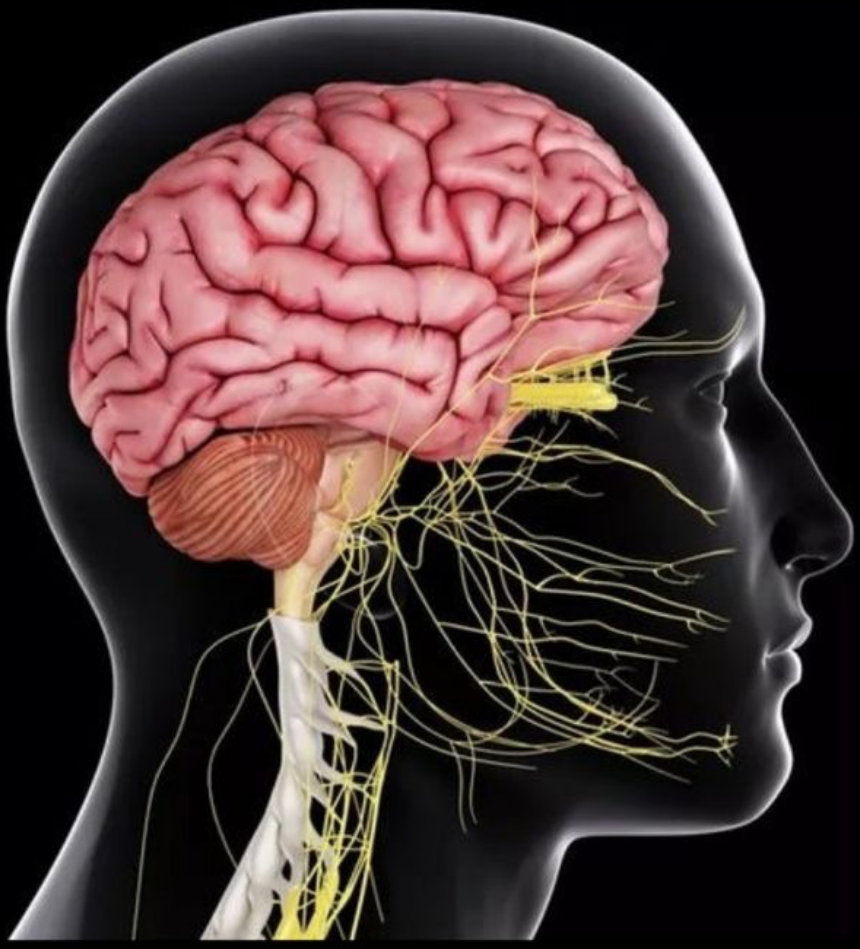
CENTRAL NERVOUS SYSTEM



SUBJECT : Pharmacology

LEC NO. : 1

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وَقُل رَّبِّ زِدْنِي عِلْمًا

Introduction

Pharmacology and Toxicology

Central Nervous System Module

Third Year Medical Students

Tareq Saleh, MD, PhD

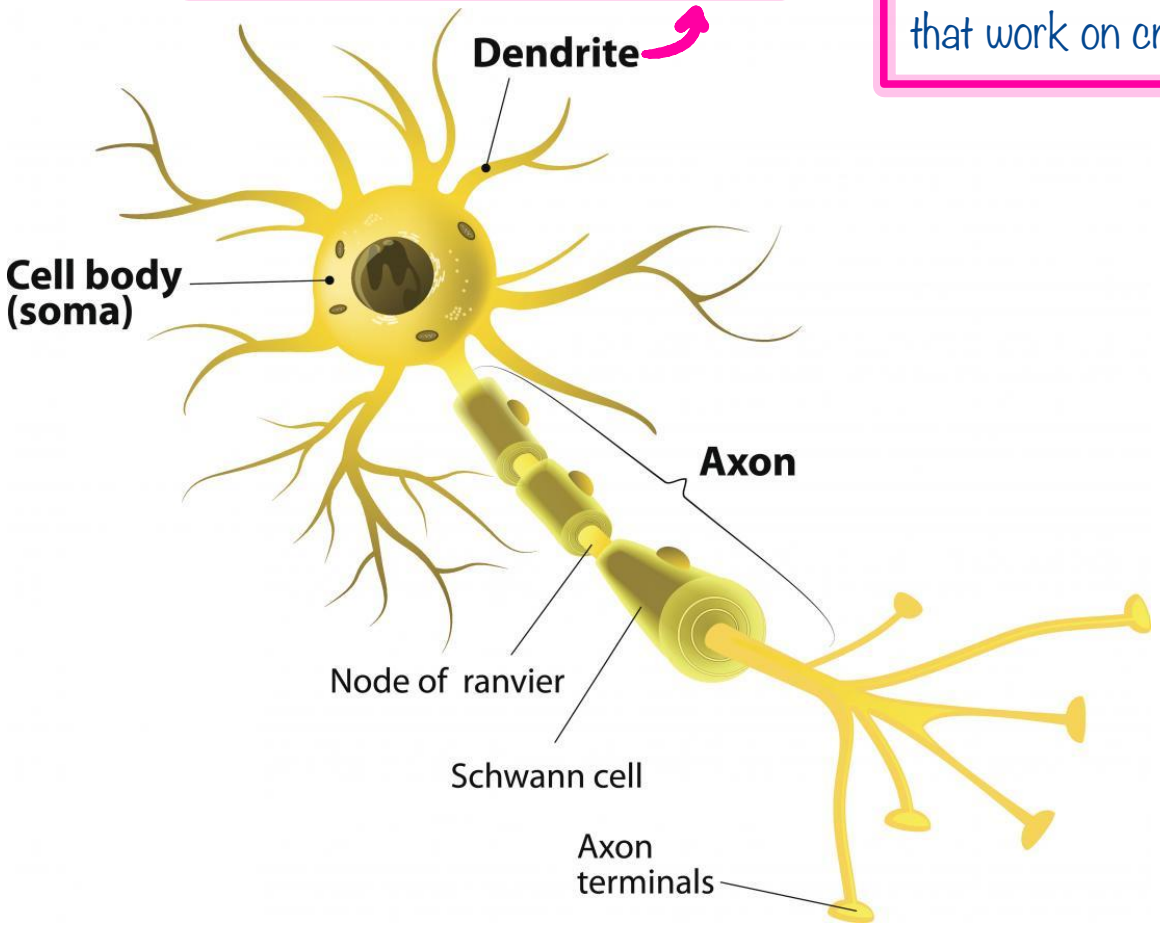
Faculty of Medicine

The Hashemite University

The Neuron

For communication and signaling

Functional unit of central nervous system, all drugs that work on cns will affect the neuron somehow



All neurons work by exhibiting an action potential but it differs wether it's inhibitory or excitatory, and from which circuit its working

Action Potential

Outward leakage of potassium from the membrane

5 Resting membrane potential

Na+ + + + + + + + + +

- - - - - - - - - - - -70mV

K+

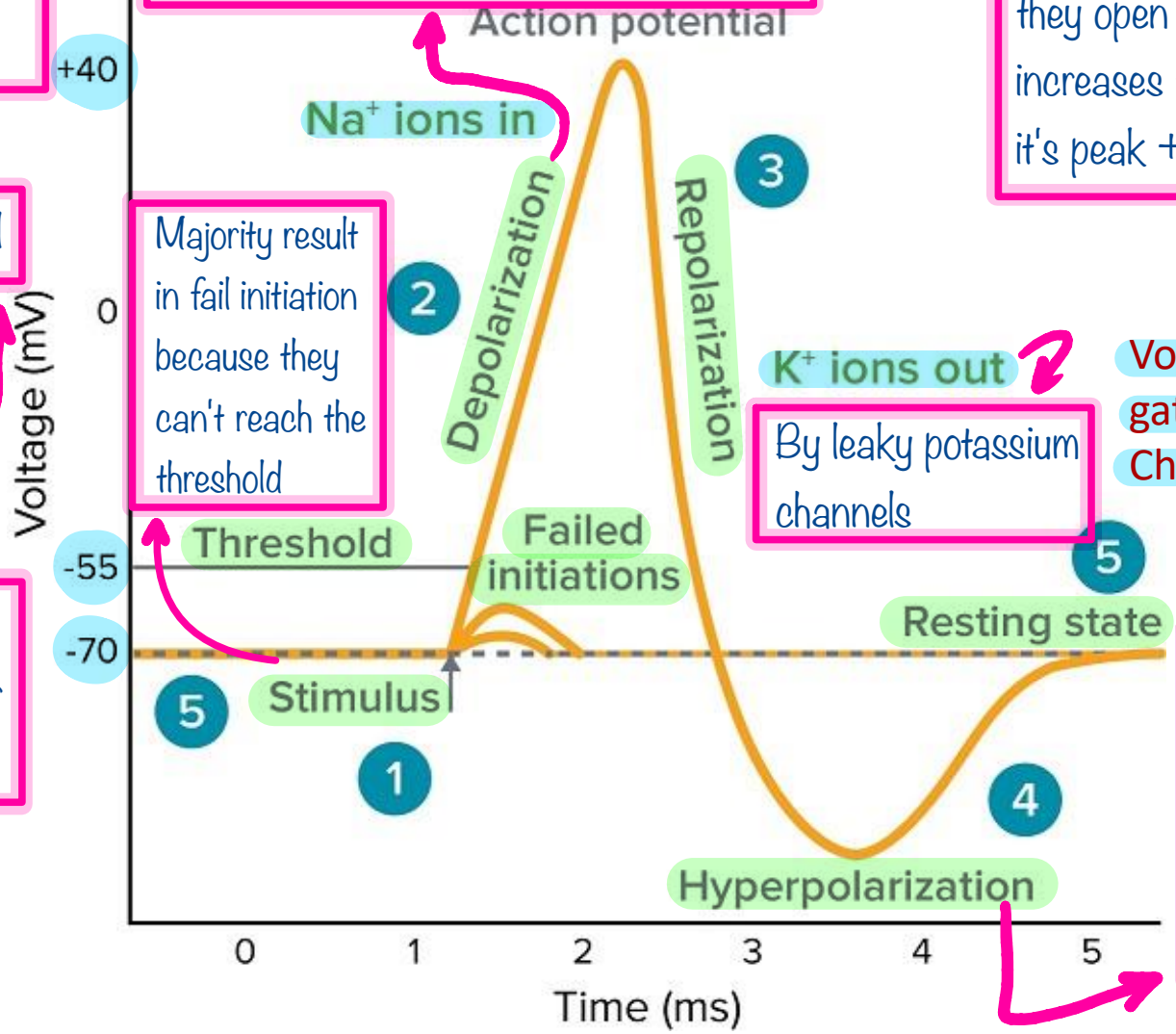
Main extracellular cation

Main intracellular cation

Main contributor to the resting membrane potential » leaky channel of potassium

Rapid influx of positive ions into the cell

Majority result in fail initiation because they can't reach the threshold



Once membrane potential reaches - 55 (threshold) they open allowing influx of sodium which gradually increases the voltage of the neuron until it reaches it's peak +40 then they start to close

By leaky potassium channels

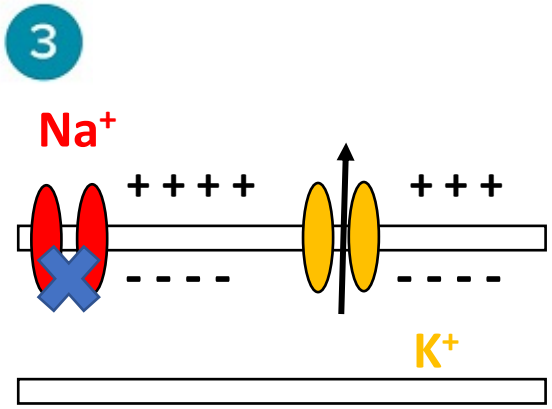
Voltage-gated Na+ Channels

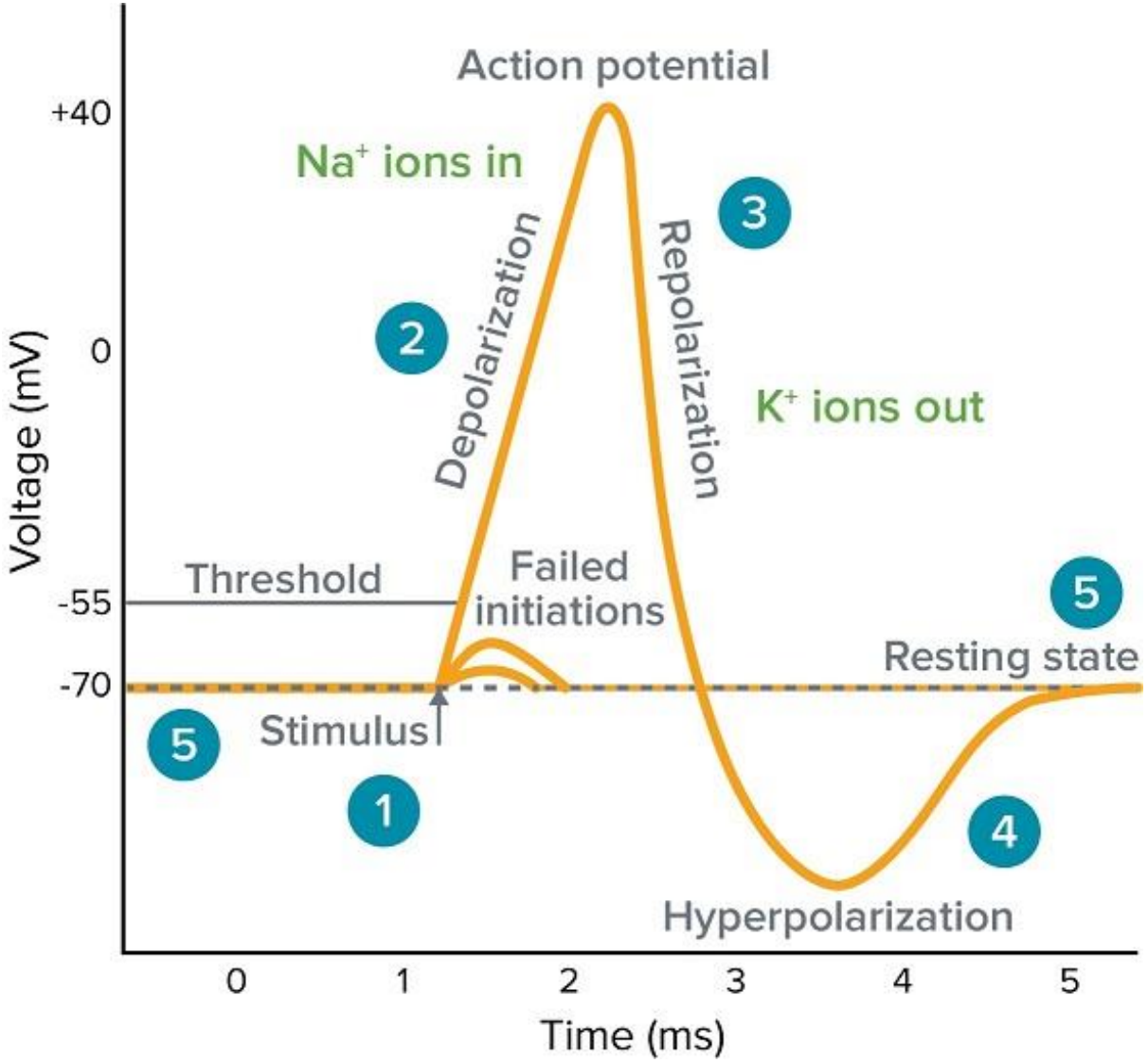
2 Na+ - - - - + + + + + + + + +40mV K+

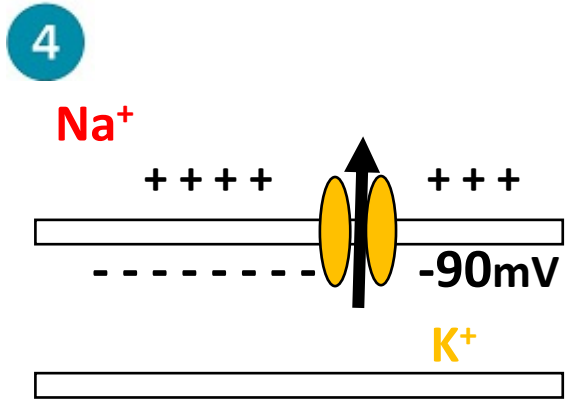
Excessive leakage of potassium ions from outside the cell voltage is about -90, the sodium potassium pump fixes the gradient to reach resting membrane potential once again

Wolters Kluwer

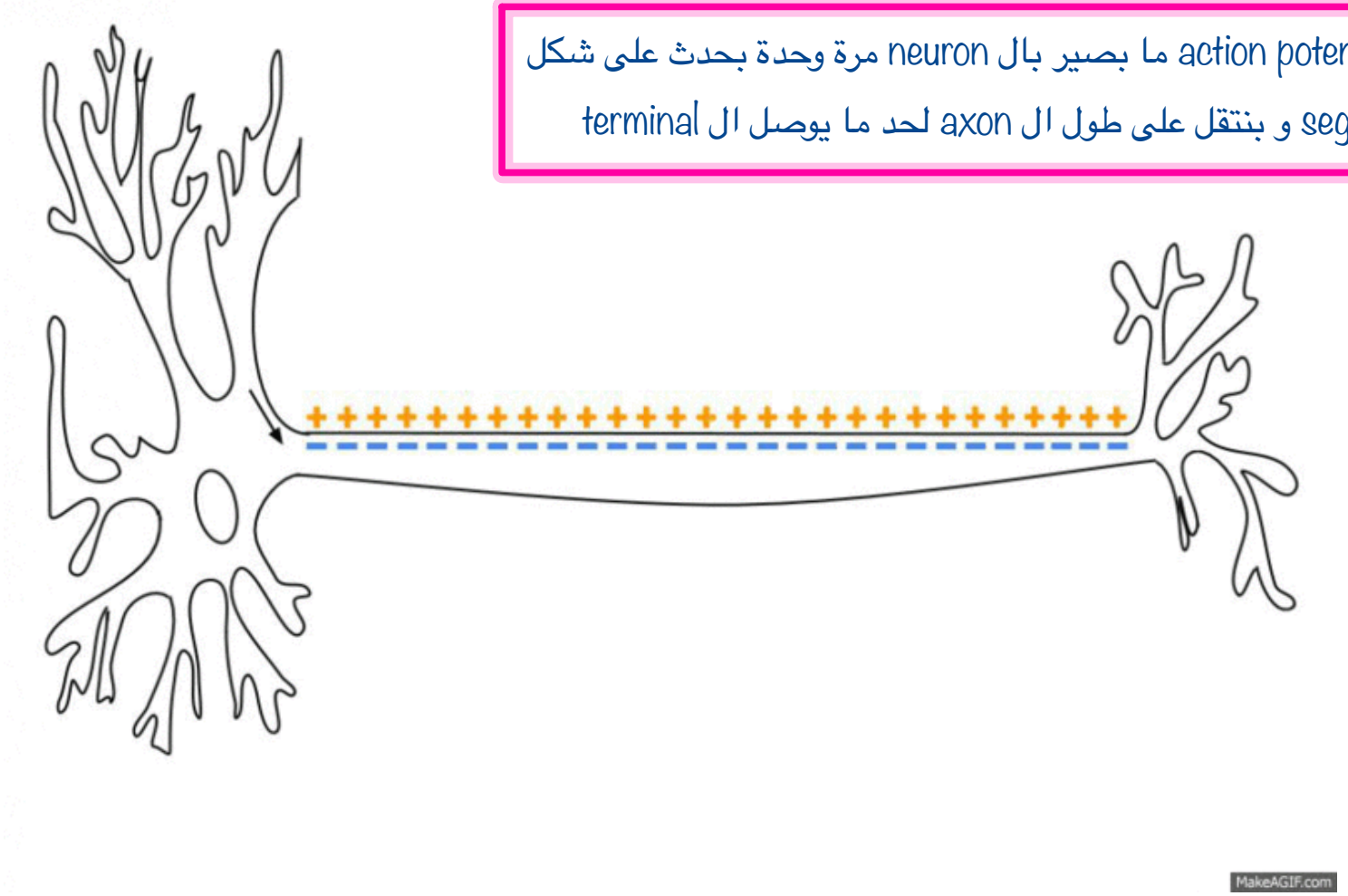
Action Potential







ال action potential ما بصير بال neuron مرة وحدة بحدث على شكل segments و بنتقل على طول ال axon لحد ما يوصل ال terminal



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^+____

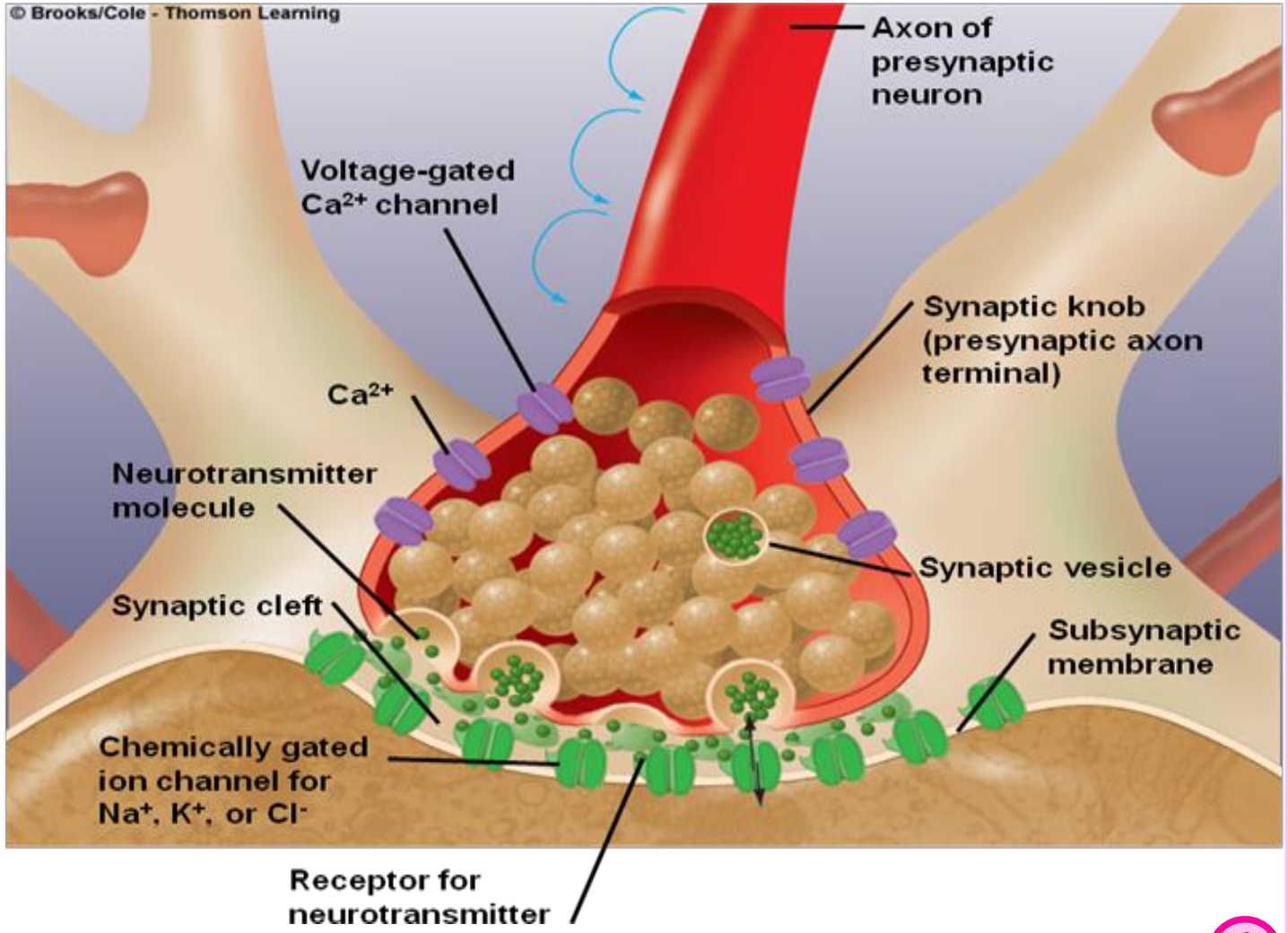
The type of ion channel that accounts for rapid depolarization is ____Voltage-gated Na^+ Channels____

Action potentials move in one direction. T or F?

In the central nervous system the post synaptic structure is a neuron

The Synapse

When action potential reaches the terminal of the neuron it will result with it's activation » the neuron will and up releasing the neurotransmitter .. There's different types of neurons depending on neurotransmitter they release which depends on the function but all of them undergo prestorage of neurotransmitters inside presynaptic vesicles so they're ready to be released as soon at the action potential reaches the terminal



action potential will also cause voltage gated calcium channels to open resulting in entry of calcium ions which play an important role in degranulating the neurotransmitter containing vesicles to the synaptic cleft where they bind to their receptors on postsynaptic neuron membrane, and it's the main site of degradation of neurotransmitters some neurotransmitters get reuptaken and degraded within the presynaptic neuron

Neurotransmitters

Action / effect of activation of presynaptic neuron differs from neuron to another » that what treats the diversity of membrane functions

Must be endogenous » must be synthesized by neurons

If substance is neuro active but not synthesized within the neuron » not a neurotransmitter

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

Not at a random time

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. → Consistency of the response
4) A mechanism must exist for removing the chemical from its site of activation after its work is done.

↓

Neurotransmitters must have pathways to synthesize it as well as to remove it (degradation and metabolism) to terminate their effect

Types of CNS neurotransmitters

- **Acetylcholine** — Excitatory
  - Nicotinic and muscarinic receptors
- **Amino acids** — Inhibitory neurotransmitter in the brain and spinal cord
  - ❖ **GABA** (gamma-aminobutyric acid)
    - $GABA_A$ and $GABA_B$ receptors
  - ❖ **Glycine** — Most dominant inhibitory
    - Glycine receptors
  - ❖ **Glutamate** — Most dominant excitatory
    - AMPA and NMDA receptors

Different receptors » different functions but it's excitatory in both cases

- **Biogenic Amines**
  - ❖ **Catecholamines**

Norepinephrine
- Adrenergic receptors

Dopamine:
- Dopamine receptors

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

Excitatory Neurotransmitters

- **Acetylcholine**

❖ **Glutamate**

Inhibitory Neurotransmitters

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

Excitatory vs Inhibitory

- **Acetylcholine**

- **Amino acids**
  - ❖ **GABA**
  - ❖ **Glycine**
  - ❖ **Glutamate**

- **Biogenic Amines**
  - ❖ **Catecholamines**

Norepinephrine

Dopamine

❖ **Serotonin**

They exert mixed function they could be excitatory or inhibitory depending on the pathway and the receptor

- **Peptides**
  - ❖ **Endogenous opioids**

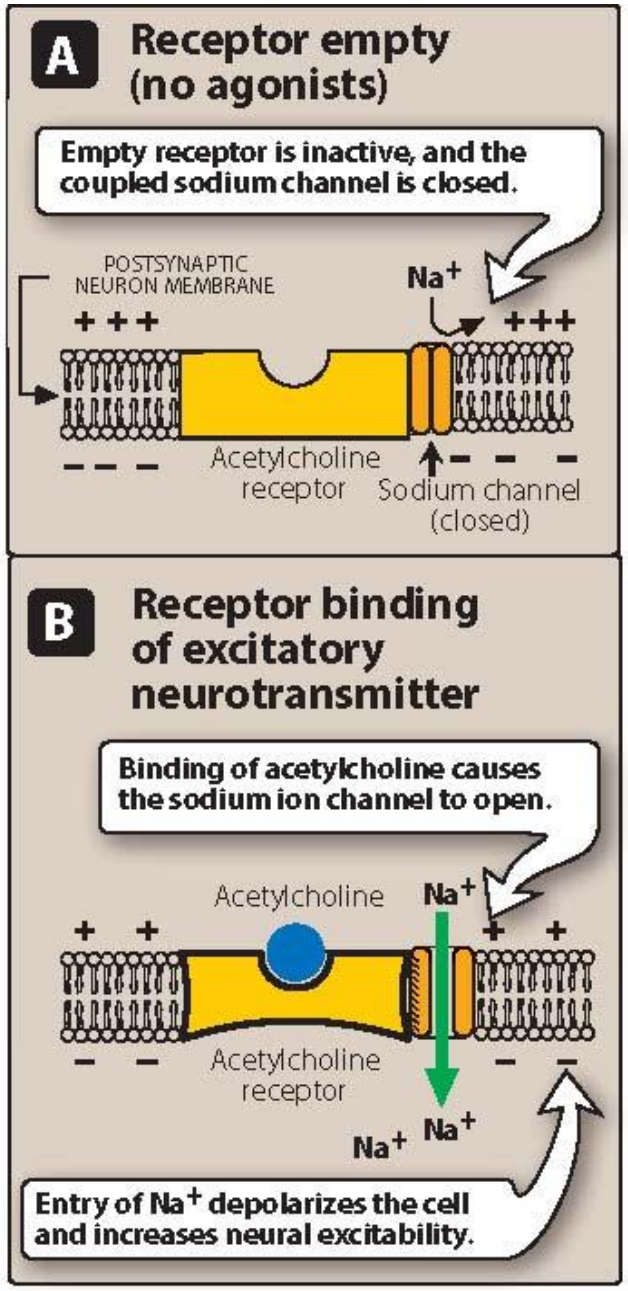
NEUROTRANSMITTER		POSTSYNAPTIC EFFECTS
	Acetylcholine	Excitatory: Involved in arousal, short-term memory, learning and movement.
BIOGENIC AMINES	Norepinephrine	Excitatory: Involved in arousal, wakefulness, mood, and cardiovascular regulation.
	Dopamine	Excitatory: Involved in emotion, reward systems 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.

① Excitatory Postsynaptic Potentials (EPSP)

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

Excitatory postsynaptic receptor

Activation

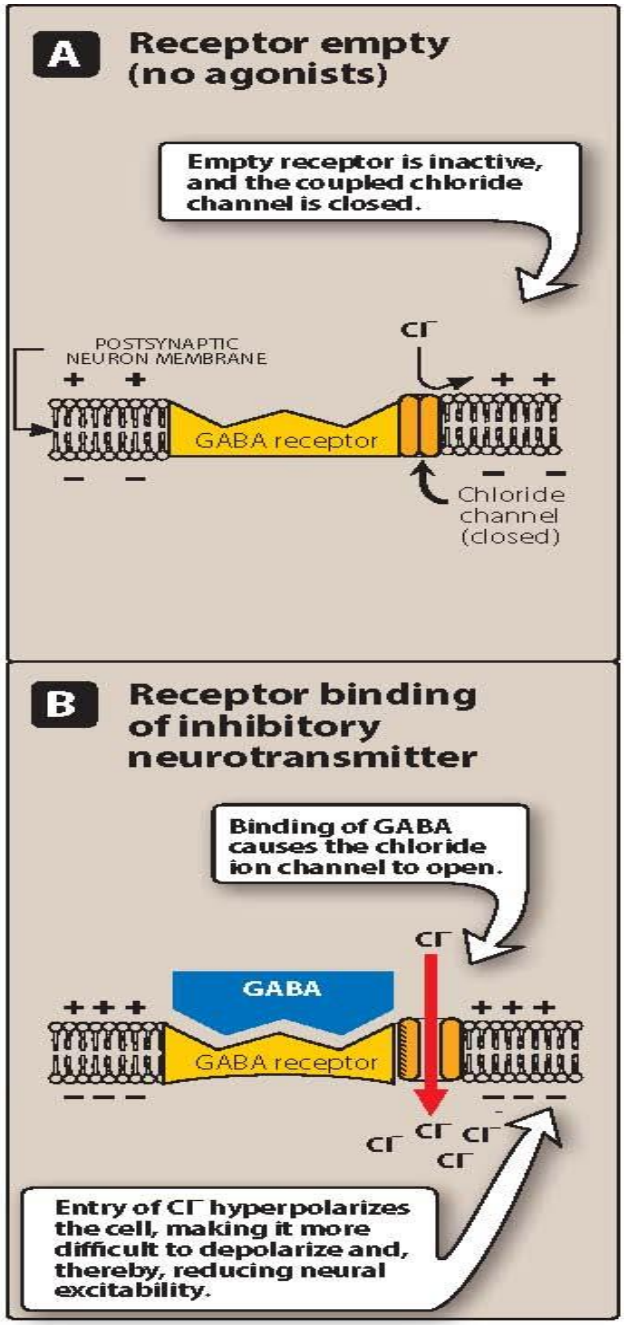


② Inhibitory Postsynaptic Potentials (IPSP)

- Release of an inhibitory NT
- NT binds to its receptor on the postsynaptic neuron

Inhibitory postsynaptic receptor

- **Influx of Cl^- or efflux of K^+** → hyperpolarization



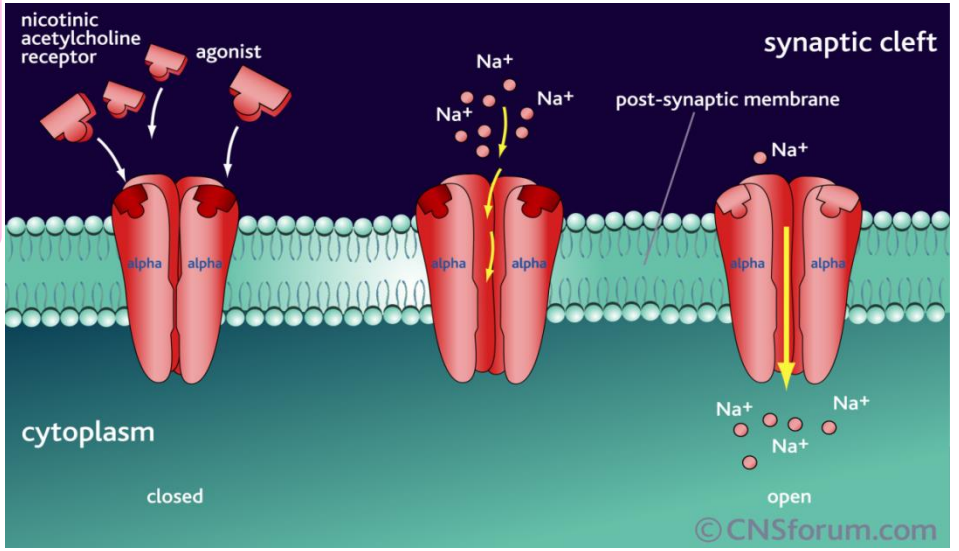
The predominant excitatory neurotransmitter in the brain is Glutamate

The predominant inhibitory neurotransmitter in the brain is Glycine

Receptors

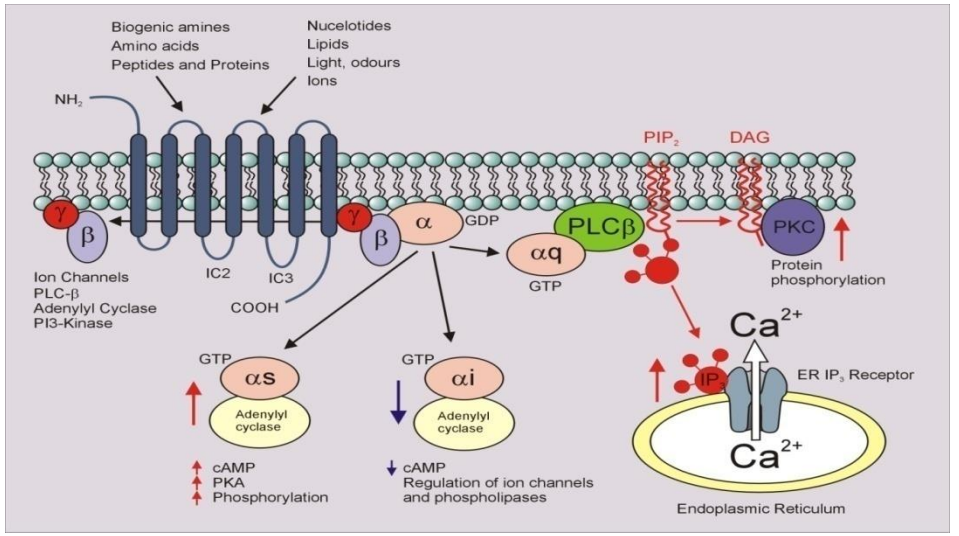
- Ionotropic
  - e.g., Ligand-gated ion channels

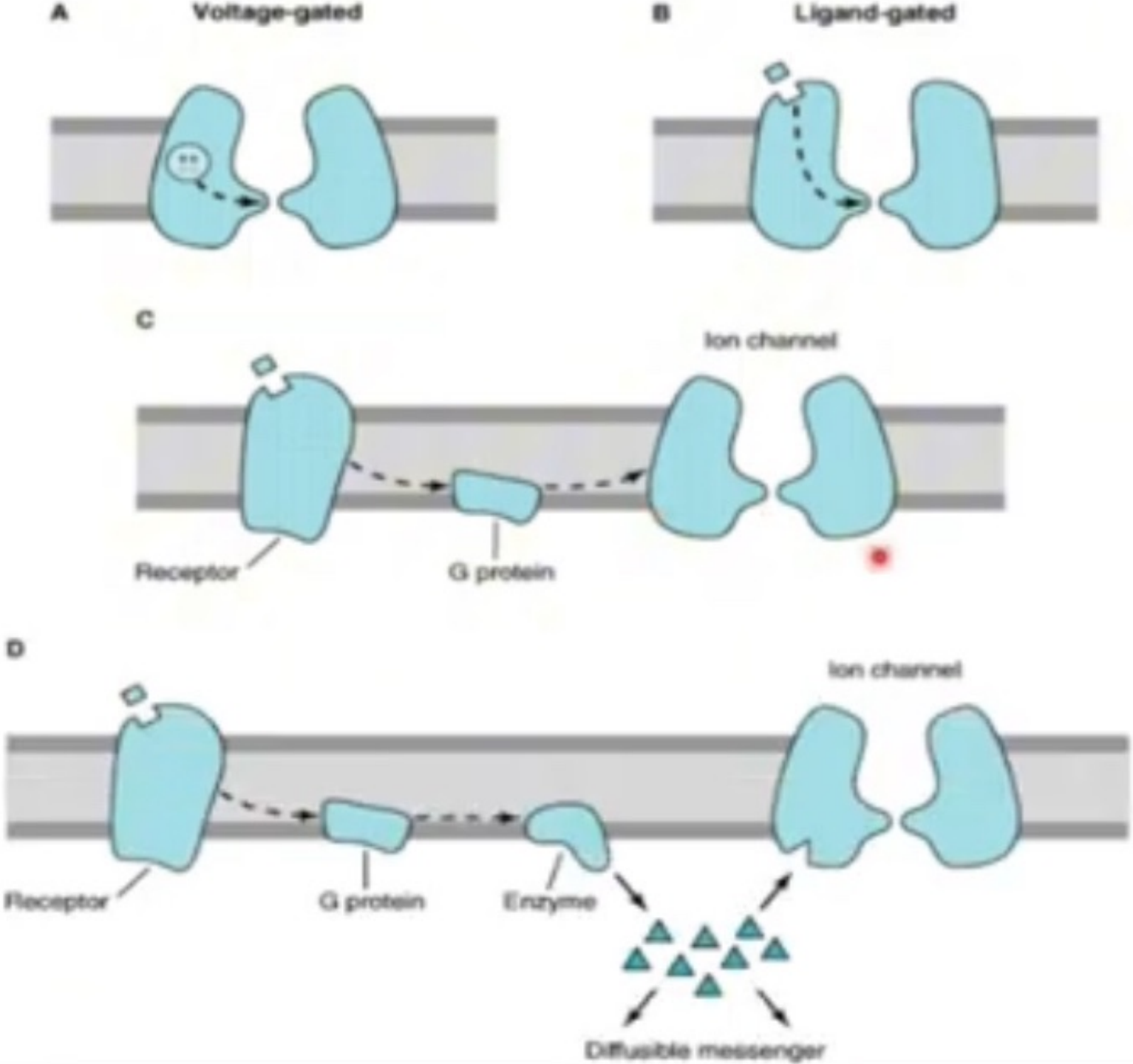
Binding of ligand (neurotransmitter or drug) will lead to their activation that will result with passage of ions like sodium, potassium, chloride



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

G-protein modulates the function of ion channel





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

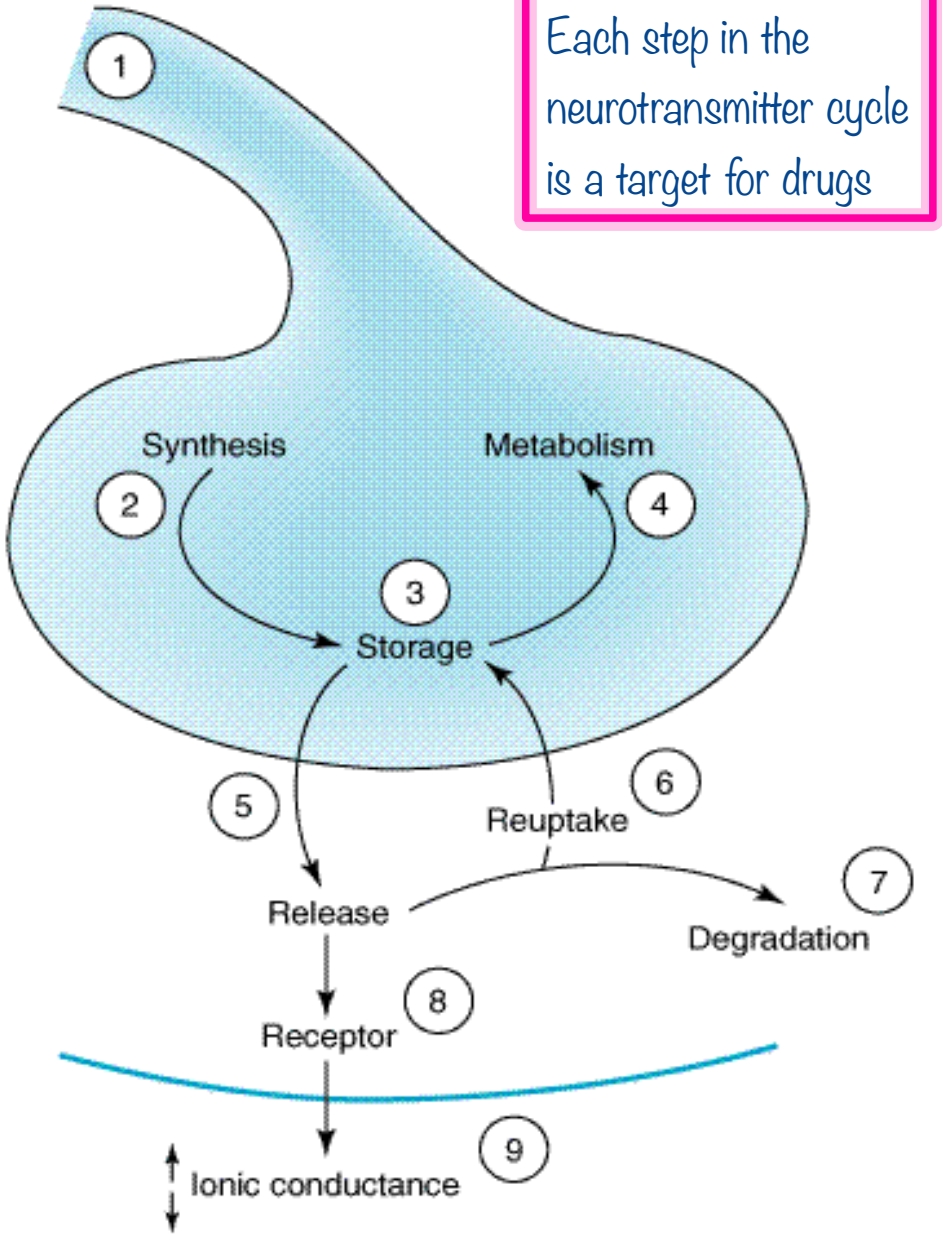
They're ligand gated ion channels, 2 molecules of acetylcholine bind to nicotinic receptor which is sodium channels which cause conformational changes in it resulting in opening of sodium channel with influx of sodium ions

They're G-protein coupled receptor with different types of actions

They're ligand gated chloride channels, binding of GABA to the receptor causes influx of chloride resulting in hyperpolarization which inhibits postsynaptic neuron

G-protein coupled receptor

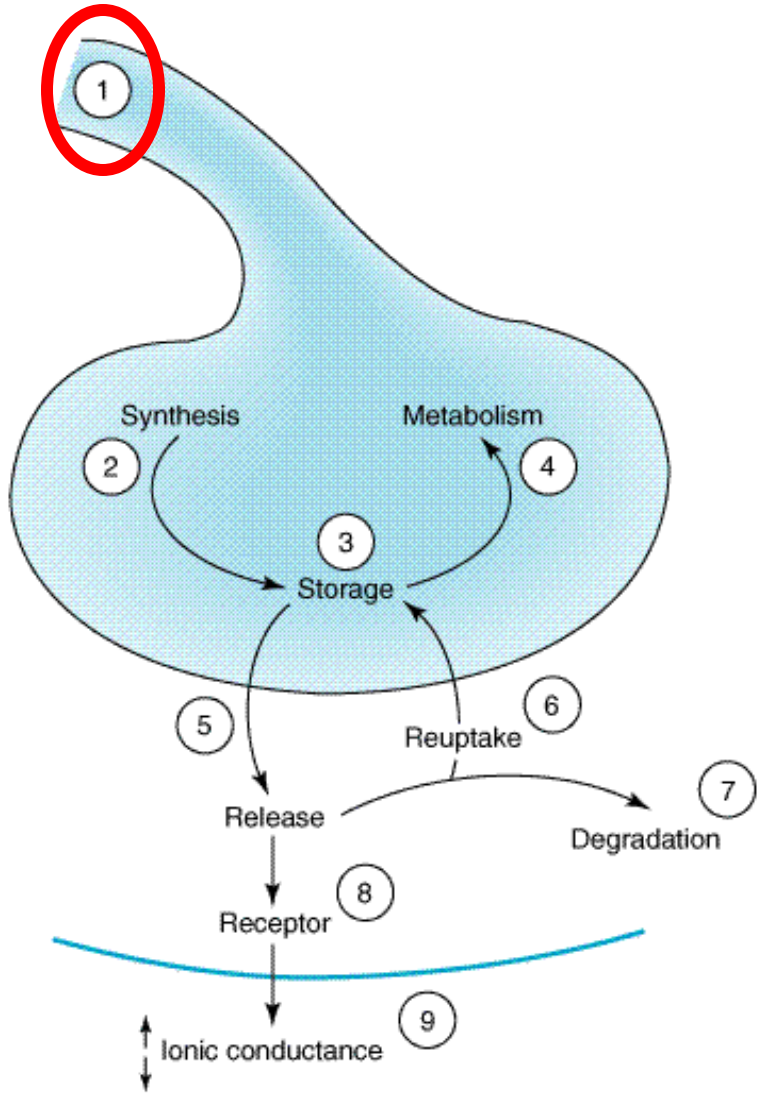
Neurotransmitter Cycle



Each step in the neurotransmitter cycle is a target for drugs

Sites and Mechanisms of CNS Drug Action

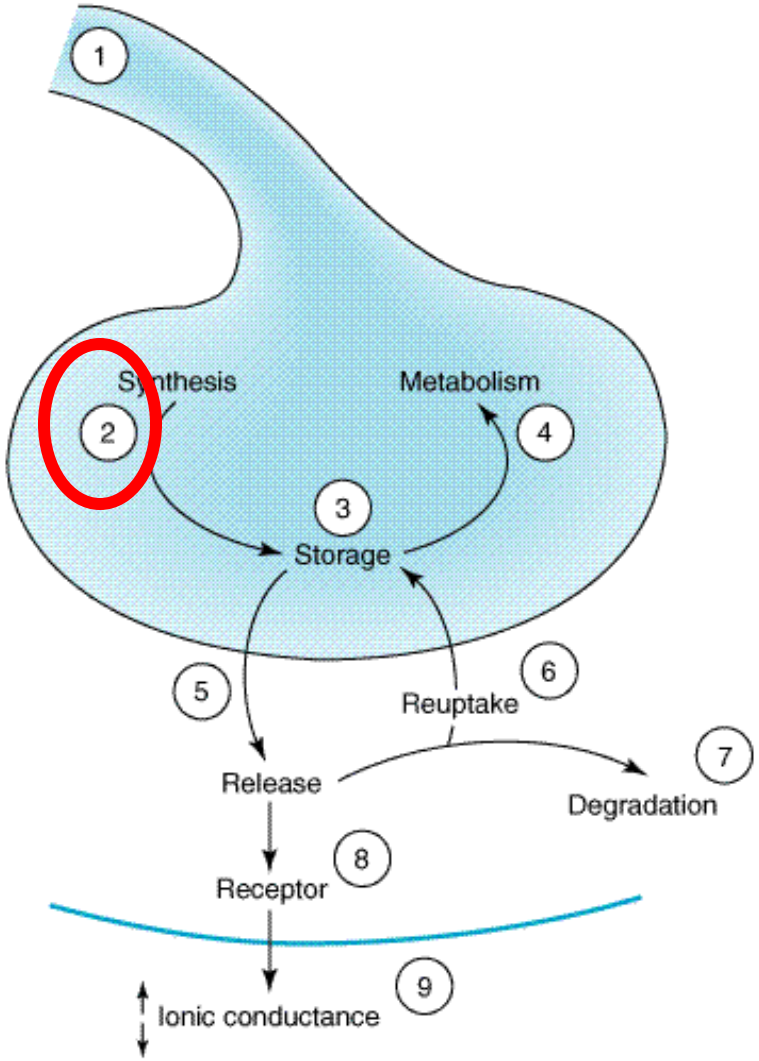
Target » voltage gated ion channels » inhibition » no depolarization » no action potential



Inhibit action potential presynaptically:

- Local Anesthetics
- General Anesthetics

Sites and Mechanisms of CNS Drug Action

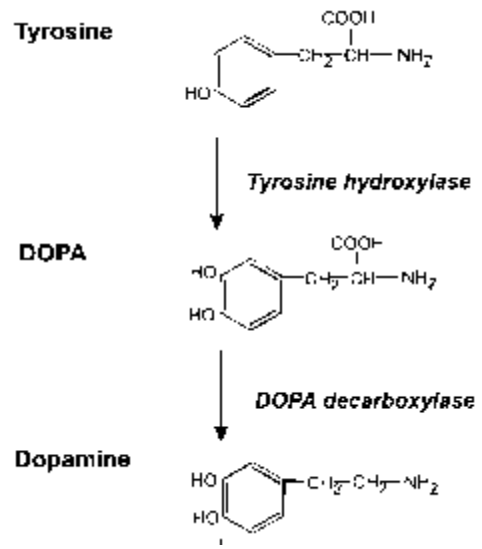


Inhibit NT Synthesis:

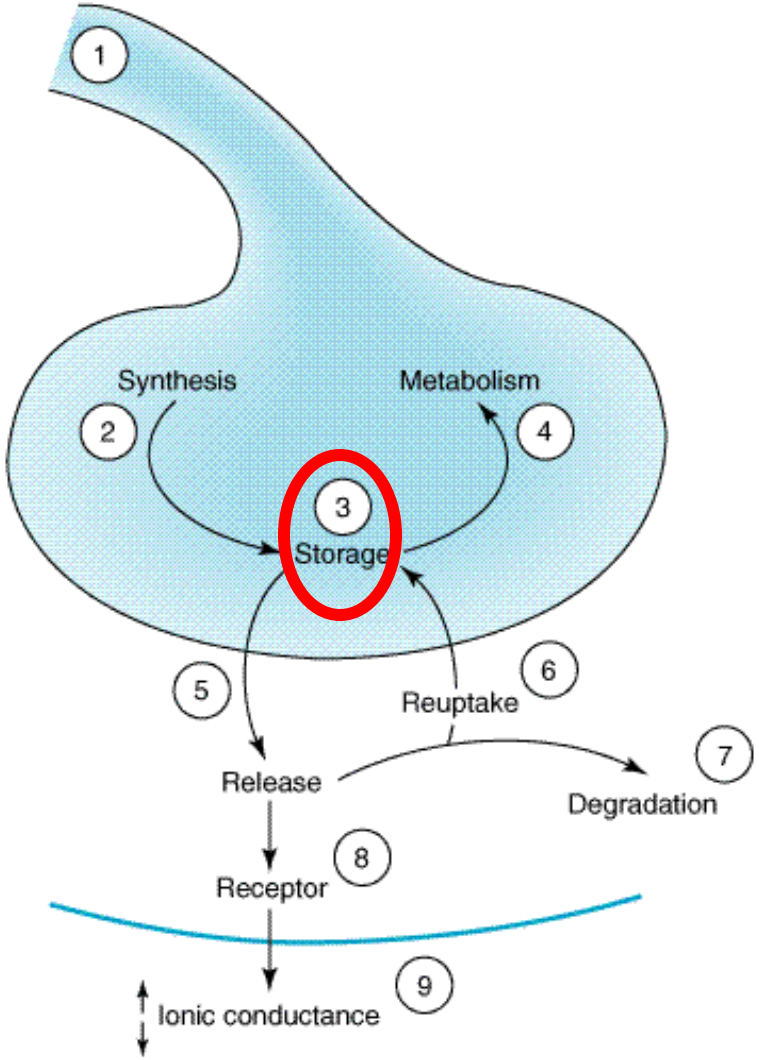
- Tyrosine hydroxylase (catecholamines)

Promote NT Synthesis:

- L-dopa
  - For depression or parkinson



Sites and Mechanisms of CNS Drug Action

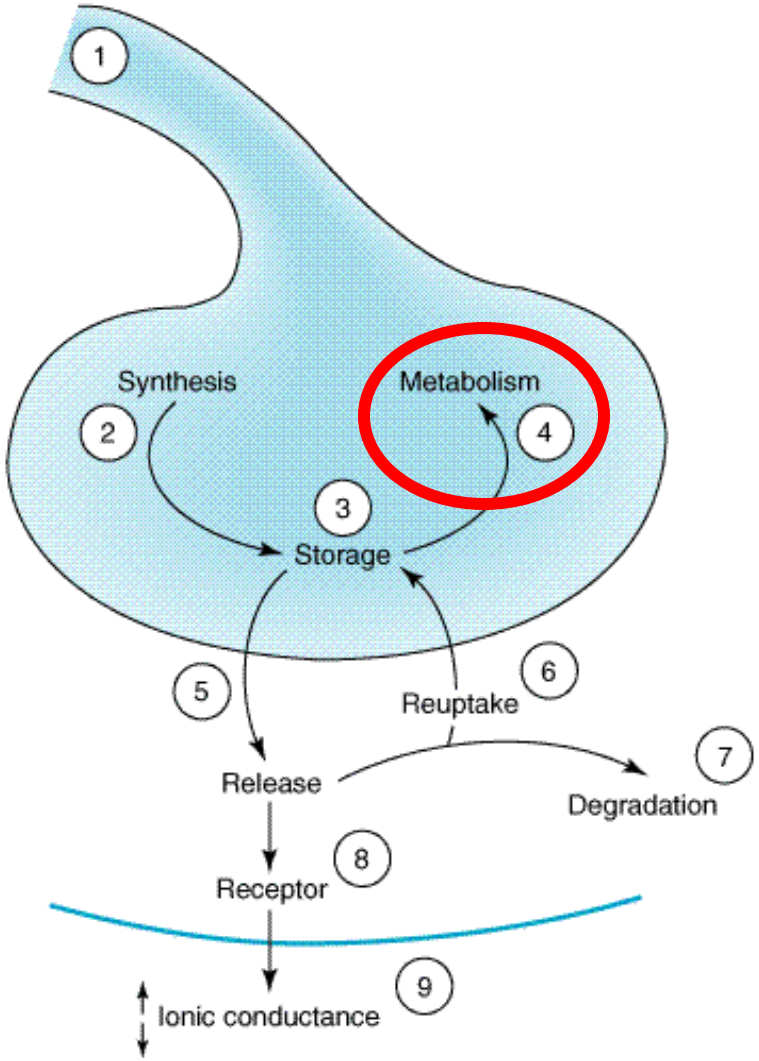


Interference with storage:

- VMAT is inhibited by *reserpine*
  - Consequences?

Preventing packaging » no neurotransmitters to be released

Sites and Mechanisms of CNS Drug Action



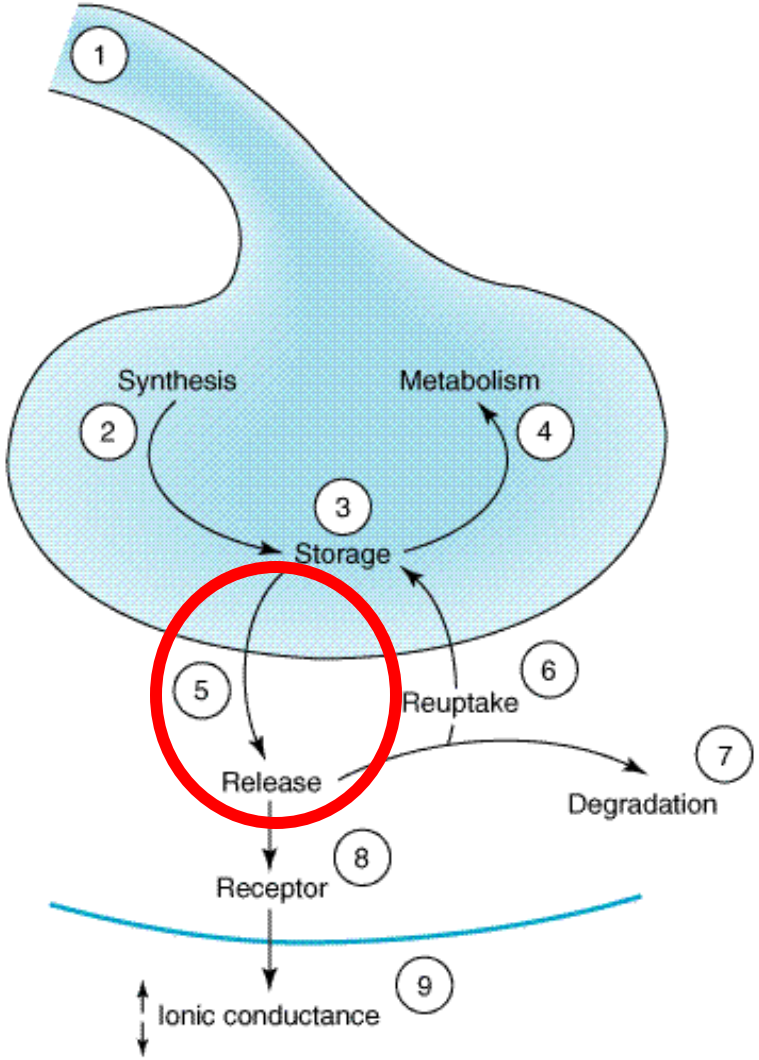
Interfering with action of these enzymes » inhibiting degradation of neurotransmitter » increase in concentration and availability of neurotransmitter at presynaptic cleft

Metabolism:

- COMT and MAO

- Antiparkinsonian
- Antidepressants

Sites and Mechanisms of CNS Drug Action

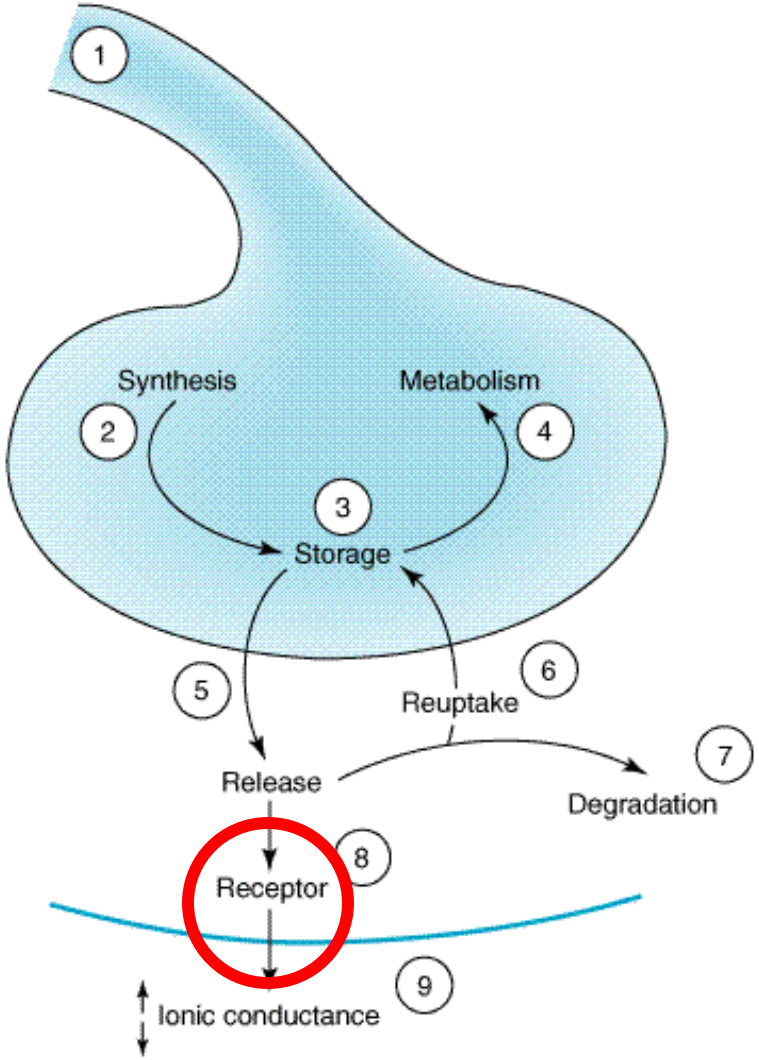


Release of NT:

- CNS stimulants

They increase release of neurotransmitter from presynaptic neuron

Sites and Mechanisms of CNS Drug Action

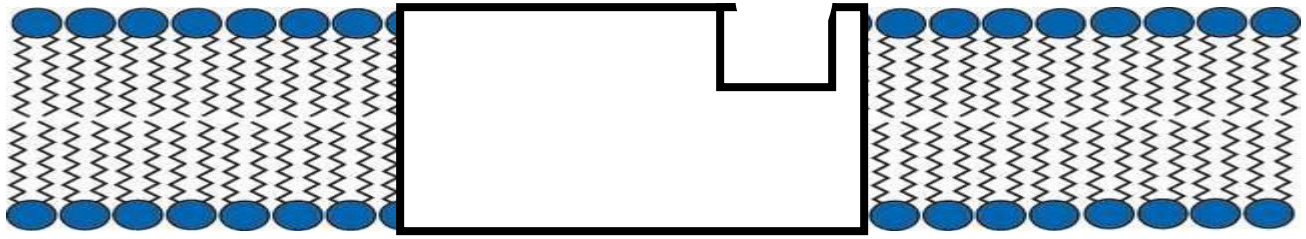


NT action on receptor:

- Agonist — Drug that binds to a receptor resulting in it's activation
- Antagonist — Drug that binds to a receptor resulting in it's inhibition
- Biased agonist
- Allosteric modulators

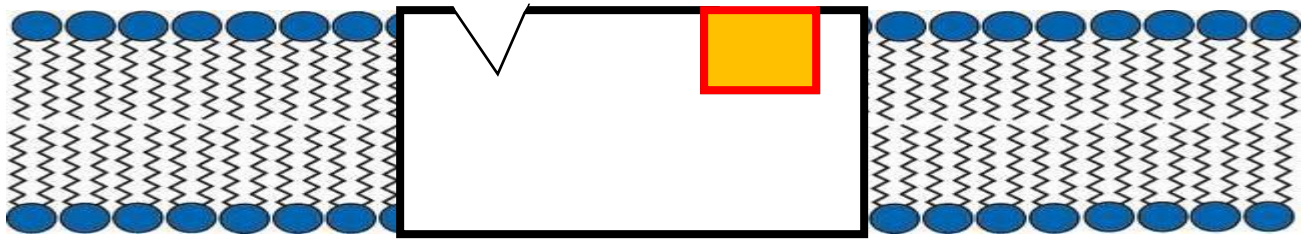
Ligand

Either agonist for activation or antagonist for inhibition



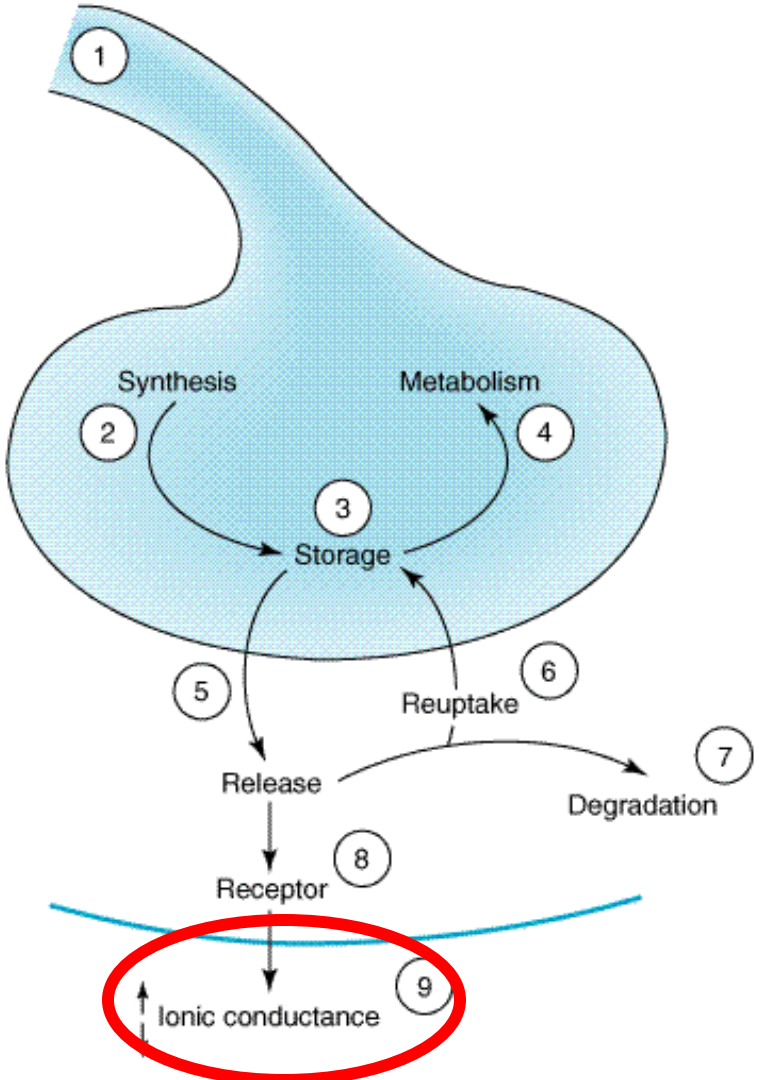
Allosteric modulator

Drugs that bind to a site other than ligand binding site, upon binding they either result with positive allosteric effect resulting in activation of receptor or with negative allosteric effect resulting in inhibition of receptor



Negative Allosteric modulator

Sites and Mechanisms of CNS Drug Action

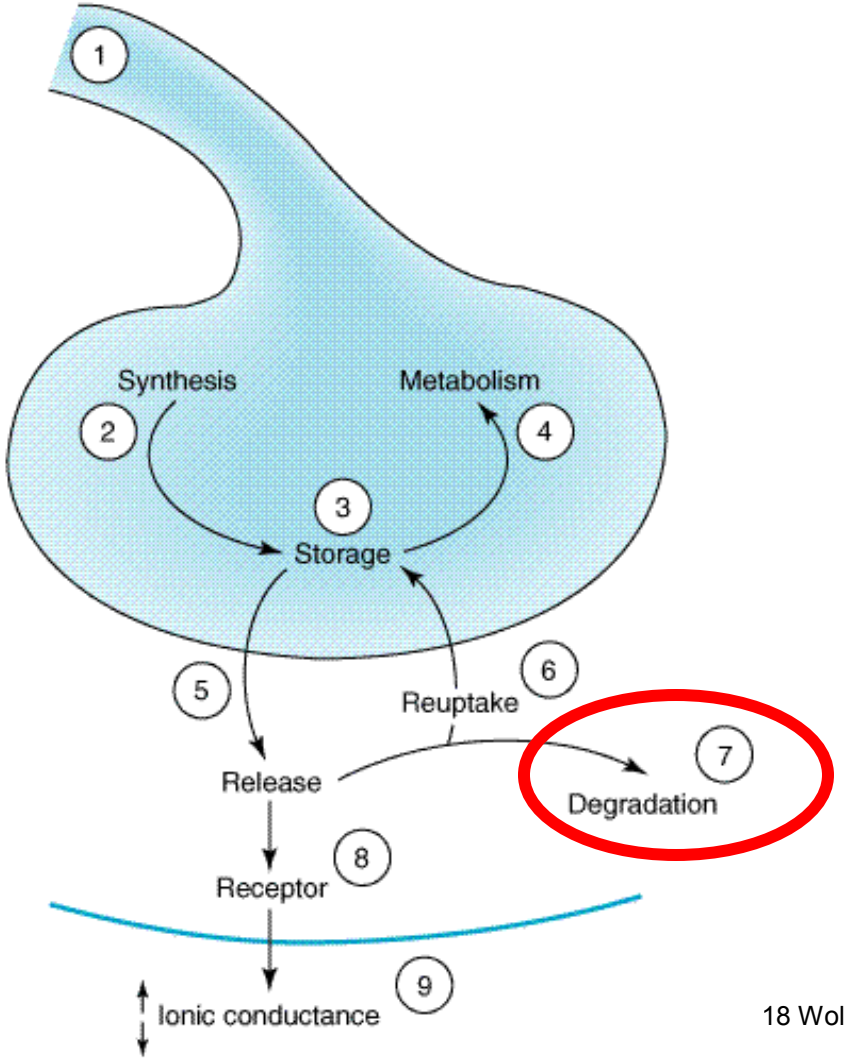


cAMP is the second messenger

Intracellular effects:

- cAMP degradation inhibitors

Sites and Mechanisms of CNS Drug Action

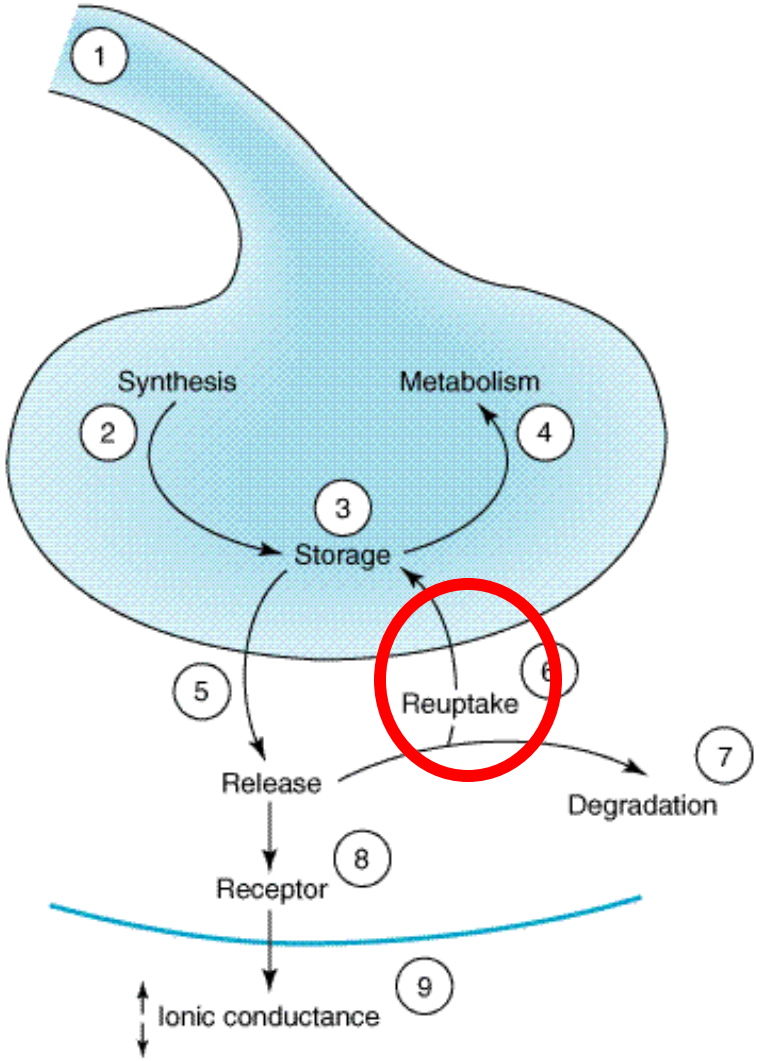


Degradation of NT:

- Acetylcholine esterase inhibitors → They cross blood brain barrier and work centrally

Alzheimer's Disease

Sites and Mechanisms of CNS Drug Action



NT reuptake:

- Antidepressants

Many neurotransmitters are reuptaken especially dopamine, epinephrine, norepinephrine » they have specialized transporters in the presynaptic neurons

$GABA_A$ 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?