

# Pharmacology of Drugs Acting on Central Nervous System

## Introduction to CNS

- The CNS consists of the brain and spinal cord, which coordinate all body activities.
- Drugs acting on the CNS affect mood, behavior, sensory perception, consciousness, motor functions, and vital body functions.
- In pharmacology, CNS-active drugs are studied for their effects on neurotransmission, receptor interaction, modulation of neuronal excitability, and clinical utility in disorders like anxiety, depression, epilepsy, schizophrenia, Parkinson's disease, etc.

## Classification of CNS-Acting Drugs

- **Sedative-hypnotics** (e.g., benzodiazepines, barbiturates)
- **Antidepressants** (e.g., SSRIs, SNRIs, TCAs, MAOIs)
- **Antipsychotics** (e.g., typical and atypical antipsychotics)
- **Antiepileptics** (e.g., phenytoin, valproate)
- **Analgesics** (e.g., opioids, NSAIDs)
- **Anesthetics** (e.g., propofol, ketamine)
- **Psychostimulants** (e.g., amphetamines, methylphenidate)
- **Cognitive enhancers** (e.g., donepezil, memantine)
- **Antiparkinsonian drugs** (e.g., levodopa, dopamine agonists)

## Neurohumoral Transmission In The CNS

- Neurohumoral transmission refers to the chemical communication between neurons via neurotransmitters across synapses.

## Steps in CNS Neurotransmission:

1. Synthesis of neurotransmitter in the presynaptic neuron.
2. Storage in synaptic vesicles.
3. Release into synaptic cleft via exocytosis (triggered by  $\text{Ca}^{2+}$  influx).
4. Binding to specific postsynaptic receptors.
5. **Termination by:**
  - Reuptake into presynaptic terminal (e.g., serotonin, dopamine).
  - Enzymatic degradation (e.g., ACh by acetylcholinesterase).
  - Diffusion away from synapse.

## Types of Neurotransmitters

- Neurotransmitters can be broadly categorized into:
  - **Excitatory** (e.g., Glutamate)
  - **Inhibitory** (e.g., GABA, Glycine)
  - **Modulatory** (e.g., dopamine, serotonin, norepinephrine)
- Each neurotransmitter has specific receptors and associated second messenger pathways which determine the cellular response.

## Neurotransmitters In The CNS

### **γ-Aminobutyric Acid (GABA)**

#### **Function:**

- Primary inhibitory neurotransmitter in the CNS.
- Reduces neuronal excitability and prevents overstimulation.
- Maintains balance with excitatory glutamate.

#### **Receptors:**

- **GABA-A (ionotropic):** Ligand-gated  $\text{Cl}^-$  channels → fast inhibition.
- **GABA-B (metabotropic):** G-protein-coupled → opens  $\text{K}^+$  channels, inhibits  $\text{Ca}^{2+}$  channels → slow inhibition.

#### **Synthesis Pathway:**

1. Glucose (via Krebs cycle) → α-Ketoglutarate
2. α-Ketoglutarate → Glutamate
3. Glutamate → GABA
  - **Enzyme:** *Glutamic Acid Decarboxylase (GAD)*
  - **Cofactor:** *Pyridoxal phosphate (Vitamin B6)*

#### **Drug examples:**

- Tiagabine (blocks GAT-1 re-uptake).
- Vigabatrin (irreversible GABA-transaminase inhibitor).
- Propofol and etomidate (direct gating in β subunits of GABA-A).

#### **Clinical Uses:**

- Anxiety disorders
- Epilepsy

- Insomnia
- Muscle spasms

## Glutamate

### Function:

- Primary excitatory neurotransmitter.
- Crucial for synaptic plasticity, learning, and memory.

### Receptors:

- **Ionotropic:**
  - NMDA (N-Methyl-D-Aspartate)
  - AMPA
  - Kainate
- **Metabotropic:** mGluRs (G-protein-coupled)

### Synthesis Pathway:

1. Glutamine (from astrocytes) → Glutamate
  - **Enzyme:** *Glutaminase*
2. Glutamate is packed into vesicles by VGLUT

### Excitotoxicity:

- Overactivation of glutamate receptors → neuronal injury/death.
- Implicated in stroke, ALS, Alzheimer's disease.

## Glycine

### Function:

- Inhibitory neurotransmitter, especially in spinal cord and brainstem.
- Facilitates  $\text{Cl}^-$  influx, similar to GABA-A.

### Receptors:

- Glycine receptor (ionotropic  $\text{Cl}^-$  channel)
- Also co-agonist for NMDA glutamate receptor (excitatory role there)

### Synthesis Pathway:

- Serine → Glycine



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