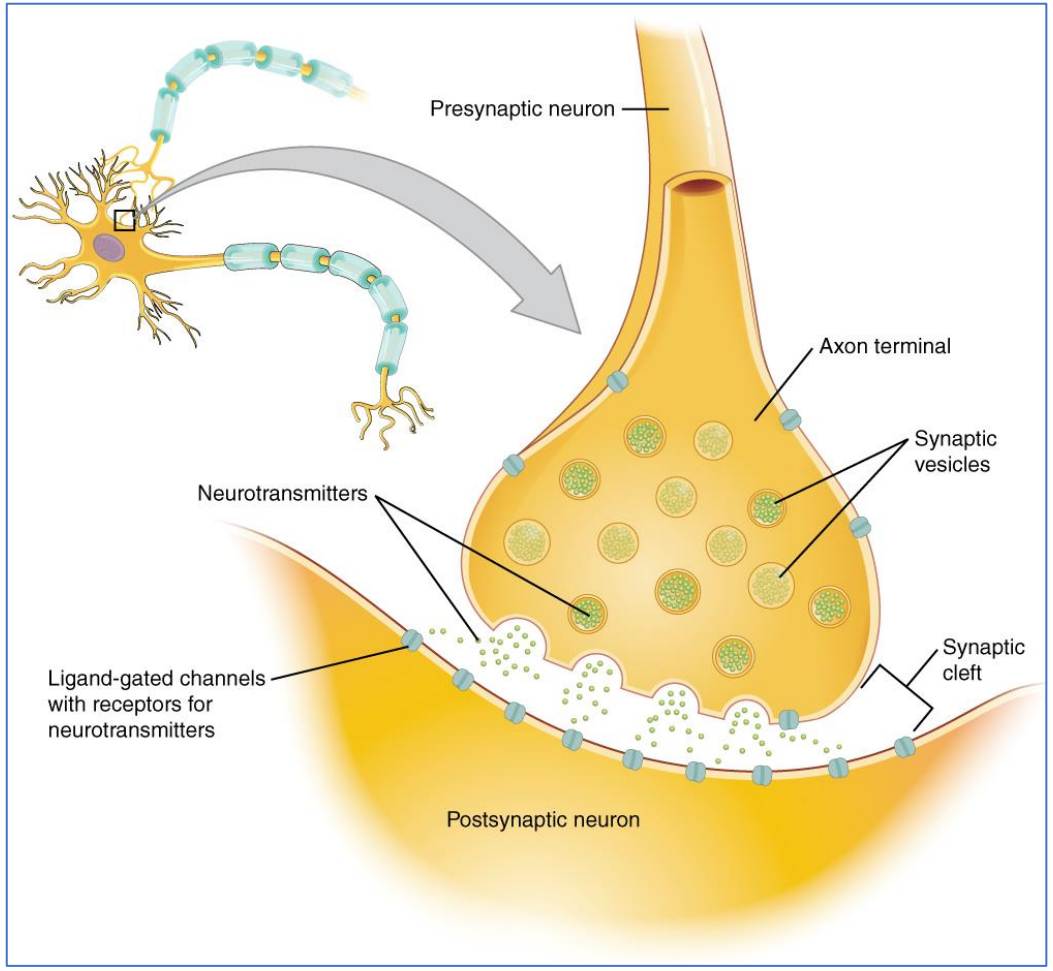
- Most drugs that act on the central nervous system (CNS) appear to do so **by changing ion flow** through transmembrane channels of nerve cells.

- CNS Drug Action depend on :

A. Types of **Ion Channels**

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

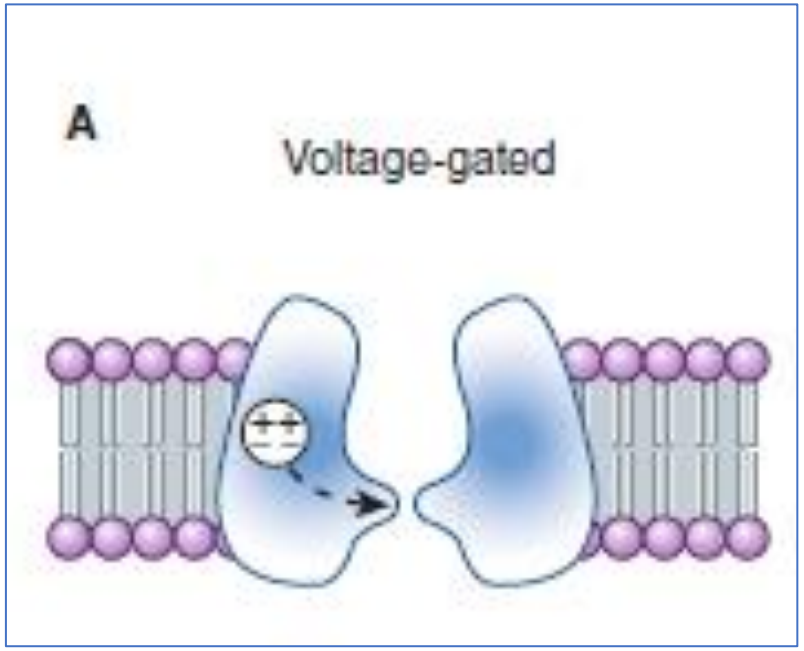
C. Role of the **Ion Current** Carried by the Channel



A. Types of Ion Channels

1. Voltage-gated ion channels:

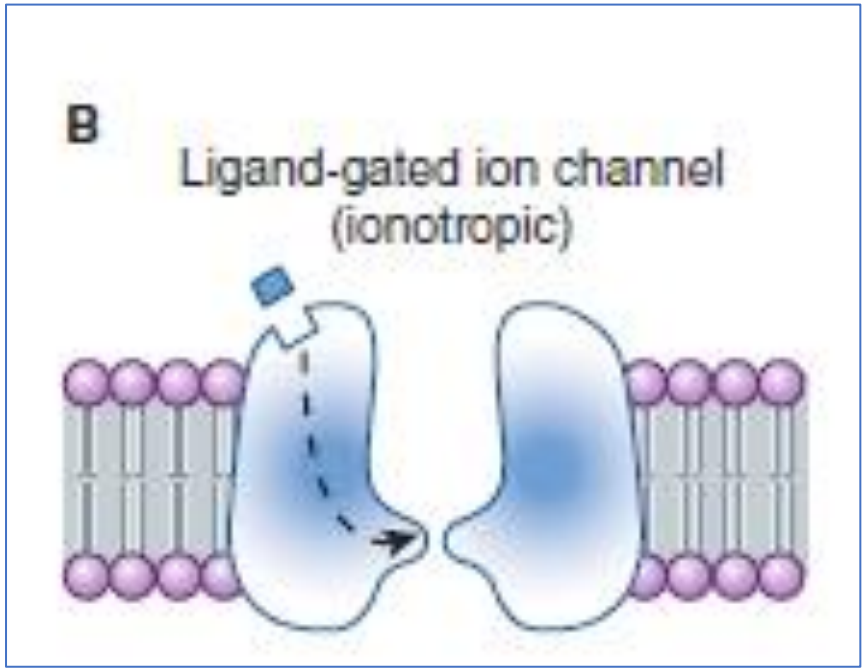
- These channels respond to **changes** in membrane **potential**.
- They are **concentrated** on the **axons** of nerve cells and include the **sodium channels** responsible for action potential propagation.
- **Cell bodies** and dendrites also have voltage-sensitive ion channels for **potassium and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



A. Types of Ion Channels

2. Ligand-gated ion channels:

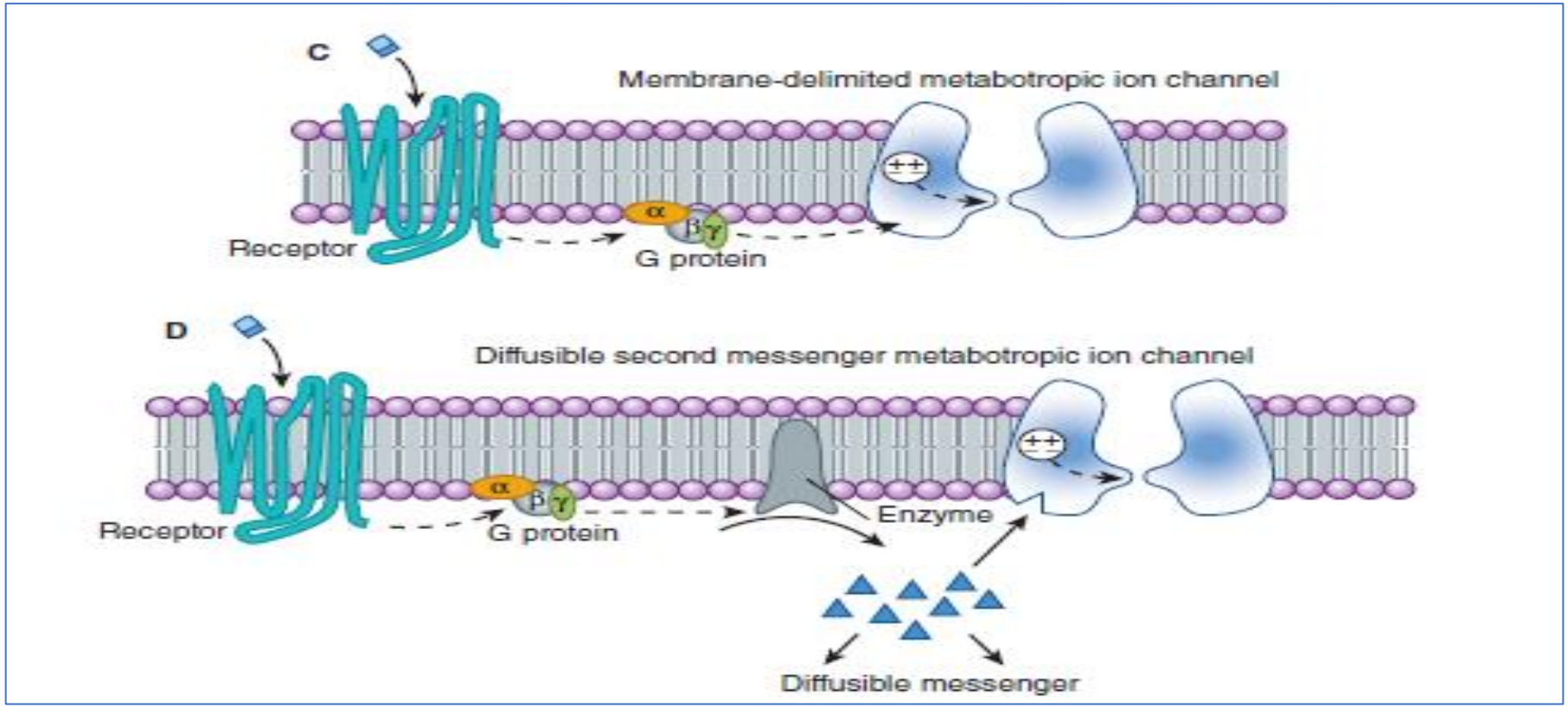
- also called **ionotropic** receptors, respond to chemical **neurotransmitters** that bind to **receptor** subunits present in their macromolecular structure.
- Neurotransmitter-coupled ion channels are found on **cell bodies** and on both the **presynaptic** and **postsynaptic** sides of synapses.



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.

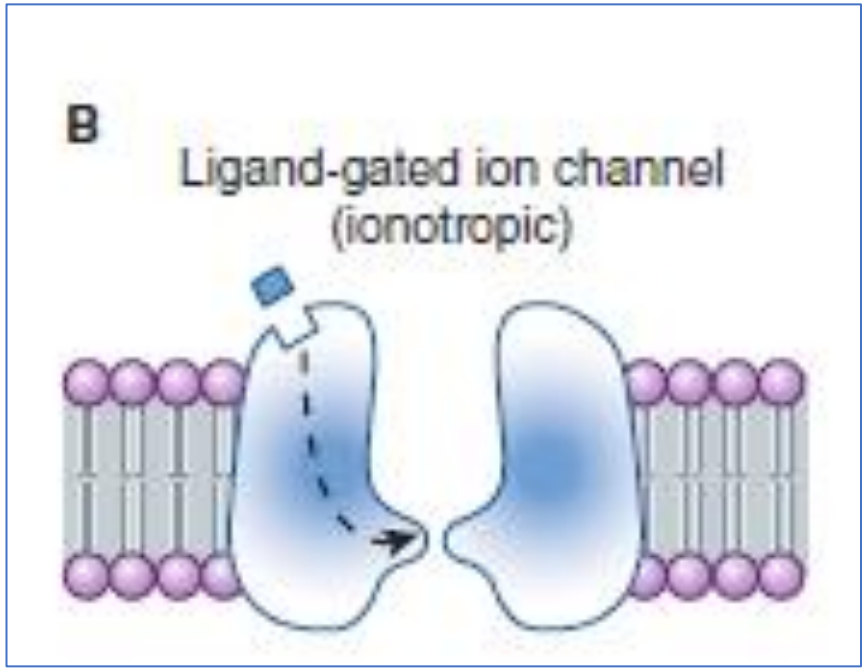


B. Types of Receptor-Channel Coupling:

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

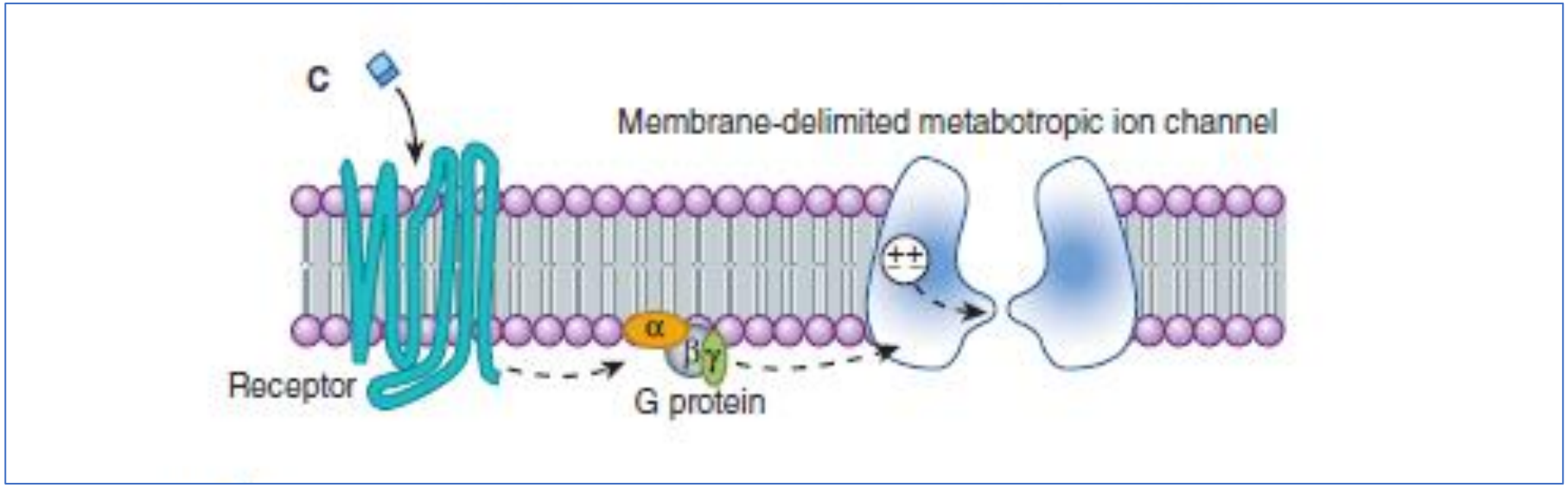
- **Coupling may be through a receptor :**

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



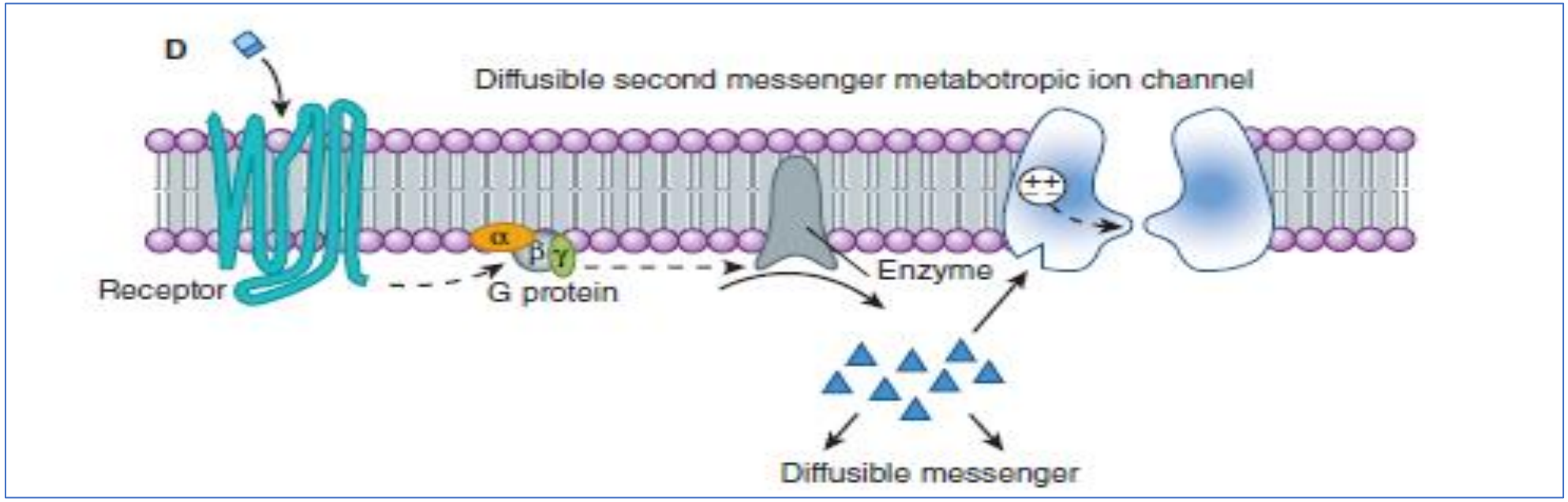
B. Types of Receptor-Channel Coupling:

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



B. Types of Receptor-Channel Coupling:

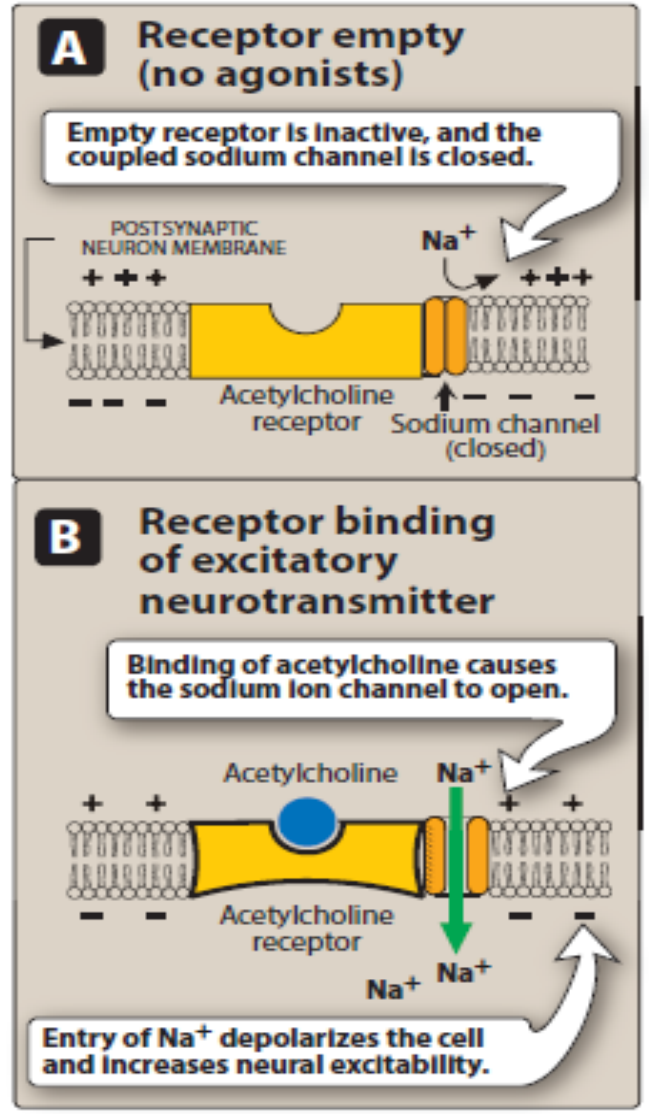
3. Coupled to a G protein that modulates the formation of **diffusible second messengers**, including cyclic adenosine monophosphate (cAMP), inositol trisphosphate (IP3), and diacylglycerol (DAG), which secondarily modulate ion channels (D)



C. Role of the Ion Current Carried by the Channel

1. Excitatory postsynaptic potentials (EPSPs):

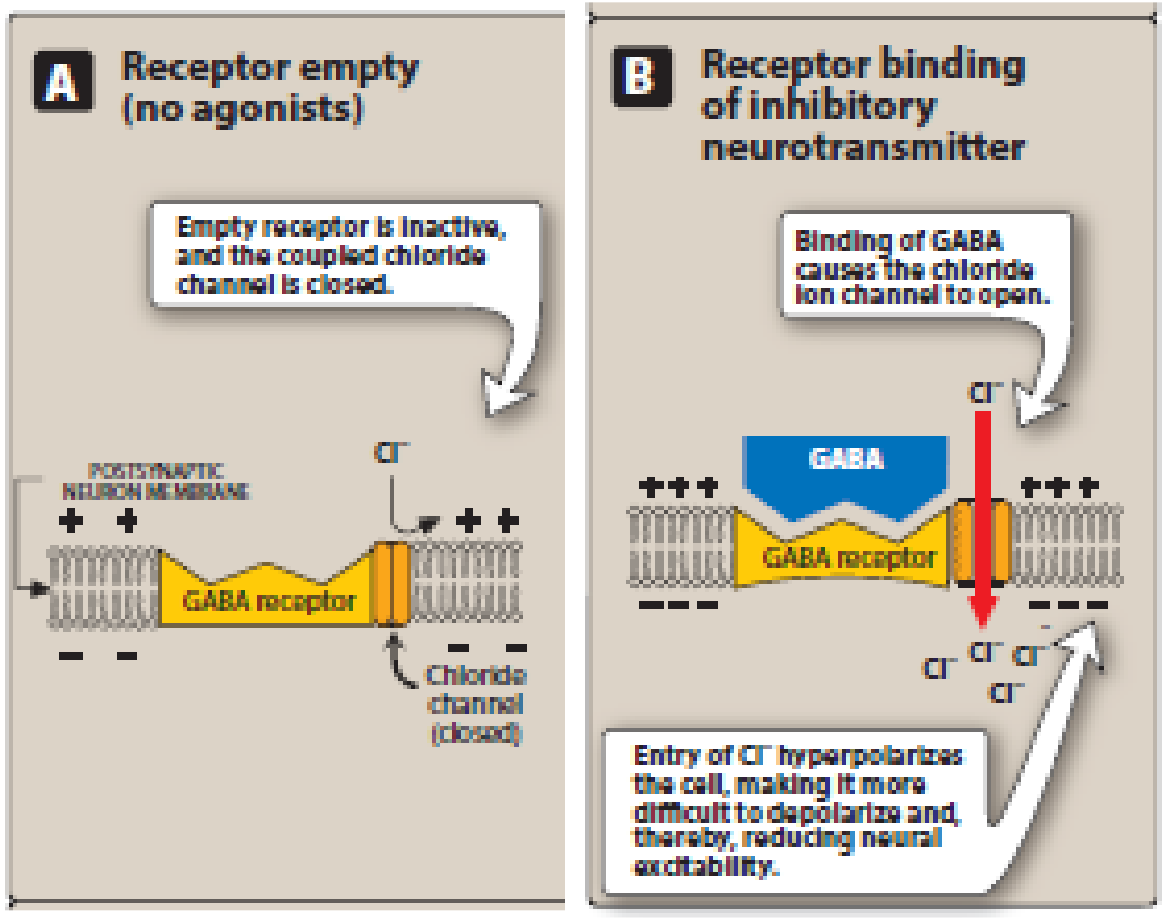
- These potentials are usually generated by the **opening** of **sodium** or **calcium** channels.
- In some synapses, similar depolarizing potentials result from the **closing** of **potassium** channels.



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.



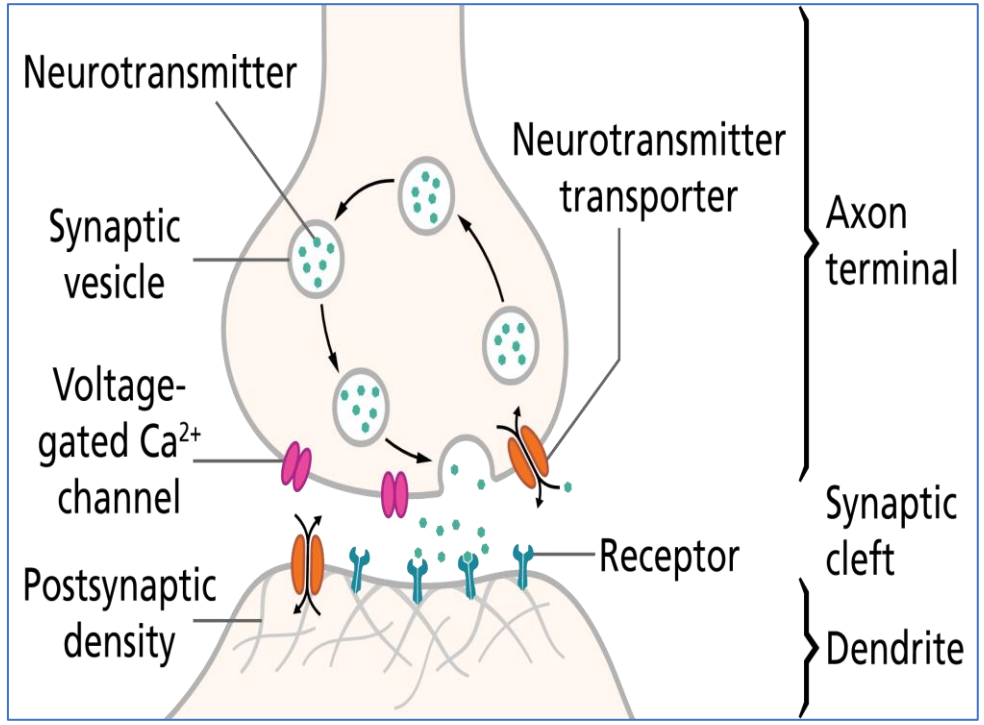
SITES & MECHANISMS OF DRUG ACTION

- 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**.

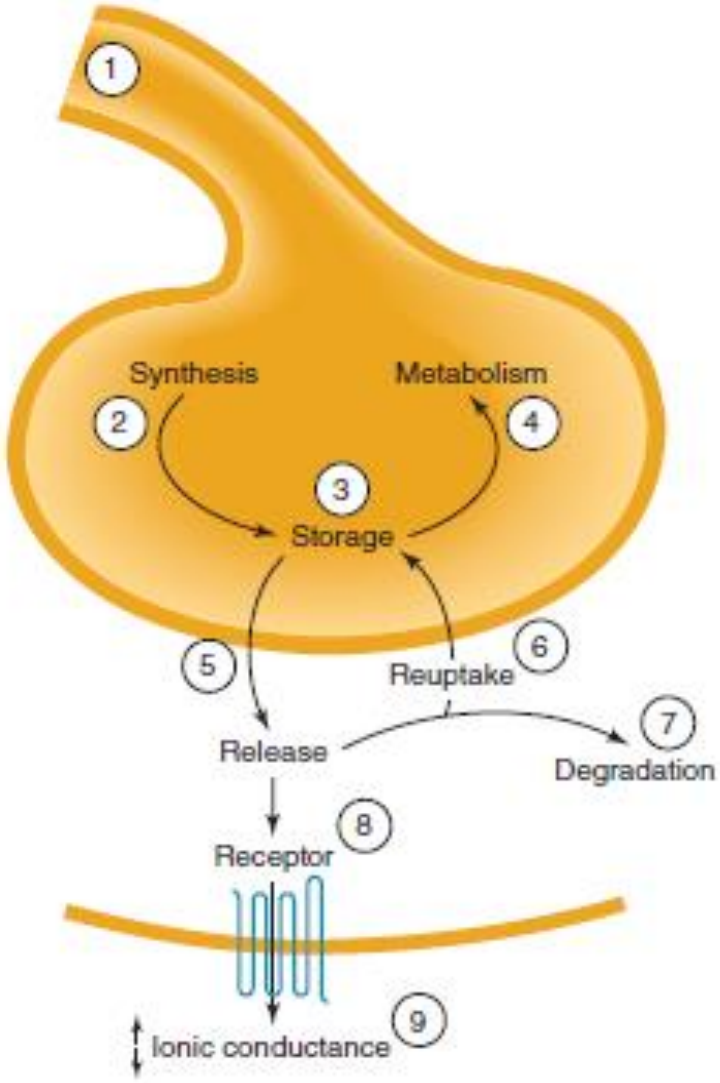
- The **selectivity** of CNS drug action is largely based on the fact that **different** groups of **neurons** use **different neurotransmitters** and that they are segregated into **networks** that subserve different CNS functions.



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:

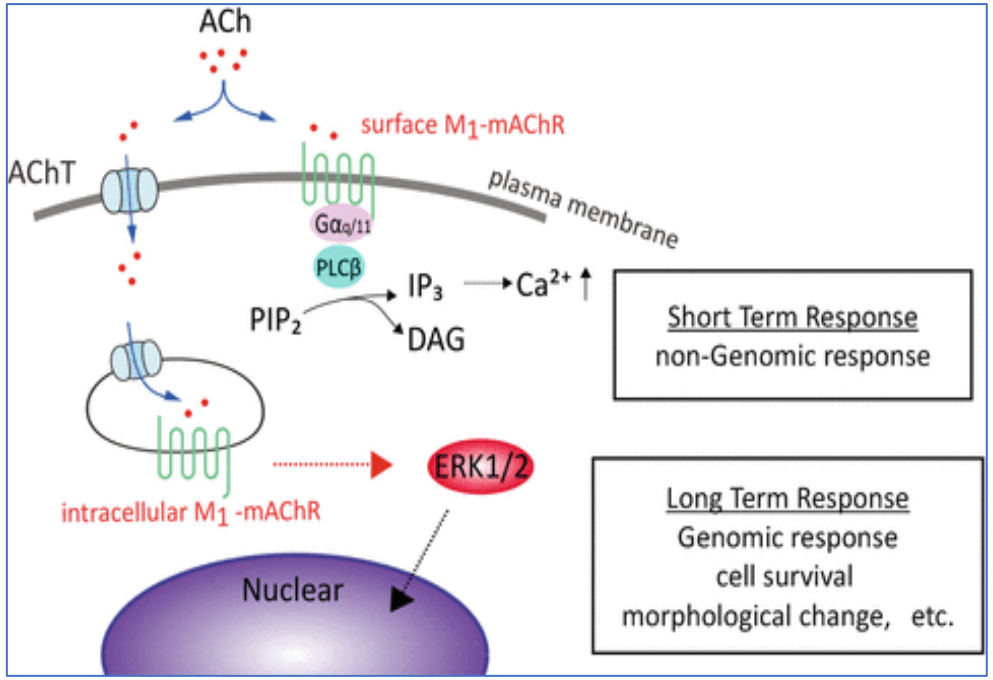
- To be **accepted** as a neurotransmitter, a candidate chemical **must**:

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:

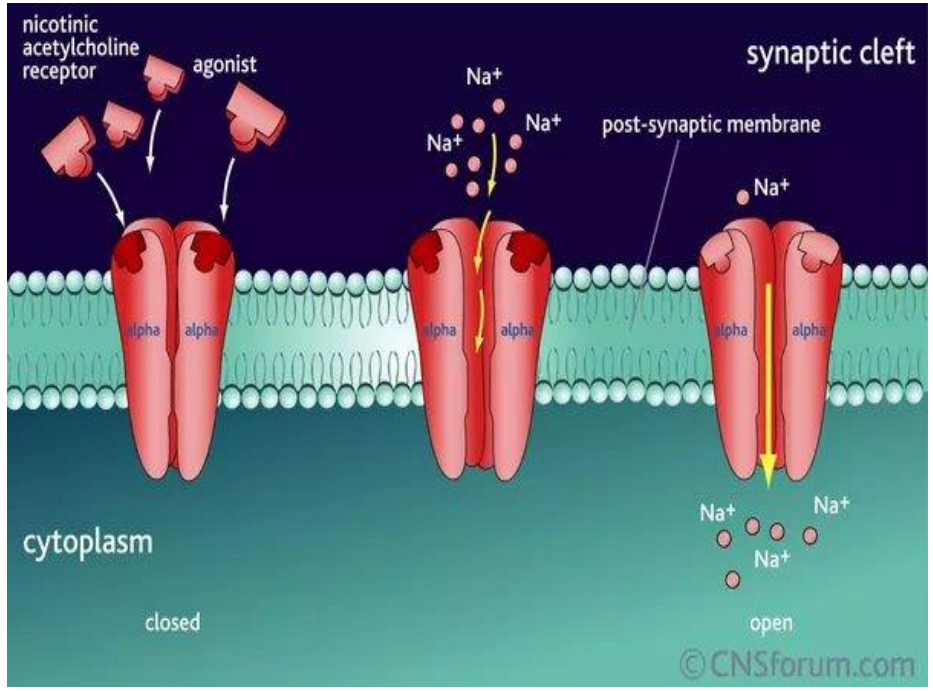
- Approximately **5%** of brain neurons have receptors for acetylcholine (ACh).
- Most CNS responses to ACh are mediated by a large family **of G protein-coupled muscarinic M1 receptors** that lead to slow **excitation** when activated.
- The ionic mechanism of slow excitation involves a **decrease in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



TRANSMITTERS AT CENTRAL SYNAPSES

Acetylcholine:

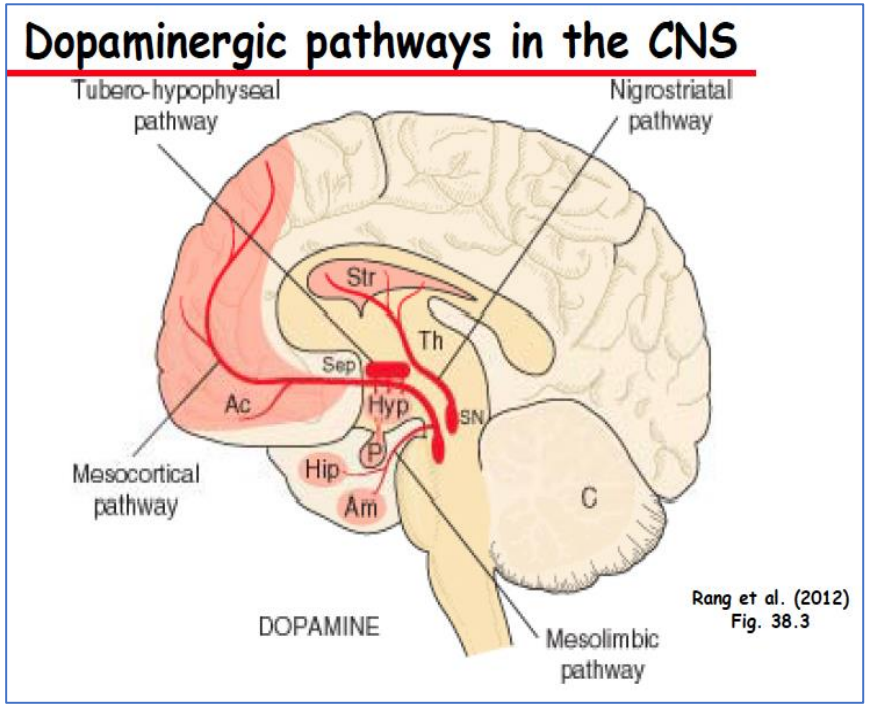
- Of the **nicotinic** receptors present in the CNS are **less common** than muscarinic receptors.
- **Drugs** affecting the activity of cholinergic systems in the brain include the **acetylcholinesterase inhibitors** used in Alzheimer's disease (eg, tacrine) and the **muscarinic blocking agents** used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

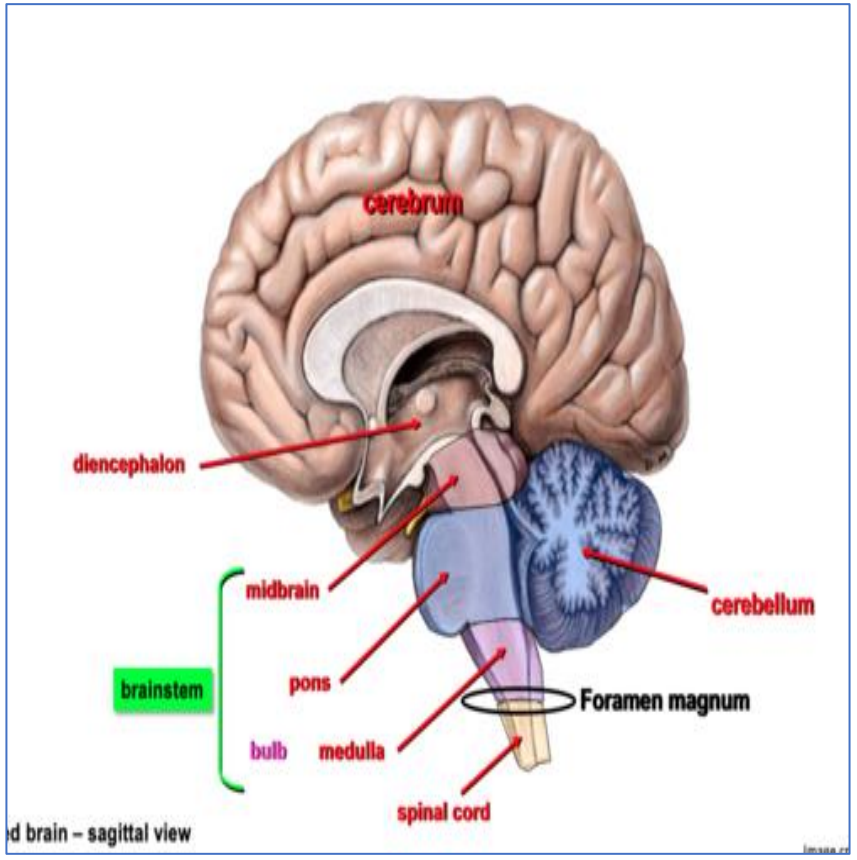
- **Drugs** that **block** the activity of dopaminergic pathways include older **antipsychotics** (eg, chlorpromazine, haloperidol), which may cause **parkinsonian** symptoms.

- **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.

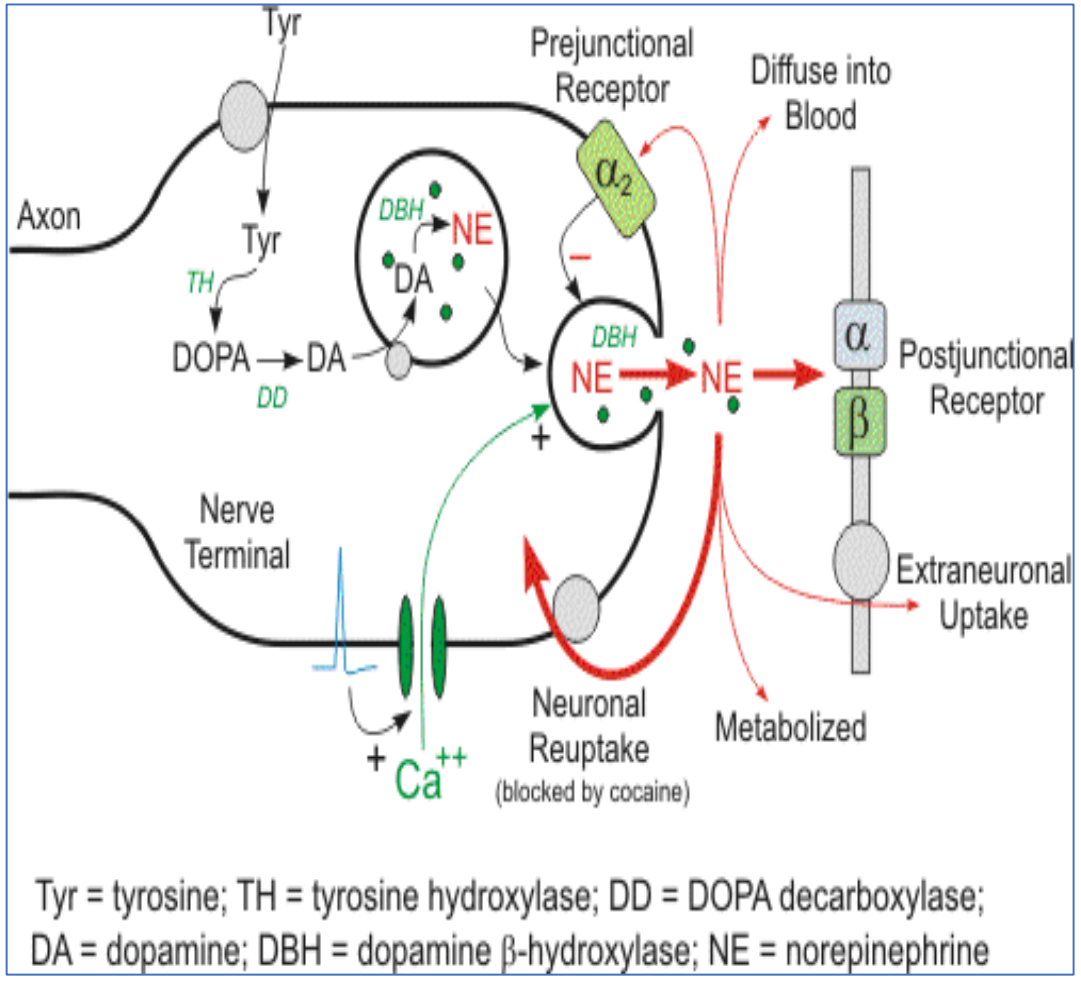


TRANSMITTERS AT CENTRAL SYNAPSES

Norepinephrine:

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

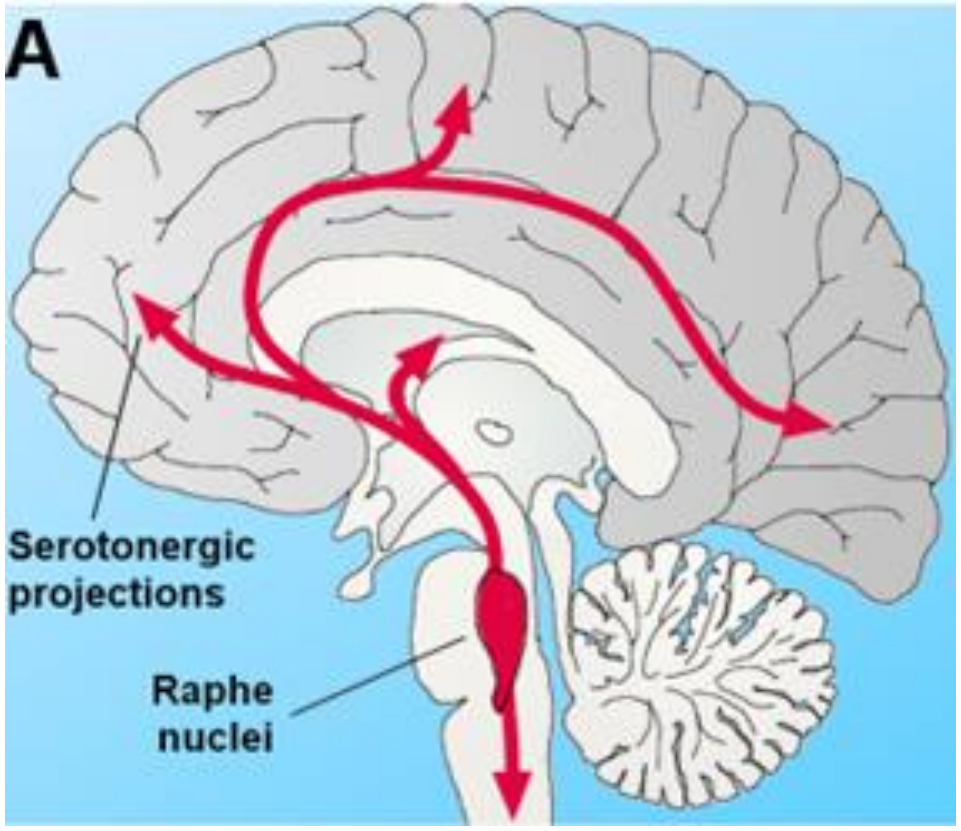
1. **CNS stimulants** such as amphetamines & cocaine.
2. **Monoamine oxidase inhibitors** like phenelzine.
3. **Tricyclic antidepressants** like amitriptyline



TRANSMITTERS AT CENTRAL SYNAPSES

Serotonin:

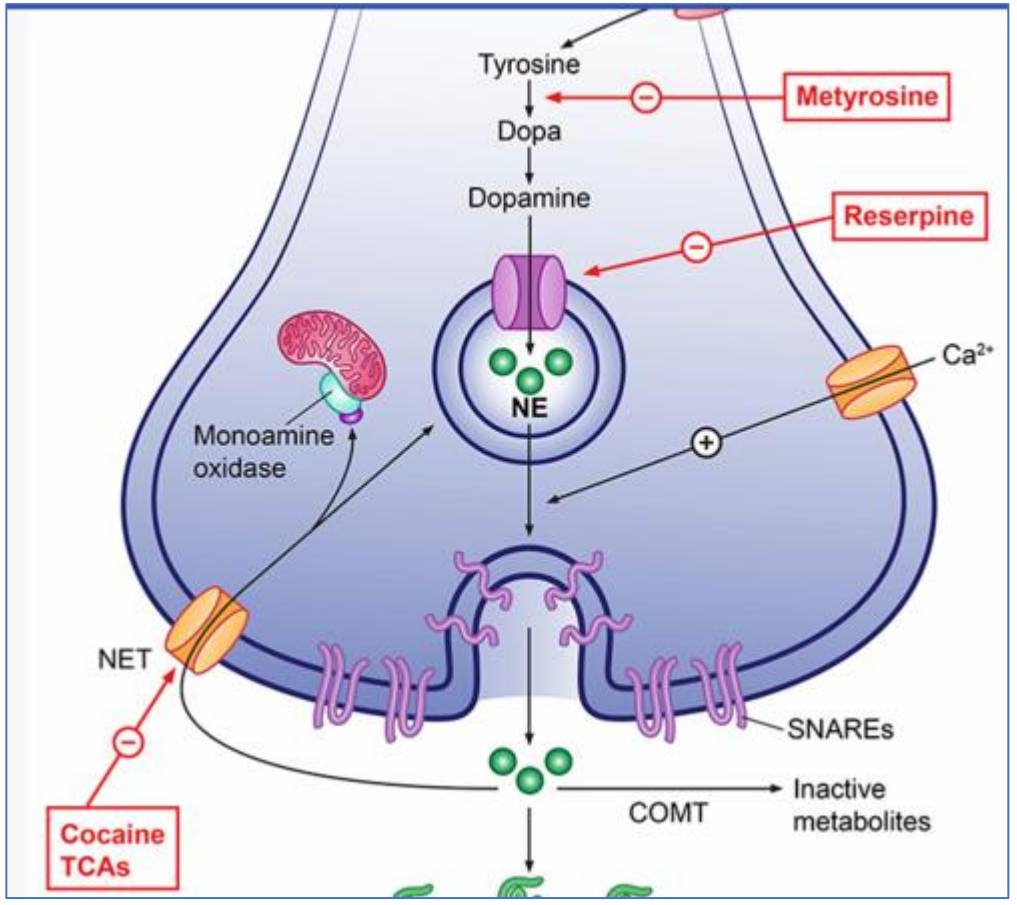
- Most serotonin (5-HT) pathways originate from cell bodies in the **raphe or midline regions** of the **pons** and **upper brain stem**; these pathways innervate most regions of the CNS.
- **Multiple** 5-HT receptor subtypes have been identified and, with the **exception of the 5-HT3** subtype, all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

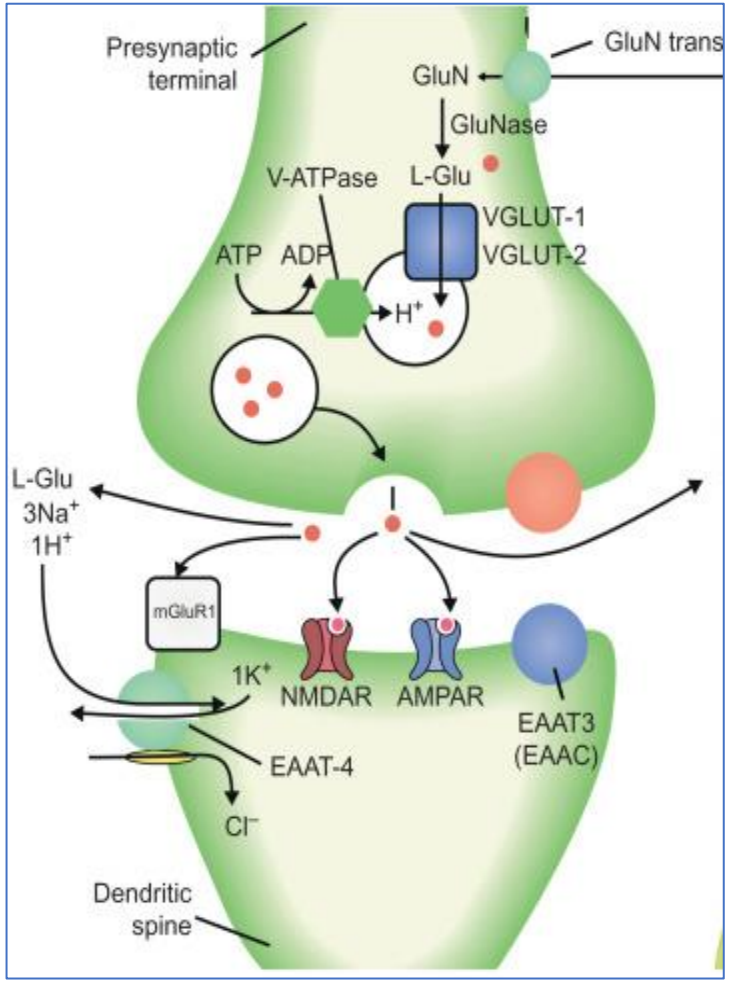
- Most of the agents used in the treatment of **major depressive disorders** affect serotonergic pathways (eg, tricyclic antidepressants, selective serotonin reuptake inhibitors).
- The actions of some **CNS stimulants** and **newer antipsychotic** drugs (eg, olanzapine) also appear to be mediated via 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:

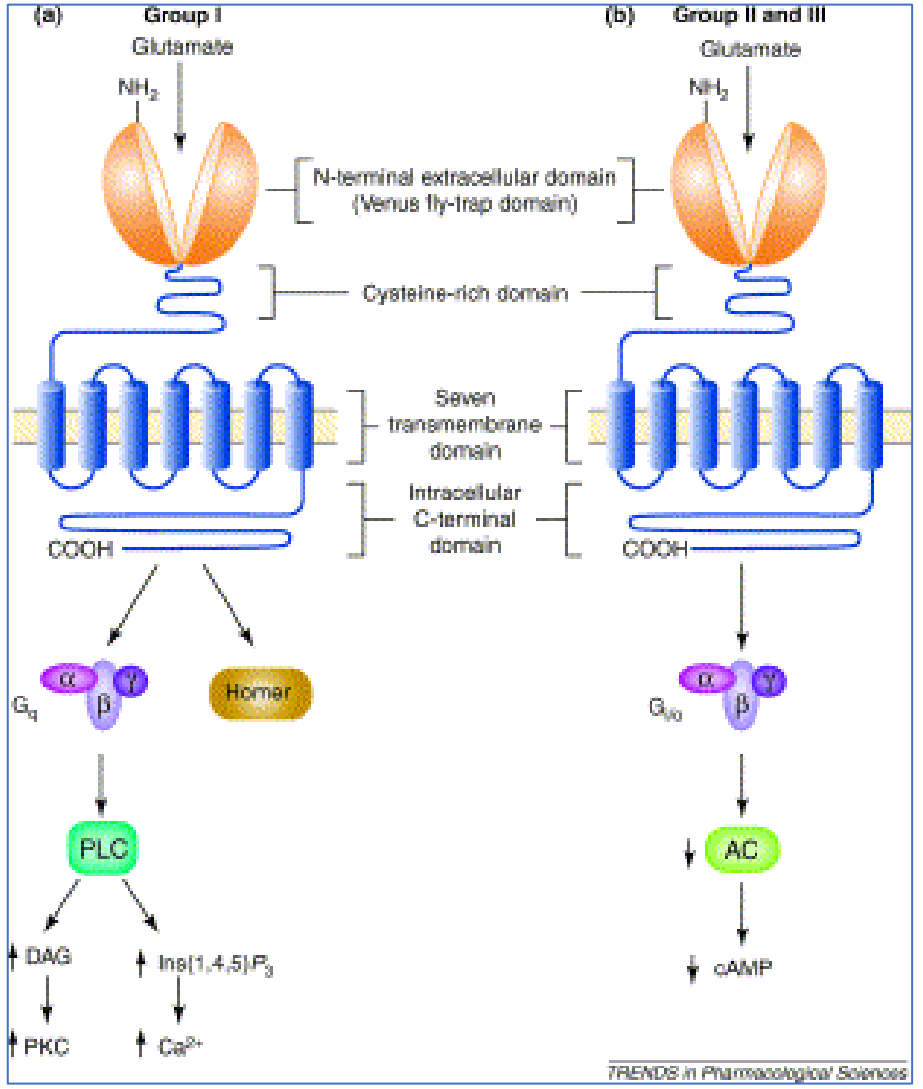
- Most neurons in the brain are **excited by glutamic acid**.
- **High** concentrations of glutamic acid in synaptic vesicles is achieved by the vesicular glutamate transporter (**VGLUT**).
- Both **ionotropic** and **metabotropic** receptors have been characterized.
- Subtypes of glutamate receptors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

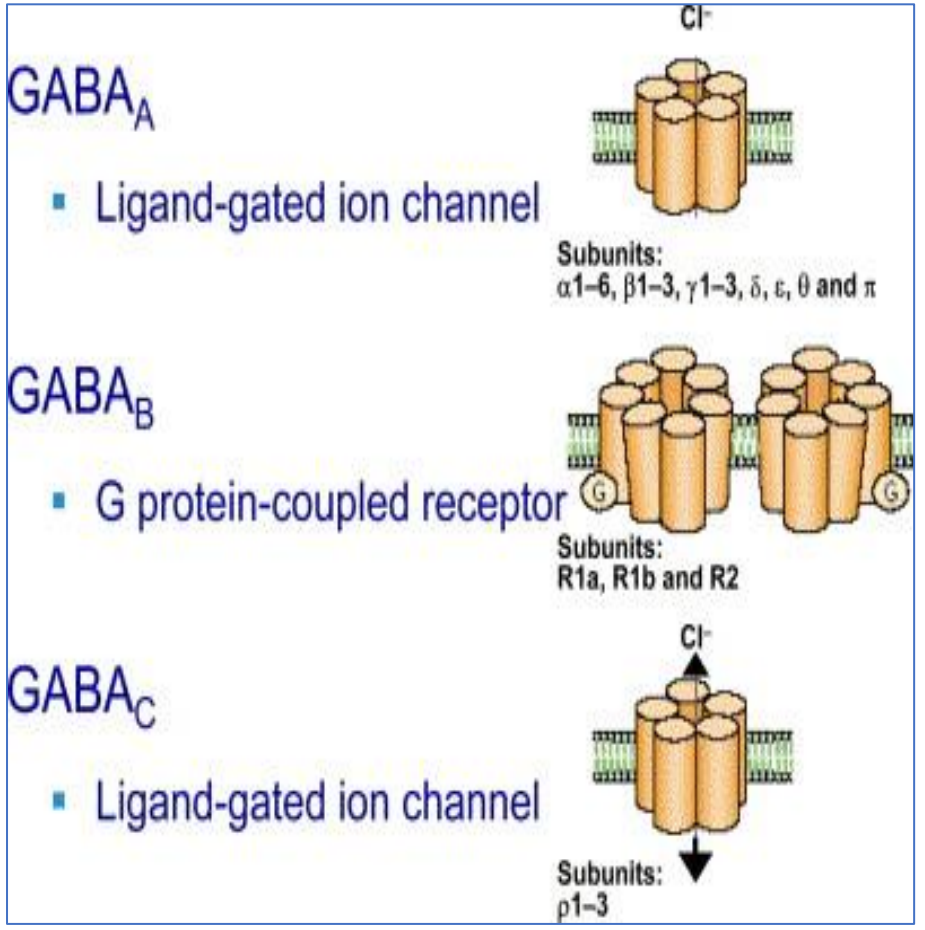
- **Memantine** is an **NMDA antagonist** introduced for treatment of **Alzheimer's dementia**.
- **Excessive activation of NMDA** receptors after neuronal injury may be responsible for **cell death**.
- Glutamate metabotropic receptor activation can result in G protein-coupled **activation** of **phospholipase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

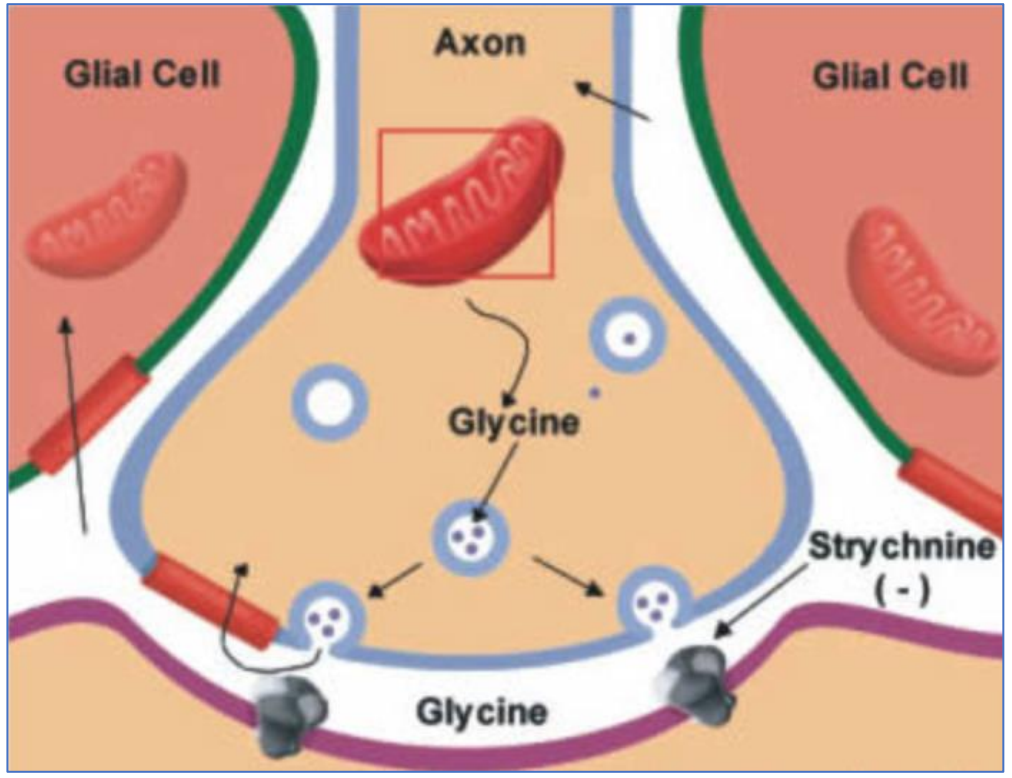


TRANSMITTERS AT CENTRAL SYNAPSES

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:

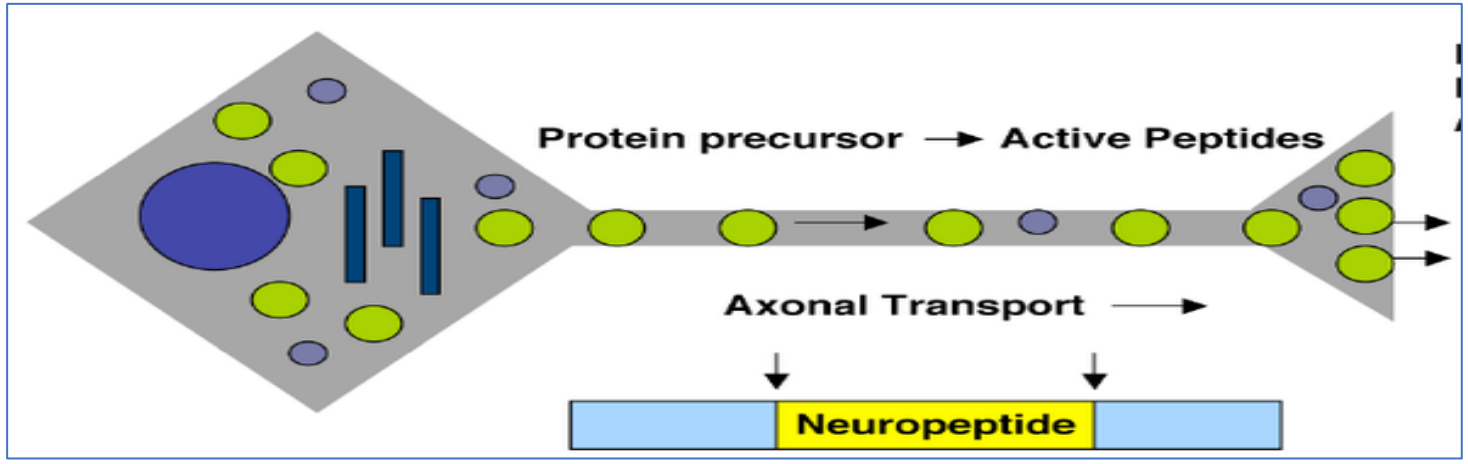
- The best-defined peptides are the **opioid peptides** (**beta-endorphin**, **met- and leu-enkephalin**, and **dynorphin)**
- Some of the important therapeutic actions of **opioid analgesics** (eg, morphine) are mediated via the **activation** of receptors for these endogenous peptides.
- Another peptide **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

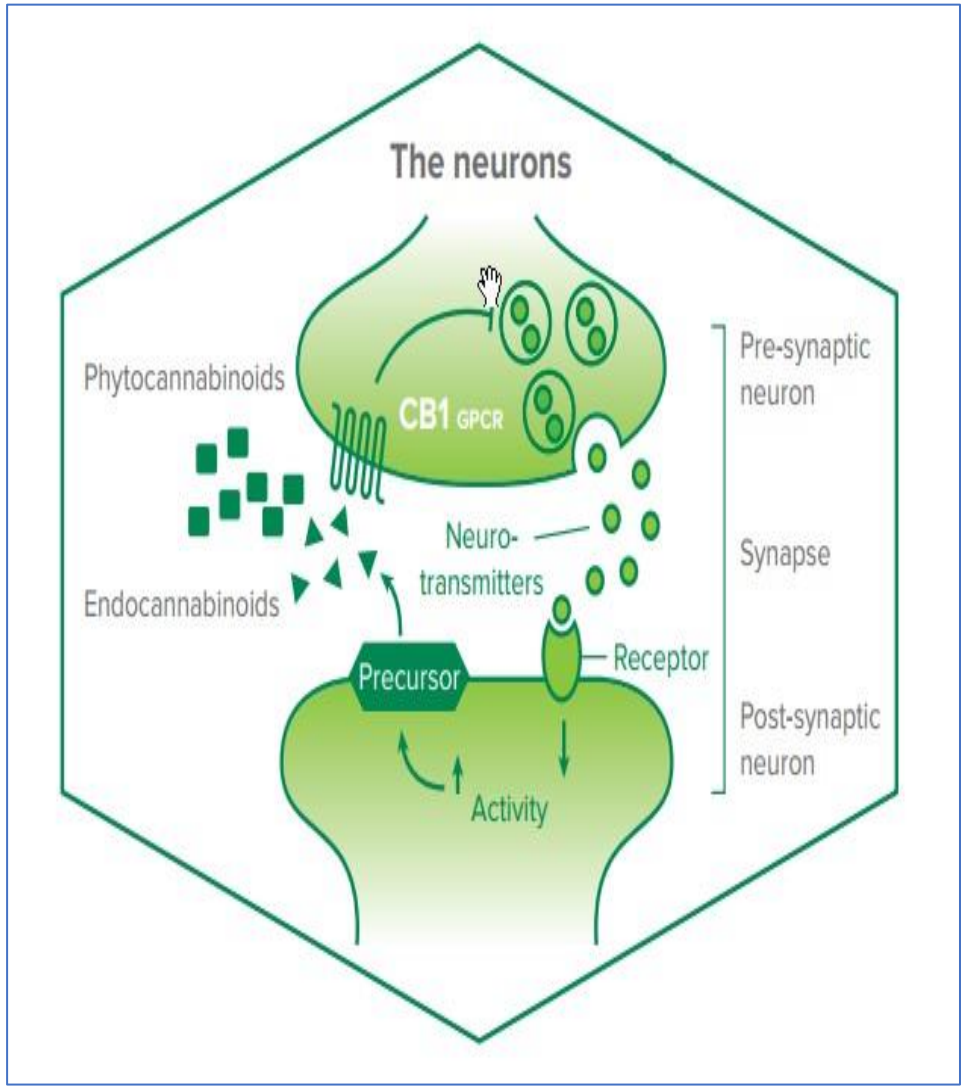
1. They are **synthesized** in the cell body and **transported** to the nerve ending via **axonal transport**
2. **No reuptake** or **specific enzyme** mechanisms have been identified for terminating their actions.



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**



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