# Introduction

Pharmacology and Toxicology

Central Nervous System Module

Third Year Medical Students

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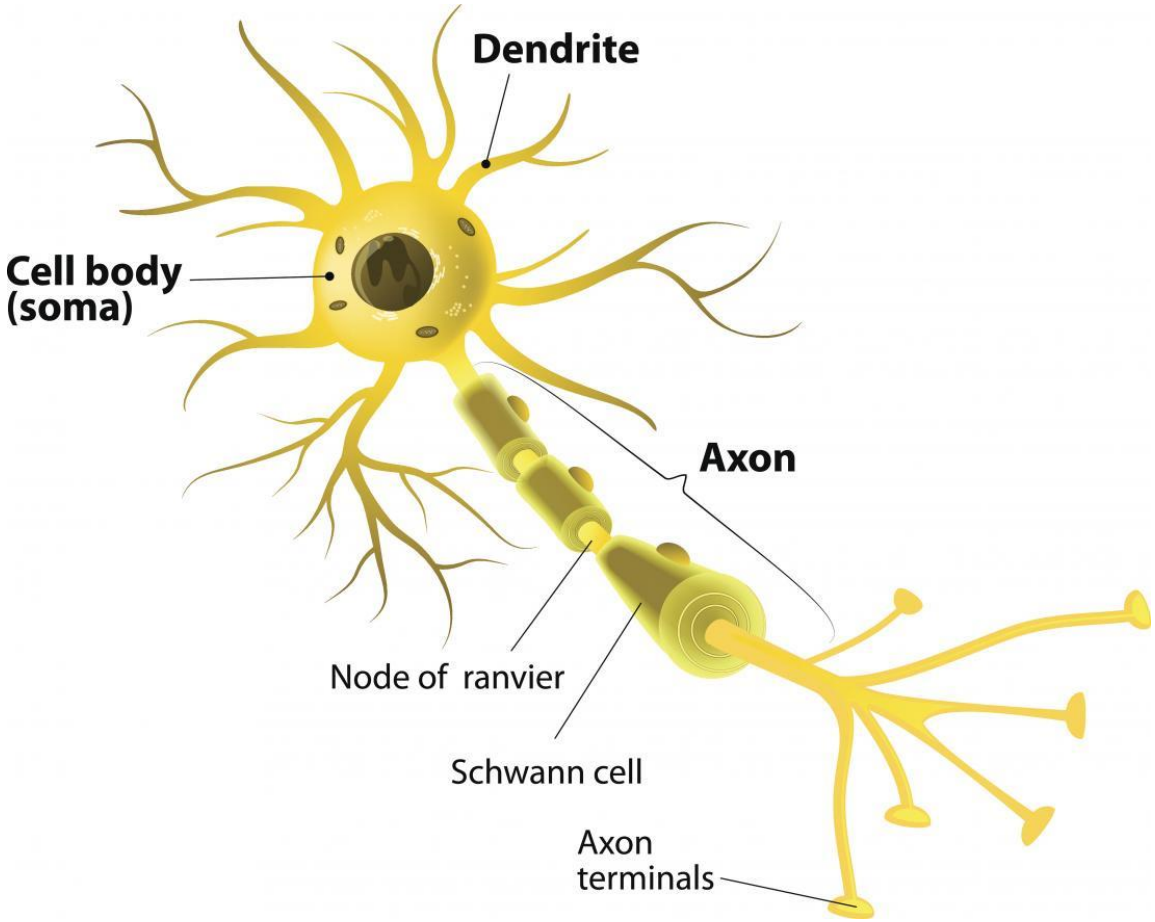
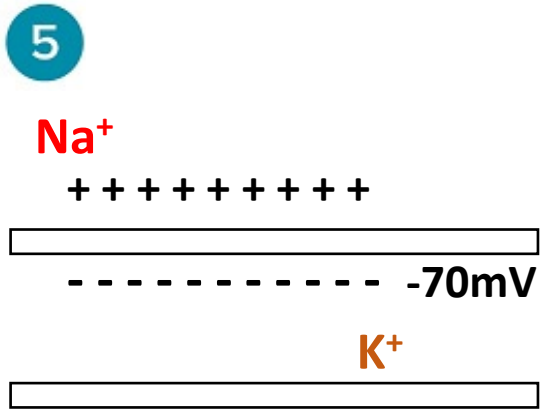
Faculty of Medicine

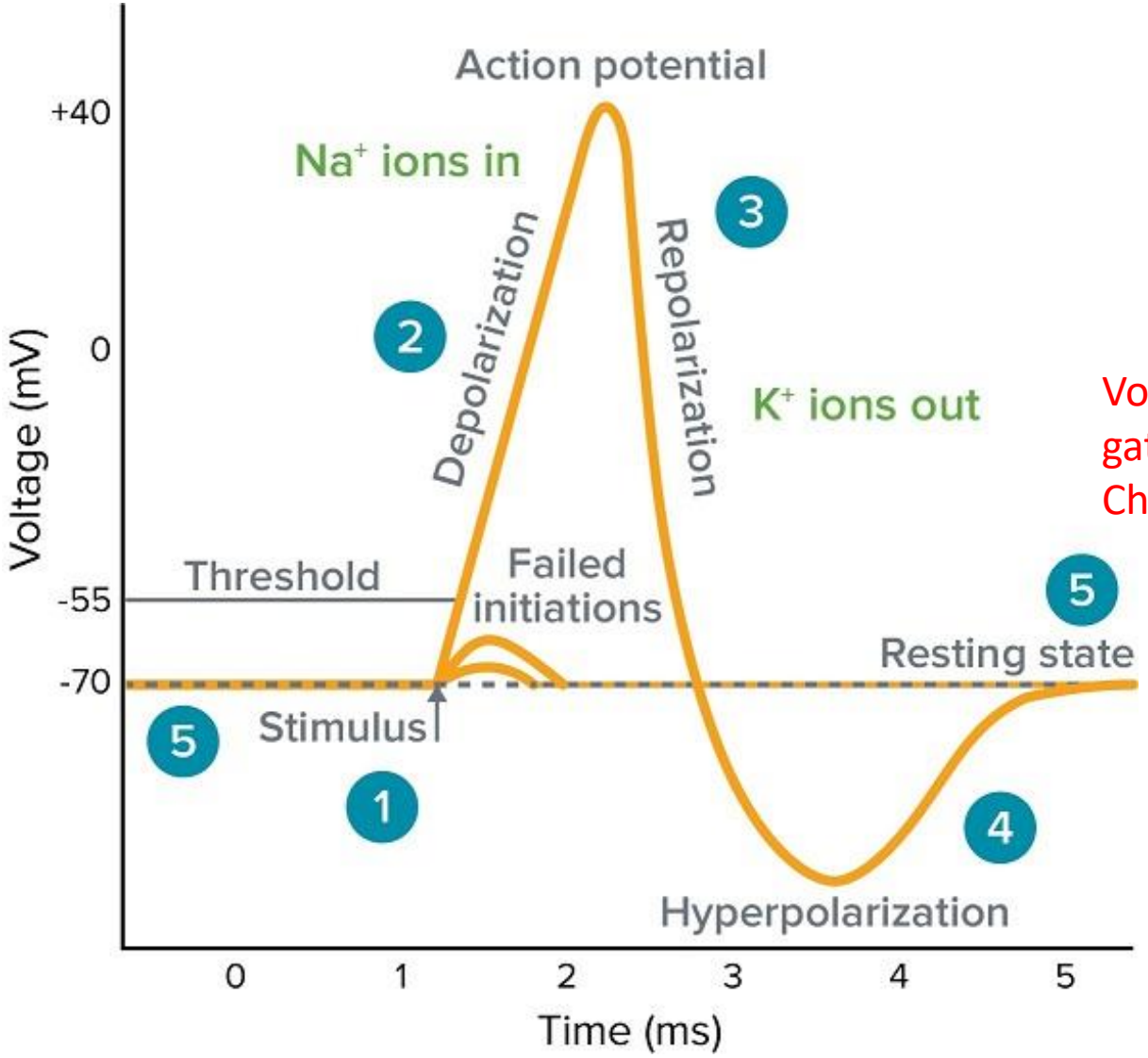
The Hashemite University

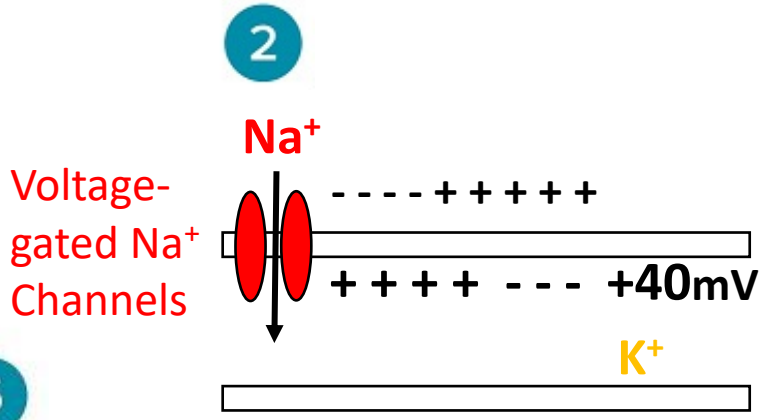
# The Neuron



# Action Potential



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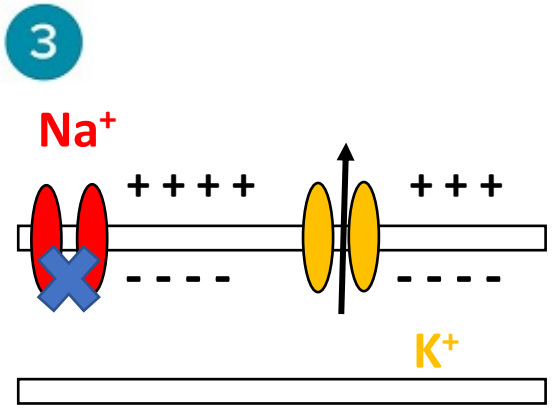
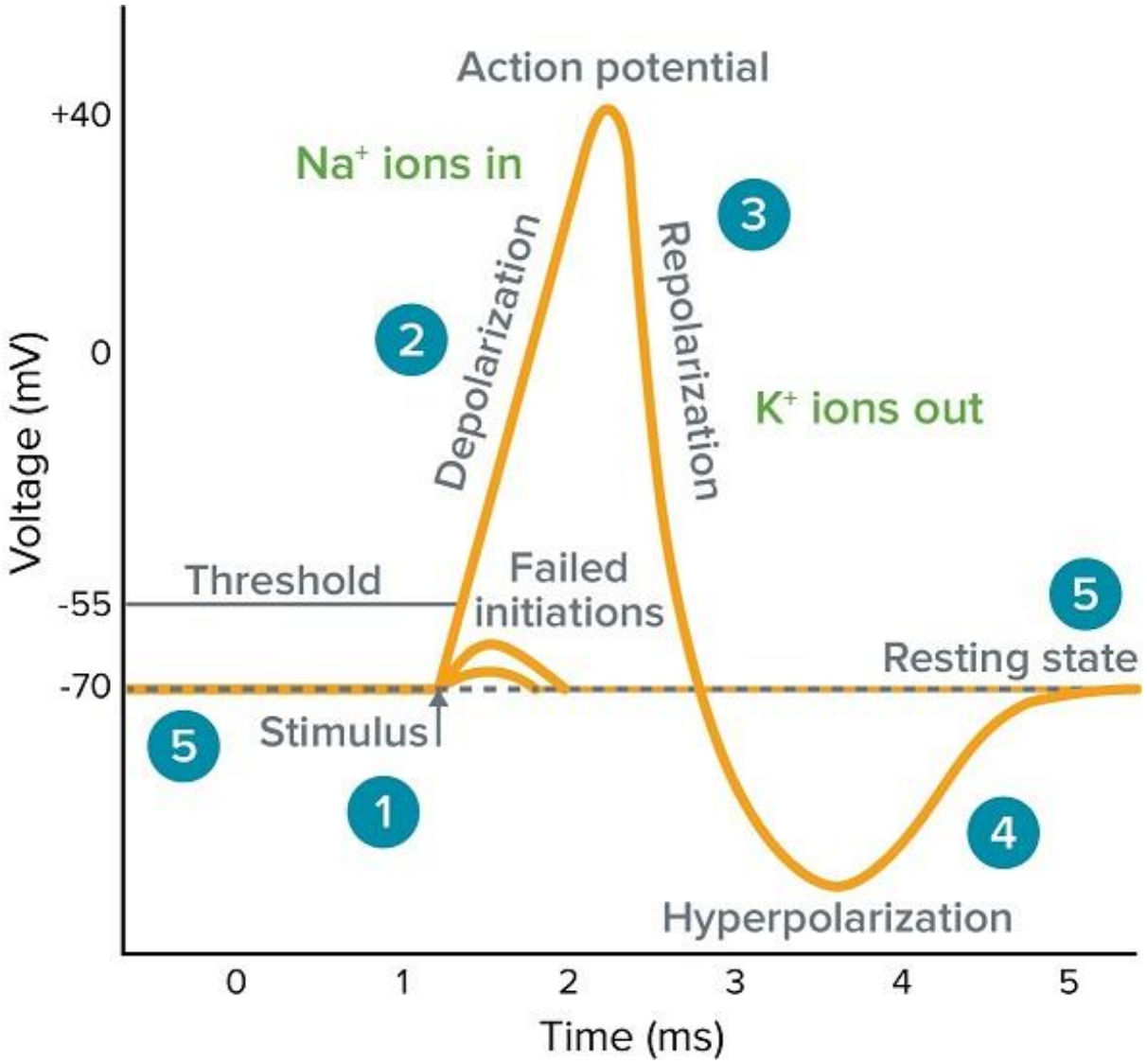
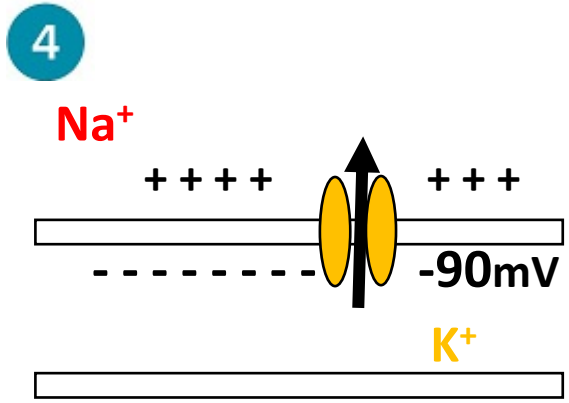
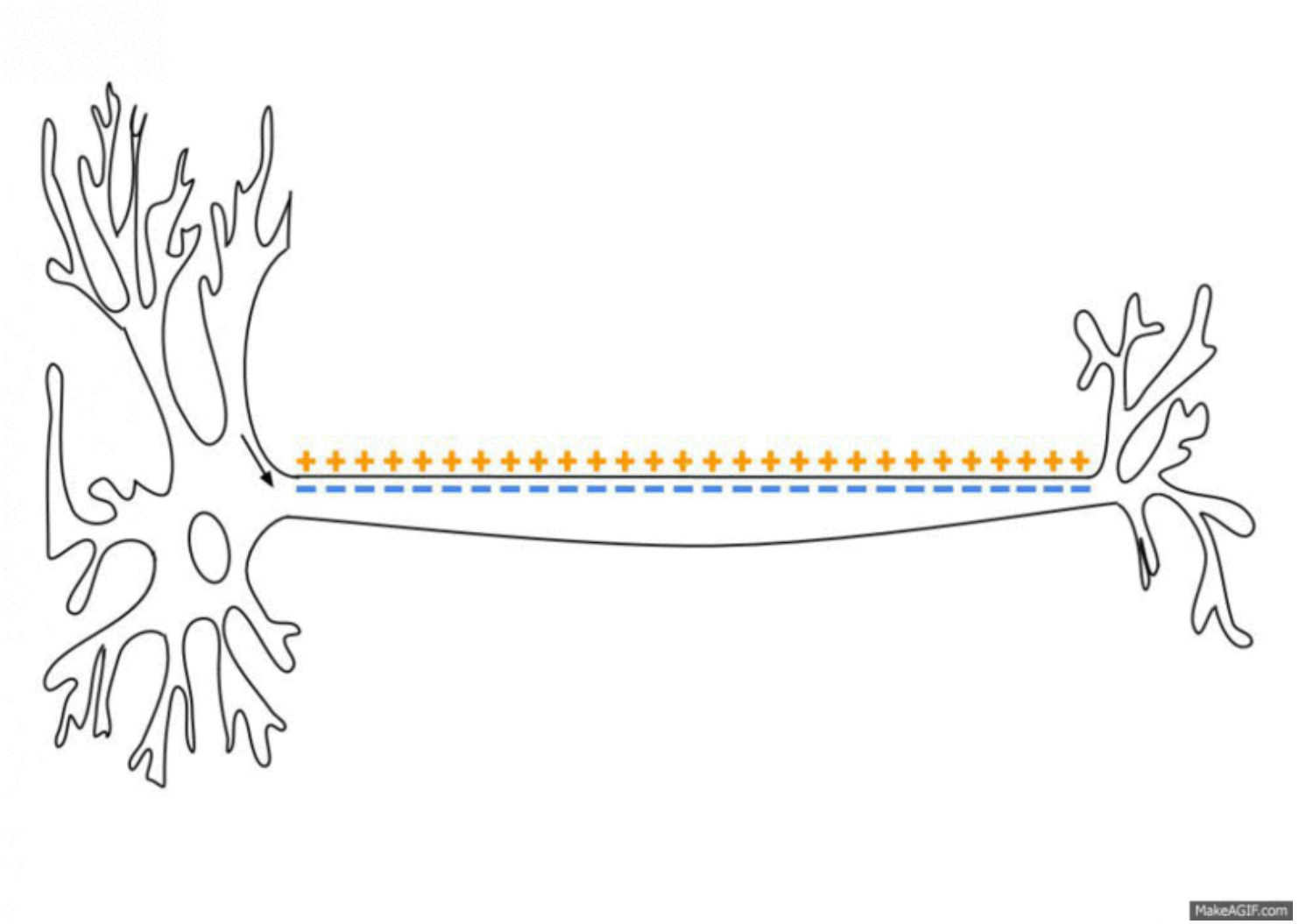




The resting membrane potential is established by the electrochemical gradient of ____$K^+$____

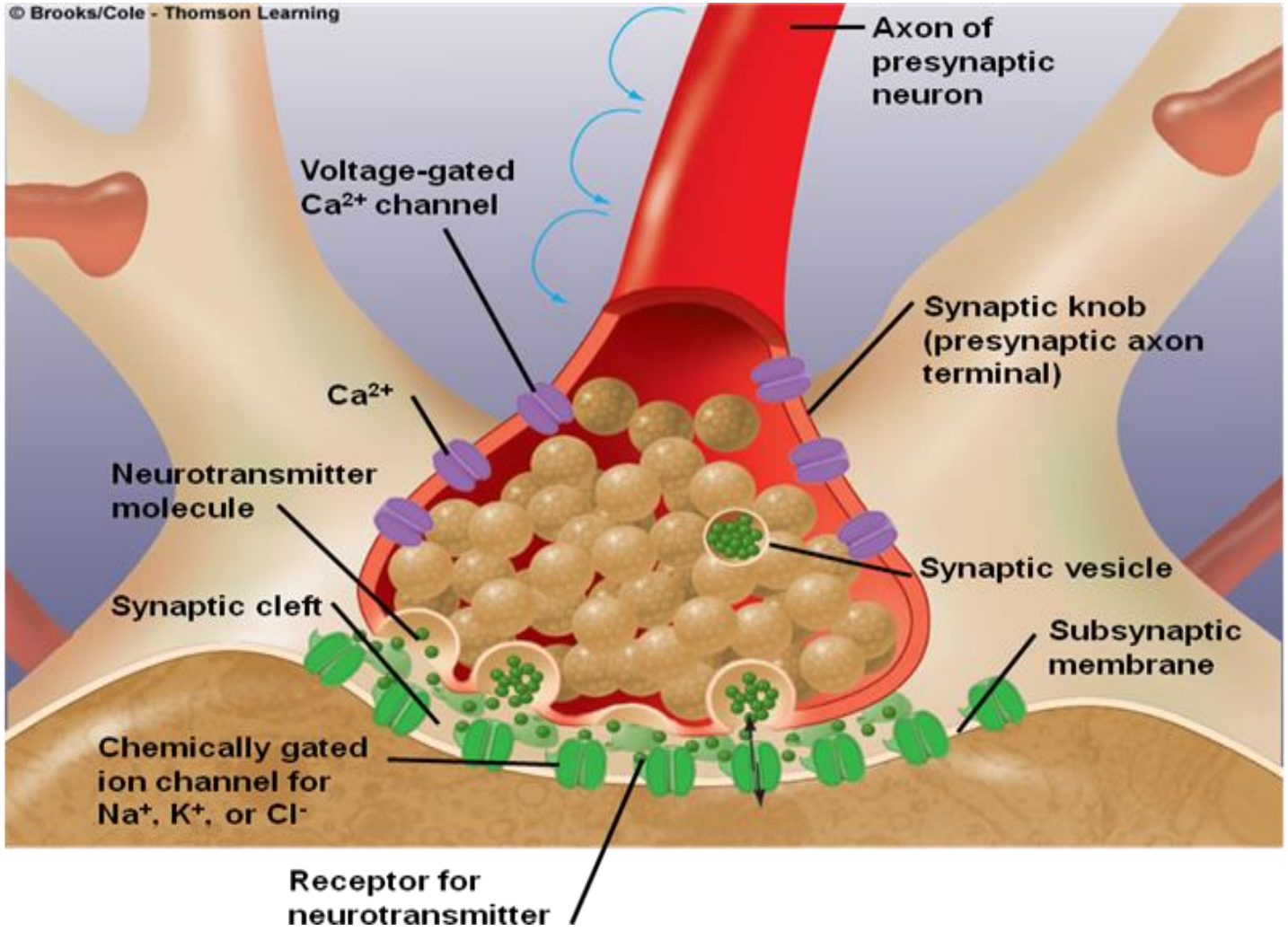
Depolarization occurs mainly due to the influx of ____$Na^+$____

Hyperpolarization occurs mainly due to the efflux of ____$K^+$____

The type of ion channel that accounts for rapid depolarization is ____Voltage-gated $Na^+$ Channels____

Action potentials move in one direction. T or F?

# The Synapse



# Neurotransmitters

- Endogenous chemicals that enable neurotransmission
- Released by the arrival of action potential (depolarization) at the nerve ending

# What Makes a Chemical Substance a Neurotransmitter?

1) The chemical must be synthesized in the neuron.
2) When the neuron is active, the chemical must be released and produce a response in some target.
3) The same response must be obtained when the chemical is experimentally placed on the target.
4) A mechanism must exist for removing the chemical from its site of activation after its work is done.

# Types of CNS neurotransmitters

- **Acetylcholine**
  - Nicotinic and muscarinic receptors
- **Amino acids**
  - ❖ **GABA** (gamma-aminobutyric acid)
    - $GABA_A$ and $GABA_B$ receptors
  - ❖ **Glycine**
    - Glycine receptors
  - ❖ **Glutamate**
    - AMPA and NMDA receptors
- **Biogenic Amines**
  - ❖ **Catecholamines**

    **Norepinephrine**
    - Adrenergic receptors

    **Dopamine**:
    - Dopamine receptors
  - ❖ **Serotonin**
    - Serotonin receptors
- **Peptides**
  - ❖ **Endogenous opioids**
    - Opioids receptors
  - ❖ **Substance P**

# Excitatory Neurotransmitters

- **Acetylcholine**

❖ **Glutamate**

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  - ❖ **Endogenous opioids**
    - Opioids receptors
  - ❖ **Substance P**

# Inhibitory Neurotransmitters

- **GABA** (gamma-aminobutyric acid)
- **Glycine**
- **Endogenous opioids**

# Excitatory vs Inhibitory

- **Acetylcholine**
- **Amino acids**
  - ❖ **GABA**
  - ❖ **Glycine**
  - ❖ **Glutamate**
- **Biogenic Amines**
  - ❖ **Catecholamines**

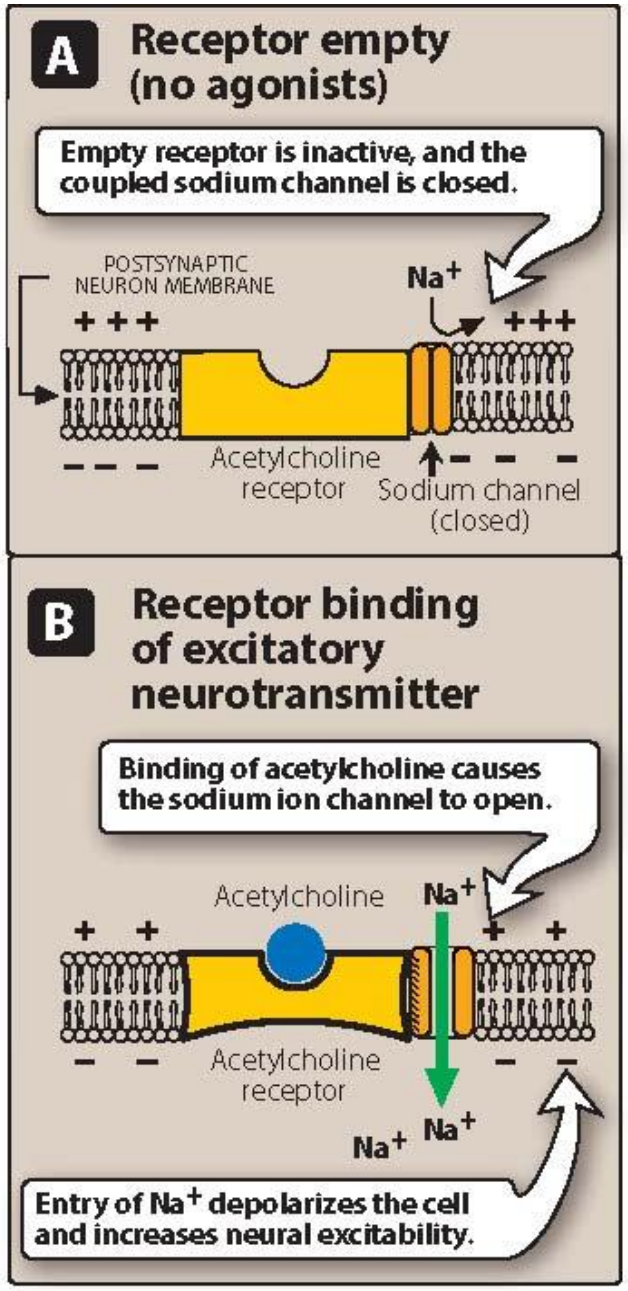
    **Norepinephrine**

    **Dopamine**
  - ❖ **Serotonin**
- **Peptides**
  - ❖ **Endogenous opioids**

| NEUROTRANSMITTER | | POSTSYNAPTIC EFFECTS |
|---|---|---|
| | Acetylcholine | Excitatory: Involved in arousal, short-term memory, learning and movement. |
| BIOGENIC AMINES | Norepinephrine | Excitatory: Involved in arousal, wakefulness, mood, and cardiovascular regulation. |
| | Dopamine | Excitatory: Involved in emotion, reward systems and motor control. |
| | Serotonin | Excitatory/Inhibitory: Feeding behavior, control of body temperature, modulation of sensory pathways including nociception (stimulation of pain nerve sensors), regulation of mood and emotion, and sleep/wakefulness. |
| AMINO ACIDS | GABA | Inhibitory: Increases $Cl^-$ flux into the postsynaptic neuron, resulting in hyperpolarization. Mediates the majority of inhibitory postsynaptic potentials. |
| | Glycine | Inhibitory: Increases $Cl^-$ flux into the postsynaptic neuron, resulting in hyperpolarization. |
| | Glutamate | Excitatory: Mediates excitatory $Na^+$ influx into the postsynaptic neuron. |
| NEURO-PEPTIDES | Substance P | Excitatory: Mediates nociception (pain) within the spinal cord. |
| | Met-enkephalin | Generally inhibitory: Mediates analgesia as well as other central nervous system effects. |

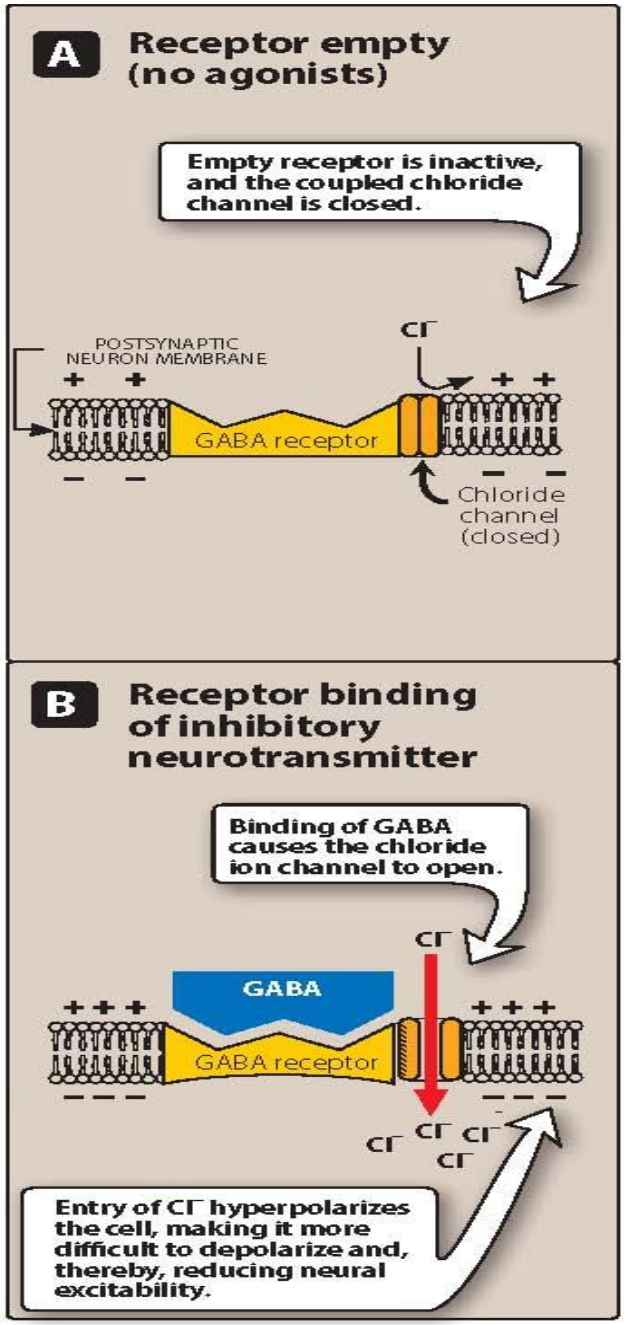
# Excitatory Postsynaptic Potentials (EPSP)

- Release of an excitatory NT
- NT binds to its receptor on the postsynaptic neuron
- **Influx of $Na^+$ or $Ca^{++}$ →** depolarization



# Inhibitory Postsynaptic Potentials (IPSP)

- Release of an inhibitory NT
- NT binds to its receptor on the postsynaptic neuron
- **Influx of $Cl^-$ or efflux of $K^+$ →** hyperpolarization

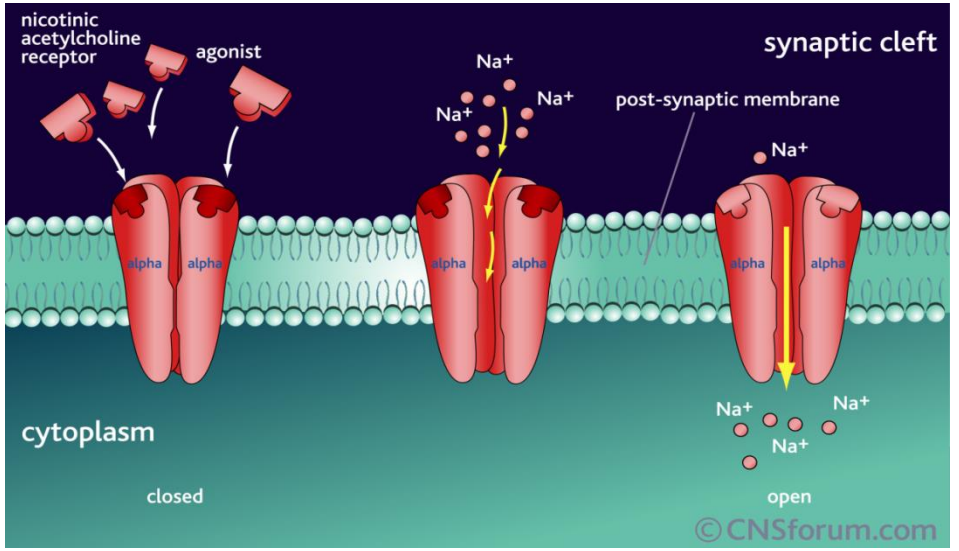


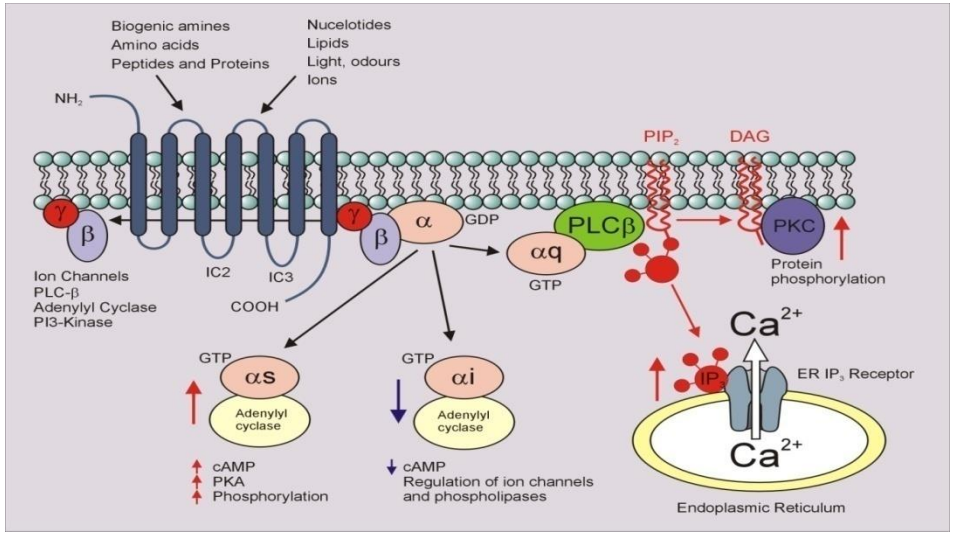
The predominant excitatory neurotransmitter in the brain is Glutamate

The predominant inhibitory neurotransmitter in the brain is Glycine

# Receptors

- Ionotropic
  - e.g., Ligand-gated ion channels
- Metabotropic
  - e.g., G-protein coupled receptors (GPCRs)
  - May or may NOT lead to ion channel opening.



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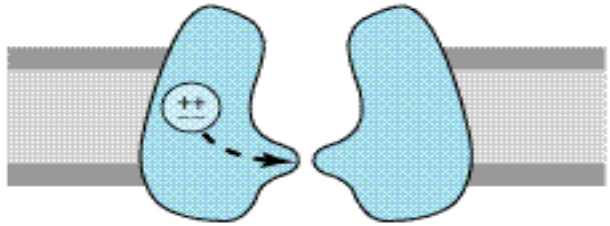

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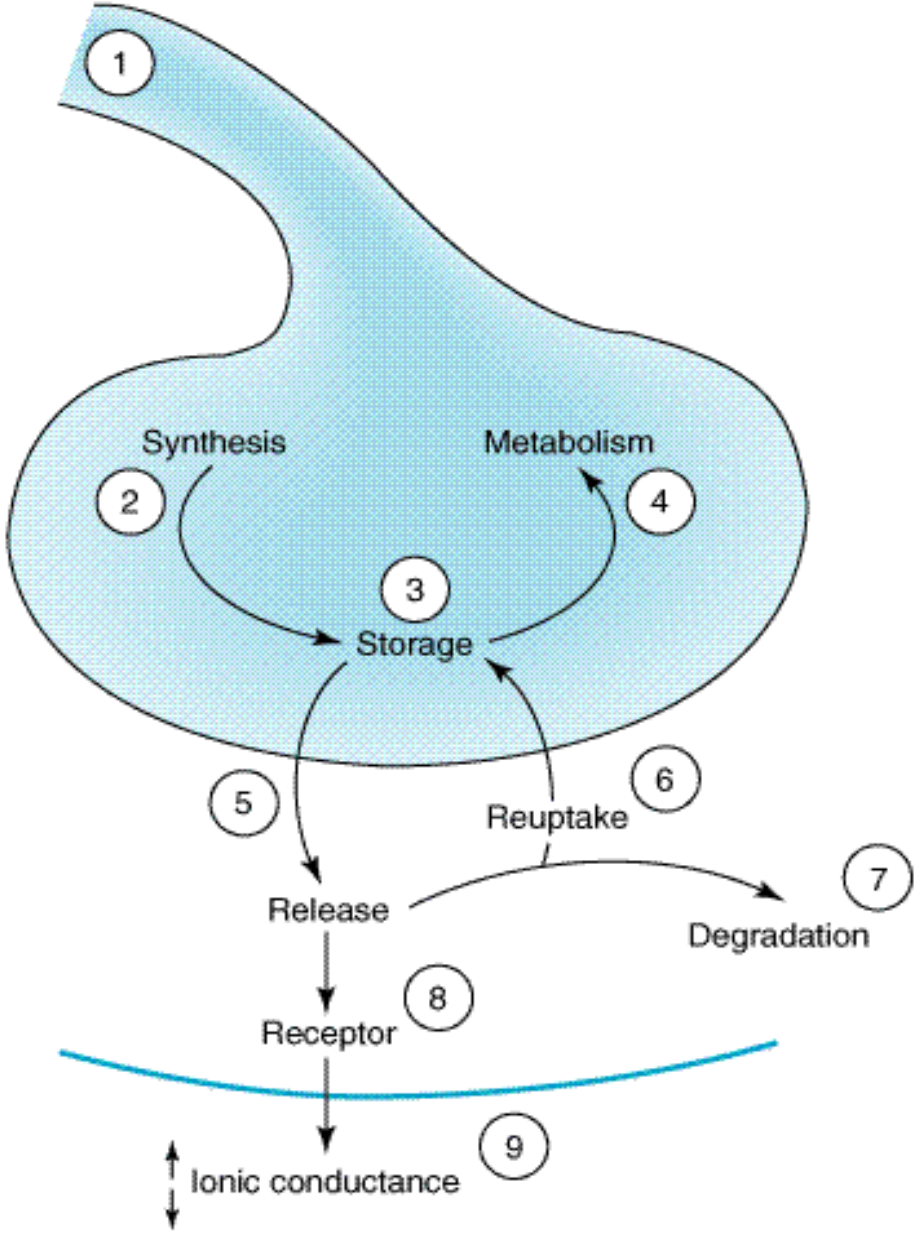
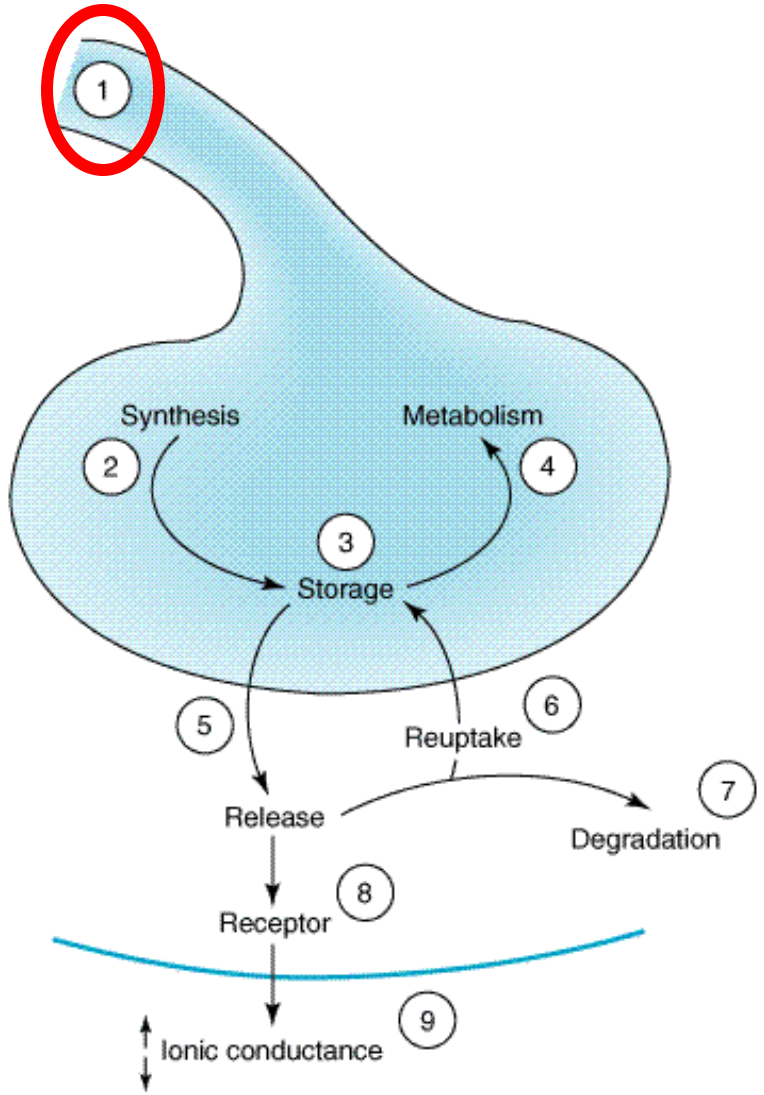
# Types of CNS Receptors

- **Excitatory**:
  - Ionotropic receptors:
    - Nicotinic acetylcholine receptors
  - Metabotropic receptors:
    - Muscarinic acetylcholine receptors
    - Dopamine ($D_1$) receptors
- **Inhibitory**:
  - Ionotropic receptors:
    - $GABA_A$ receptors
  - Metabotropic receptors:
    - Opioid receptors
    - $GABA_B$ receptors

# Neurotransmitter Cycle



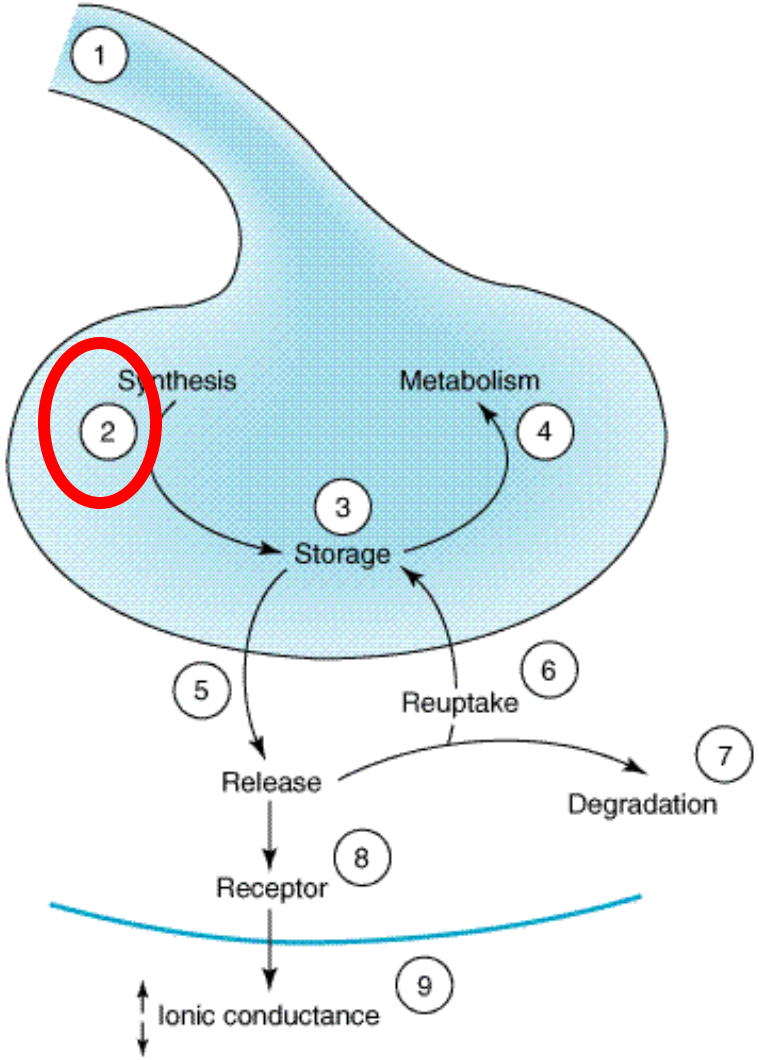
# Sites and Mechanisms of CNS Drug Action




Inhibit action potential presynaptically:

- Local Anesthetics
- General Anesthetics

# Sites and Mechanisms of CNS Drug Action

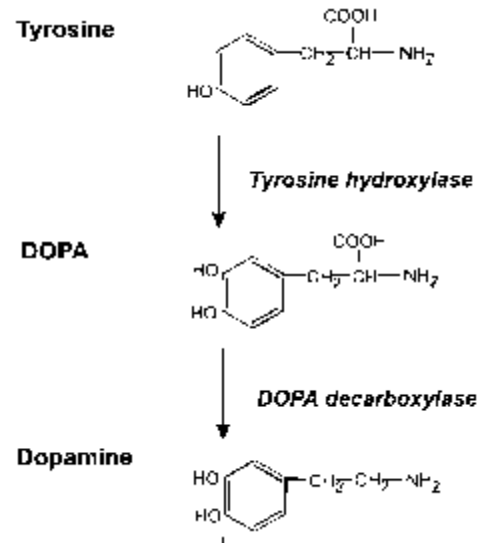



## Inhibit NT Synthesis:

- Tyrosine hydroxylase (catecholamines)

## Promote NT Synthesis:

- L-dopa



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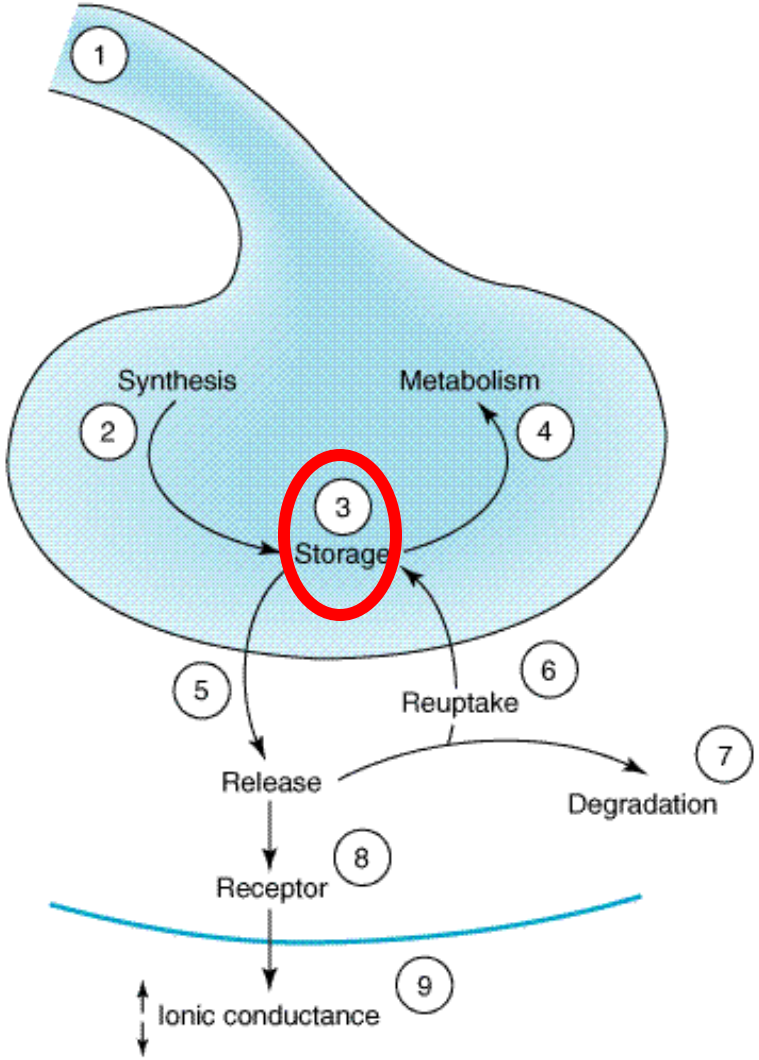
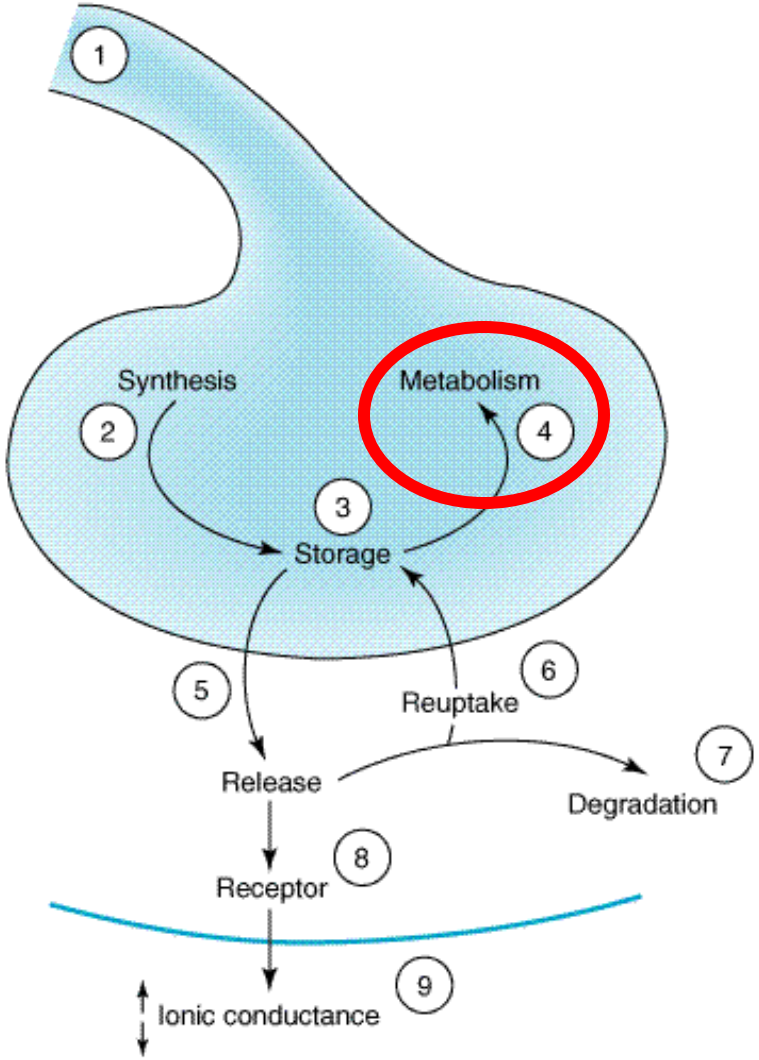



## Interference with storage:

- VMAT is inhibited by *reserpine*
  - Consequences?

# Sites and Mechanisms of CNS Drug Action

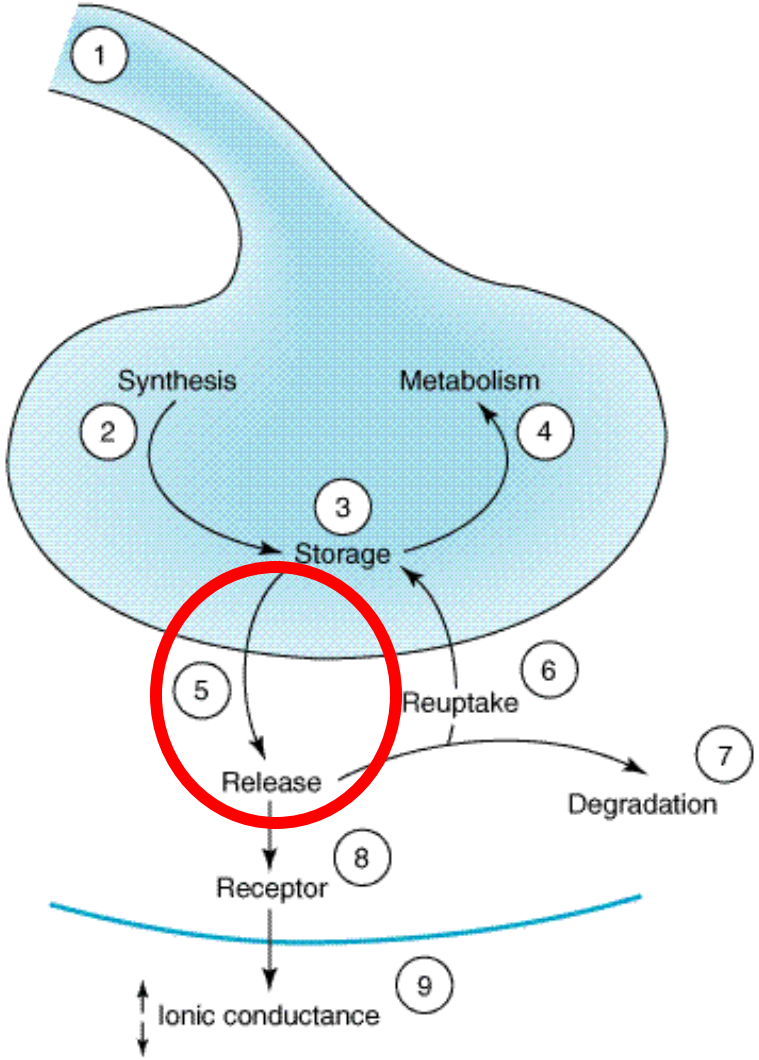



## Metabolism:

- COMT and MAO

- Antiparkinsonian
- Antidepressants

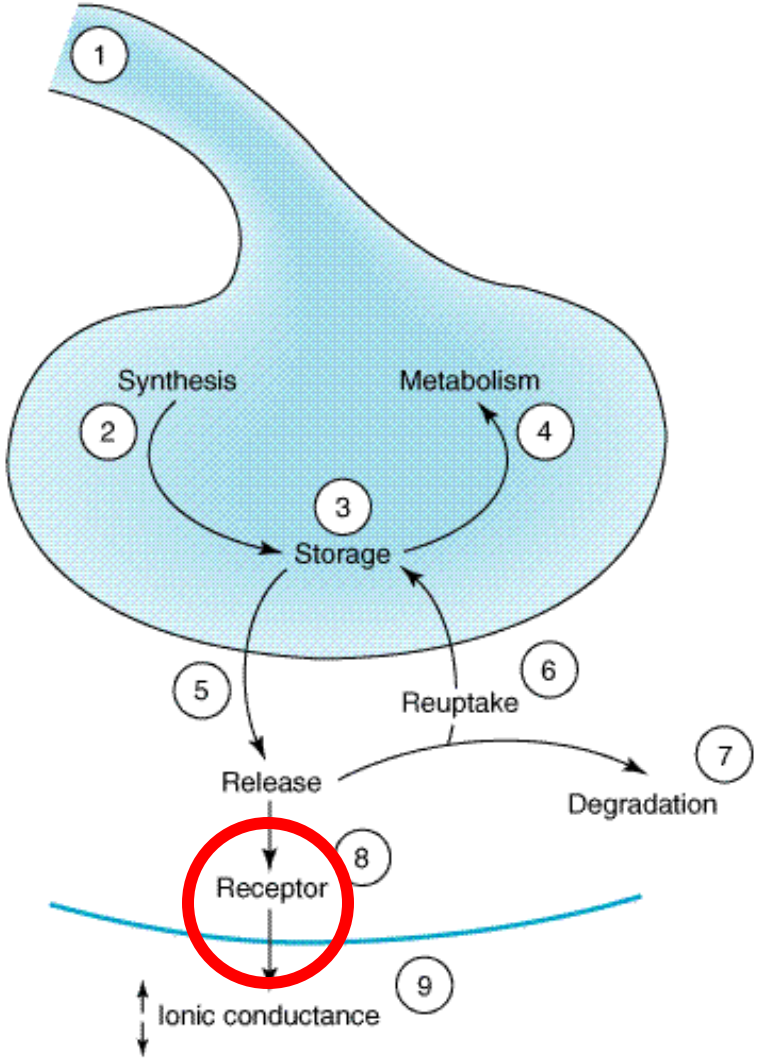
# Sites and Mechanisms of CNS Drug Action




## Release of NT:

- CNS stimulants

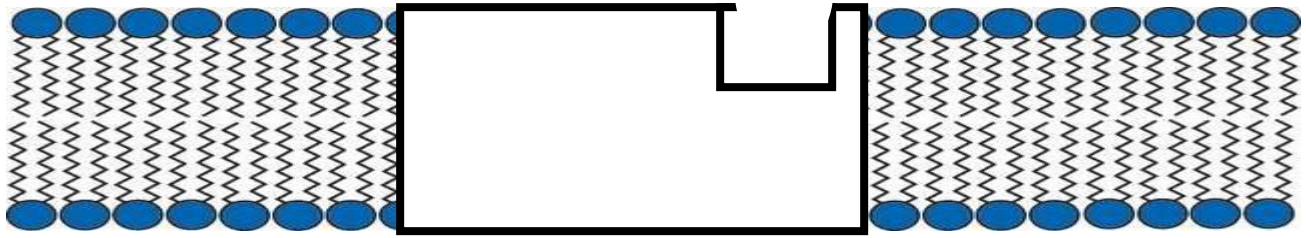
# Sites and Mechanisms of CNS Drug Action



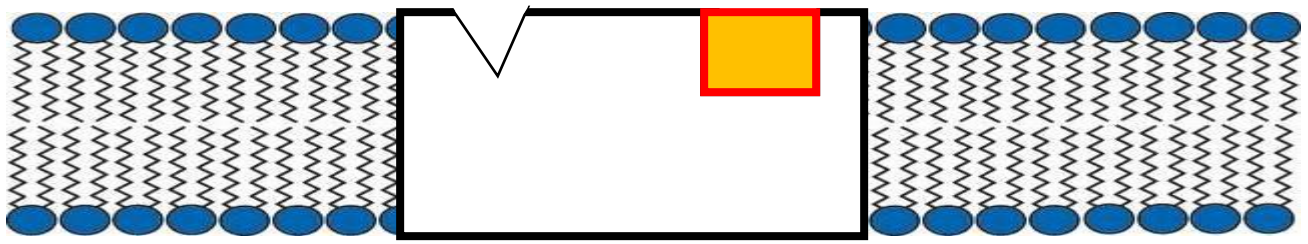

## NT action on receptor:

- Agonist
- Antagonist
- Biased agonist
- Allosteric modulators

Ligand

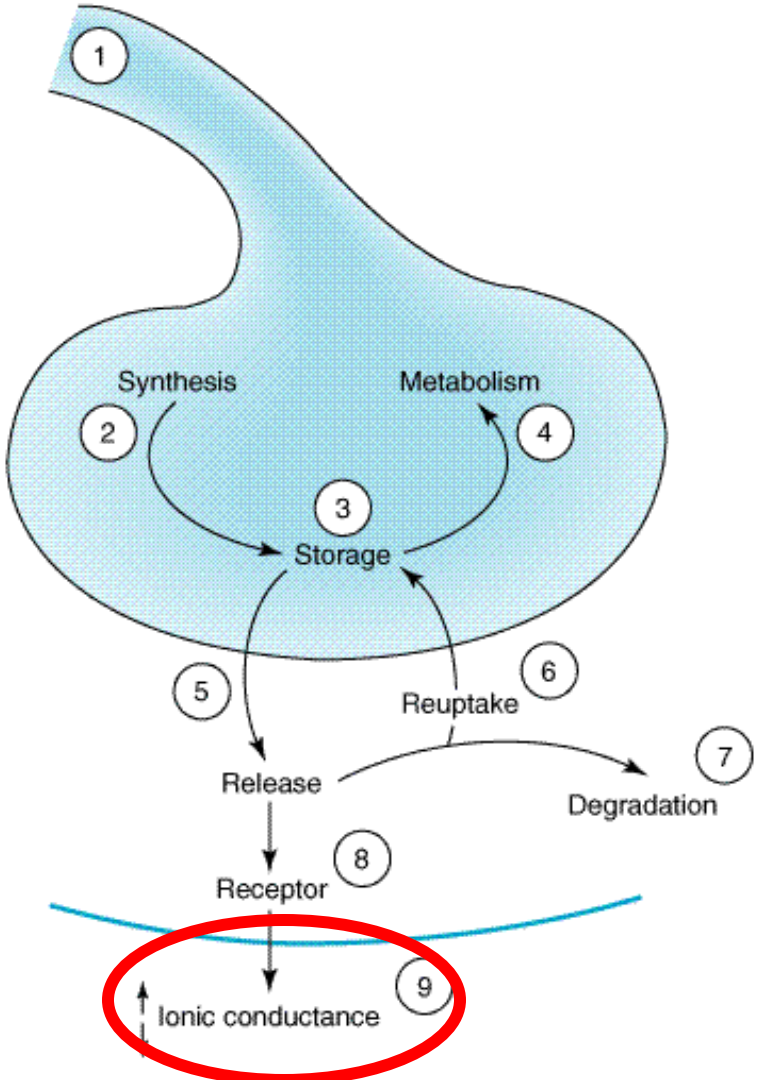


Allosteric modulator



Negative Allosteric modulator

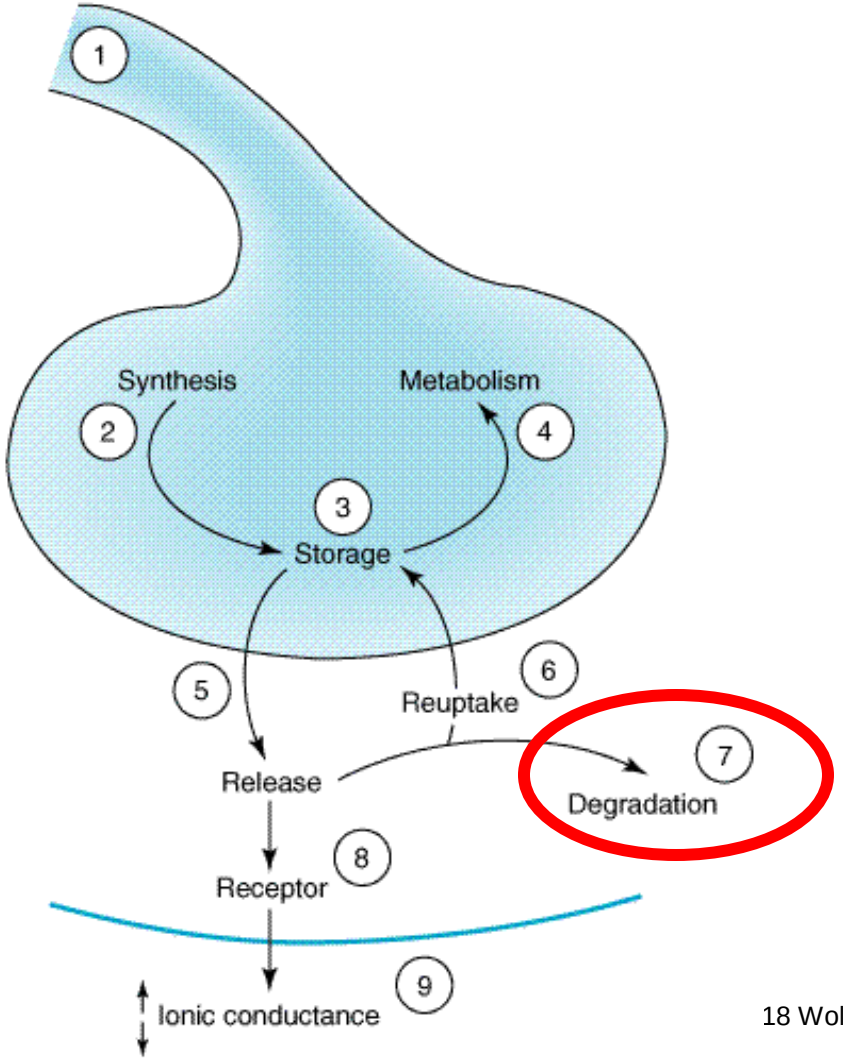
# Sites and Mechanisms of CNS Drug Action




## Intracellular effects:

- cAMP degradation inhibitors

# Sites and Mechanisms of CNS Drug Action

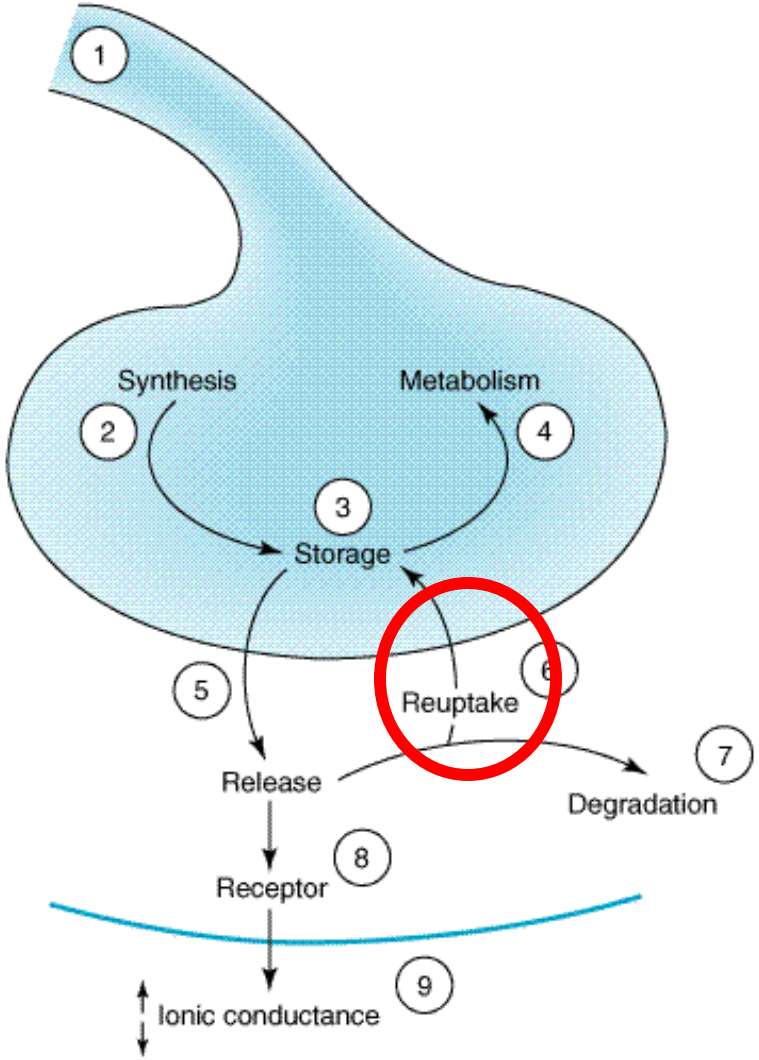



## Degradation of NT:

- Acetylcholine esterase inhibitors

Alzheimer's Disease

# Sites and Mechanisms of CNS Drug Action




NT reuptake:

•Antidepressants

$GABA_A$ receptors are example of:

a) Excitatory ionotropic receptors.
b) Inhibitory metabotropic receptors.
c) Voltage-gated channels
d) Inhibitory ionotropic receptors.
e) Excitatory metabotropic receptors

Which ion is allowed inside the cell upon $GABA_A$ receptor stimulation?

You are the leading physician-scientist of the research and development team in a pharmaceutical company. Your team is working on the development of novel therapies to treat Parkinson's disease. Parkinson's disease is characterized by decreased dopaminergic stimulation in the brain. In your research proposal, you include several strategies to improve parkinsonism by targeting different biochemical processes of dopamine signaling. Which of the following mechanisms will NOT be included in your proposal?

a) Inhibition of the vesicular monoamine transporter 2 (VMAT-2).
b) Inhibition of catechol-O-methyltransferase (COMT)
c) Designing more efficacious $D_2$ receptor agonists.
d) Designing novel therapies that promote the regeneration of substantia nigra dopaminergic neurons.


- Thank you
- Questions?