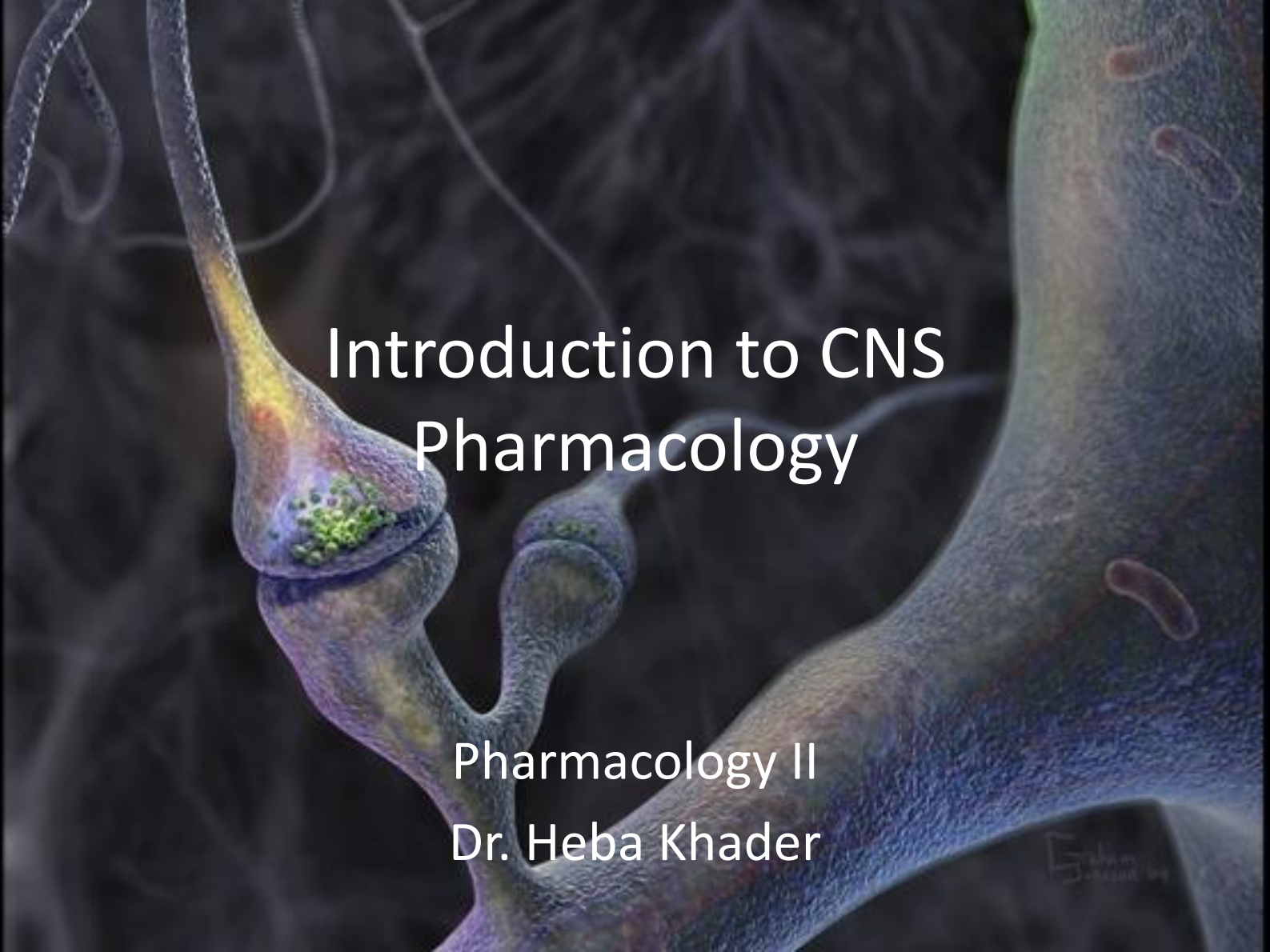


Introduction to CNS Pharmacology

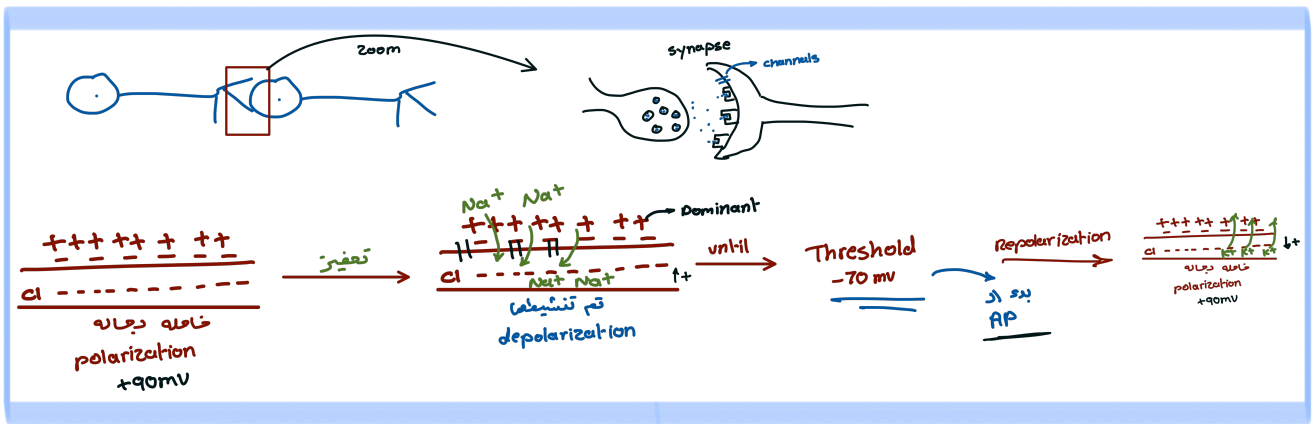
Pharmacology II

Dr. Heba Khader

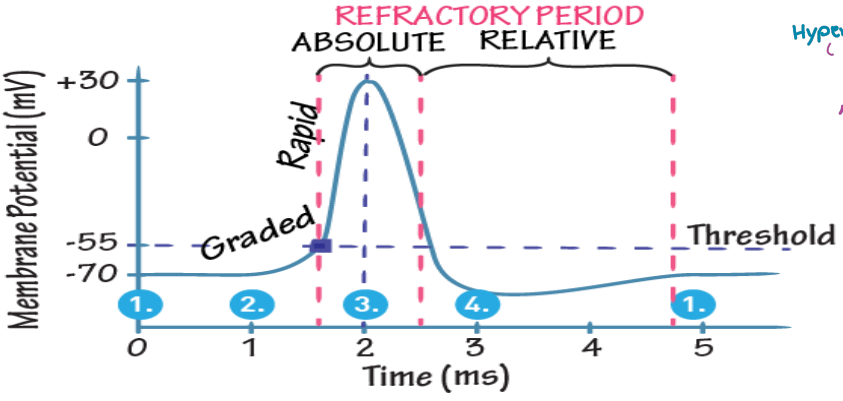
Introduction

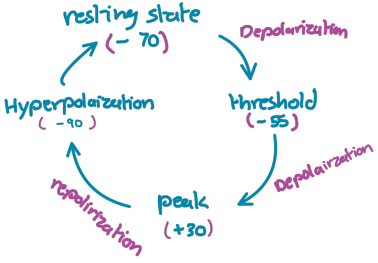
- Drugs acting in the central nervous system (CNS) include medications used to treat a wide range of neurologic and psychiatric conditions as well as drugs that relieve pain, suppress nausea, and reduce fever.

- Drugs with CNS effects act on specific receptors that modulate synaptic transmission.



Action Potentials

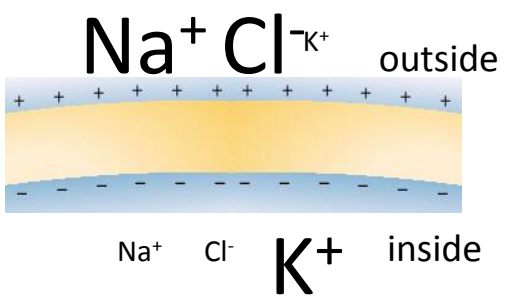




1. Resting state - All gated ion channels closed
2. Depolarization - Na+ channels open, K+ channels closed
3. Repolarization - Na+ channels inactivated, K+ channels open
4. Hyperpolarization - Na+ channels reset and closed, K+ channels still open

Neurotransmission in the CNS

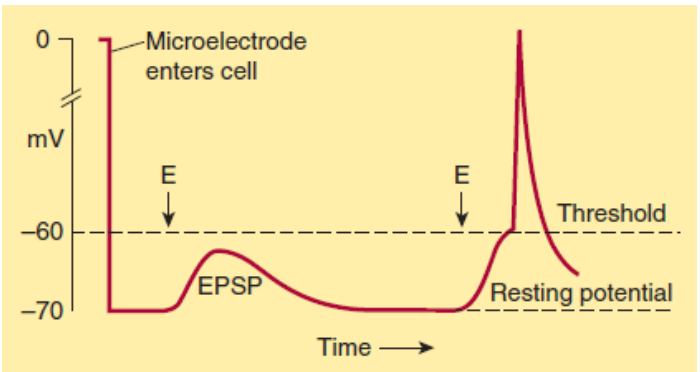
- Most drugs that act on the central nervous system (CNS) appear to do so by changing ion flow through transmembrane channels of nerve cells.
- Ion flow across the membrane of the neuron alters the postsynaptic potential, producing either depolarization (EPSP) or hyperpolarization (IPSP) of the postsynaptic membrane, depending on the specific ions that move and the direction of their movement.

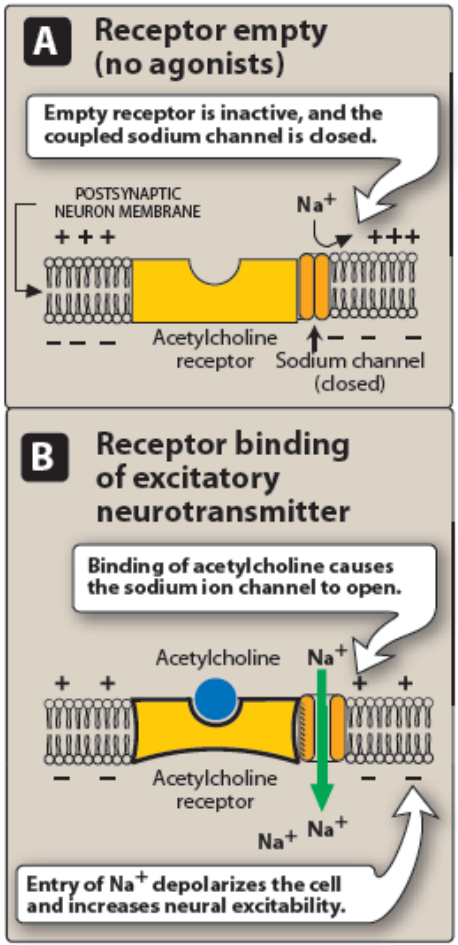


① depolarization

Excitatory postsynaptic potential (EPSP)

- Excitatory postsynaptic potentials (EPSPs) are usually generated by the opening of sodium (Na^+) or calcium (Ca^{++}) channels. ↑ ⊕ inside → depola.
- In some synapses, similar depolarizing potentials result from the closing of potassium channels.

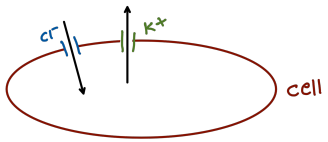


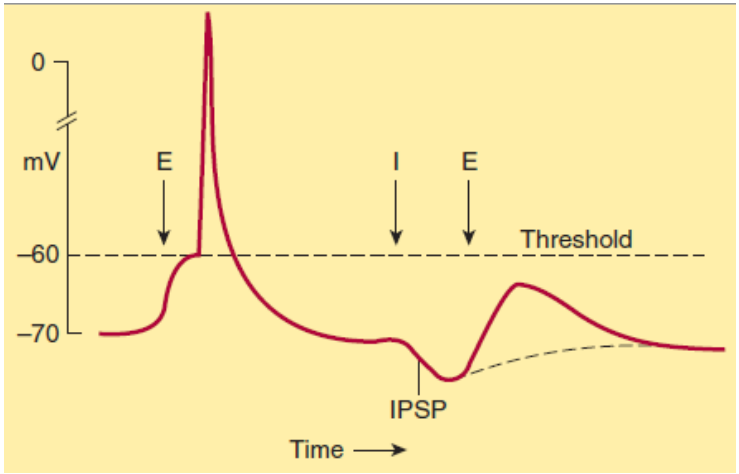


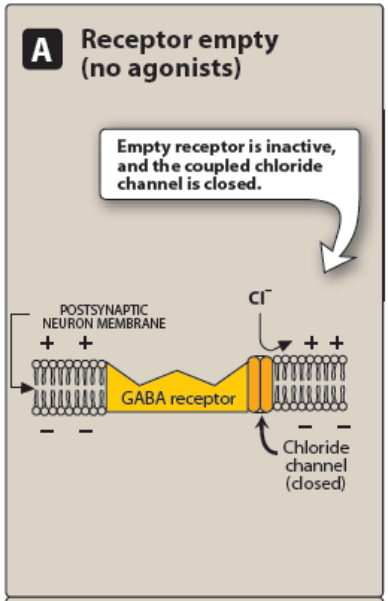
hyperpolarization

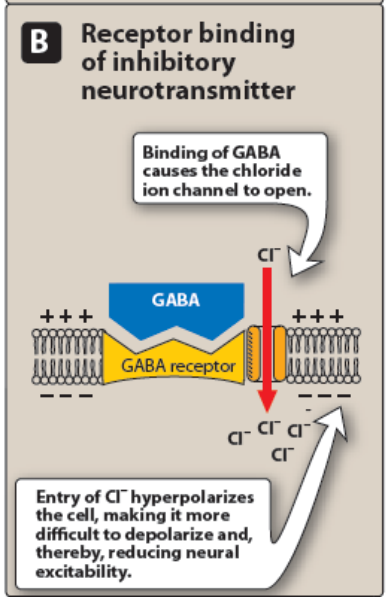
Inhibitory postsynaptic potential (IPSP)

- Inhibitory postsynaptic potentials (IPSPs) are usually generated by the opening of potassium or chloride channels (efflux of K+ or influx of Cl-, respectively).









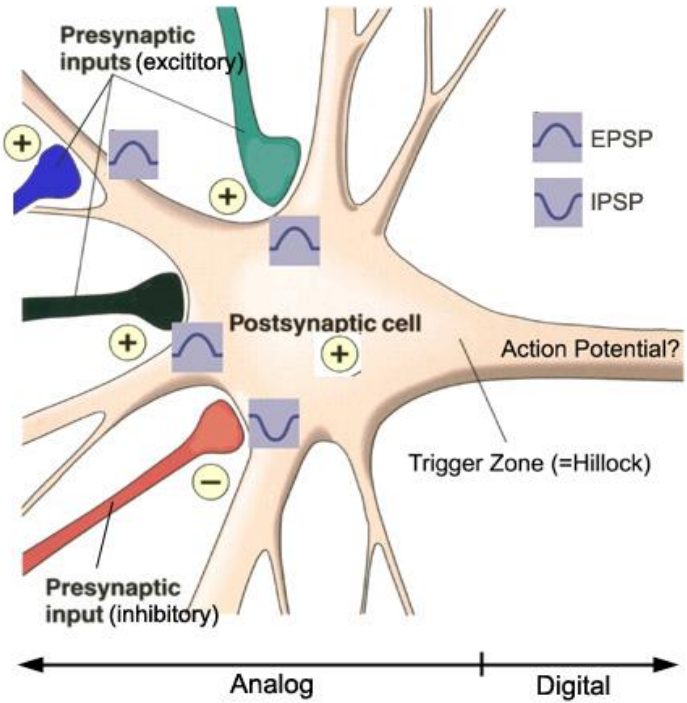
Combined effects of the EPSP and IPSP

- The overall resultant postsynaptic potential is due to the summation of the individual actions of the various neurotransmitters on the neuron.

الجهد بعد المشبكي الكلي الناتج (Overall resultant postsynaptic potential) ينتج عن **تجميع (summation)** التأثيرات الفردية لمختلف **النواقل العصبية** على العصبون.

وبصياغة أوضح:

الجهد النهائي الذي يحدث في الخلية بعد المشبكية هو نتيجة جمع تأثيرات جميع النواقل العصبية المختلفة التي أثّرت عليها.

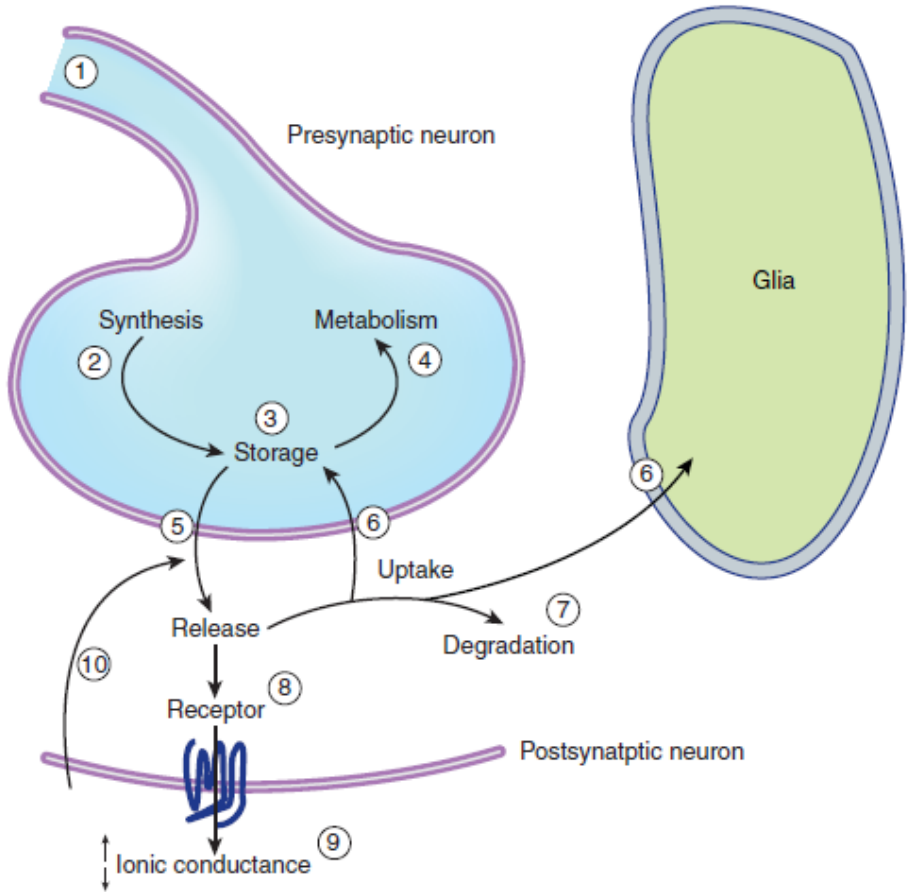


Transmitters at central synapses

1. Acetylcholine (+/-)
2. Dopamine (-)
3. γ-Aminobutyric acid (GABA) (-)
4. Glutamate (+/-)
5. Glycine (-)
6. 5-hydroxytryptamine (Serotonine) (-/+)
7. Opioid peptides (-)

(+/-)	(-)
Acetylcholine	Opioid peptides
5-hydroxytryptamine (Serotonine)	γ-Aminobutyric acid (GABA)
Glutamate	Dopamine
—	Glycine

Sites of drug action in CNS



Sedative-Hypnotic Drugs

Pharmacology II

Dr. Heba Khader

Terms to know…

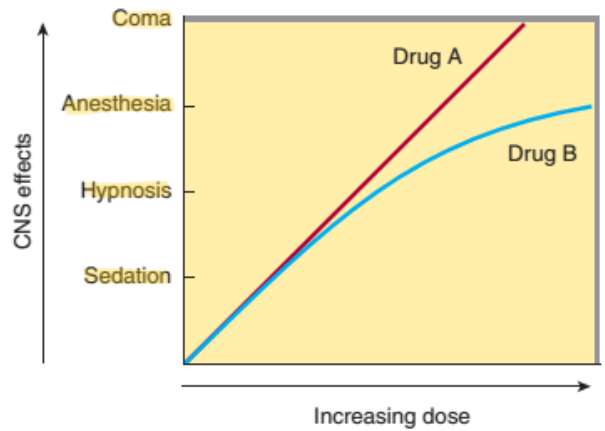
High-Yield Terms to Learn

Sedation	Reduction of anxiety
Addiction	The state of response to a drug whereby the drug taker feels compelled to use the drug and suffers anxiety when separated from it
Anesthesia	Loss of consciousness associated with absence of response to pain
Anxiolytic	A drug that reduces anxiety, a sedative
Dependence	The state of response to a drug whereby removal of the drug evokes unpleasant, possibly life-threatening symptoms, often the opposite of the drug's effects
Hypnosis	Induction of sleep

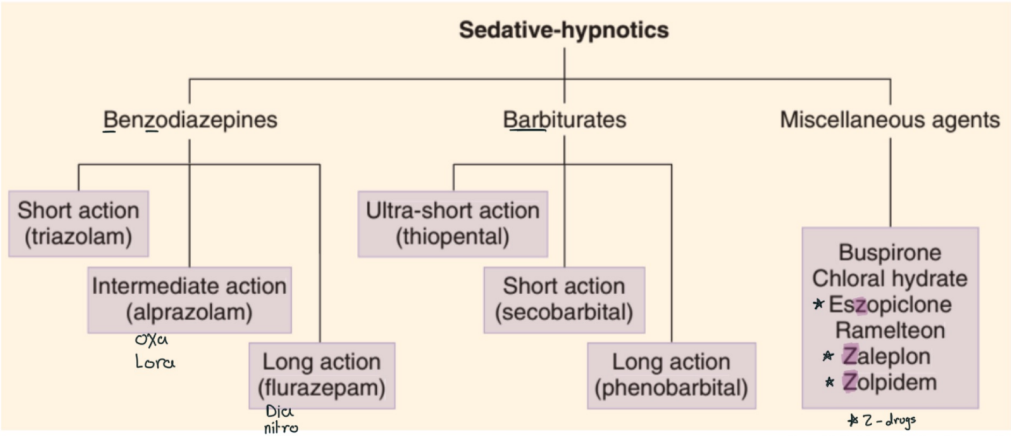
- What is anxiety?
- Anxiety is a state characterized by psychological symptoms, and often accompanied by physical symptoms such as fatigue, dizziness, vague pains, palpitations, headache, irritability and indigestion.

Basic Pharmacology of Sedative-Hypnotic Drugs

- An effective **sedative** (anxiolytic) agent should reduce anxiety and exert a calming effect.
- A **hypnotic** drug should produce drowsiness and encourage the onset and maintenance of a state of sleep.
- Hypnotic effects involve more pronounced (واضح) depression of the central nervous system than sedation, and this can be achieved with many drugs in this class simply by increasing the dose.



Classification of Sedative-Hypnotic



1. Benzodiazepines (BZ) suffix: zepam / zolam
   - Long-acting: diazepam, flurazepam, nitroazepam
   - Intermediate-acting: lorazepam, oxazepam, alprazolam
   - Short-acting: triazolam

2. Barbiturates (largely replaced by BZ)

The barbiturates induce tolerance, drug-metabolizing enzymes, and physical dependence, and they show severe withdrawal symptoms.

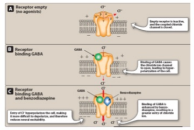
3. Zolpidem, zaleplon and eszopiclone "the Z-drugs" (more recent drugs with MOA similar to BZ)
4. Ramelteon
5. Buspirone
6. Ethanol (alcohol) and chloral hydrate
7. Antipsychotics, antidepressants and antihistamines

other drugs

Mechanism of action

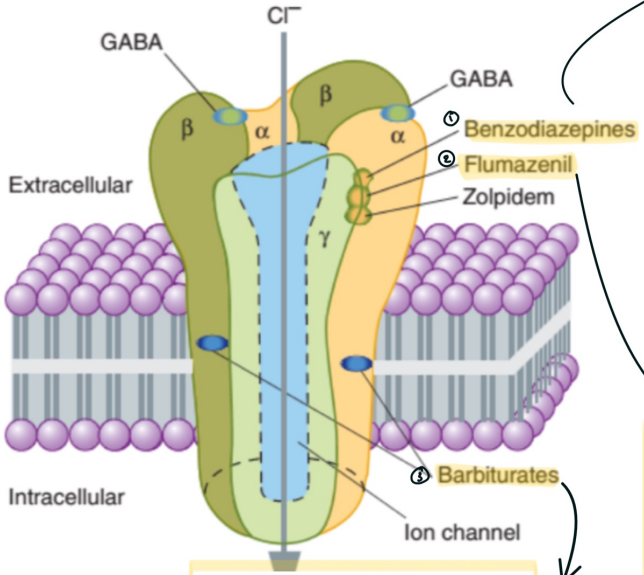
A. Benzodiazepines

- The BZ receptors form part of a $GABA_A$ receptor chloride-ion channel macromolecular complex.
- GABA (γ-aminobutyric acid) is a major inhibitory in the CNS.
- Benzodiazepines increase the *frequency* of GABA-mediated chloride ion channel opening.
- Benzodiazepines enhance the binding of of GABA to its receptor, which increases the permeability of chloride.



C. Other Drugs

- The hypnotics **zolpidem, zaleplon,** and **eszopiclone** are not benzodiazepines but appear to exert their CNS effects via interaction with certain benzodiazepine receptors.
- Their CNS depressant effects can be antagonized by flumazenil.



- **Flumazenil** reverses the CNS effects of benzodiazepines and is classified as an **antagonist at BZ** receptors.
- **Flumazenil** is available for intravenous (IV) administration only.
- Onset is rapid, but duration is short, with a half-life of about 1 hour. Frequent administration may be necessary to maintain reversal of a long-acting benzodiazepine.
- Administration of *flumazenil may* precipitate withdrawal in dependent patients or cause seizures if a benzodiazepine is used to control seizure activity.

إعطاء **فلومـازينيل (Flumazenil)** قد يسبّب ظهور أعراض انسحاب عند المرضى الذين لديهم اعتماد (إدمان) على البنزوديازيبينات، أو قد يؤدي إلى حدوث نوبات صرع إذا كان البنزوديازيبين يُستخدم للسيطرة على النوبات.

- Barbiturates also bind to multiple isoforms of the $GABA_A$ receptor but at different sites from those with which benzodiazepines interact.
- Their actions are <u>not</u> antagonized by flumazenil.
- Barbiturates increase the *duration* of GABA-mediated chloride ion channel opening.