POLTAVA STATE MEDICAL UNIVERSITY
Department of Pharmacology, Clinical Pharmacology and Pharmacy

General Pharmacology (continuation)

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2. Drugs doses
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PHARMACODYNAMICS

Pharmacodynamics is a section of Pharmacology which study how the drug acts on the body.

It studies:

- Effects
- Mechanisms of action
- Drugs interactions
- Doses
- Dose-effect dependence
- Factors influencing drug action.

TYPES OF DRUGS DOSES

A ***dose*** is the amount of drug administered into the body.

The dose may be:

- single (for single administration), daily (for the day of treatment), total (for the course of treatment)
- threshold (minimal dose which begins to act)
- therapeutic (minimal, average, maximal) (the dose which has therapeutic action)
- toxic (minimal, average, maximal) (the dose which causes toxic action)
- mortal (the dose which causes the death of animals in experiments), LD-50 and LD-100.

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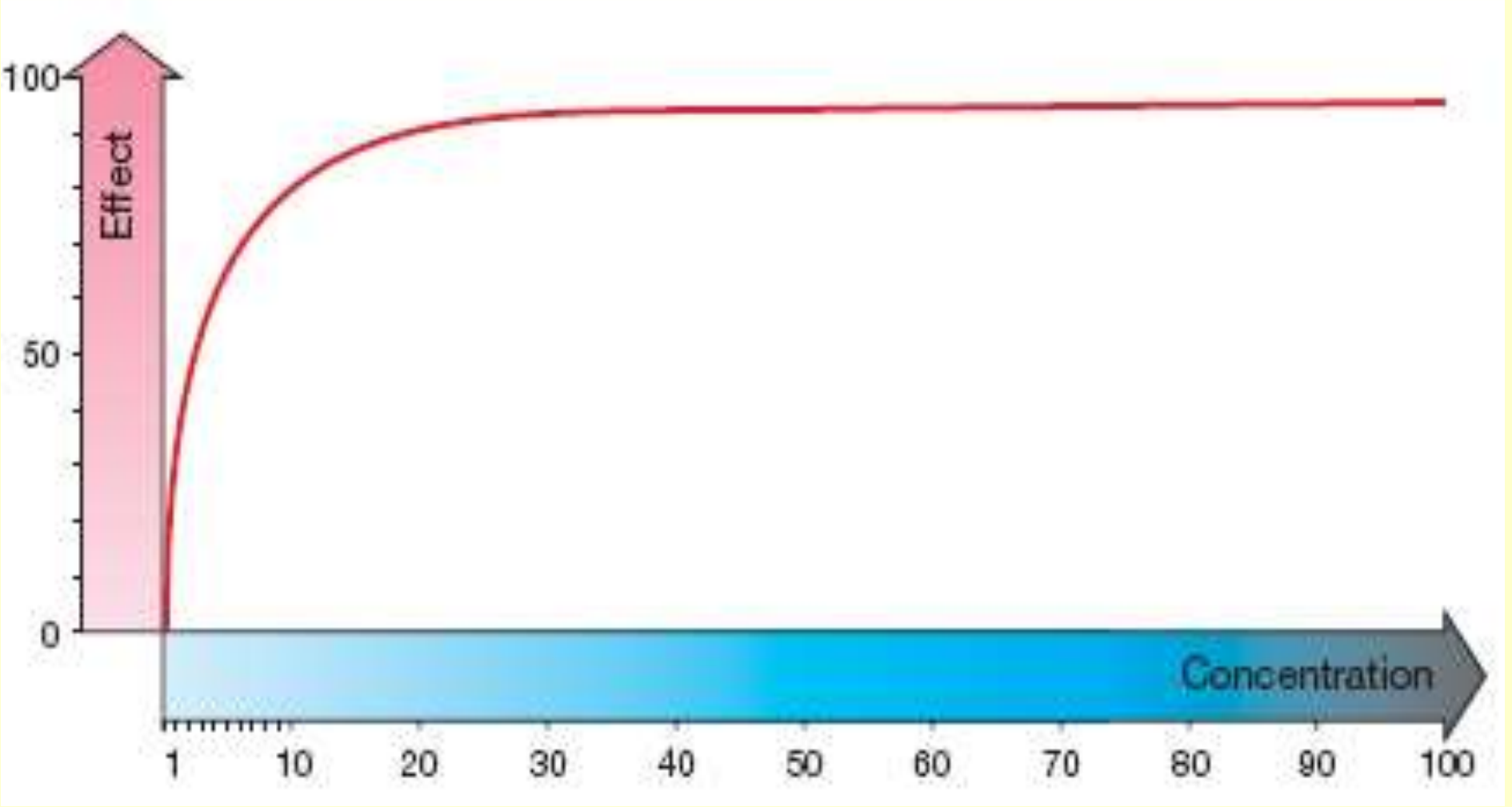
TYPES OF DRUGS ACTION

Drugs action is displayed as changes in the function of organs and systems.

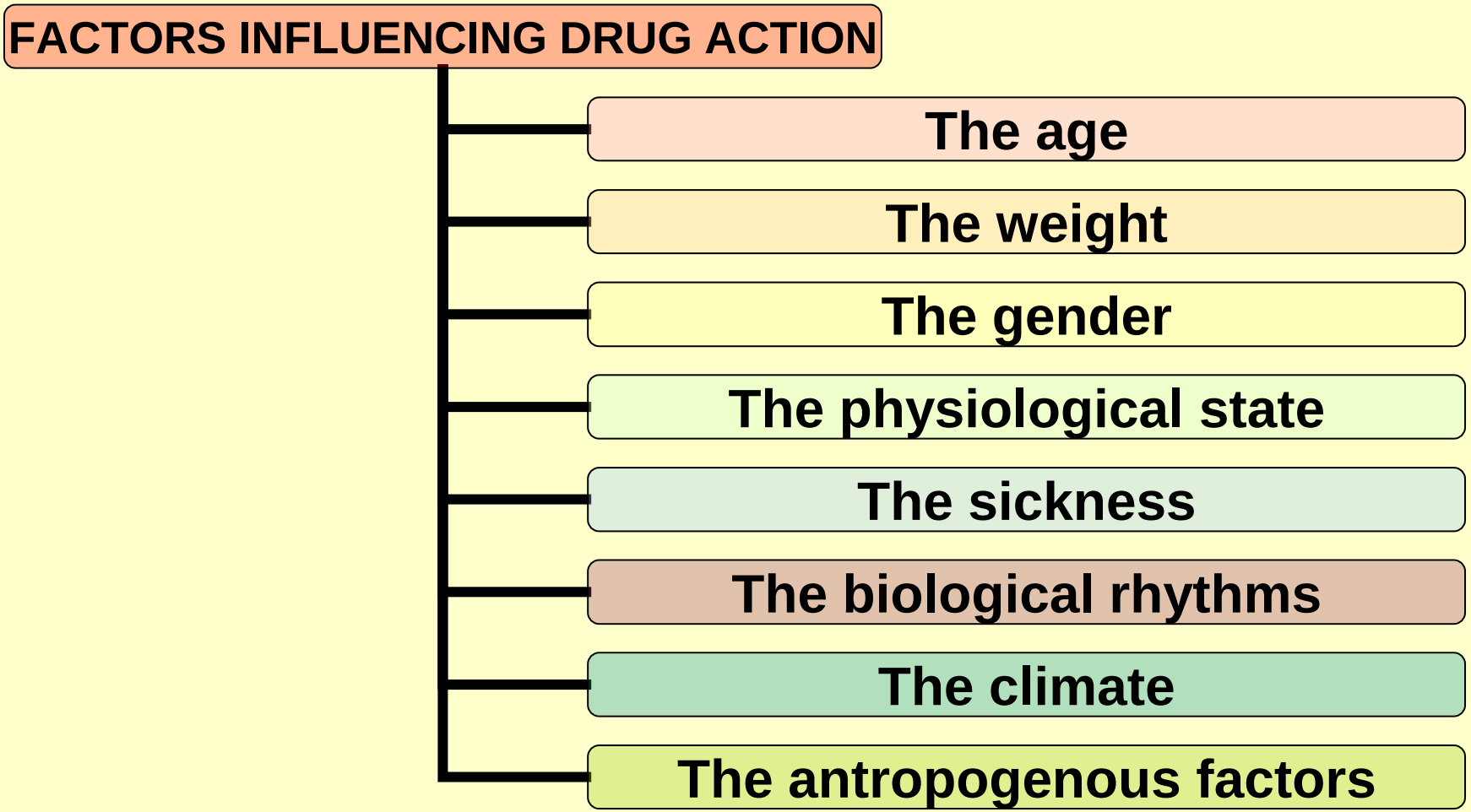
There are such ***types of drugs action***, as:

- local and resorptive
- direct, indirect and reflexive
- non-selective and selective
- reversible and irreversible
- main effects and side effects

DRUG ACTION DEPENDS ON DOSE AND CONCENTRATION



FACTORS INFLUENCING DRUG ACTION



GENETIC POLYMORPHISM AND DRUGS ACTION

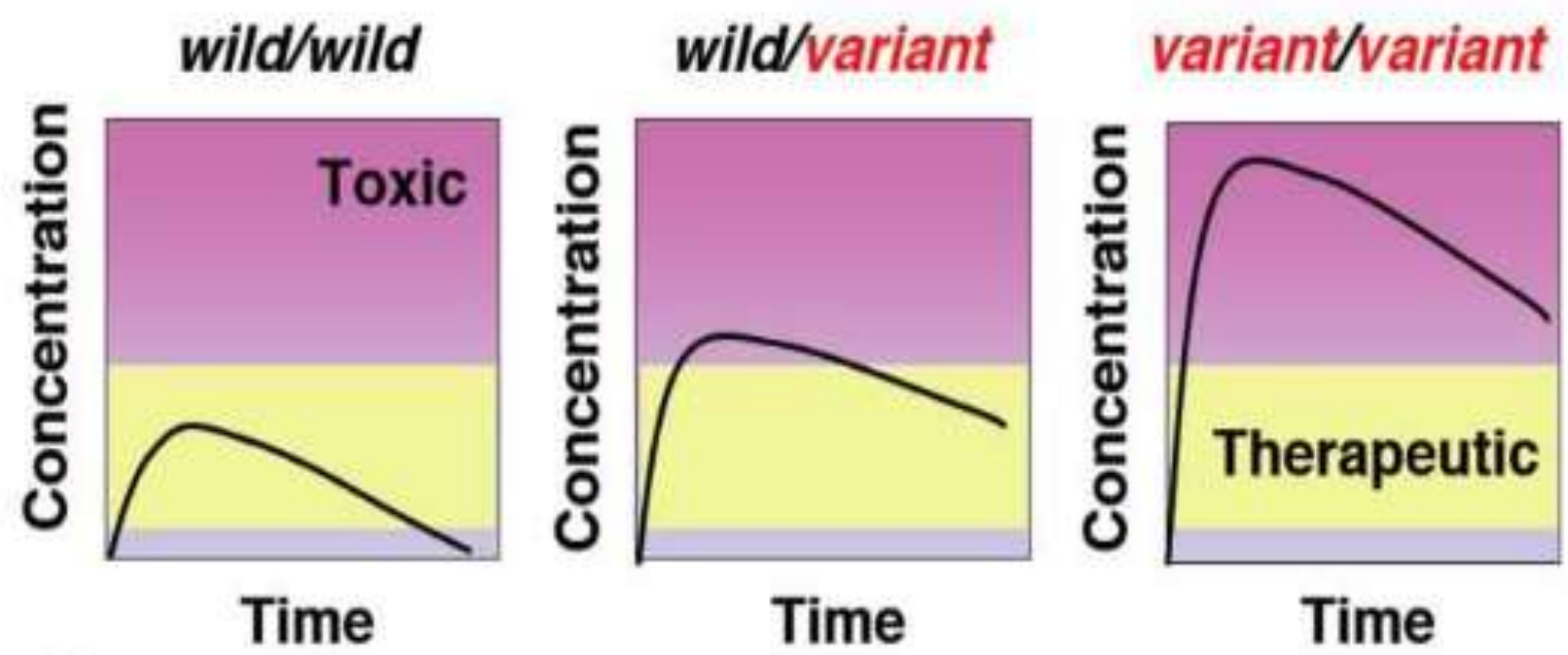
Patients can respond differently to the same medicine

Antidepressants (SSRIs)	38% failure
Asthma drugs	40% failure
Diabetes drugs	43% failure
Arthritis drugs	50% failure
Alzheimer's drugs	70% failure
Cancer drugs	75% failure

PSYCHIATRY RELATED GENES (example)

- **Pharmacokinetic**
  - CYP450 1A2, 2C9, 2C19, 3A4, 3A5, 2D6—Drug Metabolism
  - COMT (catechol-O-methyltransferase-S and MB)—O-Methylation of Catecholamines
- **Pharmacodynamic**
  - SLC6A2—Norepinephrine Transport
  - SLC6A3—Dopamine Transport
  - SLC6A4—Serotonin Transport
  - HTR1A—Serotonin 1A Receptor
  - HTR2A—Serotonin 2A Receptor
  - HTR2C—Serotonin 2C Receptor
  - DRD2—Dopamine D2 Receptor
  - DRD3—Dopamine D3 Receptor

EFFECTS OF POLYMORPHISM OF DRUG-METABOLIZING ENZYMES ON PLASMA CONCENTRATION



MECHANISMS OF ACTION

Mechanisms of action are events in the cells caused by the drug.

Medicinal substances realize their action by:

- ***changing of the enzyme's activity*** (e.g.: neostigmine as acethylcholinesterase inhibitor)
- ***interaction with receptors*** (e.g.: atropine as M-cholinoblocker)
- ***influence on ion channels*** (e.g.: local anesthetics)
- ***influence on the transport systems***
- ***antimetabolic mechanism*** (e.g.: methatrexate)
- ***the action in the genes level*** (e.g.: anti-cancer drugs).

RECEPTOR THEORY

Drug receptor is a specialized target macromolecule.

Receptors are located:

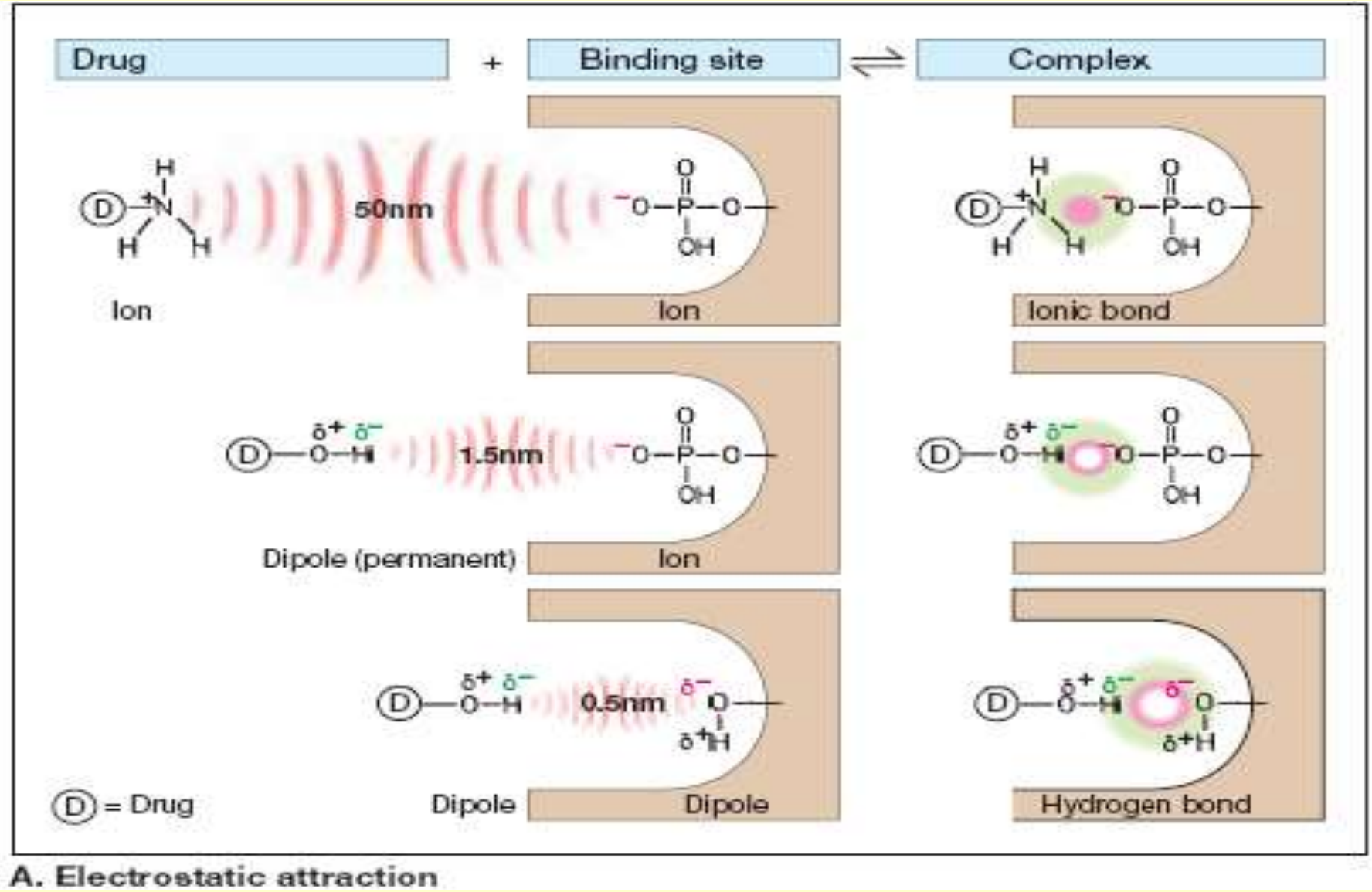
- in the membrane
- in the cytoplasma
- in the nuclei.

Drug + Receptor →

Drug-receptor complex →

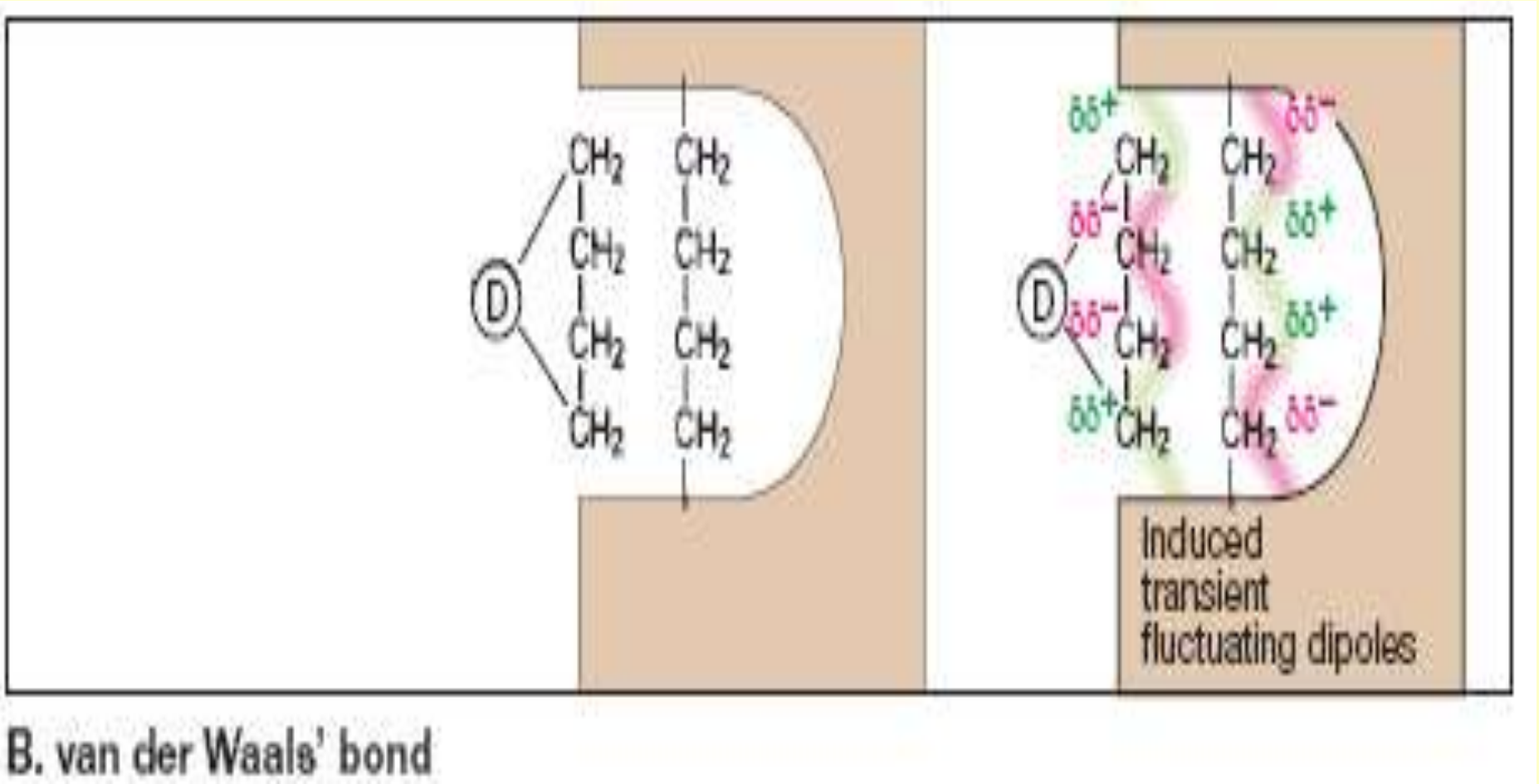
Effect

DRUG-RECEPTOR COMPLEX



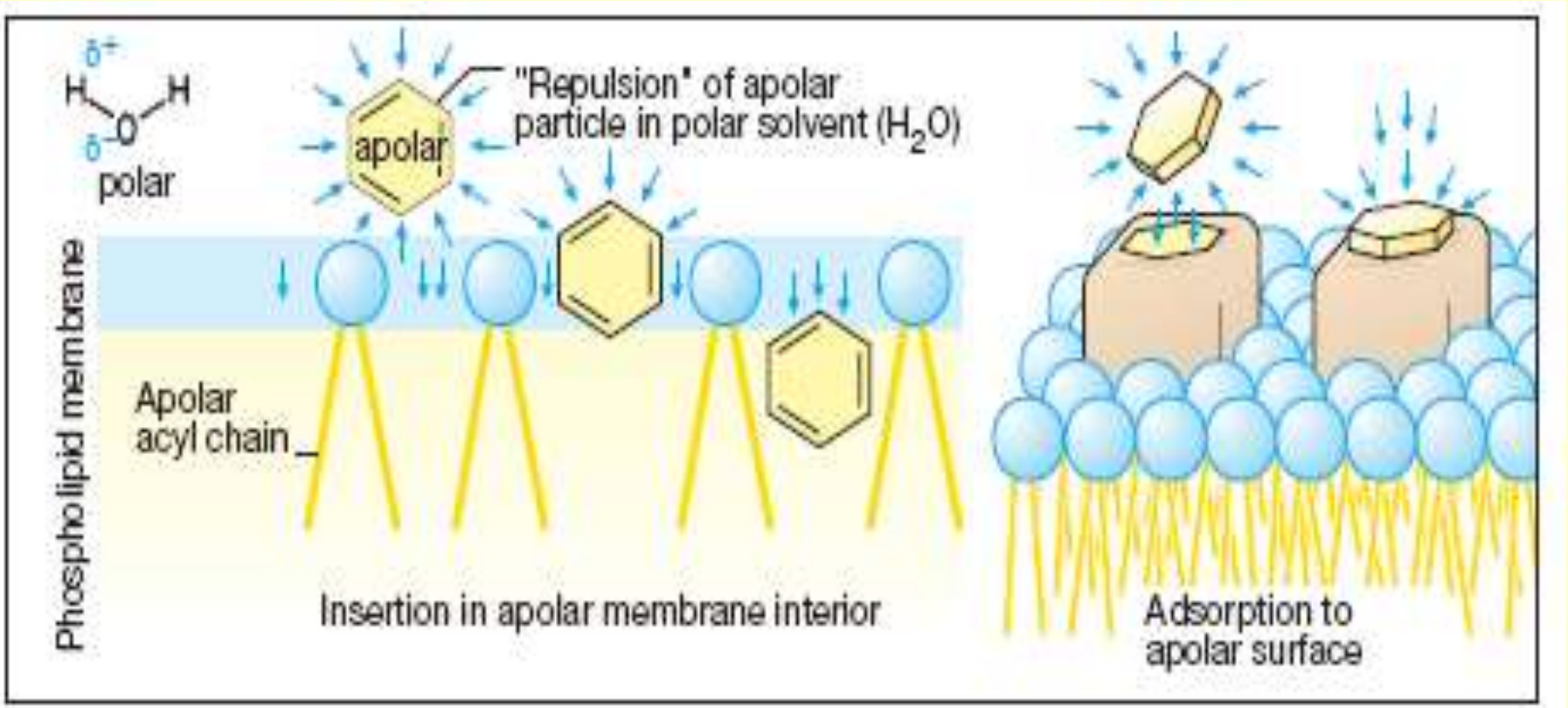
A. Electrostatic attraction

DRUG-RECEPTOR COMPLEX



B. van der Waals' bond

DRUG-RECEPTOR COMPLEX



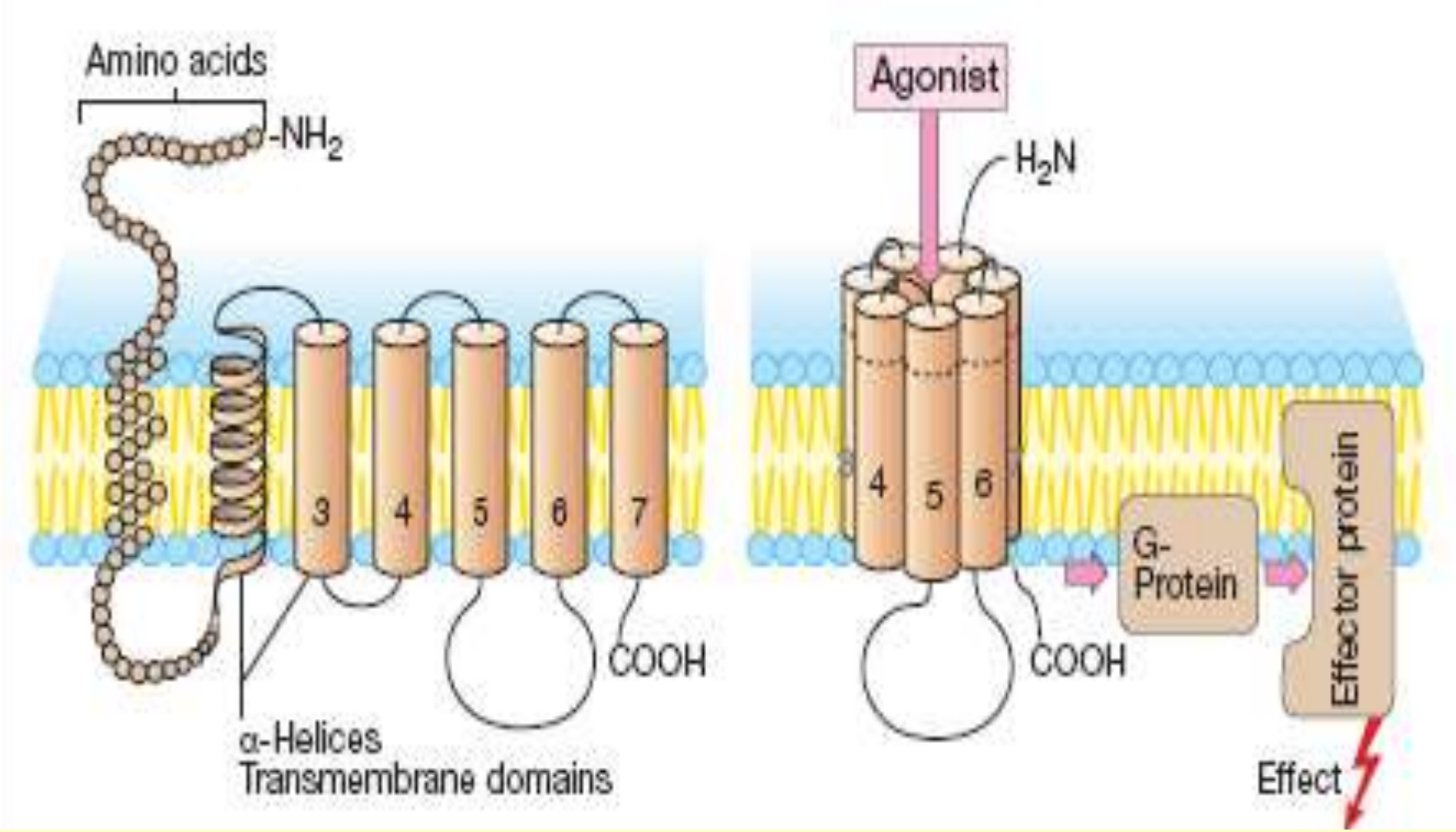
C. Hydrophobic interaction

RECEPTORS FUNCTIONS

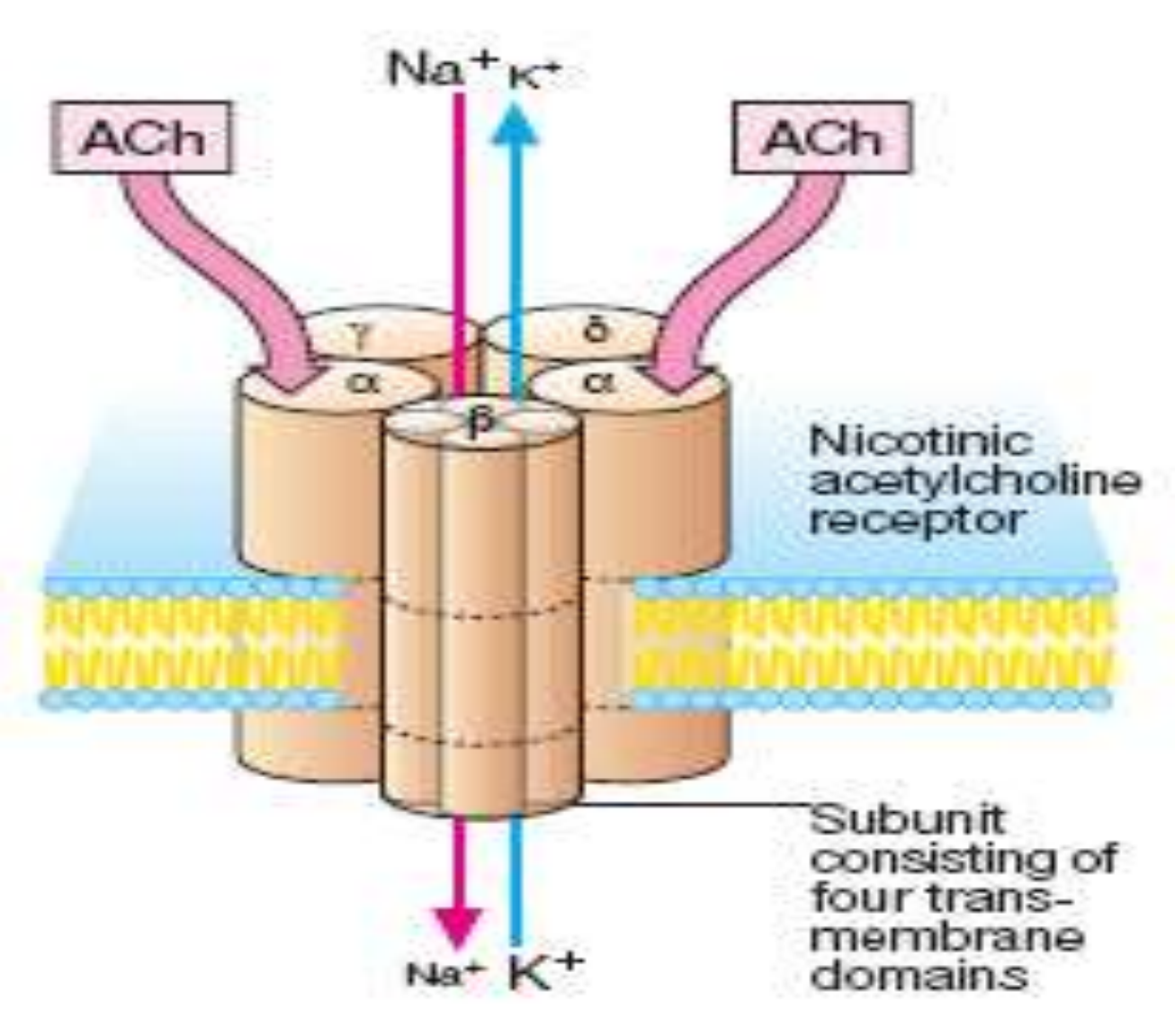
Receptors functions are achieved by:

- ion channels
- cyclic nucleotides (c AMP)
- G- proteins
- Ca++ and protein-kinases.

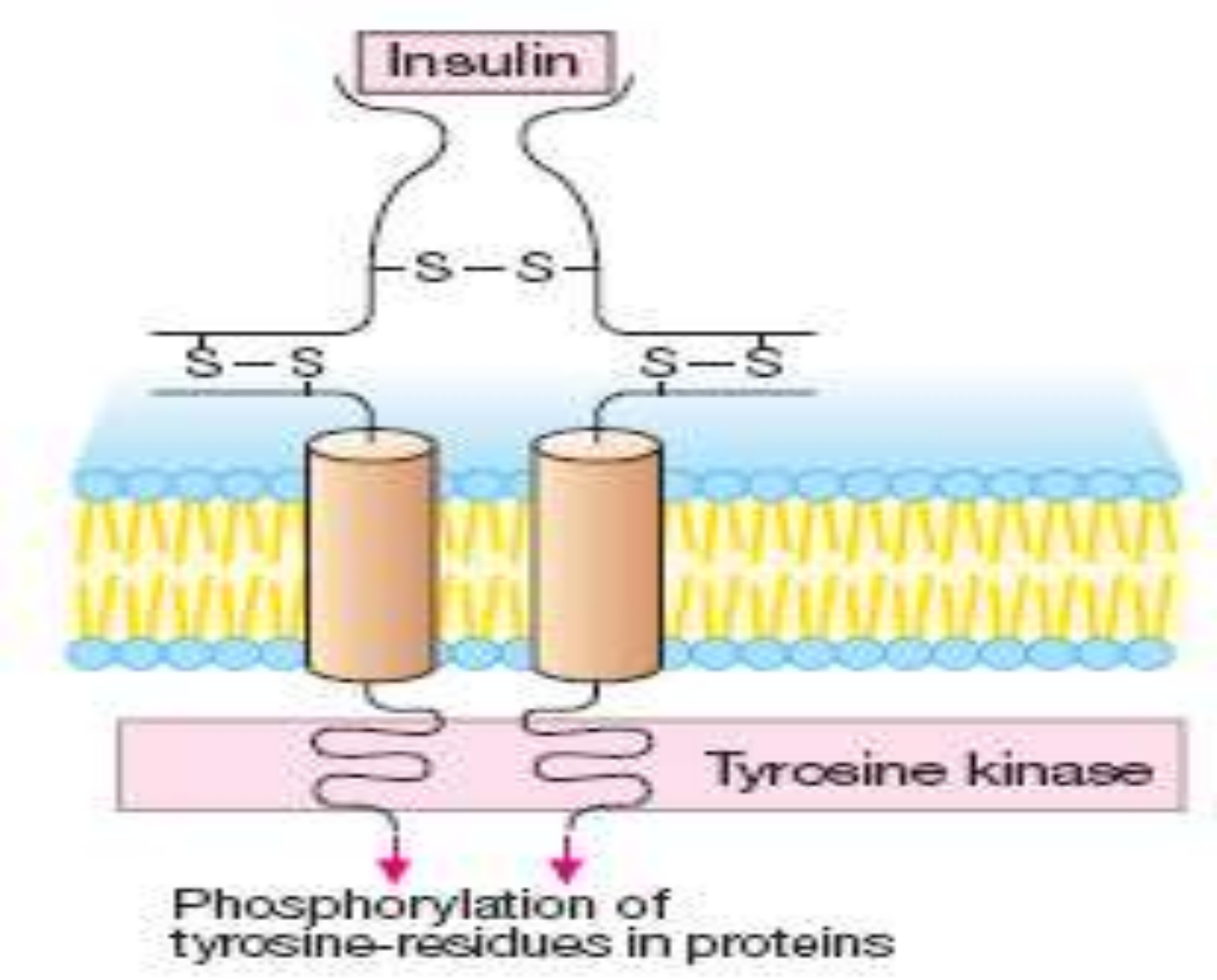
G-PROTEIN COUPLED RECEPTOR



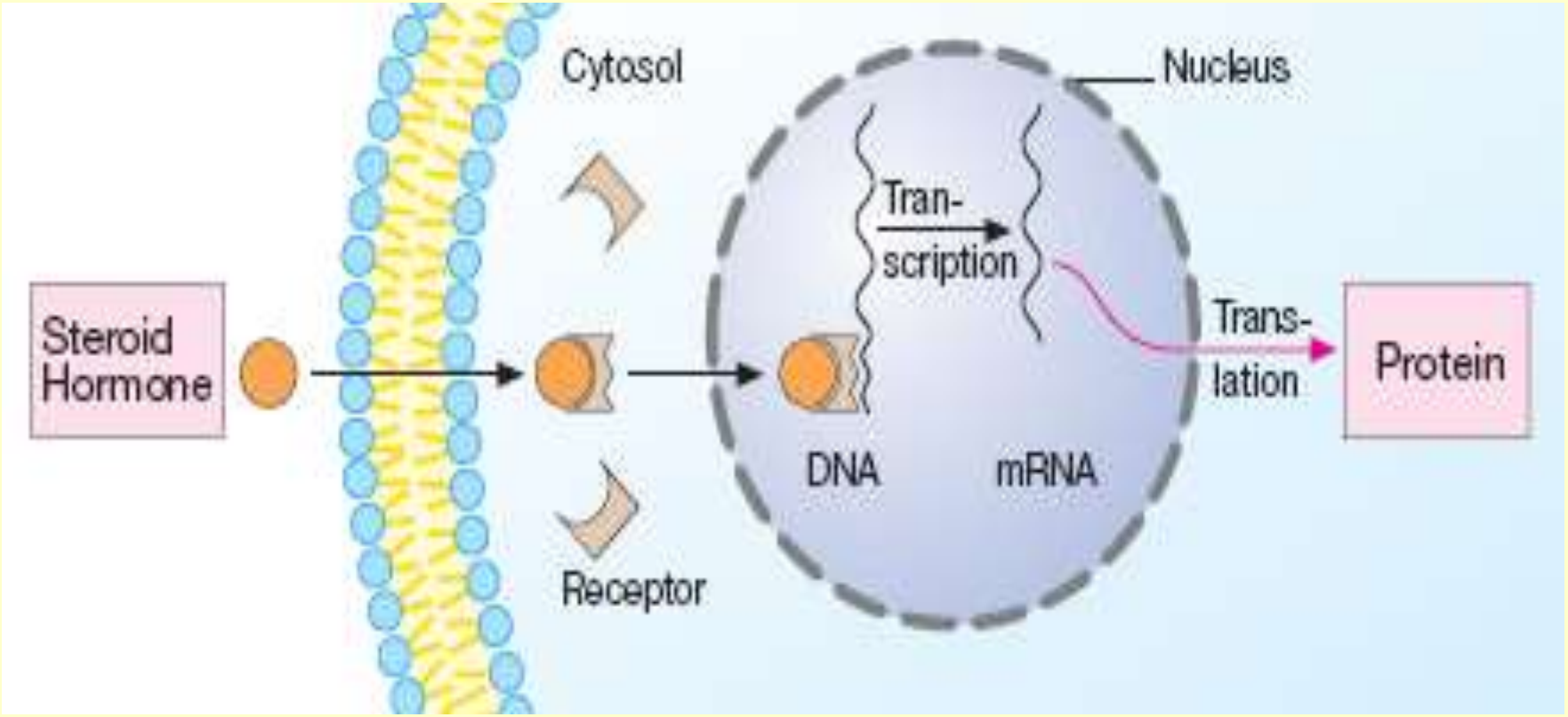
LIGAND-GATED ION CHANNEL



LIGAND-REGULATED ENZYME

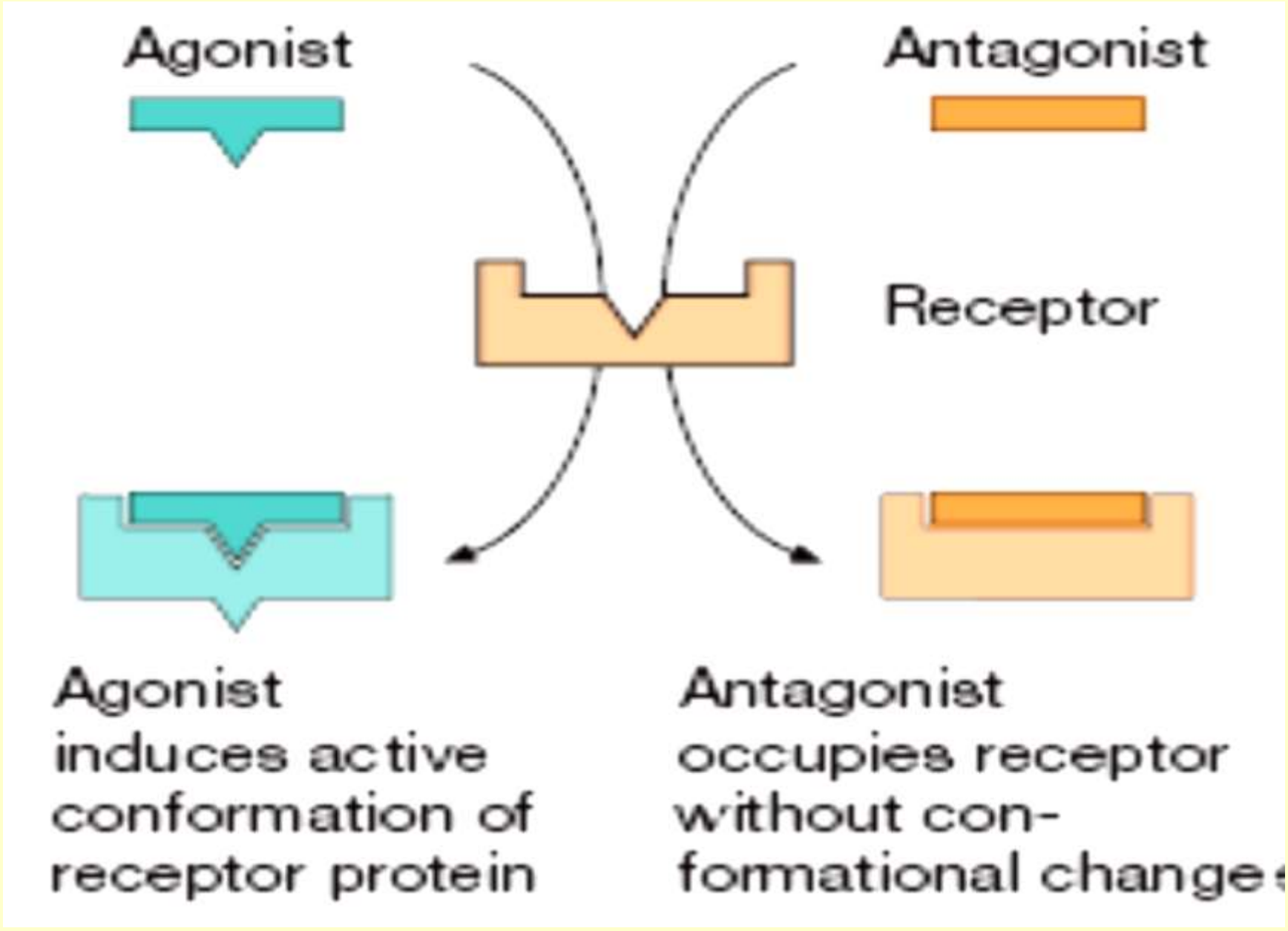


PROTEIN SYNTHESIS REGULATING RECEPTOR



DRUGS INTERACTION WITH RECEPTORS

- ***Agonist*** is a drug which stimulates receptor, induces its conformation and causes specific cell answer.
- ***Antagonist*** is a drug which inhibits receptor – it interacts with receptor without its conformation, prevents binding of ligand to receptor resulting in absence of specific cell answer.
- ***Agonist-antagonist*** is a drug which stimulates one subtype of receptor, but blocks the another one.


Agonist
Antagonist
Receptor
Agonist
induces active
conformation of
receptor protein
Antagonist
occupies receptor
without con-
formational change

DRUGS INTERACTION

Drugs interaction is an action of the drug on another one:

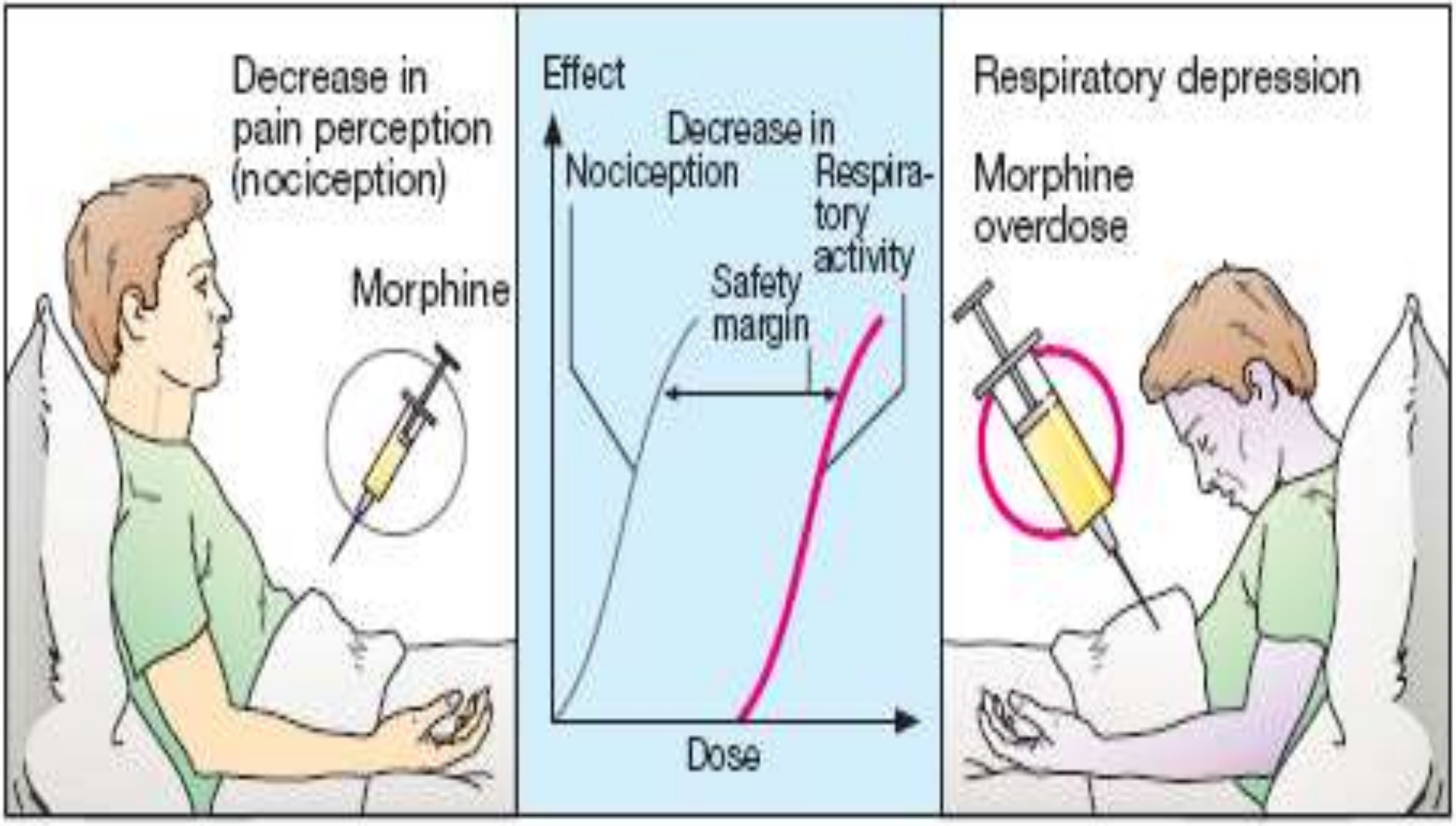
- ***Pharmaceutical*** (before the administration, extra the body)
  1. Physical
  2. Chemical
- **Pharmacological** (after the administration, intra the body)
  1. Pharmacokinetic
  2. Pharmacodynamic

COMBINED ACTION OF DRUGS

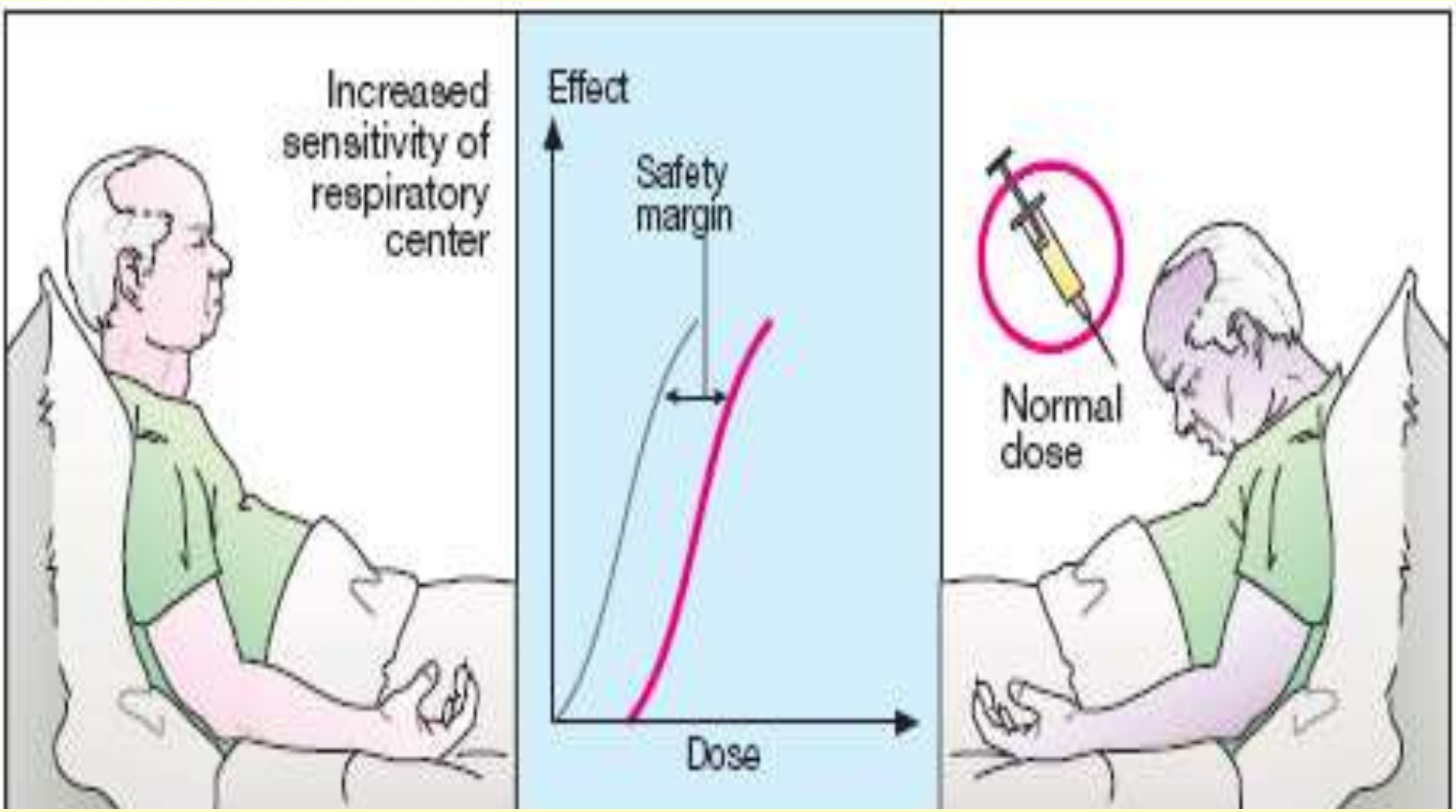
Combined action of drugs is the action of two or more co-administered drugs on the organism.

- ***Synergism*** is ***a*** strengthening of effect
  1. Addition (C = A + B)
  2. Potentiation (C > A + B)
- ***Antagonism*** is ***a*** weakening of effect
  1. Chemical
  2. Physical
  3. Physiological (competition in binding to receptors, action on different receptors with the opposite effect)

OVERDOSE AS THE ACTION OF LARGE (TOXIC) DOSE OF DRUG



SIDE EFFECTS AS UNWANTED ACTION OF THERAPEUTIUC DOSE OF THE DRUG

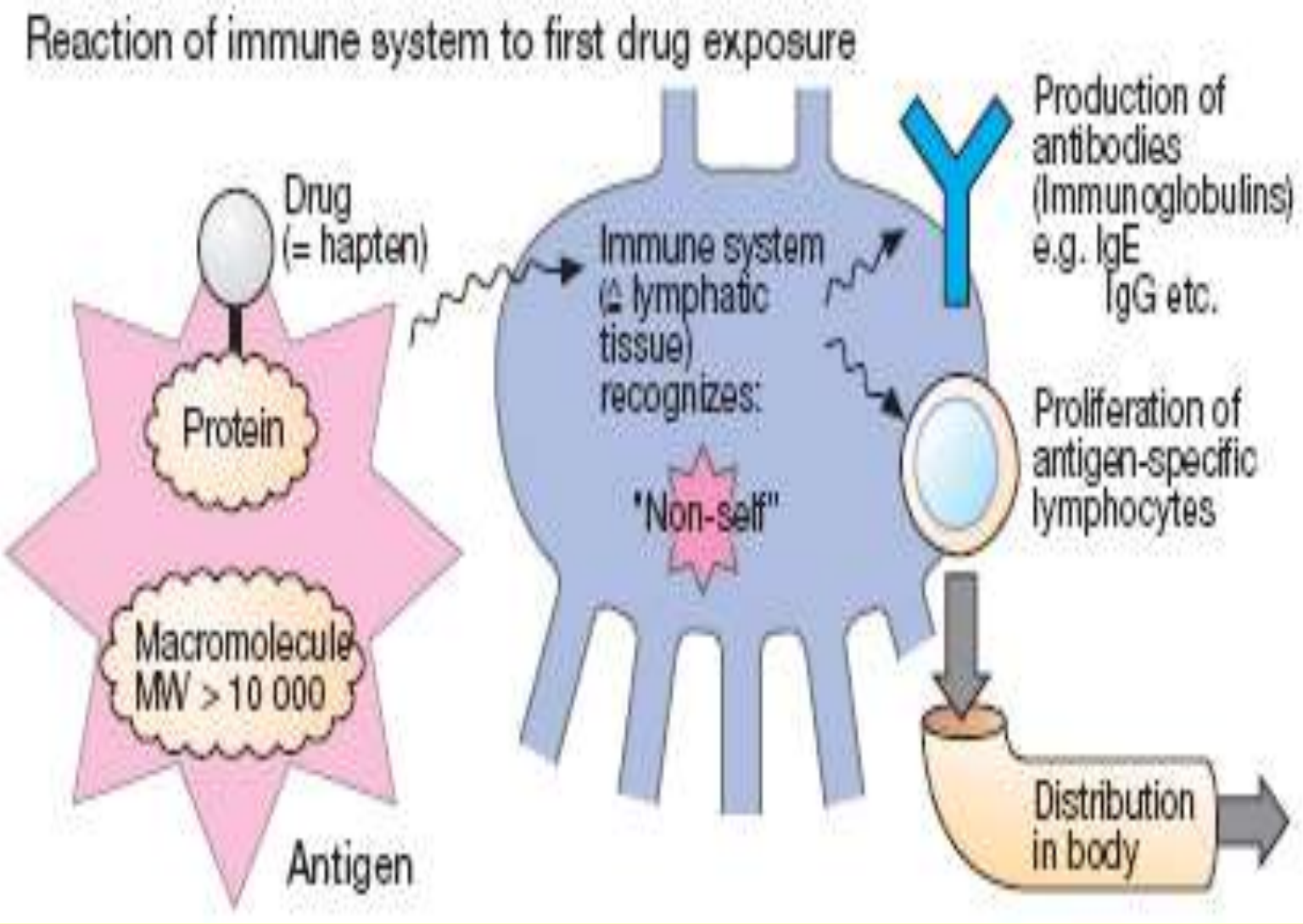


SIDE EFFECTS

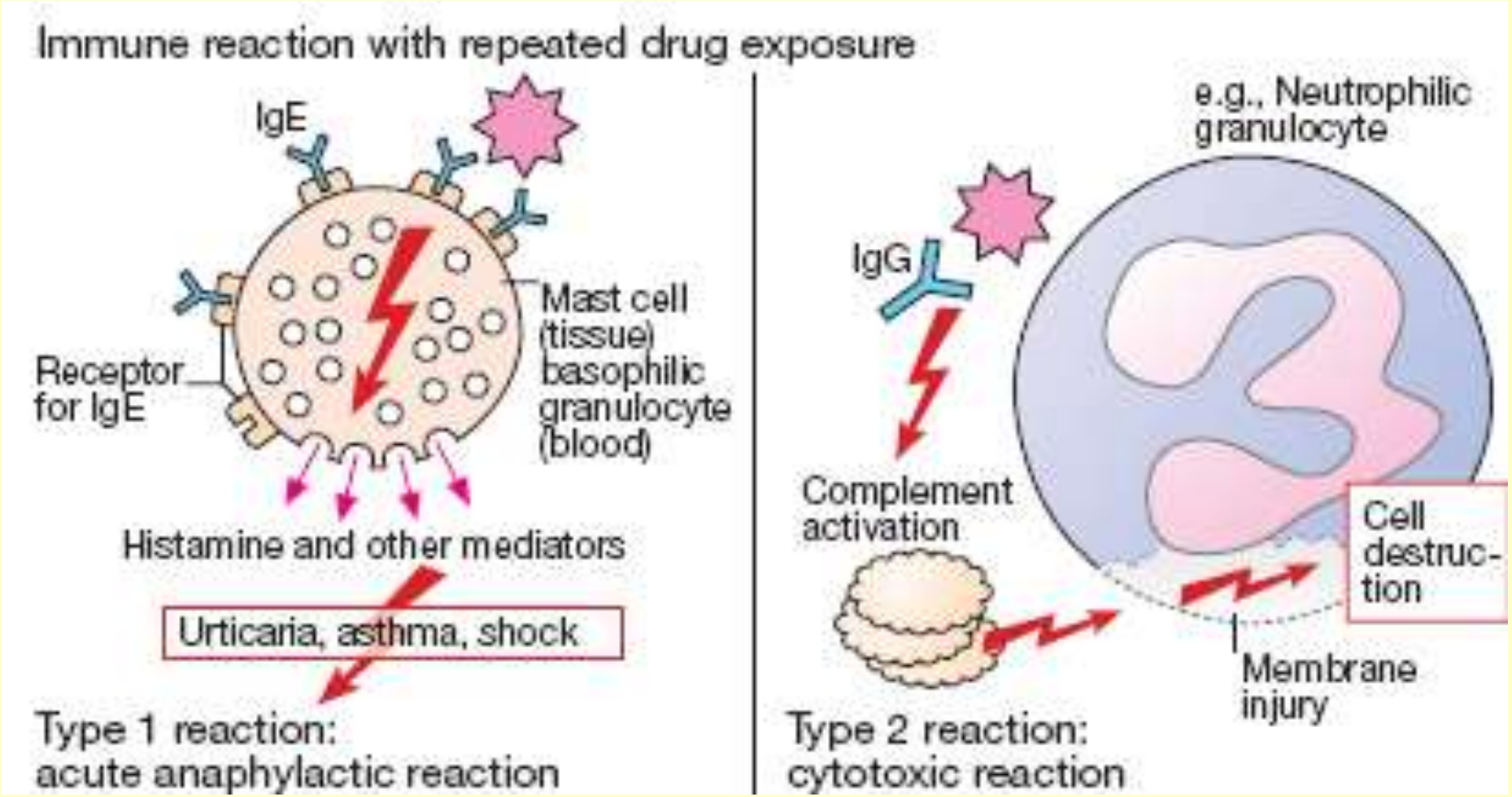
Side effects are non-useful effects of drugs in therapeutic doses:

- ***direct toxic effects***
- ***allergic reactions*** (immune reaction of hypersensitivity)
- ***idiosyncrasy*** (abnormal reaction occurred after the fist drug administration and caused by genetic factors)
- ***embryotoxic, fetotoxic and teratogenous effects*** (negative influence on the embrio and fetus during pregnancy)
- ***cancerogenous and mutagenous action.***

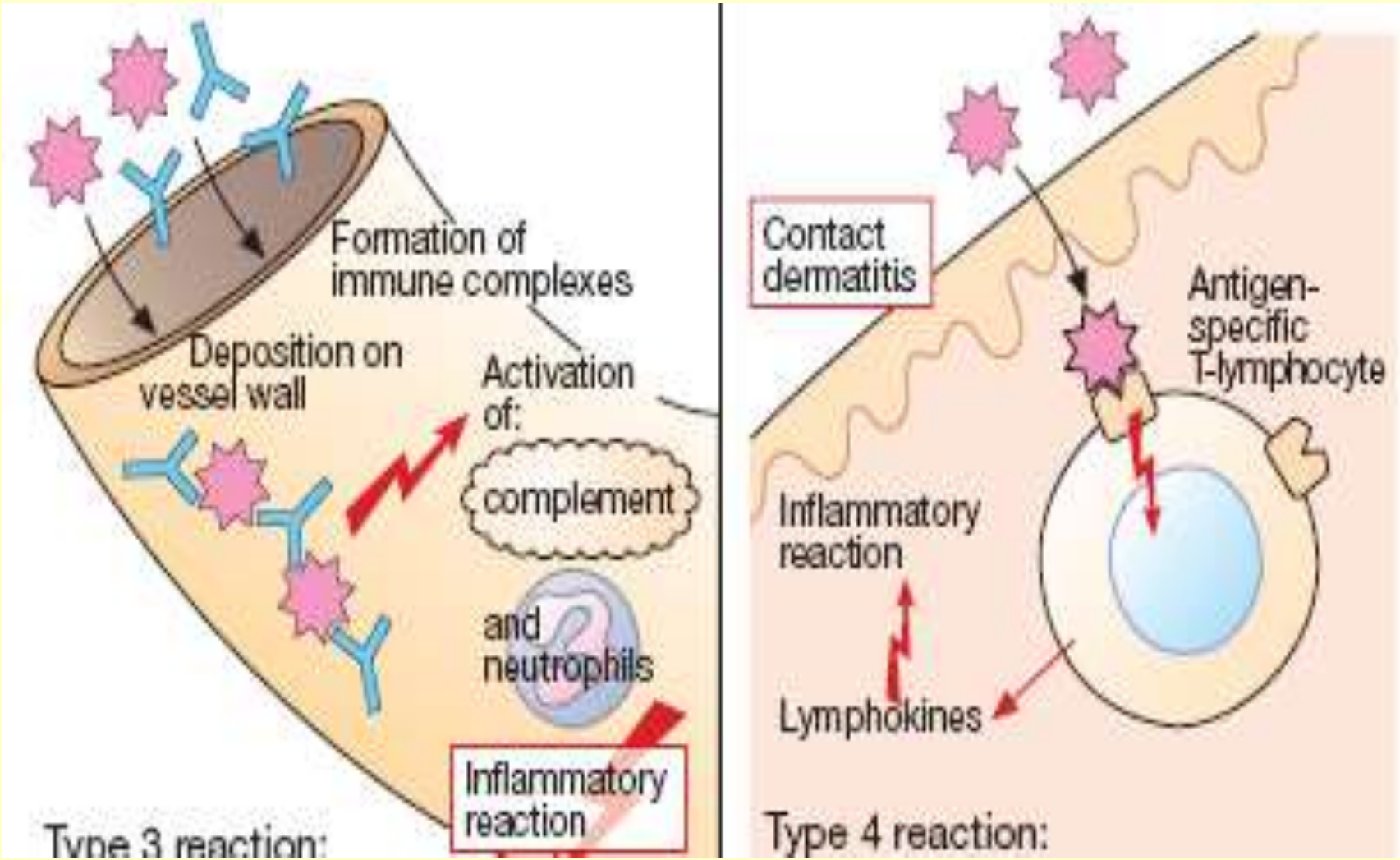
ALLERGIC REACTIONS AS SIDE EFFECTS OF PHARMACOTHERAPY



ALLERGIC REACTIONS AS SIDE-EFFECTS OF PHARMACOTHERAPY

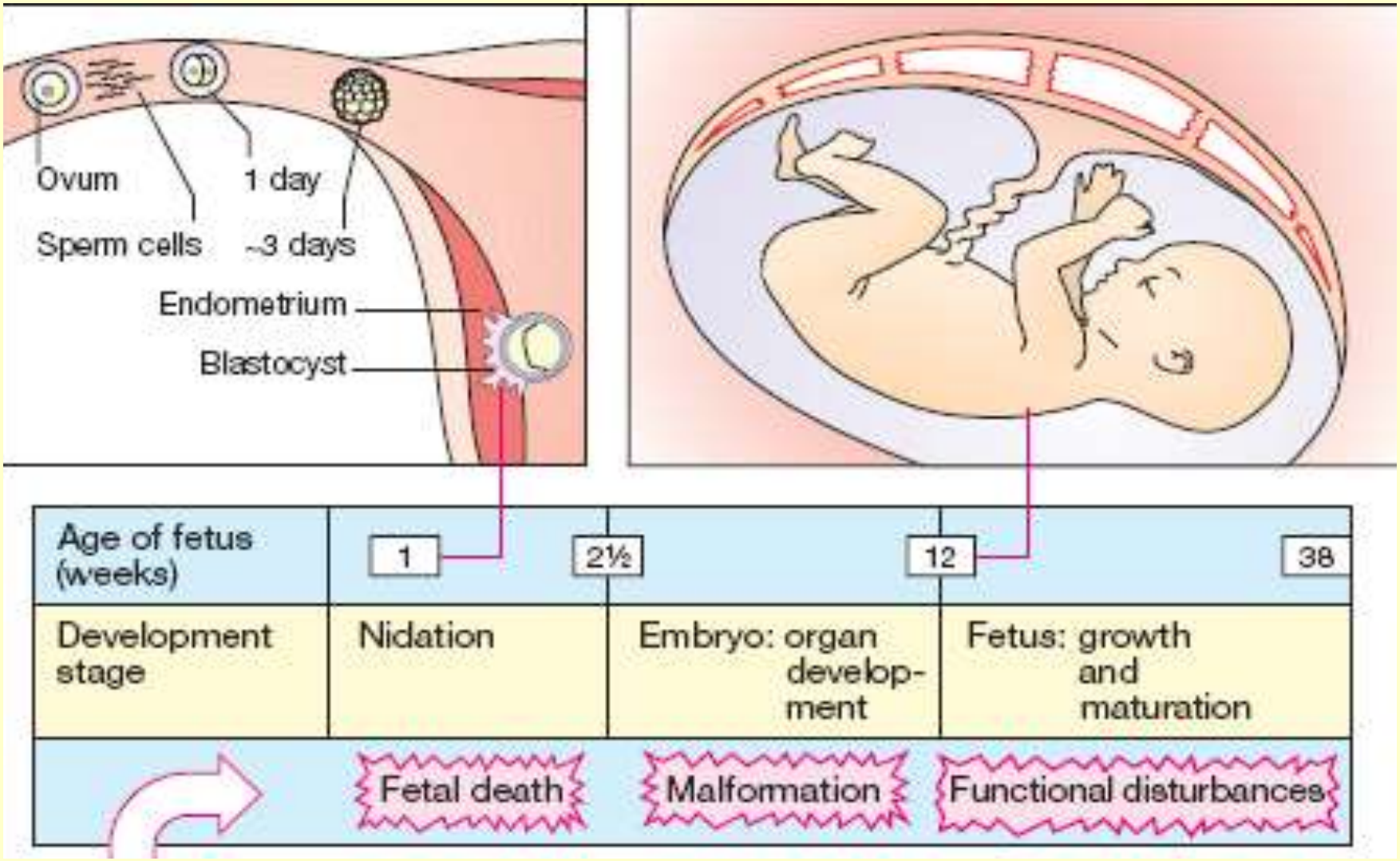


ALLERGIC REACTIONS AS SIDE EFFECTS OF PHARMACOTHERAPY



ALLERGIC REACTIONS:
from skin rash to anaphylactic shock

NEGATIVE INFLUENCE ON THE EMBRIO AND FETUS



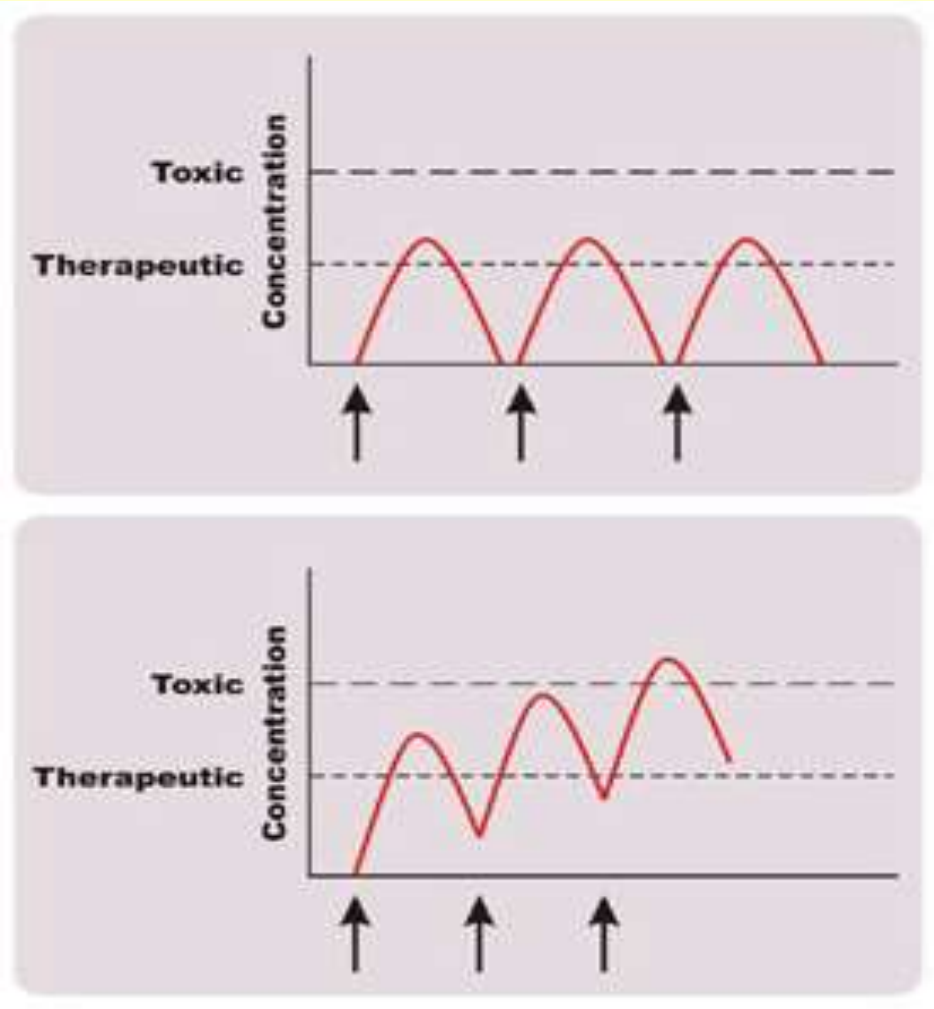
SIDE EFFECTS OF DRUGS:

teratogenous action (focomelia caused by talidomide and tetracyclin teeth)

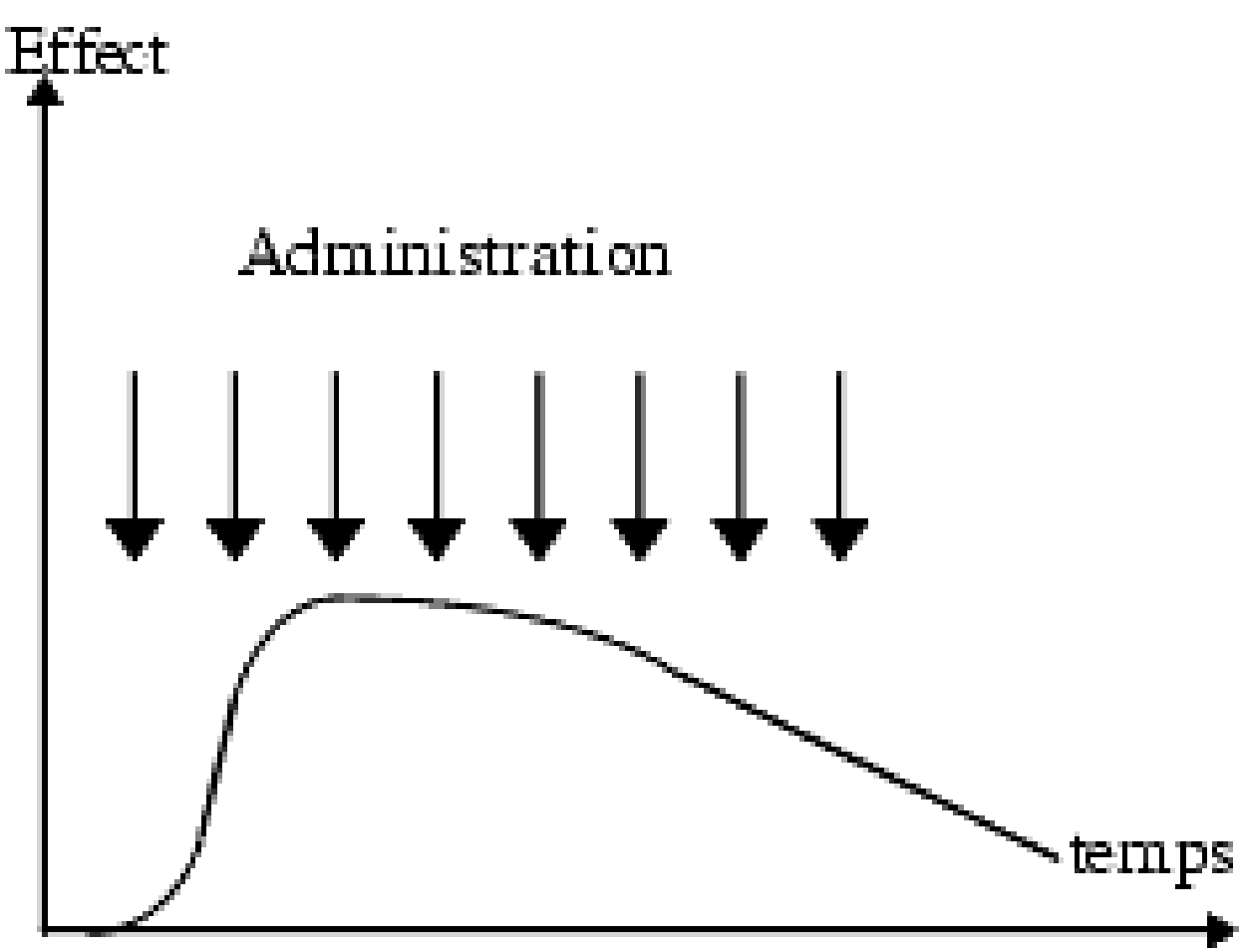
EFFECTS OF REPEATED DOSES OF DRUGS

- ***Accumulation*** (material and functional) is the accumulation of the drug or its effects.
- ***Tolerance*** (habituation) is a decrease in drug's action after its repeated administration.
- ***Tachyphylaxis*** is a rapid form of tolerance developing in the first day of treatment.
- ***Drug dependence*** is un-resistless aspiration to take a drug for euphoria or improvement of condition.

DRUG ACCUMULATION



DRUG TOLERANCE



DRUG DEPENDENCE

Drug dependence

Physical dependence –
if the patent wants to take the drug for altering general state and mood (e.g.: ethyl alcohol, morphine)

Psychological dependence –
if the patient wants to take the drug for altering the mood (for euphoria) (e.g.: psychomotor stimulants)

ABSTINENCE

Abstinence is a phenomenon of deprivation.

- It accompanies physical dependence
- It is due to disturbances in the synthesis of neurotransmitters and neuropeptides in the brain after a quick abolishing of the agent caused drug dependence.

CONTROL TASKS

- Cardiac glycoside was used for emergency help to the patient with acute heart failure. It acts on the heart muscle and increases the force of contractions. How is such type of action called?

A. Direct action

B. Indirect action

C. Local action

D. Reflexive action

E. Irreversible action.

(A)

CONTROL TASKS

- An attack of malaria was treated with quinine. The treatment was complicated by hemolytic anemia (black-water fever). Laboratory analysis has shown the deficit of glucose-6-phosphate dehydrogenase. What kind of side effects is displayed in this case?

A. Direct toxic action

B. Allergic reaction

C. Physical drug dependence

D. Idiosyncrasy

E. Functional accumulation.

(D)

CONTROL TASKS

- The eye drops containing atropine were prescribed to a patient with trauma of the eye. It is known that atropine blocks M-cholinoreceptors. What kind of mechanism of action has this preparation?

A. Genom-tropic

B. Membrane-tropic

C. Receptor mechanism

D. Enzyme-tropic

E. Other of listed.

(C)