PHARMACOKINETICS
2018.

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PHARMACOLOGY

Pharmacodynamics

What the drug „makes” with the organs

Pharmacokinetics

What the organs „makes” with the drug

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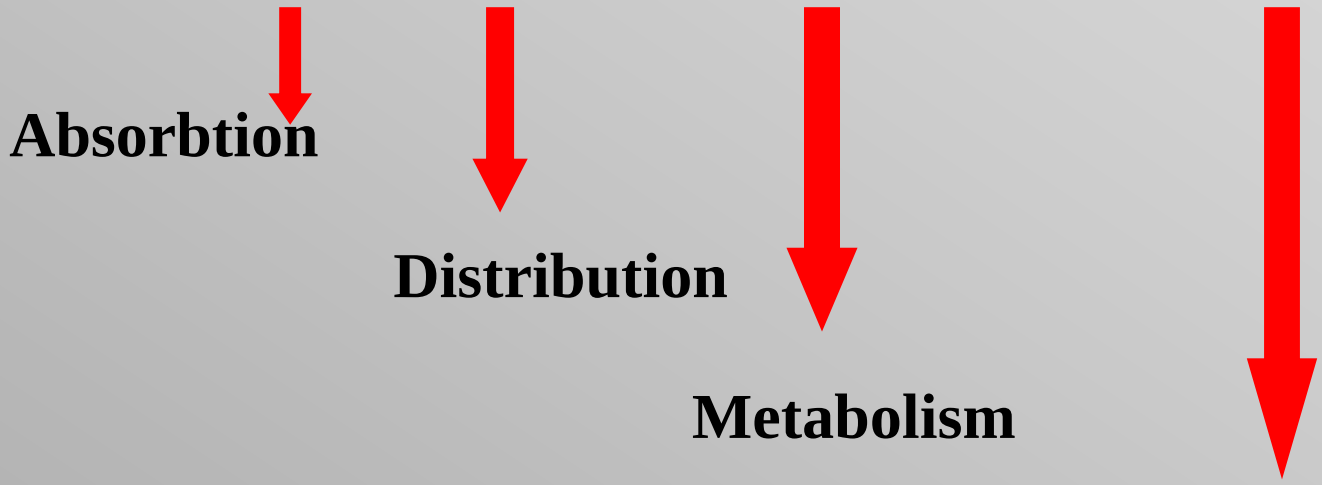
PHARMACOKINETICS



(ADME)

DEPENDS ON MEMBRANE-TRANSPORT

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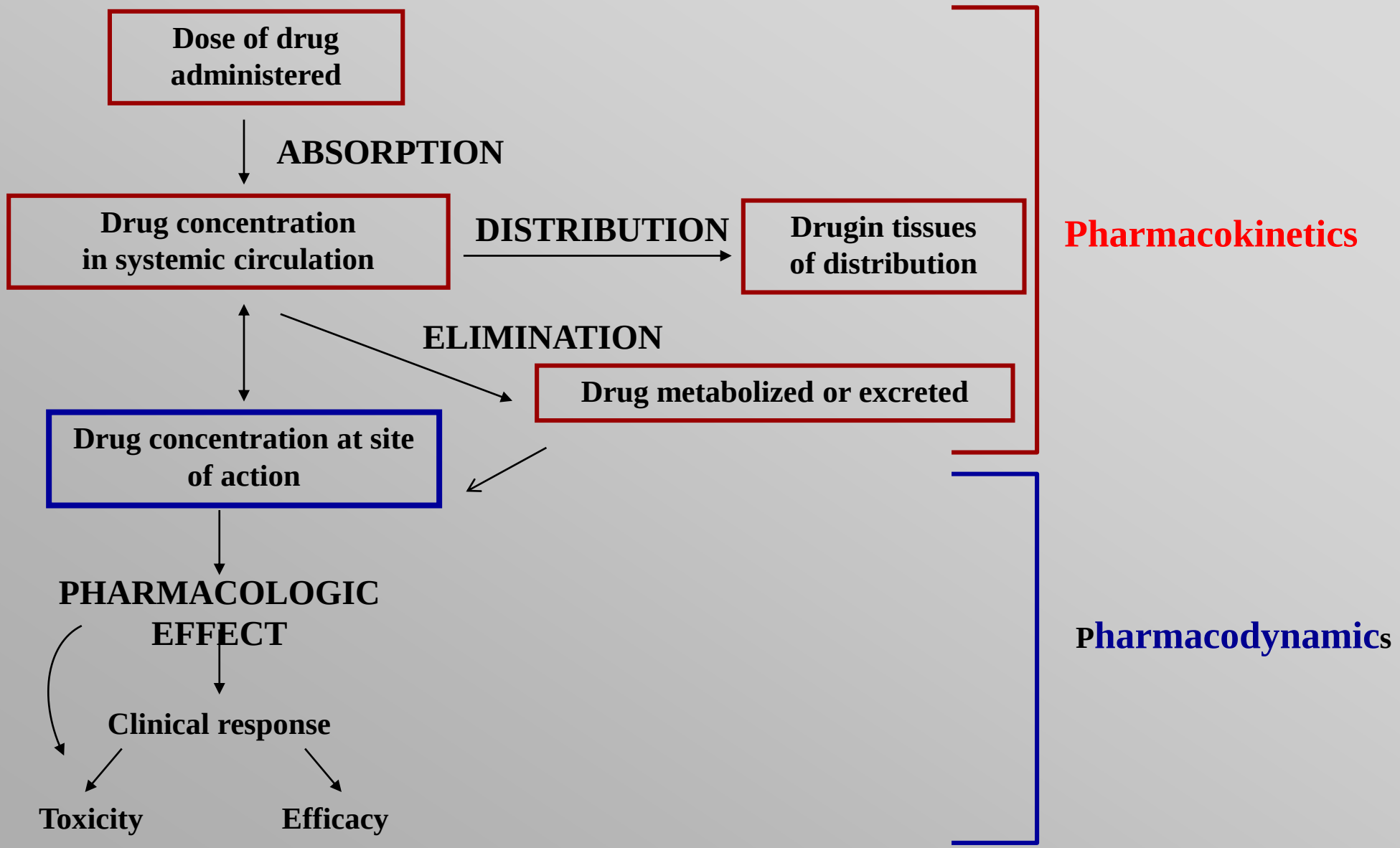

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I. TRANSPORT MECHANISMS 1.
Passive

1. AQUEOUS-DIFFUSION

Small molecules (d:<0.4 nm)
Through epithelial membrane pores
Through endothelial pores

(*Execption: blood-brain, blood- testis!*
intestinal, cutan epithel: minimal permeation
placenta: below 1 kDa permeation
)

2. LIPID-DIFFUSION!!!

lipid barriers separate water-compartments

Determinant factors:
concentration gradient,
lipid/aeqous partition coefficent of the drug memembrane

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I. TRANSPORT MECHANIZMS 2.
Active

3. CARRIER-MEDIATED TRANSPORT

selective, saturable, inhibitable

⬇ ⬇

facilited diffusion **active transport**

-Large endogenous molecules, non-lipid soluble moleules
e.g. peptides, amino acid, glucose, L-DOPA
-Xenobiotics

Number of carrier molecules can be changed; e.g. inhibitors of protein synthesis.

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I. TRANSPORT MECHANIZMS 3.

Active

4. ENDOCYTOSIS, EXOCYTOSIS

ENDOCYTOSIS

Bound to cell surface receptor, engulfed by the cell-membrane, and the newly formed vesicle carried out the into the cell. Large molecules, e.g. iron-, B12 vitamine – protein complex

EXOCYTOSIS

Fusion of the vesicle with cell membrane, expulsion of its content extracellularly, e.g. transmitter release, mast cell degranulation

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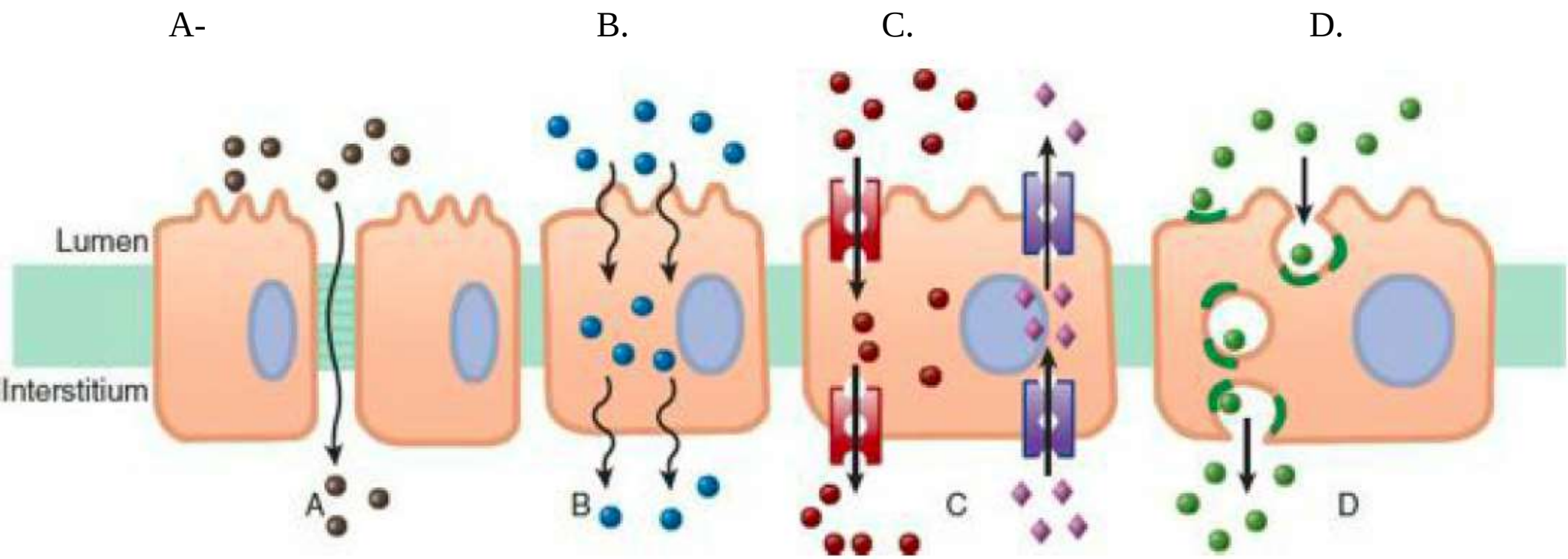
TRANSPORT MECHANIZMS



From B. Katzung 13 Ed., 2014

A: Aeqous diffusion B: **Lipid diffusion C. carrierr-mediated**

D. Endo-, exocytozis

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LIPID DIFFUSION

Importance of ionised, non-ionised molecules in membrane transport

Ionised molecule: weak lipid solubility

Non-ionised molecule: lipid-soluble
(exception: aminoglycoside)

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Henderson-Hasselbach equation

Weak acids

$$pK_a - pH = \log \left[\frac{\text{non-ionized}}{\text{ionized}} \right]$$

Weak bases

$$pK_a - pH = \log \left[\frac{\text{ionized}}{\text{non-ionized}} \right]$$

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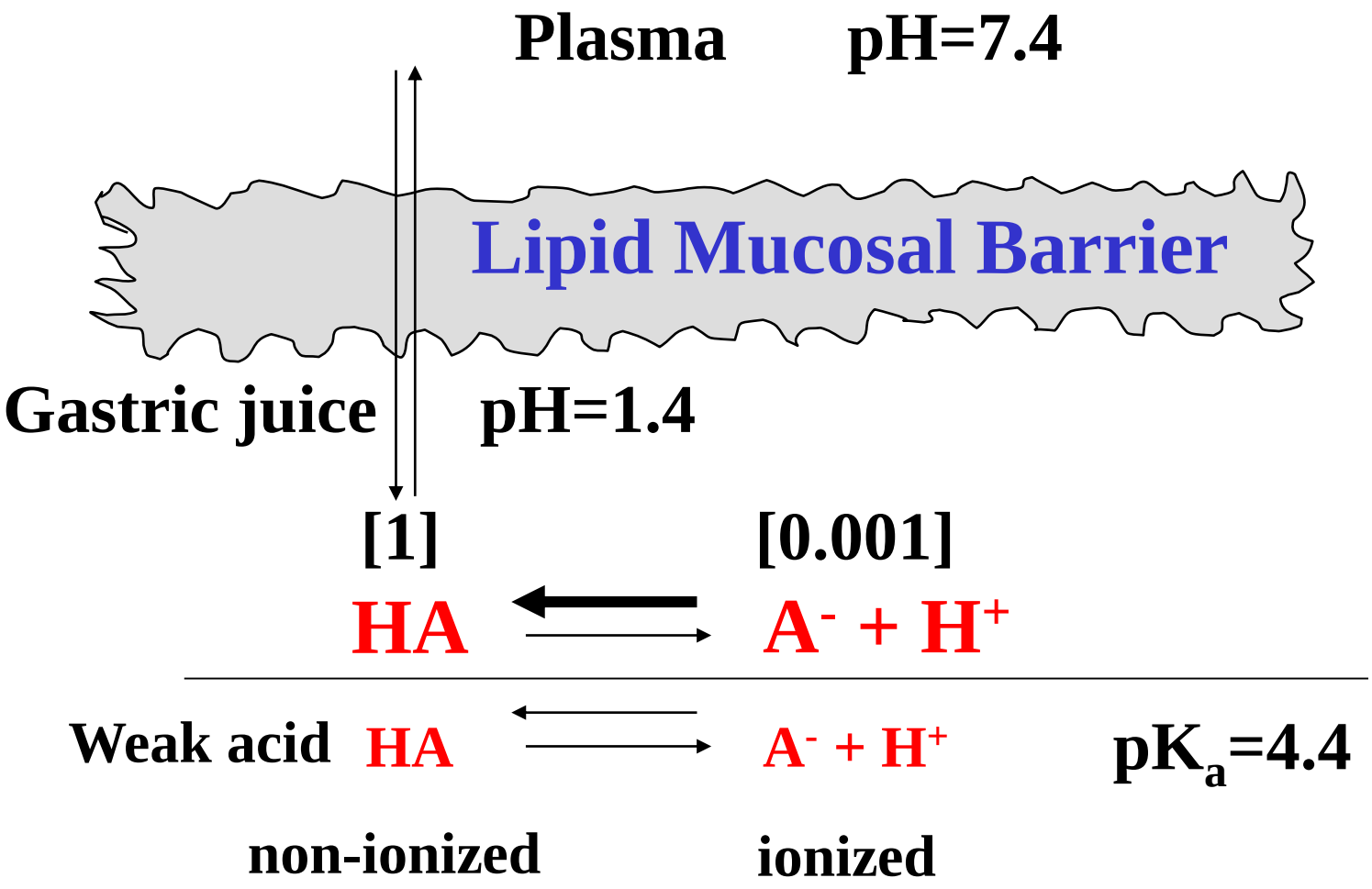
EXAMPLE 1.

Salicylates

pKa:4.4; **pH: 1.4 (Stomach)**

$$pKa - pH = \log \left(\frac{\text{non-ionized molecules}}{\text{ionized molcules}} \right)$$

$$4.4 - 1.4 = 3 = \log \frac{1000}{1}$$


Plasma pH=7.4
Lipid Mucosal Barrier
Gastric juice pH=1.4
[1]
[0.001]
HA
A- + H+
Weak acid HA
A- + H+
pKa=4.4
non-ionized
ionized

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EXAMPLE 2.

Salicylates

pKa: 4.4 **pH: 7.4 (mucosal cell)**

$$pKa - pH = \log\left(\frac{\text{non-ionized molecules}}{\text{ionized molecules}}\right)$$

$$4.4 - 7.4 = -3 = \lg\frac{1}{1000}$$

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EXAMPLE 3.

Salicylates

pK:4.4; **pH:8.4 (urine)**

$$pKa - pH = \lg\left(\frac{\text{non-ionized molecules}}{\text{ionized molecules}}\right)$$

$$4.4 - 8.4 = -4 = \log\frac{1}{10000}$$

Conclusion

Alkalisation of the urine enhances the excretion of weak acids, acidification enhances the excretion of weak bases

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TRANSPORTERS

ATP binding casett (ABC)

Solute carrier (*SLC*)

transporter superfamilies

EFFLUX

Energy: ATP

7 families

INFLUX, EFFLUX

Use ion gradient to drive transport

48 families

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TRANSPORTERS

ATP binding casett transporter large family

7 families

EFFLUX

- **Multidrug resistance protein (MDR): MDR1 or P-glycoprotein (**intestine. brain, placenta, testis)
- Multidrug resistance-associated protein (MRP) (excretion of drugs to urine, bile)
- White" transporter: BCRP (Breast Cancer Resistance Protein)

Role: Excretion of drug into urine, bile, intestine,
Drug resistence of tumor to chemotherapy

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MDR1 – P-glycoprotein

- INTESTINAL EPITHELIAL
  Reverese transport toward to the intestinal lumen

Inhibitors of MDR1 transporter

Increased toxic effect:
grapefruit: enhance intestinal absorbtion of cyclosporin – increased toxicity

***Increased therapeutic effect*:**
ritonavir (anti-HIV agent, protease inhibitor: combined with other protease inhibitors enhance their absorbtion and therapeutic effect (e.g.: lopinavir+ritonavir; atazanavir+ritonavir)

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MDR1 – P-glycoprotein

- ENDOTHELIAL

BLOOD-BRAIN BARRIER: in endothel cells;

e.g. loperamide can not enter the CNS

PLACENTA - does not allow entry of drugs to the phoetus (not absolutely)

TESTIS

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TRANSPORTERS

SLC transporter superfamily

Use ion gradient to drive transport,
primary **INFLUX**
48 families

Primarily involved in the uptake of small molecules into cells.

Organic anion transporters (OAT, OATP).
Organic cation transporters (OCT).

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TRANSPORTERS

In one cell more transporters:

e.g. in liver cell influx transporter facilitate the drug entry and its metabolism

The efflux transporters enhance the polar glucoronid-derivative excretion to the bile

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SUMMARY OF DRUG MOVEMENT ACROSS MEMBRANES

Drug cross lipid membranes mainly by **passive transport** and carrier-mediated transfer.

The most important factor that determines the passive transport is the **lipid solubility** of the drug.

Only the **uncharged** molecules can diffuse the lipid membranes.

Carrier-mediated transporters (renal tubule, GI epithelium, blood-brain barrier) play a role in efflux (ABC) and influx (SLC) of drugs that are chemically related to endogenous substance or xenobiotics.

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CONSEQUENCES OF Ph PARTITION

- Urinary acidification accelerates excretion of weak bases and retards weak acids
- Urinary alkalisation has the opposite effect.
- Increasing plasma pH (Na bicarbonate) causes weak acidic drugs to be extracted from CNS into the plasma.
- Reducing plasma pH causes weak acidic drugs to be concentrated in CNS.

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II. ABSORBTION

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II. ABSORPTION

Routs of administration

Oral

Sublingual absorption: devoids portal circulation

Gastric absorption: weak acids !!
But: enormous absorptive area of intestinal villi

Intestineal absorption: weak bases!!!

Influenced by : GI motility, splanchnic blood flow
particle size and formulation (e.g. digoxin)
physico-chemical factors (tetracyclin-Ca)

Carrier-mediated **influx** transzport: L-DOPA , Flurouracil

P-glycoprotein-associated **eflux, reverse** trasport: from intestinal wall to lumen

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ORAL ABSORBTION

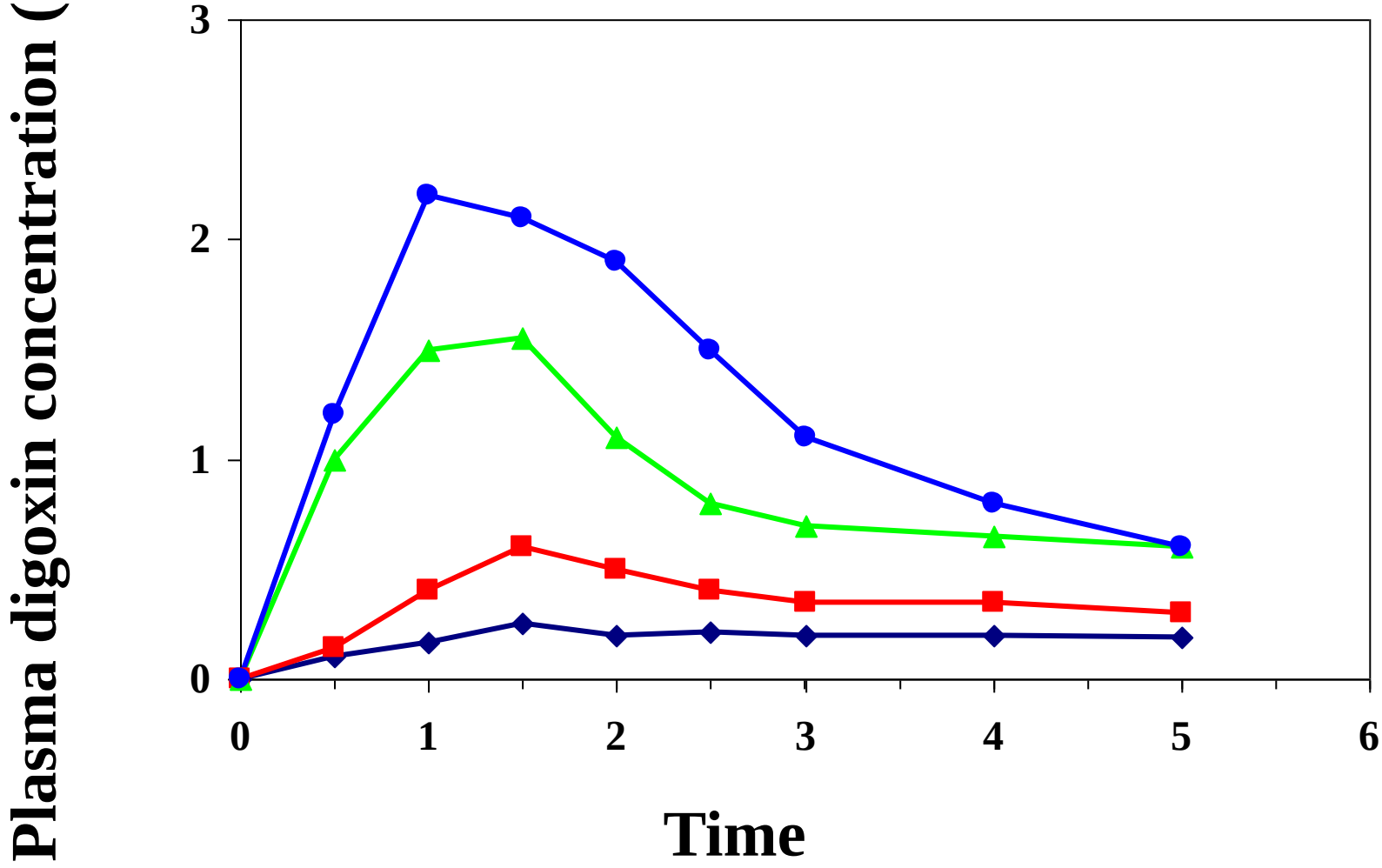
can depend on the vehicle of the drug

Different absorbtion of the same drug with different vehicle

(e.g. ampicillin, teracyclin, chloramphenicol, aspirin, digoxin)

AREA UNDER CURVE (AUC)

(represents the absorbtion)



Lindenbaum és mtsai, New Eng. J. Med.285, 1344, 1971

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II. ABSORPTION
Routs of administration

- **Rectal**
  - devoids portal circularion, first pass metabolism, local action
- **Cutan**
  - organophosphates, nitroglycerine, oestrogens
- **Nasal**
  - **ADH**
- **Eye drops**
  - glaucoma (pylocarpin, thimolol),
- **Inhalation:**
  - asthma (salbutamole, ipratropium, glucocorticoids), anaesthetics
- **Injections**
  - i.cutan, subcutan, intramuscular, intravenous
- **Intrathecal**
  - opioids, local anaesthetics baclophen, penicillin

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II. ABSORBPTION
Special systems

Pro-drug: eg. levodopa, cyclophosphamid, zidovudine

Antibody-drug conjugates: to attach a drug to antibody directed against tumor-specific antigen

Packaging to liposomes: spheric lipid layer - vesicle – drug

Coated implantable devices: intrauteri devices, coronary stents with antithrombic drugs

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III. DISTRIBUTION

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III. DISTRIBUTION

1. VOLUME OF DISTRIBUTION (V_d)

$$V_d = \frac{\text{Amount of drug in the body (mg)}}{\text{Plasma concentration (c) (mg/ml)}}$$

c: c_b, c_p, c_w

Apparent volumen

V_d (< 5) low: drug is distributed only in blood

V_d high: drug is distributed also in extravascular compartment

Eg. Digoxin V_d: 500 l; Aspirin V_d: 11 l

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III. DISTRIBUTION
2. COMPARTMENTS
based on perfusion

Central compartments: **plasma**
organs with good blood supply
(kidney, heart, liver, lung, brain)

Peripheral compartments: **organs with poor blood supply**
(fatty tissue, skin, muscle)

Deep compartments: **organs with very bad blood supply**
(bone, cartigle, joint)

III. DISTRIBUTION

2. COMPARTMENTS

TOTAL BODY WATER (0.6 l/kg):

Small, water soluble molecules, eg. ethanol, phenytoin, diazepam

EXTRACELLULAR WATER (0.2 l/kg):

Biger, water soluble molecules eg. gentamycin, tubocurare

BLOOD (0.08L/KG**), PLASMA** (0.04 l/kg)!:

drugs bound in plasma protein and very big molecules (heparin, insulin, warfarin)

FAT (0.2-0.35 l/kg):

highly lipidsoluble molecules e.g. DDT, thiopental

BONE (0.07 l/kg)**:** ions, e.g. lead, fluor, tetracyclin

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III. DISTRIBUTION

3. IMPORTANCE OF PLASMA PROTEINS-BINDING

Ionic, van der Waals, hydrogen - bindings

One albumine molecule can bind two acidic molecules

NON-SPECIFIC BINDING SITES – COMPETITION FOR BINDING

Warfarin - NSAIDs: NSAID displaces warfarin

Sulfonamide-bilirubine: sulfonamide displaces bilirubine

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III. DISTRIBUTION

3. IMPORTANCE OF THE BINDING TO PLASMA PROTEINS

Compound	Binding in %	Occupied binding site in %
DICLOFENAC	99.5	<1
DIAZEPAM	95-99	<1
TOLBUTAMID	90-95	50-60
ASPIRIN	50	50
SULPHISOXAZOL	90-95	50-60

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III. DISTRIBUTION

3. IMPORTANCE OF THE BINDING TO PLASMA PROTEINS

ONLY THE UNBOUND FORM OF DRUGS IS PHARMACOLOGICALLY ACTIVE!!

The amount of bound-form depends on the:

- concentration of free drug
- affinity for binding site
- concentration of protein

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III. DISTRIBUTION

3. IMPORTANCE OF THE BINDING TO PLASMA PROTEINS

METABOLISM, EXCRETION

CAN BE SLOWER

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III. DISTRIBUTION

4. CENTRAL NERVOUS SYSTEM

FUNCTIONAL BARRIER – BLOOD BRAIN BARRIER

ENDOTHEL CELLS ARE TIGHTLY → transcellular transport

↓

NON-IONISED, LIPID SOLUBLE MOLECULES ENTER THE CNS

Drug designe

- First, second generation antihistamines
- atropin, benztropin – ipratropium
- Physostigmine - neostigmine

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III. DISTRIBUTION

4. CENTRAL NERVOUS SYSTEM

- **TRANSPORT- OUTWARD**

  on capillar endothel a carrier (P-glycoprotein)

  e.g. Loperamide –transport outward

  Inhibited by: verapamil

- **SPECIAL UPTAKE MECHANISM**

  endogenous substances

Inflammation (meningitis): increased permeability

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III. DISTRIBUTION

5. PLACENTA

Plasma pH is more acidic in phoetus

(7 vs. 7.2) → bases are retained

Capillar endothel-cells are tightly

water soluble molecules cannot enter above 1 KDa

P-glycoprotein also in placenta

transport-out

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III. DISTRIBUTION

6. FATTY TISSUE

Thiopental: accumulation in body fat

↓

Limited effect as a short – term induction of anaestheisa

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IV. BIOTRANSFORMATION

1. Apolar compound → polar one

2. Inactivation

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IV. BIOTRANSFORMATION

PHASE I. REACTIONS:

OXIDATION, REDUCTION, HYDROLYSIS

oxydative reactions catalysed by the mixed function oxygenase system,

the most important is the cytochrom P-450, a hem protein

Metabolite can be active or toxic!!!

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IV. BIOTRANSFORMATION
Formation of active compounds

Active compound –active metabolite

Diazepam →oxazepam

Codeine →morphine

Phenacetin →paracetamol

Inactive compound (PRO-DRUG) – active compound

Enalapril → Enalaprilát

Active compound – toxic metabolite

Paracetamol →N-acetylbenzoquinon

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CYP450 DEPENDENT AND INDEPENDENT OXYDATIVE REACTIONS

DEPENEDENT:

Aromatic hydoxylation aliphyatic hdroxylation, epoxidation, N-dealkylation, O-dealkylation, N-oxysation, S-oxydation, desulfuration, dechlorination, deamination

INDEPENDENT:

Flavin monooxygenase, amine oxydases, dehydrogenases

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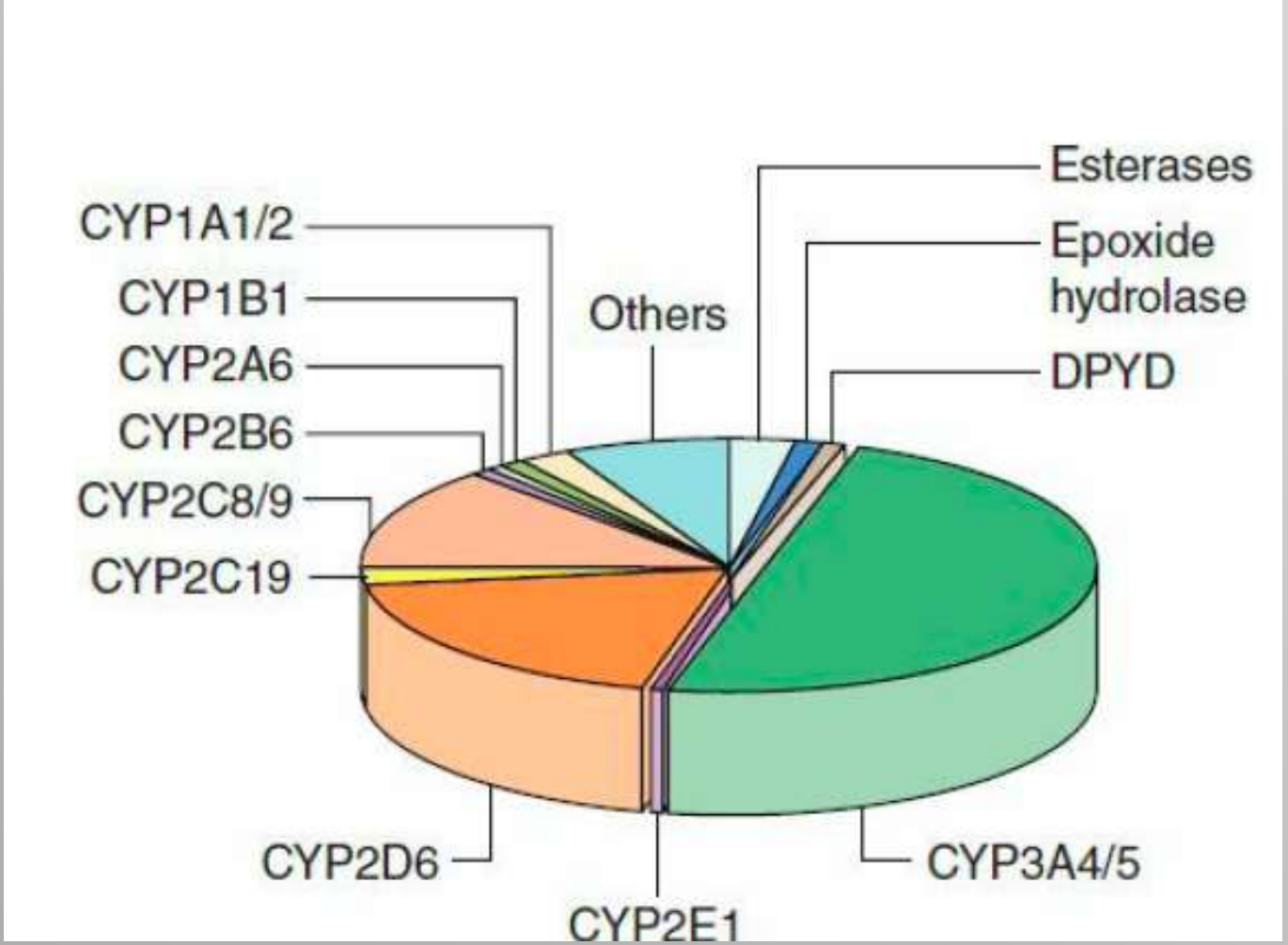
DIFFERENT ISOFORMS OF CYP450

CYP1A2, CYP2A6, CYP2C19, CYP2E1, **CYP2B8, CYP2D6, CYP 3A4!**



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REDUCTION AND HYDROLYSIS

REDUCTIONS: Azo-, nitro- carbogen reduction

HYDROLYSIS: esters. amides

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IV. BIOTRANSFORMATION METABOLISM 2.

PHASE II. REACTION

CONJUGATION

glucoronide, sulphate, acetyl, methyl, glycole

Metabolit inactive, water soluble!!!

Exceptions:
morphine-6-OH glucoronide conjugation
izonicid N-acetylation

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IV. BIOTRANSFORMATION
ENZYME INDUCTION, INHIBITION

Enzyme induction: increased gene transcription

inhibtion of degradation

e.g. phenobarbital, rifampicin, ethanol, smoke, ritonavir (CYP 1A2**) , grapefruit juice, air pollution**

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IV. BIOTRANSFORMATION
ENZYME INDUCTION, INHIBITION

Enzim inhibition: **cimetidine, ketokonazol, cloramphenicol, ritonavir (**3A4 and 2D6)

Suicide inhibitors: the formed metabolite inhibits CYP enzyme (e.g. ethinylestrediol, clopidogrel)

P-glycoprotein* inhibition in the intestines → incerased drug absorption

(claritromycin, nicardipin, verapamil, grapefruit, ritonavir)

.

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IV. BIOTRANSFORMATION

FIRST-PASS (pre-systemic) METABOLISM

After oral adminsitration drugs can be metabolised before raching the systemic circulation

- **in the liver (e.g. morphine, meperidine, lidocain (toxic metabolite), verapamil, propranolol)**

to avoid portal circultion: sublingual, transdermal, rectal administration

- **in intestines (clonazepam, midazolam)**
- **gastric acid (penicillin)**
- **digestive enzyme (poliypeptides).**

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IV. BIOTRANSFORMATION
BIOAVAILABILITY

Fraction of unchanged drug reaching the systemic circulation

Intravenous	**100%**
Intramuscular	**75 - 100%**
Oral	**5 - < 100%**
Rectal	**30 - < 100%**
Transdermal	**80 - 100%**

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PHARMACOGENETICS

Different isoforms of CYP450

CYP1A2, CYP2A6, CYP2B8, CYP2C19, CYP2D6, CYP2E1, CYP3A4!

Extensive metabolism (EM), Poor metabolism (PM)

Genetic polimorphism

1. Oxydation - CYP2D6!

antidepressants, antipsychotics (haloperidol), antiarrythmic (propafenon)

Asian population 1-2%: PM

Caucasian population: 5-10% PM

→high risk factor

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PHARMACOGENETICS

Oxydation - CYP2C19

diazepam, omeprazol

Asian population 14-22%: PM

Caucasian population: 2-6% PM

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PHARMACOGENETICS

N-acetylation:

isoniazide, procainamide, nitrazepam,

Slow acetylators: Egypt: 90%

Asian population: 10-20%
Caucasian population: 40-70%

Side effect (isoniazid): hepatoxicity,
SLE

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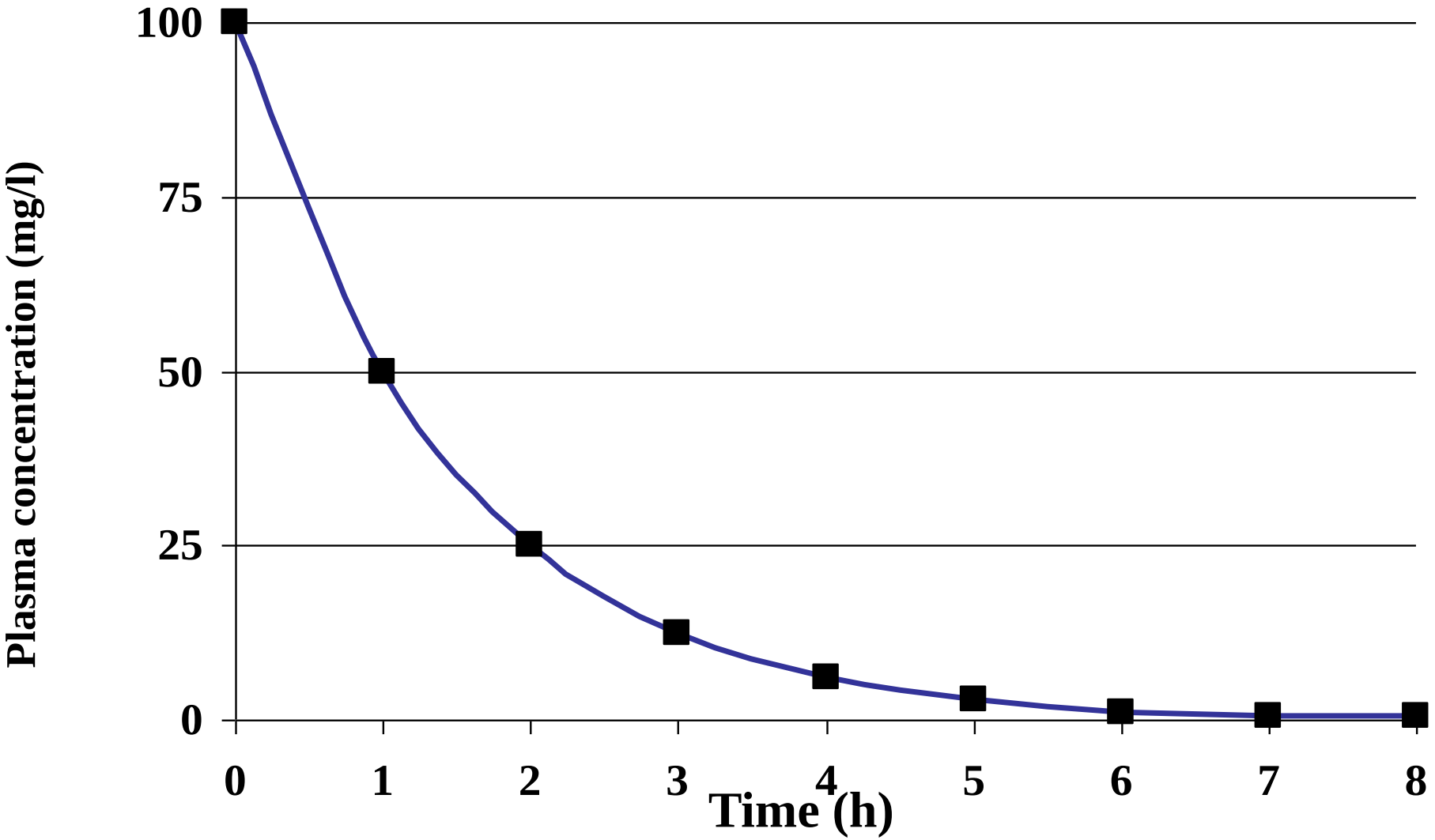
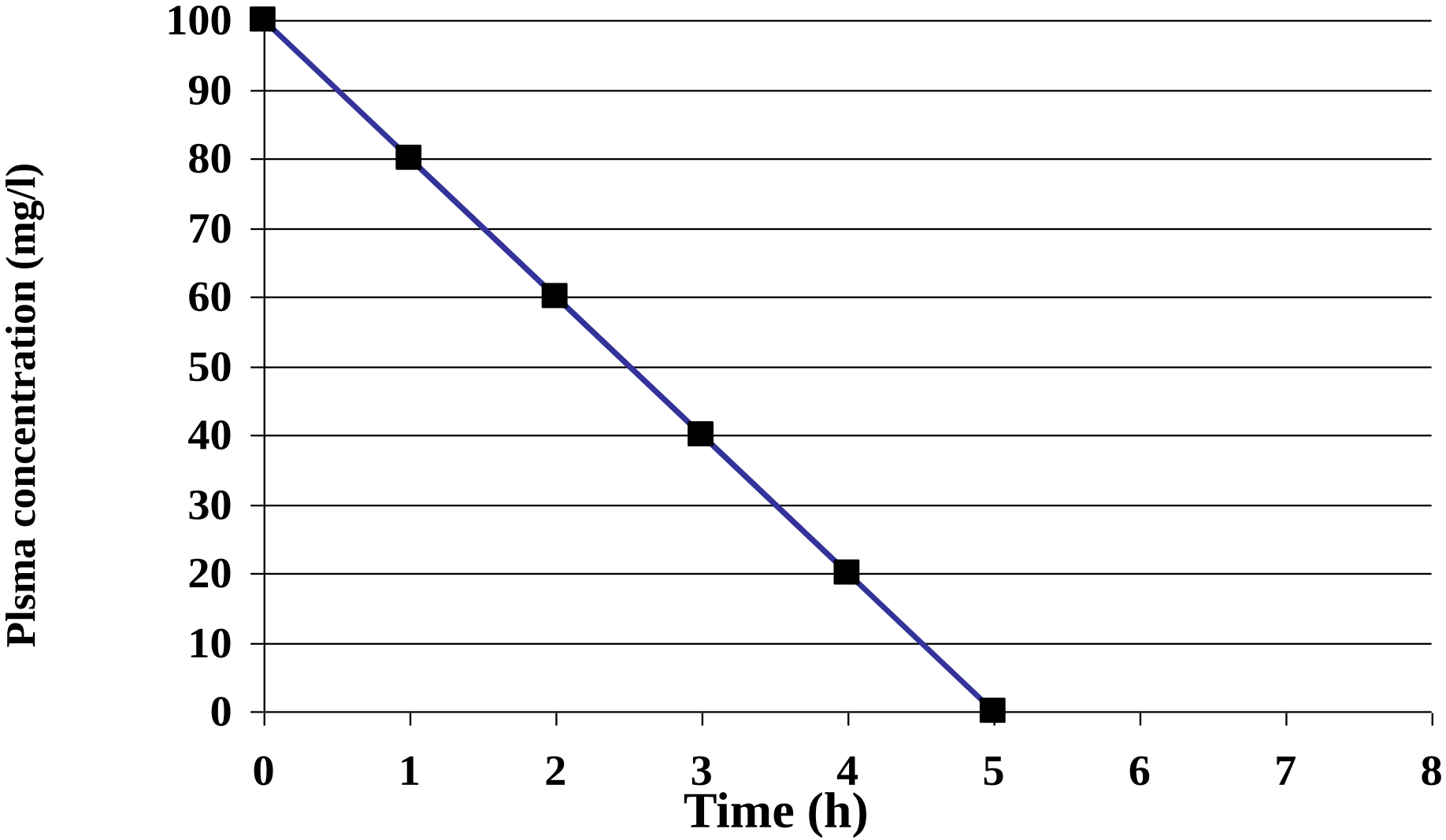
First-order kinetics!!



ELIMINATION: CONSTANT FRACTION/TIME UNIT

RATE OF ELIMINATION IS A LINEAR FUNCTION OF PLASMA DRUG CONCENTRATION!!

Zero-order kinetics



ELIMINATION: CONSTANT AMOUNT OF DRUG/TIME UNIT

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V. EXCRETION

1. KIDNEY

- glomerular filtration

- active tubular secretion/reabsorbtion (carrier mediated (penicillin – probenicid)

- passive tubular diffussion
  (pH dependent; apolar compounds are reabsorbed polar ones remain in tubules)

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V. EXCRETION

2. BILIAR EXCRETION/ENTEROHEPATIC CIRCULATION

eg. digoxin, morphine, chloramphenicol, ethyniloestradiol

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„TAKE HOME MESAGE”

1. Absorbtion: passive
   carrier-mediated

2. V_d: Amount of drug/plasma cc.

3. I. phase reactions (oxydation, reduction, hydrolysis)
   II. phase recations (conjugation)

4. „First-pass” metabolism- Bioavailability

5. Excretion - glomerular filtration, tubular (passive -active)