THE NATIONAL UNIVERSITY OF PHARMACY
Pharmacology department

Lecture topic:

“GENERAL PHARMACOLOGY II”

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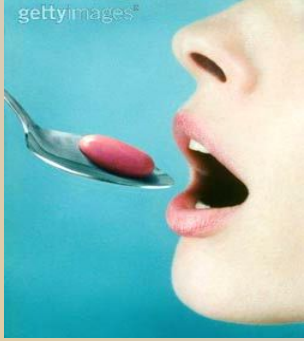
Objectives

I. Pharmacokinetics

- ✔Absorption
- ✔Bioavailability
- ✔Distribution
- ✔Drug metabolism
- ✔Excretion

II. Combined action of drugs

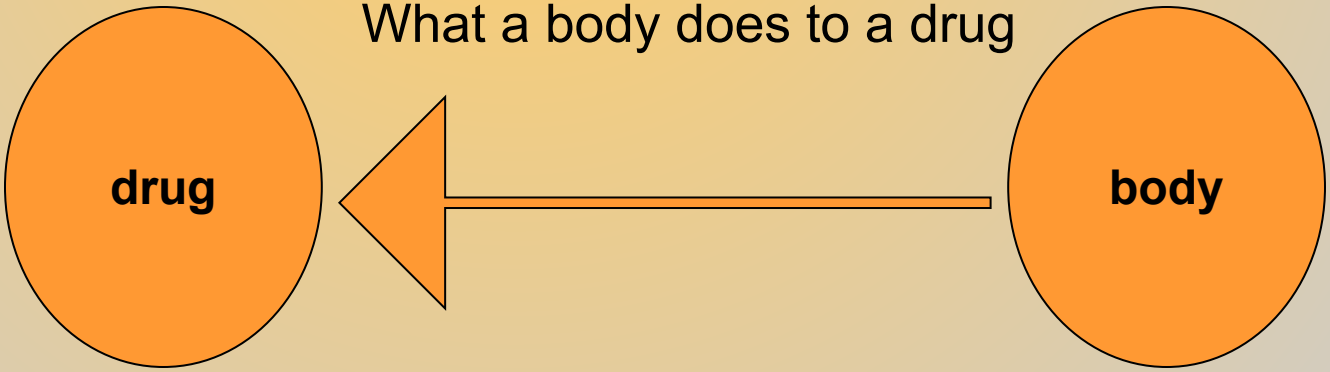
Pharmacokinetics



Pharmacokinetics
(from Greek *pharmakon* - medicine,
kineo - move)

Pharmacokinetics is the part of pharmacology that deals with compound absorbtion, distribution in the body, storage, metabolism and exretion.

What a body does to a drug



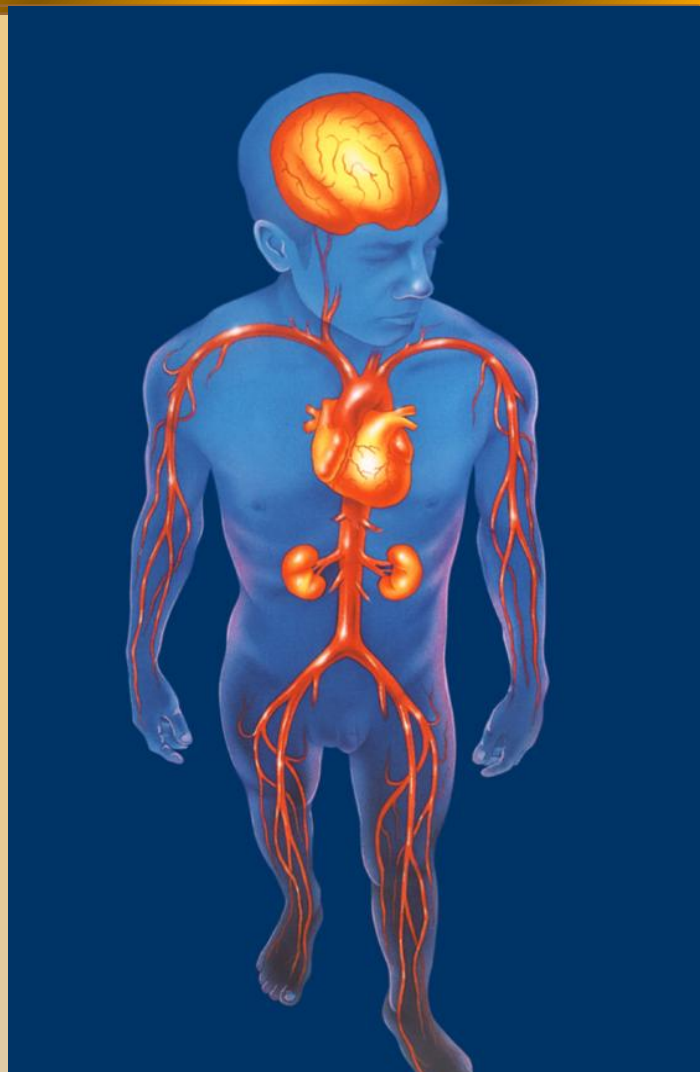
Pharmacokinetics

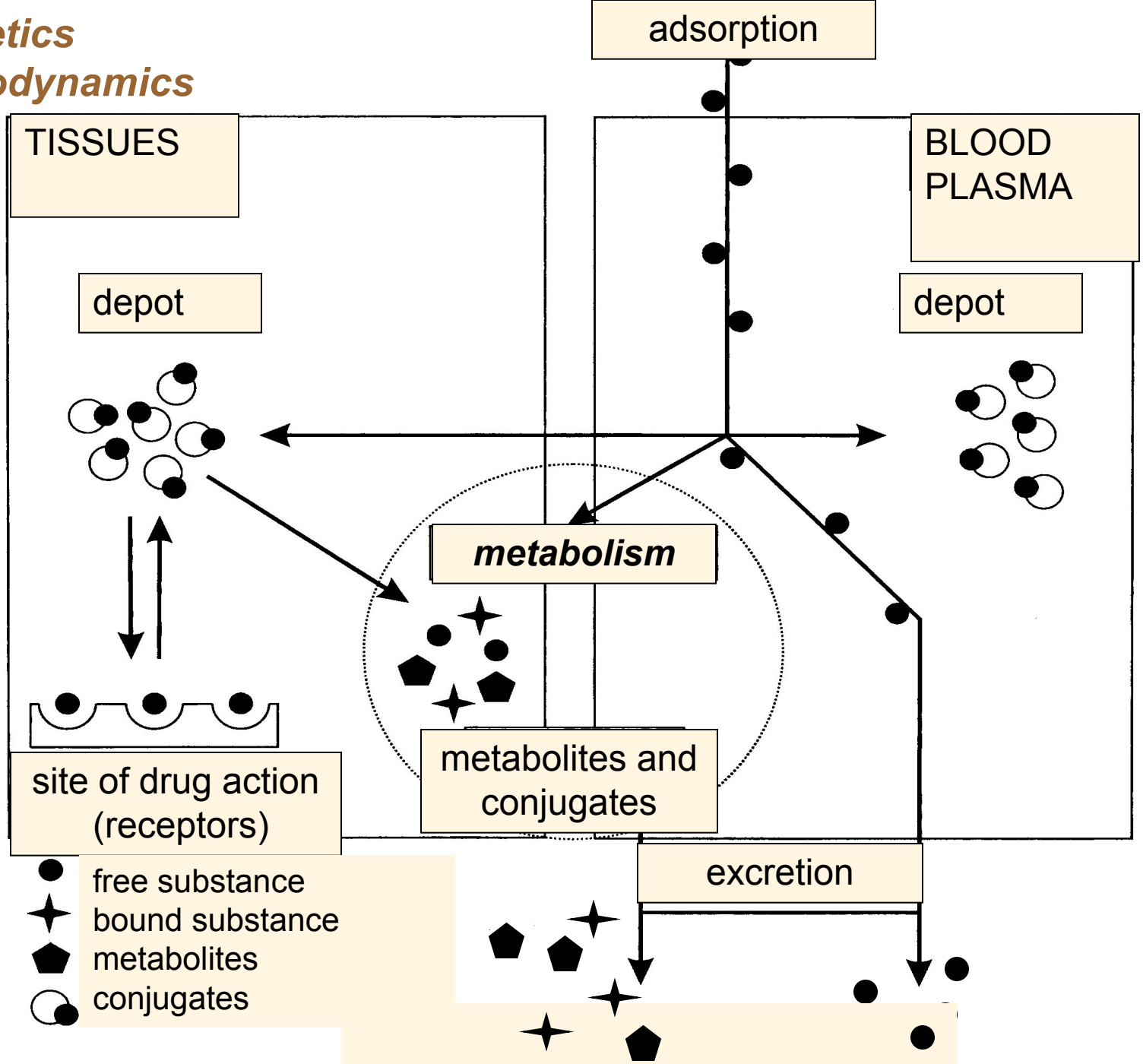
- Based on the hypothesis that **the action of a drug requires presence of a certain concentration in the fluid surrounding the target tissue**.
- In other words, the magnitude of response (desirable or undesirable) depends on the concentration of the drug at the site of action

Pharmacokinetics
Drug Movement in the Body

ADME profile

- Absorption
- Distribution
- Metabolism
- Excretion




adsorption
TISSUES
BLOOD PLASMA
depot
depot
metabolism
site of drug action (receptors)
metabolites and conjugates
excretion
free substance
bound substance
metabolites
conjugates

Absorption

Step 1 in ADME profile

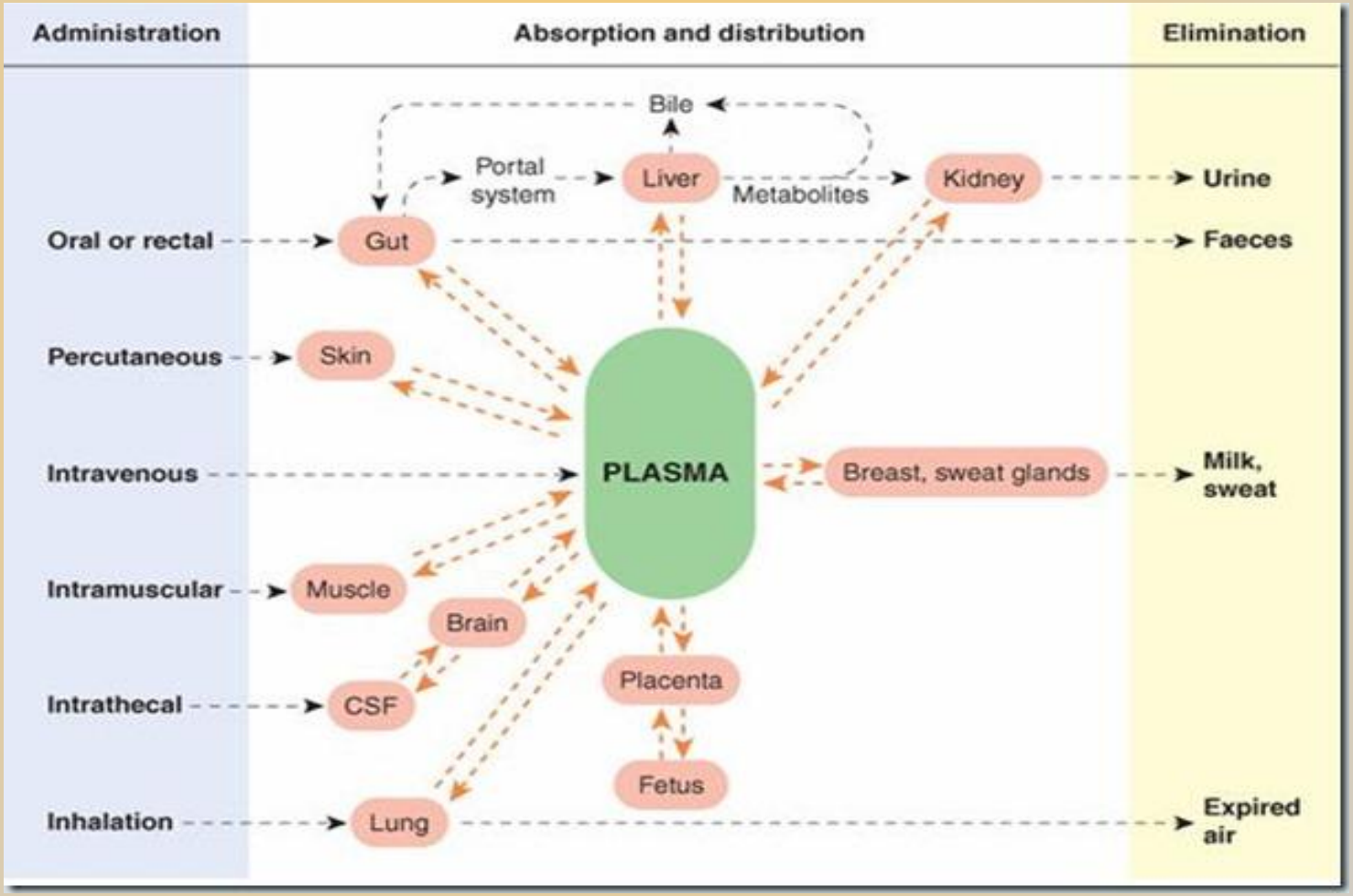
The usage of drugs starts with their administration into the organism or application onto body surface

The route of administration defines the speed of onset of effect, its intensity and duration and, in certain cases, the drug activity

There are several known absorbtion mechanisms

Absorption

Absorption

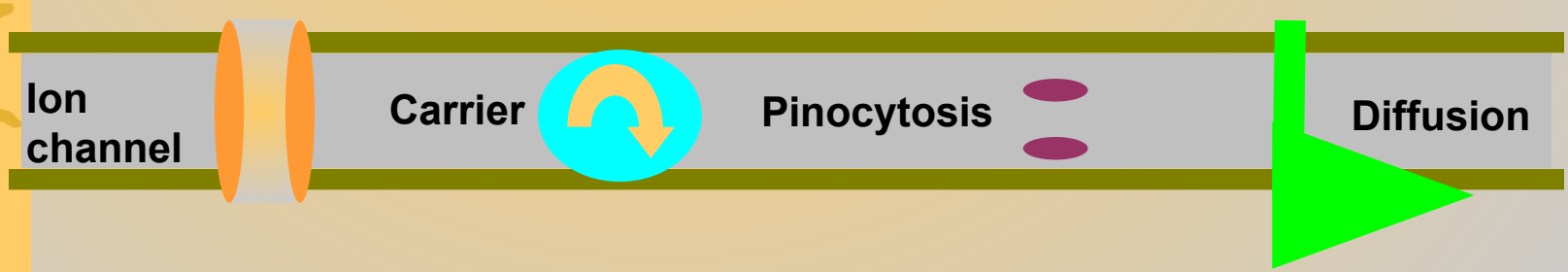

Administration
Absorption and distribution
Elimination
Bile
Portal system
Liver
Metabolites
Kidney
Urine
Oral or rectal
Gut
Faeces
Percutaneous
Skin
Intravenous
PLASMA
Breast, sweat glands
Milk, sweat
Intramuscular
Muscle
Brain
Placenta
Intrathecal
CSF
Fetus
Inhalation
Lung
Expired air

Absorption

Absorption of drugs from the gastrointestinal tract through the skin, respiratory and vascular walls is connected with several known mechanisms.

Types of transport:

- **passive** transport
  (simple diffusion, facilitated diffusion, ultrafiltration)
- **active** transport
- **pinocytosis**



Absorption

Passive diffusion: substances move from the area with high concentration to the area with low concentration
(*small neutral molecules, oxygen*)

Facilitated diffusion: involves transport systems (specific carriers) functioning without energy consumption,
along the concentration gradient (*adenilyc nucleotides*)

Active transport: can occur against the concentration gradient and with energy consumption. Involves transport systems that are selective to certain compounds and saturable
(*Na^+ and K^+ ions, sugars, aminoacids*)

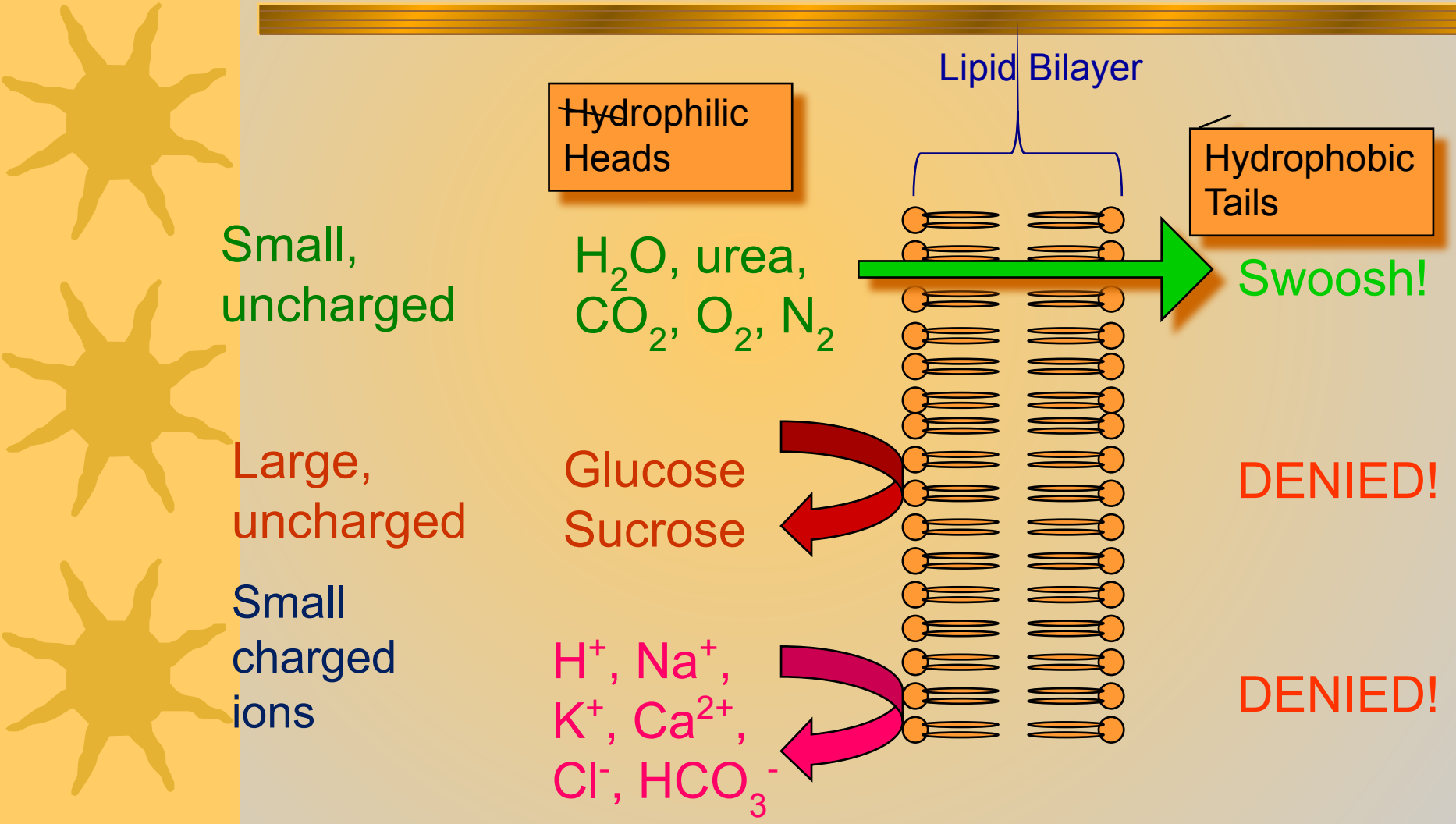
Pinocytosis: involves formation of a vesicle filled with fluid and large molecules of transported substances. The vesicle migrates via the cytoplasm to the opposite side of the cell where the vesicle content is expelled from the cell

Absorption

Mechanism	*Direction*	*Energy required*	*Carrier*	*Saturability*
Passive diffusion	**Along the gradient**	**No**	**No**	**No**
Facilitated diffusion	**Along the gradient**	**No**	**Yes**	**Yes**
Active transport	**Against the gradient**	**Yes**	**Yes**	**Yes**

Passive transport

Membranes and Absorption

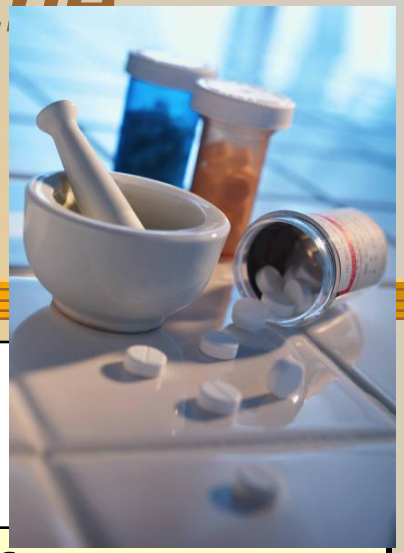


Facilitated transport

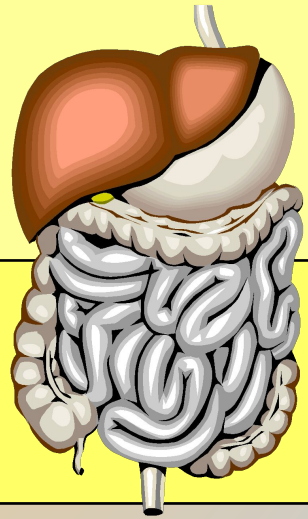
Active transport

Pinocytosis

Factors that influence the absorption



Physical properties	Physical state Solubility
Medicinal forms	Type of a medicinal form Size of drug particles Disintegration time
Physiological factors	pH of GI fluids Ionization GI transit time
Diseased state	Gastric disorders Liver disorders



Bioavailability

Systemic effect of a substance develops only after its entrance into the bloodstream from which it moves to tissues

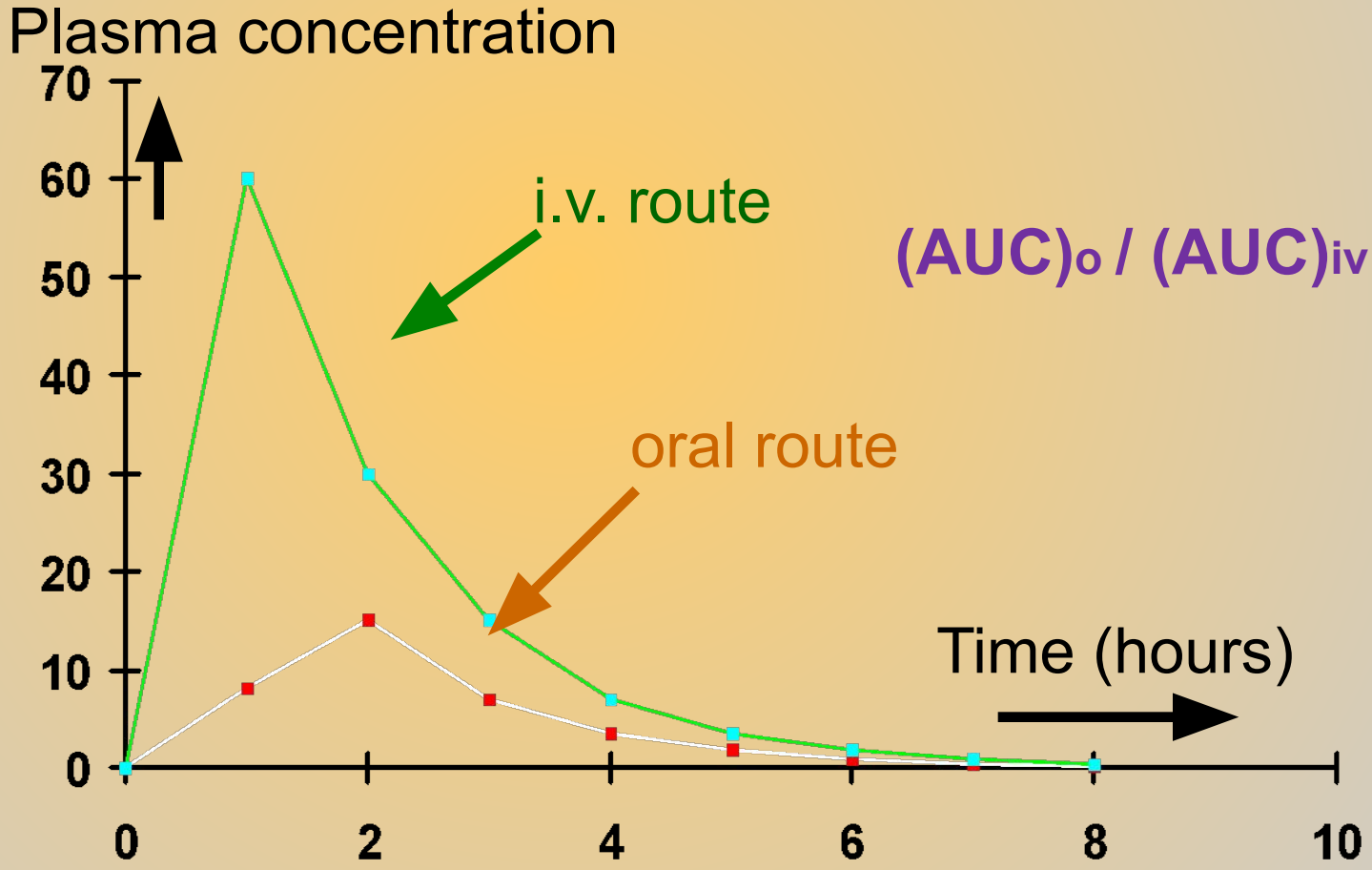
bioavailability is the proportion of the initial drug dosage that reaches blood plasma (systemic circulation) without changes

after i.v injection - 100% bioavailability

In bioavailability assessment, the area under the curve (AUC) is usually measured

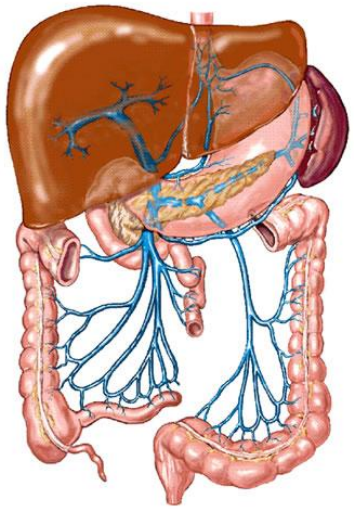
Says nothing about effectiveness

Bioavailability



$(AUC)_o / (AUC)_{iv}$

Bioavailability



Destroyed in gut

Not absorbed

Destroyed by gut wall

Destroyed by liver

Dose

to systemic circulation

Distribution

Step 2 in ADME profile

After absorption, drug enters the blood, than different organs and tissues

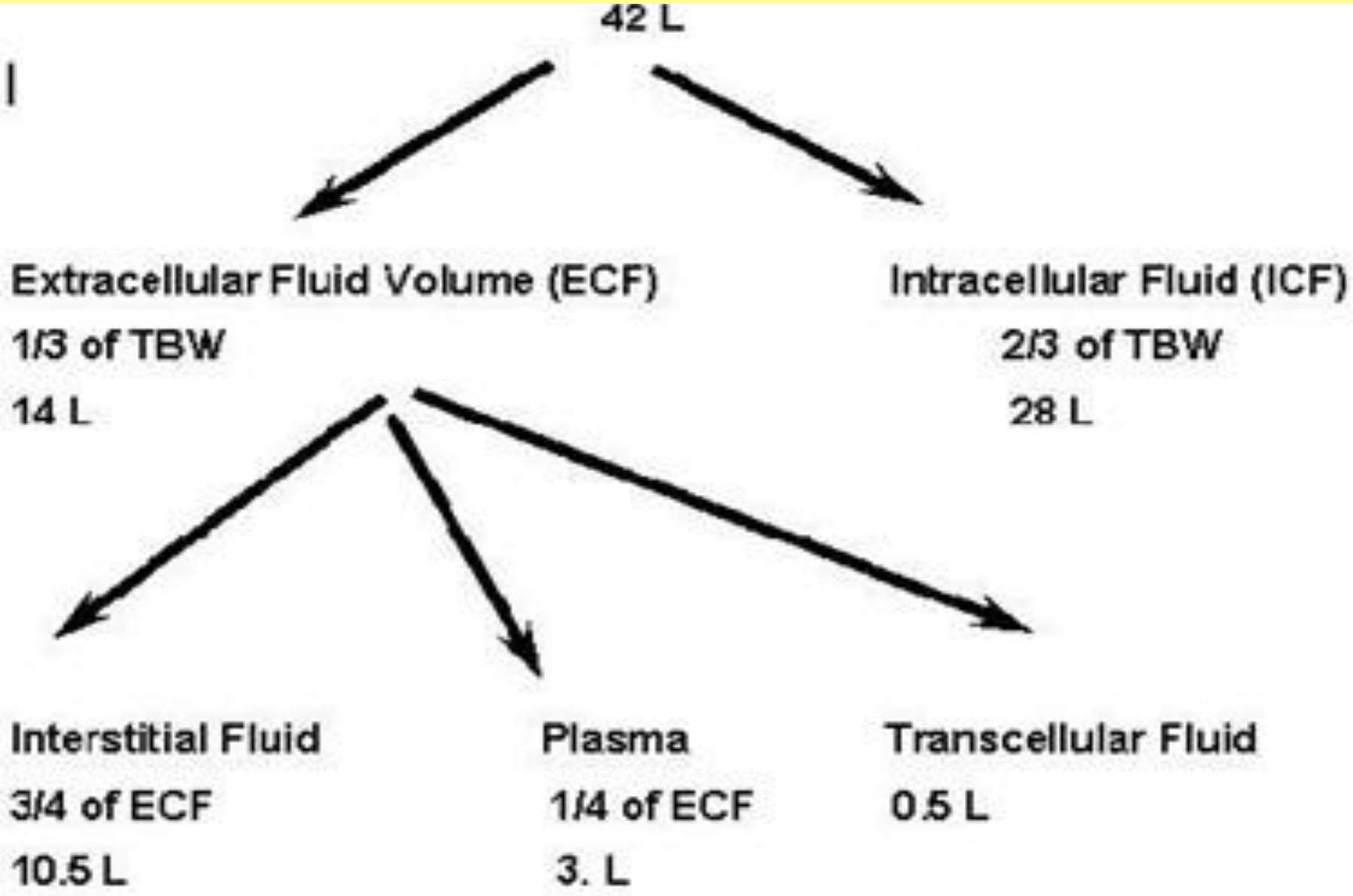
The majority of drugs are distributed unevenly

Drugs more easily penetrate into most organs with intensive blood circulation (heart, liver, kidneys)

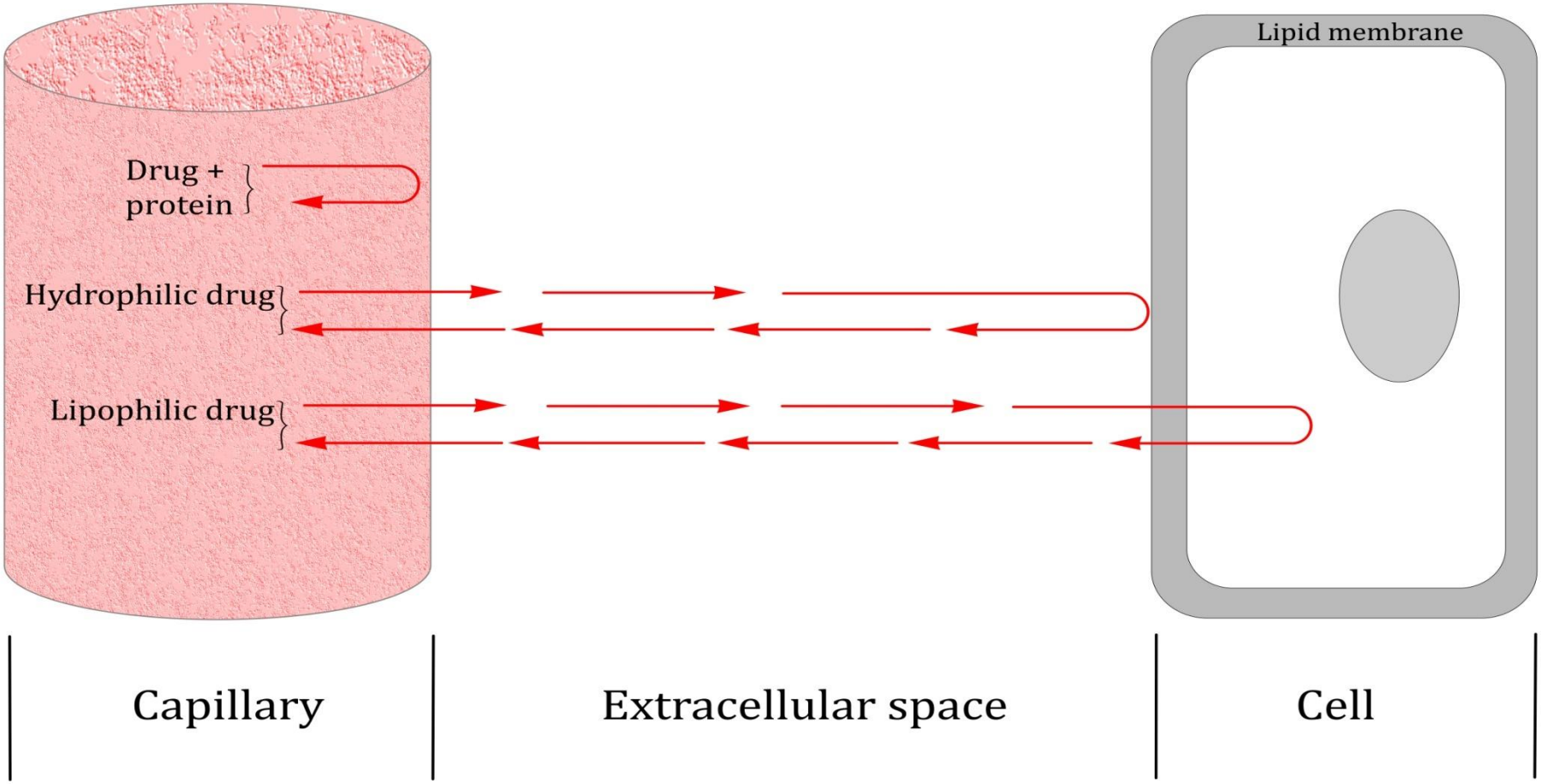
Distribution into the body compartments

- **Plasma 3.5 litres** *(heparin, plasma expanders)*
- **Extracellular fluid 14 litres**, *(tubocurarine, charged polar compounds)*
- **Total body water 40 litres** *(ethanol)*

THE BODY COMPARTMENTS



Factors influencing drug distribution



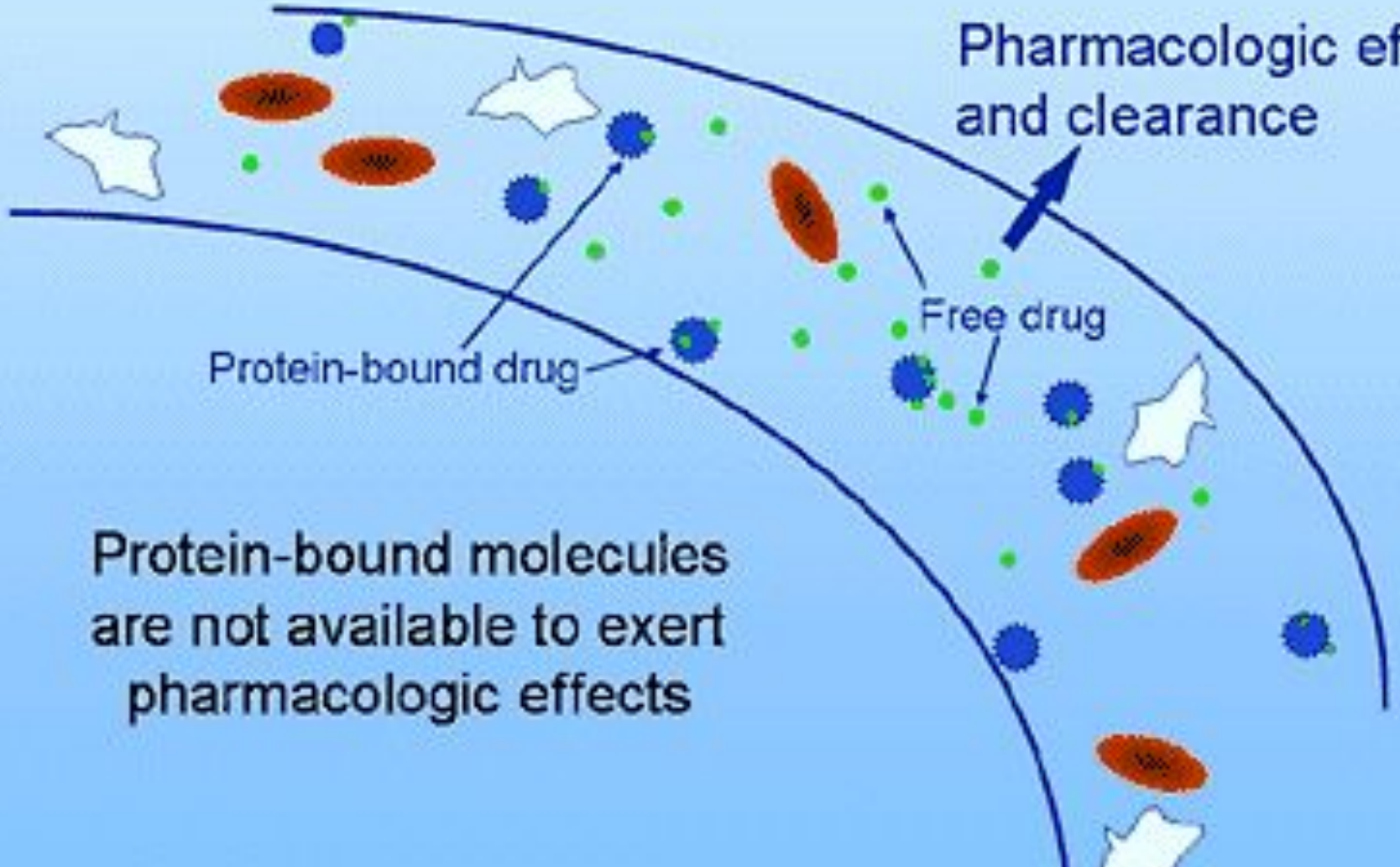
Distribution of drugs in the body

In the body drugs partially bind to other molecules and form extracellular and cellular depots
Plasma proteins (especially albumins) are the most important extracellular depots

Only free drug fraction can move through the membrane, render a pharmacological effect, undergo biotransformation and excretion

Binding of drugs to proteins may be reduced in liver and kidney diseases, sepsis, burns, gastritis, enteritis, protein deficiency, and due to the drug interaction (if two drugs get bound with the same proteins)

Schematic Representation of Protein Binding



Distribution

Distribution

The apparent volume of distribution

Important for clinical pharmacology

It is the presumed volume of liquid in which a drug can be distributed (assuming that drug concentrations in plasma and other liquid media of the body is equal)

$$V_d = \frac{\textbf{Total amount of drug in the body}}{\textbf{Drug concentration in plasma}}$$

Plasma 3.5 litres

Extracellular fluid 14 litres

Total body water 40 litres

Liphophilic compounds with wide distribution have high value of V_d

Drugs that only circulate in blood have low value of V_d

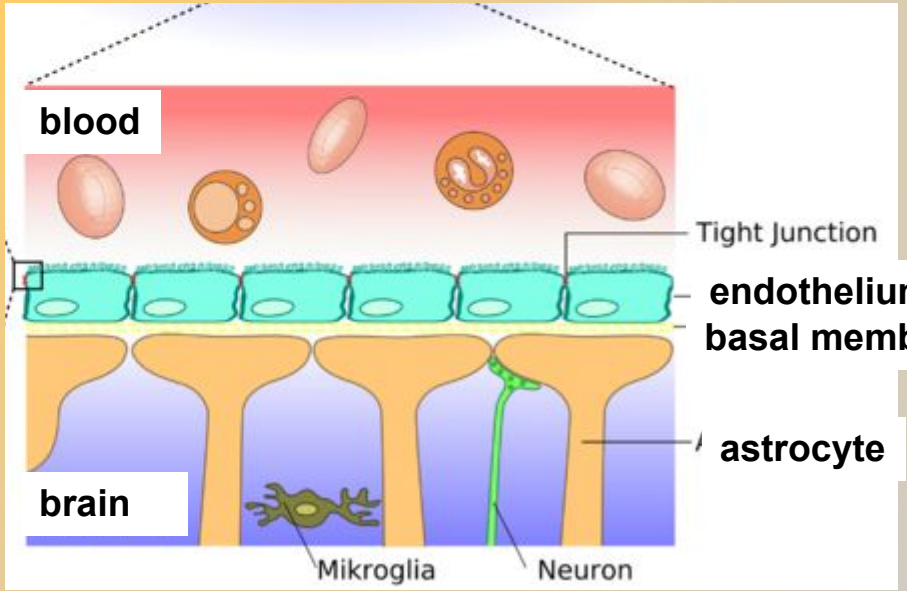
Distribution

Biological barriers

substantially influence drug distribution

There are such biological barriers:

- capillary wall
- cell membranes
- blood-brain barrier
- placental barrier



blood-brain barrier

Metabolism

Step 2 in ADME profile

Most drugs undergo biotransformation in the body

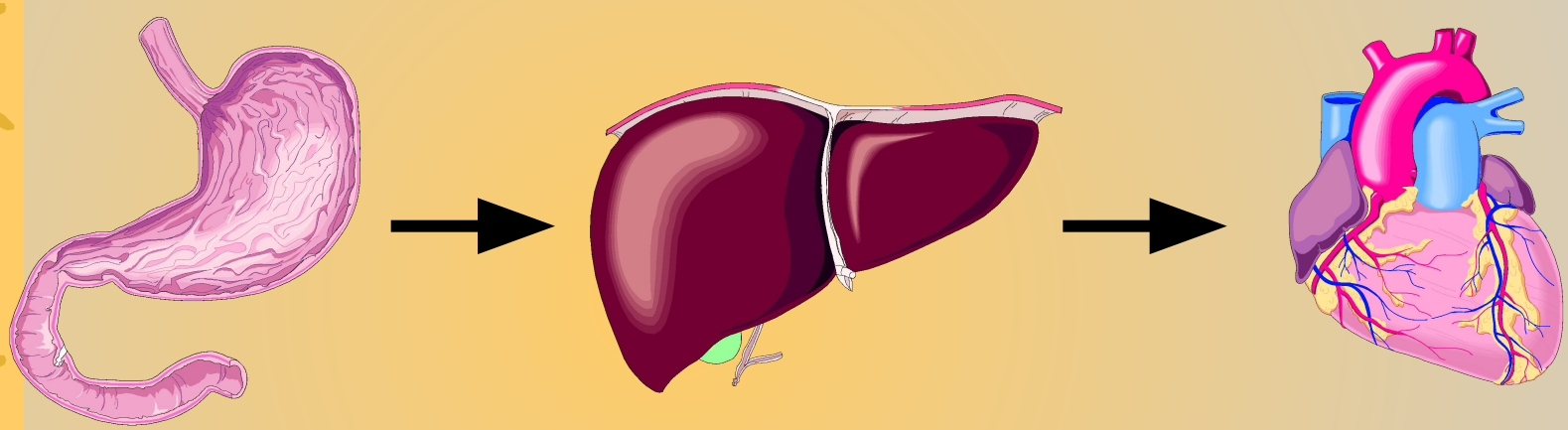
Biotransformation of drugs (drug metabolism) is the process of drugs (xenobiotics) conversion into metabolites that are easily dissolved in water and can be excreted by the kidneys.

Many enzymes participate in drug biotransformation, the most important among them are **microsomal enzymes of the liver**, they do not have substrate specifity

Non-microsomal enzymes are localized in the liver and in the intestines, lungs, kidneys, blood, placenta and others.

Drug metabolism determines drug dosage regimen.

METABOLISM



Lipid soluble drug → Water soluble drug

or

Active drug → Inactive metabolite

or

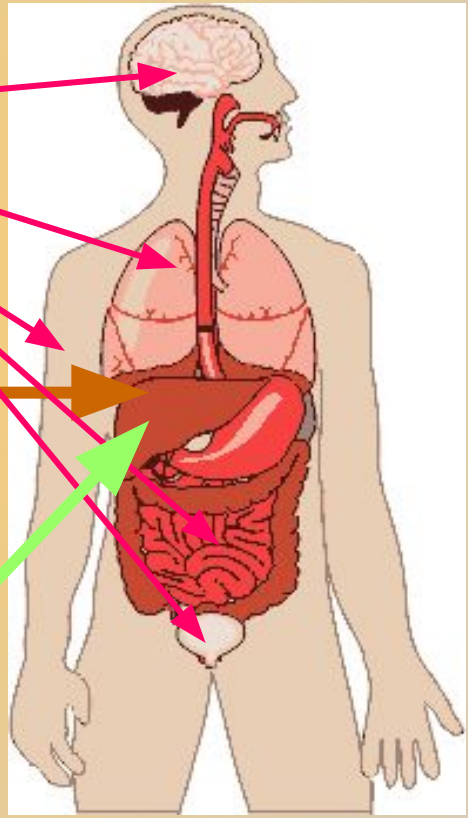
Prodrug → Active drug

Drug Metabolism

Extrahepatic microsomal enzymes (oxidation, conjugation)

Hepatic microsomal enzymes (oxidation, conjugation)

Hepatic non-microsomal enzymes (acetylation, sulfation,GSH, alcohol/aldehyde dehydrogenase, hydrolysis, ox/red)



Metabolism

Step 3 in ADME profile

There are two main types of drugs biotransformation

1. Metabolic transformation

occurs through oxidation, reduction, hydrolysis
In these reactions groups with active hydrogen atoms (oxy-, aminogroups)are formed

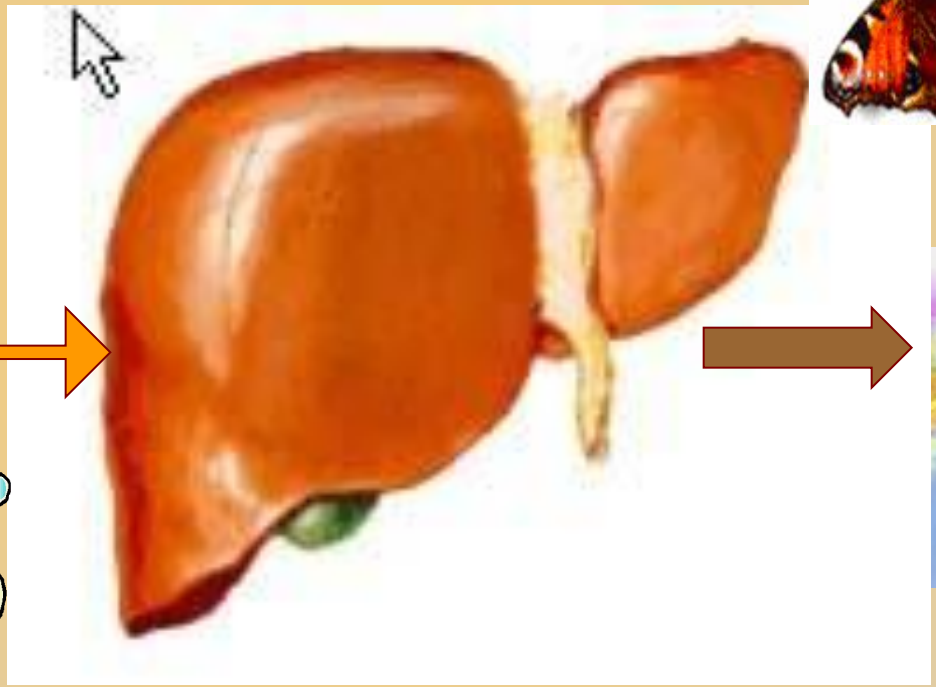
2. Conjugation

Functional groups of a drug get bound with endogenous compounds such as glucuronic residues, sulfur and amino acids. Also methylation and acetylation can take place.

Nb! *Biotransformation can increase drug activity or toxicity*
Prodrugs – active molecule is formed in the body
(sulphenamide is an active metabolite of omeprazole)

"**Lethal synthesis**" – if the toxic metabolites are formed
(acetaldehyde is the toxic metabolite of ethanol)

METABOLISM



Metabolism

Metabolic rate depends on genetic factors.

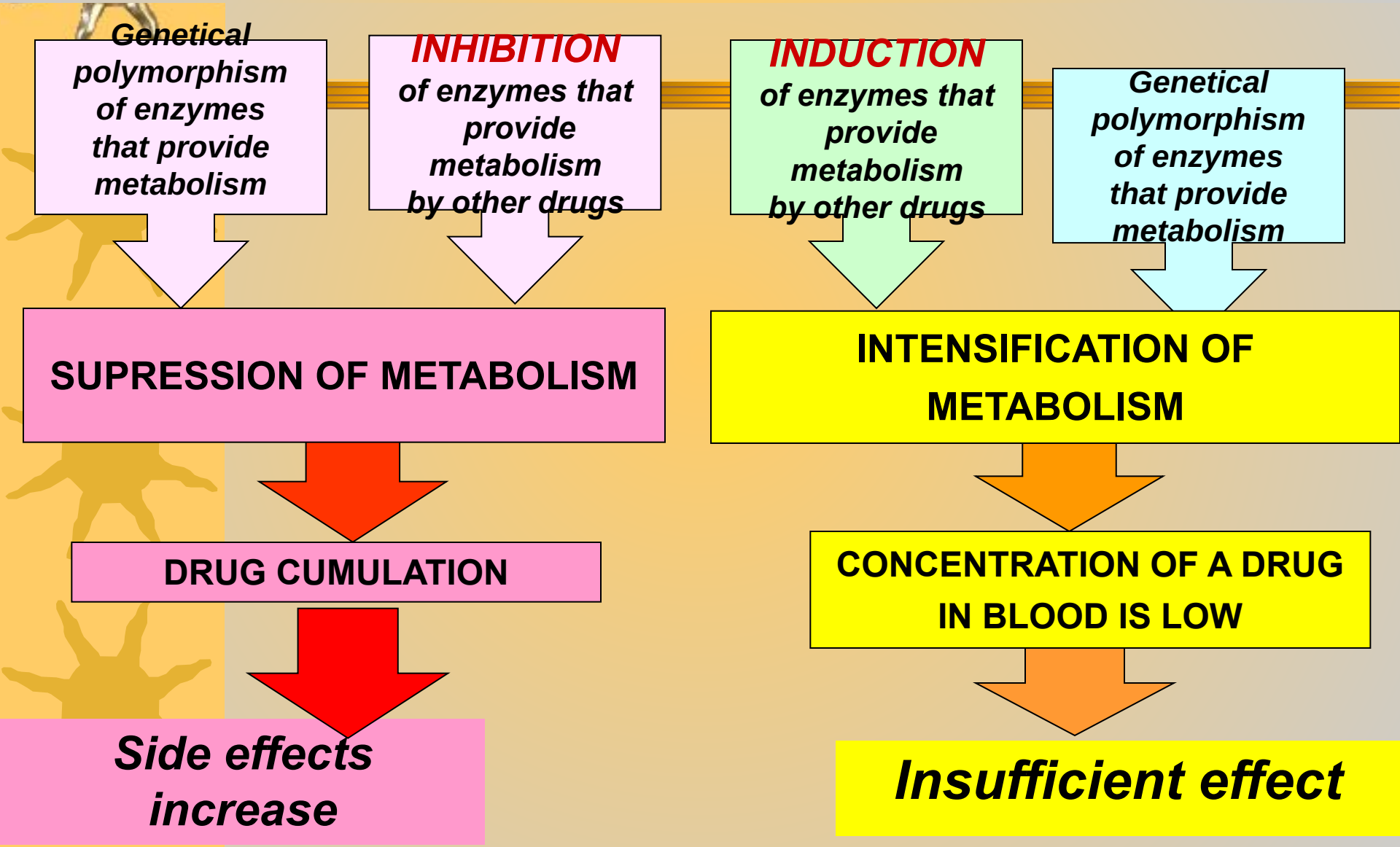
Induction and inhibition of metabolism enzymes influences the rate of metabolism of drugs.

Induction of metabolism enzymes **– increase of their activity – acceleration of the drug metabolism**

Inhibition of metabolism enzymes **– decrease of their activity – retarding of the drug metabolism**

While the use of drugs with inductors or inhibitors drug doses should be adjusted.

Concentration of a drug in blood is variable because of the changes in biotransformation processes



Excretion

Step 4 in ADME profile

Drugs and their metabolites are mainly eliminated with urine and bile

and sometimes with expiratory air, by salivary glands, sweat glands, gastric and intestinal glands, lacrimal glands, mammary glands *(caution is needed when administering drugs to a nursing mother!)*

Ways of excretion	***Drugs***
1. With urine	Most drugs in the free state
2. With bile	Penicillin, tetracycline, streptomycin, strychnine, quaternary ammonium derivatives
3. Through intestine	Doxycycline, ionized organic acids
4. By lungs	Inhalation anesthetics, iodides, camphor, ethanol, essential oils
5. With sweat	Sulfonamides, thiamine
6. With saliva	Penicillin sulfanilamides, salicylates, thiamine, benzodiazepines, ethanol
7. With milk	Anticoagulants, antibiotics, thyrostatics, carbamazepine

$t_{1/2}$ The elimination half-life or «half-life»

Important for clinical pharmacology

It shows **the time necessary to decrease drug concentration in blood plasma by 50%**

It is used to adjust doses of drugs and intervals between the times of their administration in order to achieve stable drug concentration

90% of the drug is eliminated during the period that equals 4 $t_{1/2}$

$t_{1/2}$ is defined not only by the drug elimination from the body, but also by its biotransformation and storage

EXCRETION

Drug interactions

- Based on the change in drugs pharmacokinetics
- Based on the change in drugs pharmacodynamics
- Pharmaceutical interaction

Drug interactions based on the change in drugs pharmacodynamics

- **Synergism**
  (from Greek *syn – together, ergos* – work)
  increase in effect of drugs used at the same time *(unidirectional effects)*

Two types of drug synergism

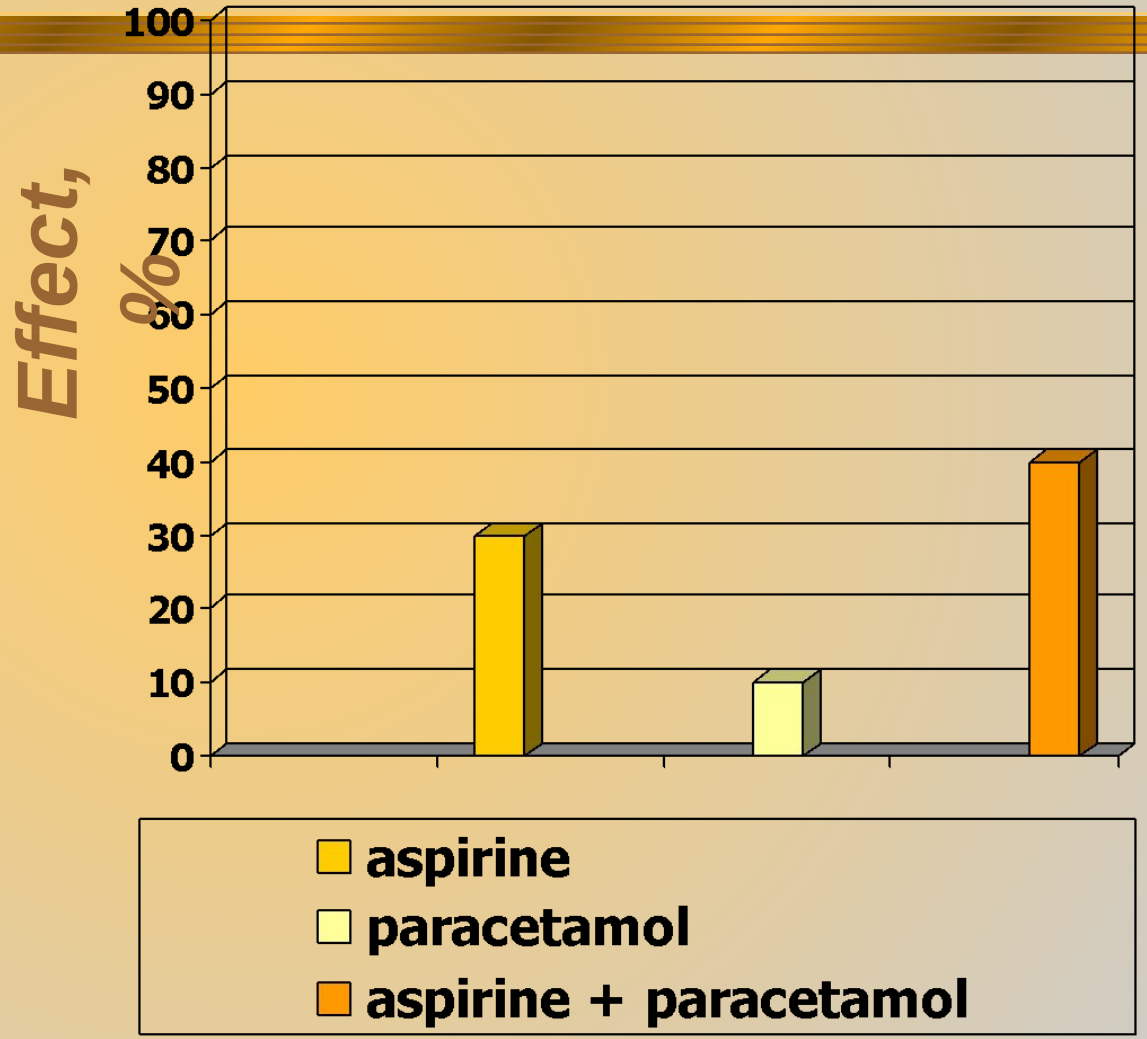
- Summing up or additive effects

- **Potentiation**

Summing up or additive effects

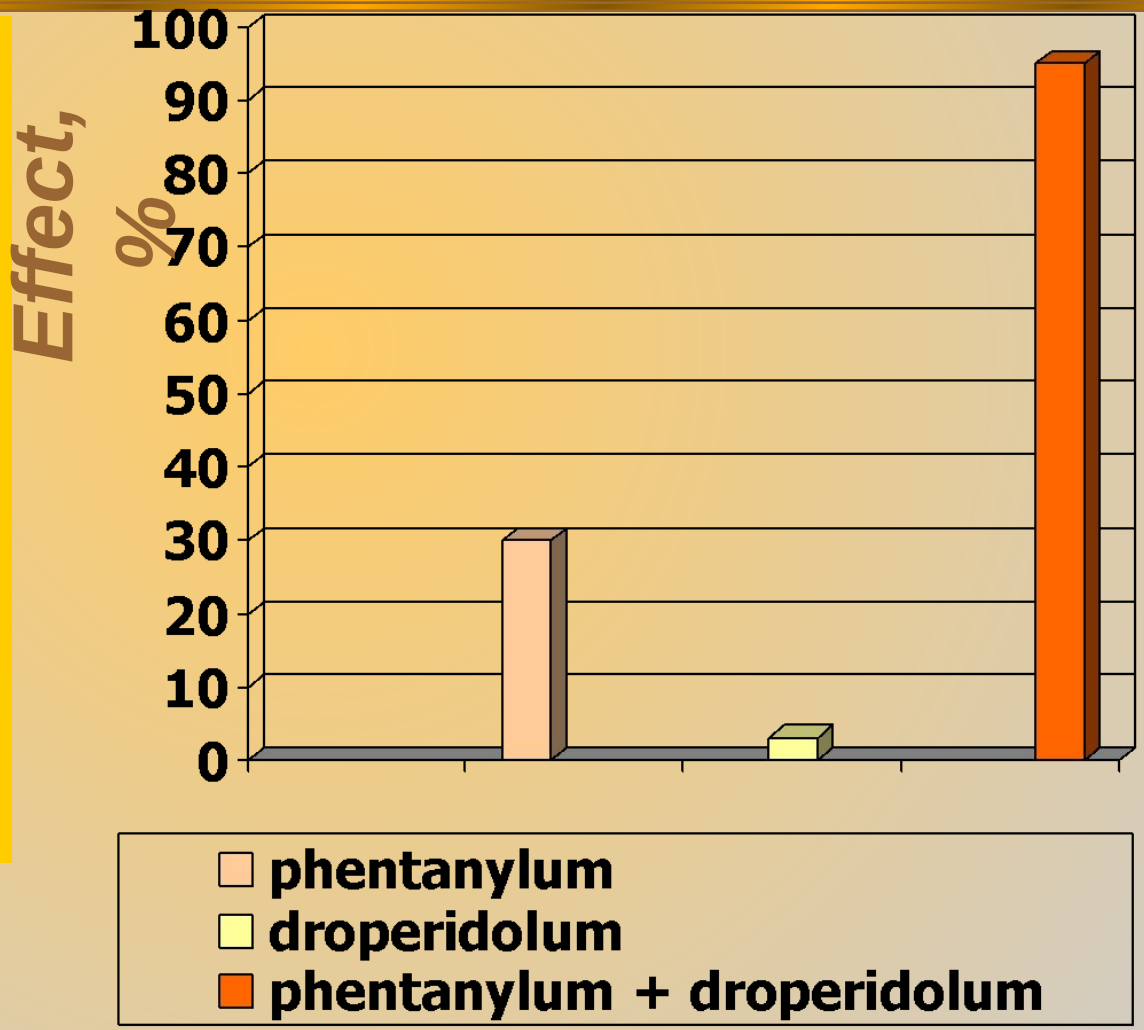
(combination of analgesics)

- The mechanisms of actions of both drugs are similar
- Summed effect represents the actual sum of effects of the individual drugs



Potentiation (neuroleptanalgesia)

- The drugs differ in mechanisms of action
- The total effect exceeds the sum of effects of the individual drugs



Drug interactions based on the change in drugs pharmacodynamics

Antagonism

(from Greek *antagōnisma* – *struggle, conflict*)

the ability of drug to decrease the effect of the other one

Types of antagonism

- **direct (competitive)**
  the same target but the opposite effect
  (contraction or relaxation of the same muscle)

- **indirect (noncompetitive)**
  different targets and the opposite effect

Drug interactions based on the change in drugs pharmacodynamics

Antagonism

Types of antagonism

- two-way and one-way antagonism

A blocker reliably eliminates the effects of a mimetic (activator)

but a mimetic (activator) usually is ineffective against a background of a blocker

Synergoantagonism

Occurs when some effects of the combined drugs are intensified, and others are weakened

Drug incompatibility

Incompatibility is the weakening, full loss or change in the pharmacotherapeutic effect, intensification of side or toxic effects

–*Pharmacological incompatibility* – in the body

- **Antagonistic combinations of drugs *(activator + blocker)* or drugs with food *(nialamide + chocolate, iron compounds + milk and others)***
- **Dangerous combinations of drugs *(astemisole + itraconazole; cardiac glycosdes + calcium salts and others)* or drugs with food (niphedipine + grapefruit and others) or drugs with herbal preparations *(drugs decreasing blood coagulation + ginkgo or garlic)***

✶ ***Pharmaceutical incompatibility*– during the production process, storage or mixing of the drugs in one syringe**

- **physical**
- **chemical**
- **physico-chemical**

Thank you!