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Basic pharmacological terminology

Drug classification

Mechanisms of drug effects

Basics of pharmacokinetics

Literature

Pharmacology. Edited by Michelle Alexia Clark. 5th ed. Baltimore: Wolters Kluwer Health/Lippincott Williams & Wilkins, 2012. xii, 612. ISBN 9781451113143.

In IS: Pharmacology for students of bachelor's programmes at MF MU (special part)

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Basic pharmacological terminology

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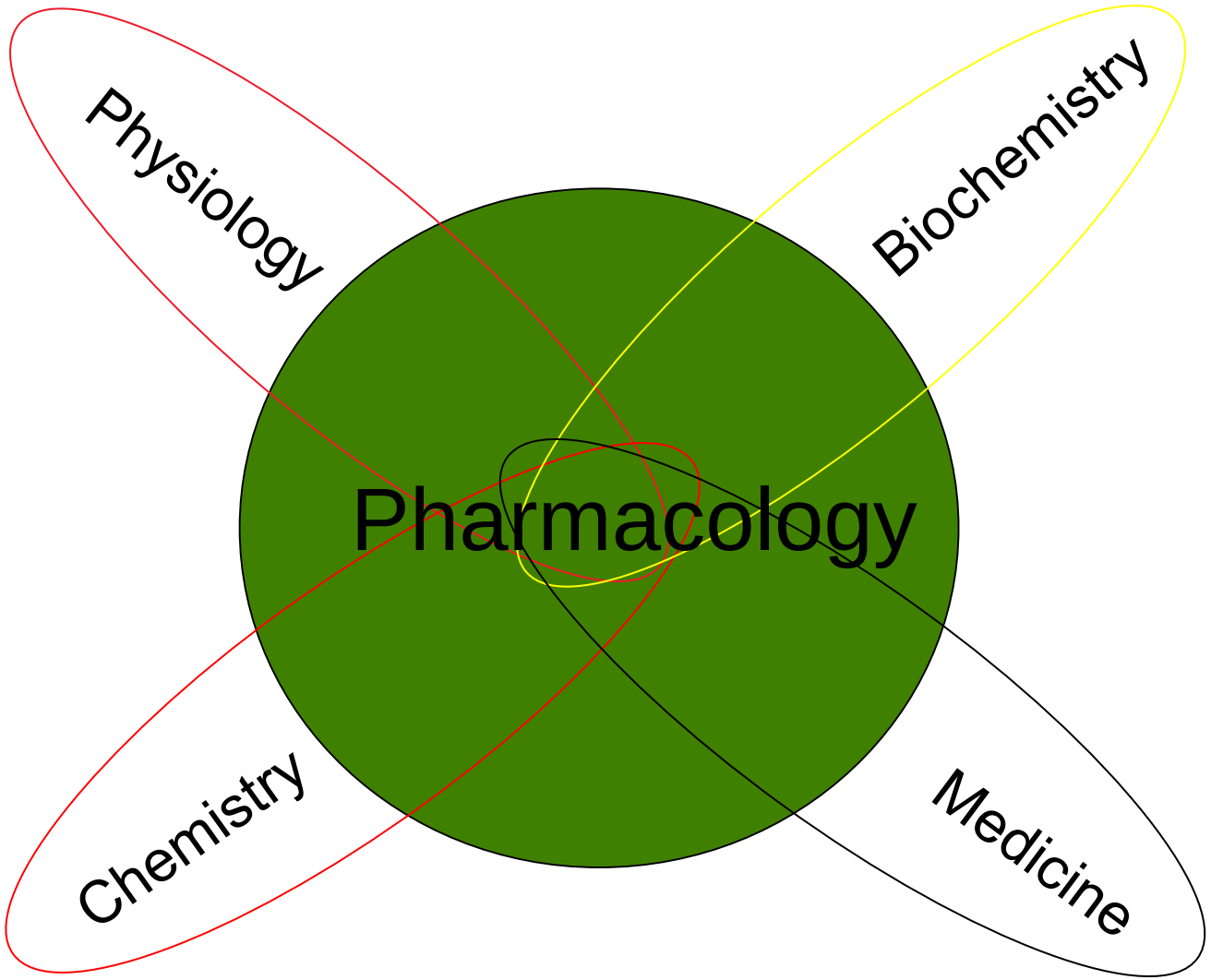
A synthesis of several biomedical sciences….



…but unique in its own right

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Pharmacology, definition, aims

„pharmacon“ + „logos“ / „logia“

Scientific discipline dealing with
INTERACTIONS BETWEEN SUBSTANCES..
introduced into the organism from the environment

..AND THE LIVING ORGANISM
on all levels of complexity:
molecular
cellular
organ
organism as a whole

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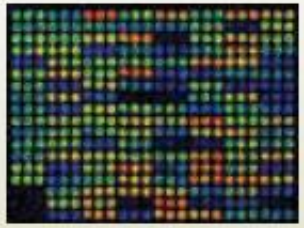
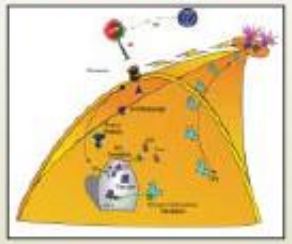
Pharmacologists study science at <u>every</u> level

Genetic



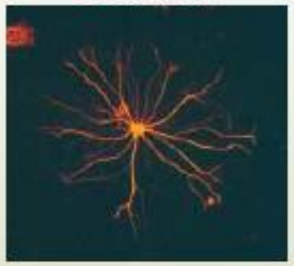
Gene Chip Microarray.
Courtesy of Annette Thelen, MSU Genomics Structure Facility.

Molecular



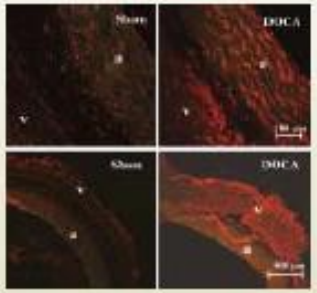
Interaction of the dopamine (D2) and dynorphin system in regulation of tuberoinfundibular neuronal function.
Courtesy of Y. Will-Murphy and K. Lookingland

Cellular



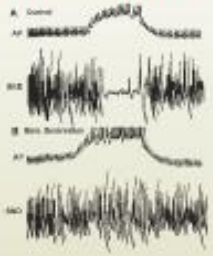
Astrocyte, labelled with Glial Fibrillary Acidic Protein
Courtesy of J. Edwards and B. Atchison.

Tissue



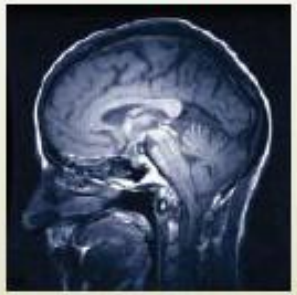
Superoxide measurement through dihydroethidium in artery (a) and vein (v) of normotensive (sham) and hypertensive (DOCA) rats.
Courtesy of H. Xu and J. Galligan

Whole Animal



Effect of sectioning baroreceptor nerves (denervation) on the inhibition of sympathetic nerve discharge during a rise in arterial pressure in an anesthetized cat.
AP = arterial pressure, SND = sympathetic nerve discharge.
Courtesy of S. Barman and G. Gebber.

Human



MRI of Human Head
Courtesy of Kevin Henley and James Potchen of the Radiology Department, MSU

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DRUG

„substance or mixture of substances, suppopsed to be administered to the humans or animals for prevention, treatment or diagnosis of diseases or its symptomes or for physiological function adjustment“

Drugs are administered for

- Prevention,
- Diagnosis,
- Treatment of disseases

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What Pharmacology is NOT...

❖ Pharmacy

This is a separate profession responsible for the preparation and dispensation of medication.

❖ Pharmaceutical Science

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Basic Pharmacology

General principles

Systems Pharmacology

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General principles

Principles which predestinate the interactions of the drug and body

Two important and interrelated areas:

- General Pharmacokinetics

- General Pharmacodynamics

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Pharmacokinetics (PK)

Deals with the fate of the drug in the body – processes of

Absorption,
Distribution
Metabolism
Excretion

„What the body makes with the drug“

…“ADME“

Pharmacodynamics (PD)

deals with the mechanism of action (e.g. receptor sites, molecular level of action..)

„How does it work“

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Systems Pharmacology

Is focused on individual organ systems and its pharmacotherapy

e.g.
Autonomic drugs
Psychoactive drugs
Drugs used in cardiovascular diseases….

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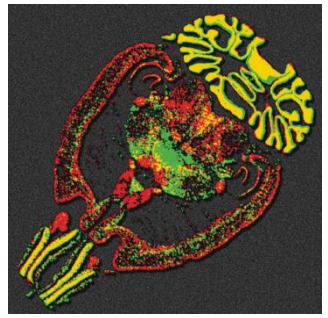
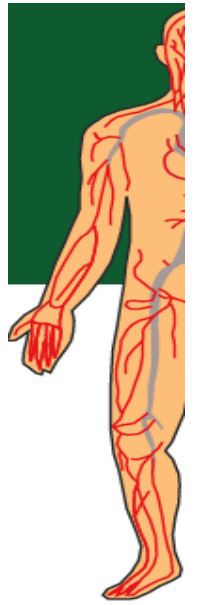
Systems Pharmacology

❖ **Neuropharmacology:** study of the effect of drugs on components of the nervous system (brain, spinal cord, nerves)



Example: treatment of Alzheimer‘s disease

❖ **Cardiovascular Pharmacology:** study of the effects of drugs on heart, vasculature, kidney, nervous and endocrine systems that participate in cardiovascular function.



Example: treatment of high blood pressure (hypertension)

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Branches of Pharmacology

Clinical pharmacology

- deals with different drugs and their varied clinical usage

- interdisciplinary branch, which integrates basic and experimental Pharmacology with the clinical and complementary branches

AIM: to study and evaluate the effect of the drug using objective methods (EBM)

Sub-branches of clinical pharmacology:
Clinical Pharmacokinetics, clin. Pharmacodynamics, Rational prescribing, Clinical toxicology

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Toxicology

the study of the toxic effects of chemicals on living organisms

study of symptoms, mechanisms, treatments and detection of poisoning

experimental (in vitro, in vivo)

clinical - poisoning prophylaxis, diagnosis, treatment

forensic toxicology…

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Pharmacogenetics

deals with the influence of genetic variation on Pharmacokinetics and Pharmacodynamics

study of the drug response in patients by correlating gene expression or single-nucleotide polymorphisms with a drug's efficacy or toxicity

consequences can be either quantitative or qualitative

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Biochemical and molecular pharmacology

detail study of the mechanism of action at molecular level

Chronopharmacology

Study of the action of the drugs with respect to the biorhythm

(antiasthmatics, glukocorticoids, statins, etc.)

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Pharmacovigilance

Pharmacological science relating to the detection, assessment, understanding and prevention of adverse effects

collecting, monitoring, researching and evaluating information from healthcare providers and patients on the adverse effects of medication

Drug safety monitoring

AIM: to minimize the risk of adverse effects

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Pharmacoepidemiology

- study of the **effect of drugs on populations**; questions dealing with the influence of genetics are particularly important

risks and benefits of the therapy using epidemiological methods

Approach of the health specialists (GP, pharmacist)

patient (compliance)

society (drug abuse, marketing, financial resources…)

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Pharmacoeconomy

- rationalize the use of sources in health care

- Compares the costs of therapeutic approaches by the pharmacoeconomical analyses

The goal is not „to decrease total money spent in health care“ , but to use the sources effectively

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Experimental pharmacology

Biological experiment

in vitro – isolated structures or organs,

cell cultures, microorganisms

- regulatory factors we have to satisfy:

☺ ethical (replacement, refinement, reduction)

☺ small amounts of drugs

☺ use of human cells

☹ elimination of systhemic reaction of the whole body

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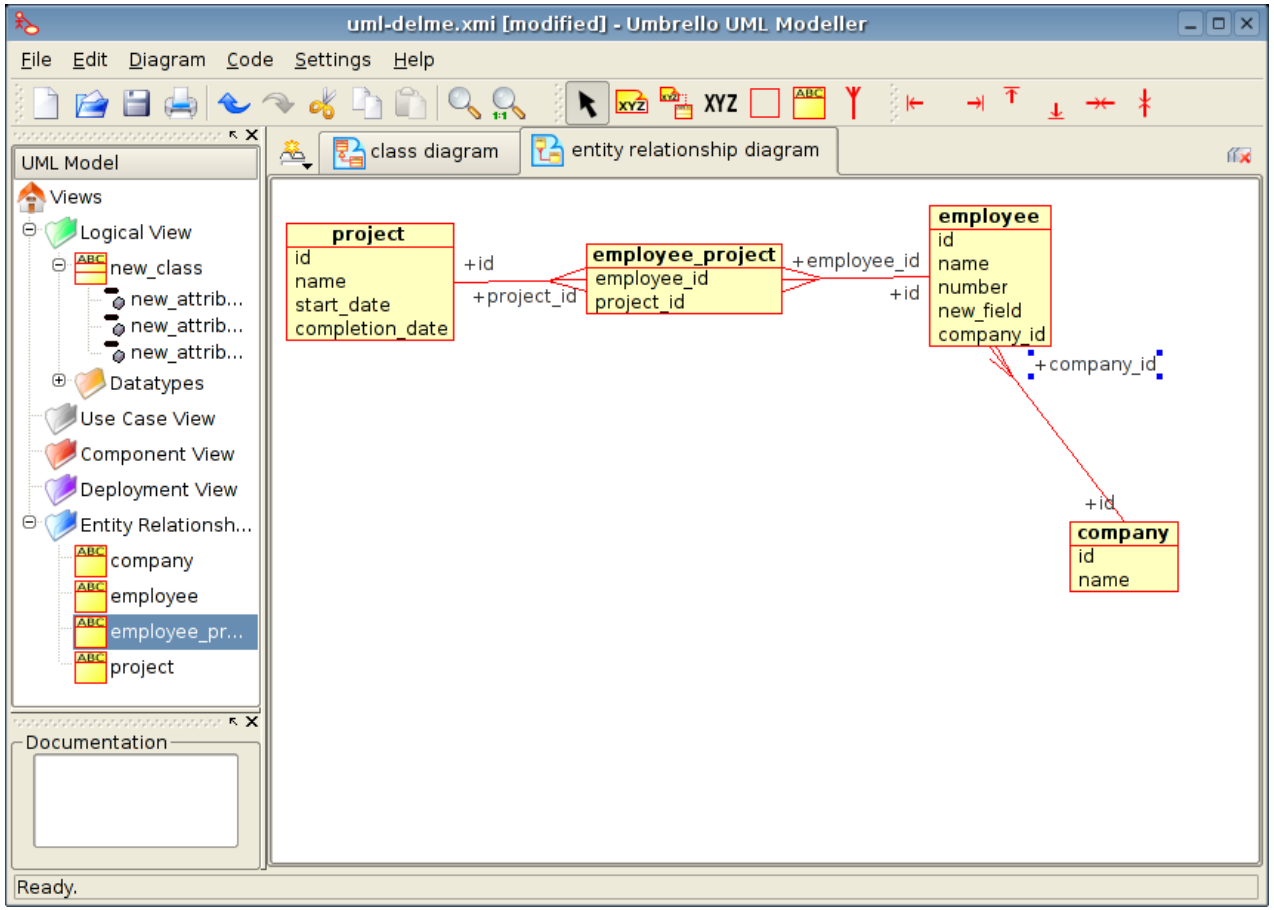
Biological experiment

in silico – use of IT, especially computer modelling (f-kinetics), databases



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Biological experiment

in vivo – whole animal

- systhemic effects

- we record toxicity, possible adverse and alergic effects

- impact on memory and other cognitive faculties, learning abilities, depression

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Drug classification

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Drug names

Chemical name
according to the IUPAC (International Union of Pure and Applied Chemistry)
nomenclature rules
e.g.: N-acetyl-para aminophenol

Generic name (non-proprietary)
INN (International Non-proprietary Name)
not registered, supposed to be used internationally
has to be printed on the packing of the drug (under the registered trade name)
for the universal terminological identification of the medicines
formed from the chemical name (shortness) accordingly with the rules (WHO)
each drug has its own CAS No (Chemical Abstracts Sevice Number)

e.g. paracetamol

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Drug names

Trade name (proprietary)

registered, patent-protected ®
has to be acompanied with the INN
e.g. Panadol, Coldrex, Paralen

Officinal name

latin name in Pharmacopoeia (e.g. Paracetamolum)
usually very similar to INN
has to be prescribed on Rx formulary in case of individually prescribed medicines
established name for a drug substance is usually found in the originating country's Pharmacopeia
Paracetamolum
…

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Some drug-family names

-olol	beta receptor antagonists
-caine	local anaestethics
-tidine	histamine receptor antagonists
-dipine	calcium channel blockers of dihydropyridine type
-statin	inhibitors of HMG CoA transferase

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„GENERICS“

Drug which is produced and distributed after ending of patent protection - mostly manufactured by other company which has not developed the original drug (the same active substance!)

Mostly cheaper than original preparation

Assumed to be identical in dose, strength, route of administration, safety, efficacy, and intended use

Bioequivalent trials are needed before registration

Registration procedures are much easier than in orig. preparation

Drug patents give 10 years of protection, but they are applied for before clinical trials begin, so the *effective* life of a drug patent tends to be between 7 and 12 years

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DOSE

A specified quantity of a therapeutic agent, prescribed to be taken at one time or at stated intervals.

If administered in the body, desintegrates, solutes, and distribute across the barriers in the body compartments. Than it is measured like „concentration“

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DOSE

DOSIS SINGULA - single dose

on Rx !

DOSIS PRO DIE - daily dose

- for 24 h !!

DOSIS CHRONICA

- (adjusted) dose in the chronic treatment (long-term)

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Basics of pharmacokinetics

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Basic principles of pharmacokinetics

Pharmacokinetics is aimed on this processes:

- absorption
- distribution
- biotransformation
- excretion of drugs

and their relation to pharmacologic (therapeutic or toxic) effects

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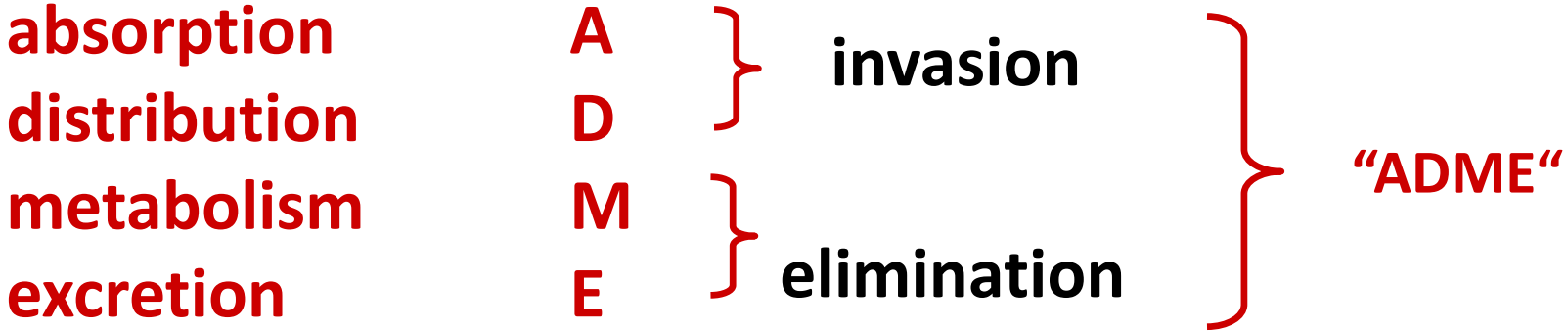
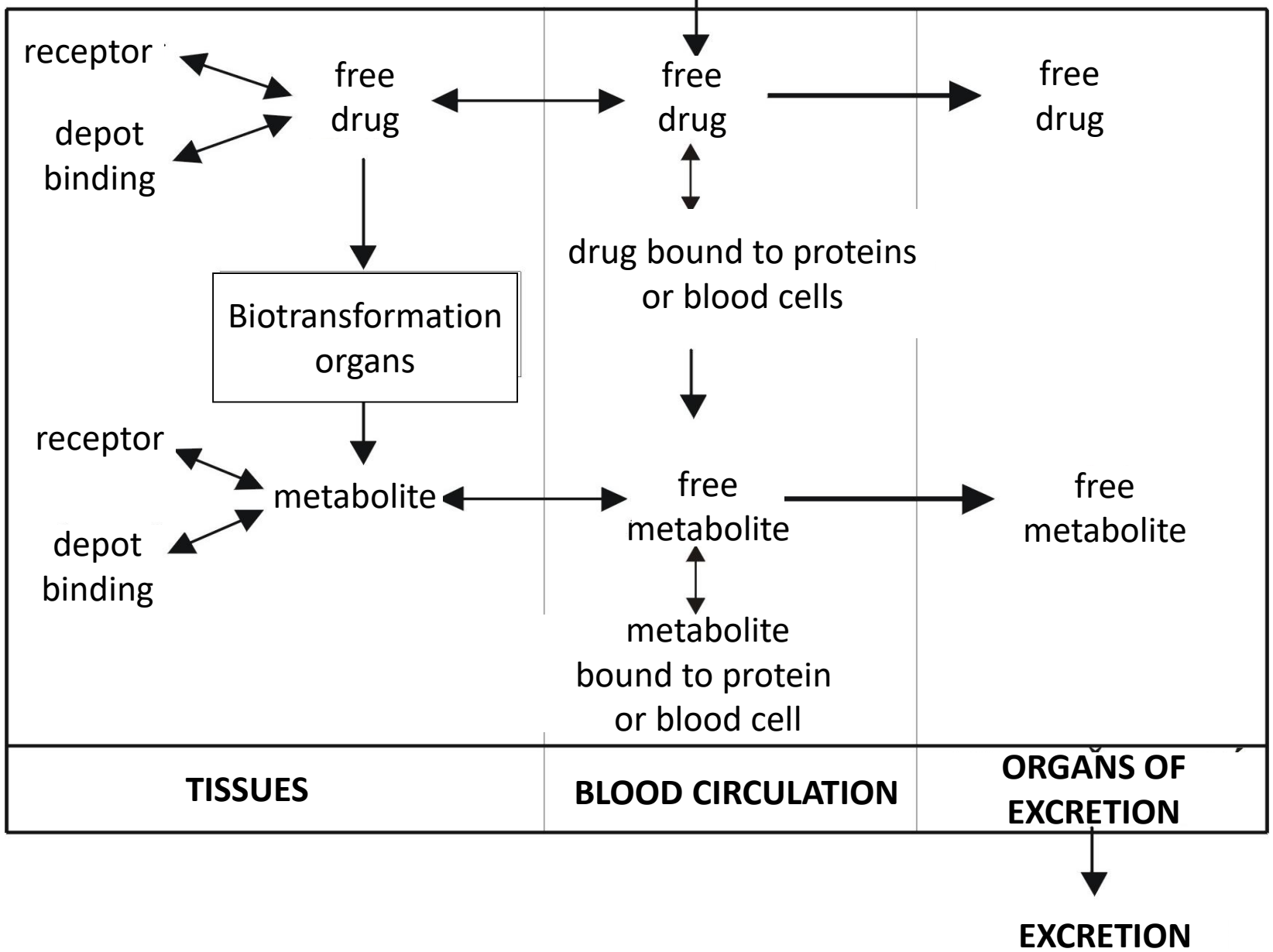
Pharmacokinetics



- processes of **ADME**

Administration of drug → Absorption



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Absorption – routes of administration

- penetration of dissolved drug from the site of administration to blood (systemic circulation) – necessary for general effect**– systemic effect**
- **Local effect:**
  - on skin, mucosas or ventricles
  - absorption is undesirable – possible AE
  - ie. local corticoids, local anesthetics

Speed and **extent** of absorption are described by P-kinetic parameters:

C_{max} max. concentration of drug in plasma after single dose

T_{max} time, when drug reach c_{max} (speed)

F bioavailability (extent)

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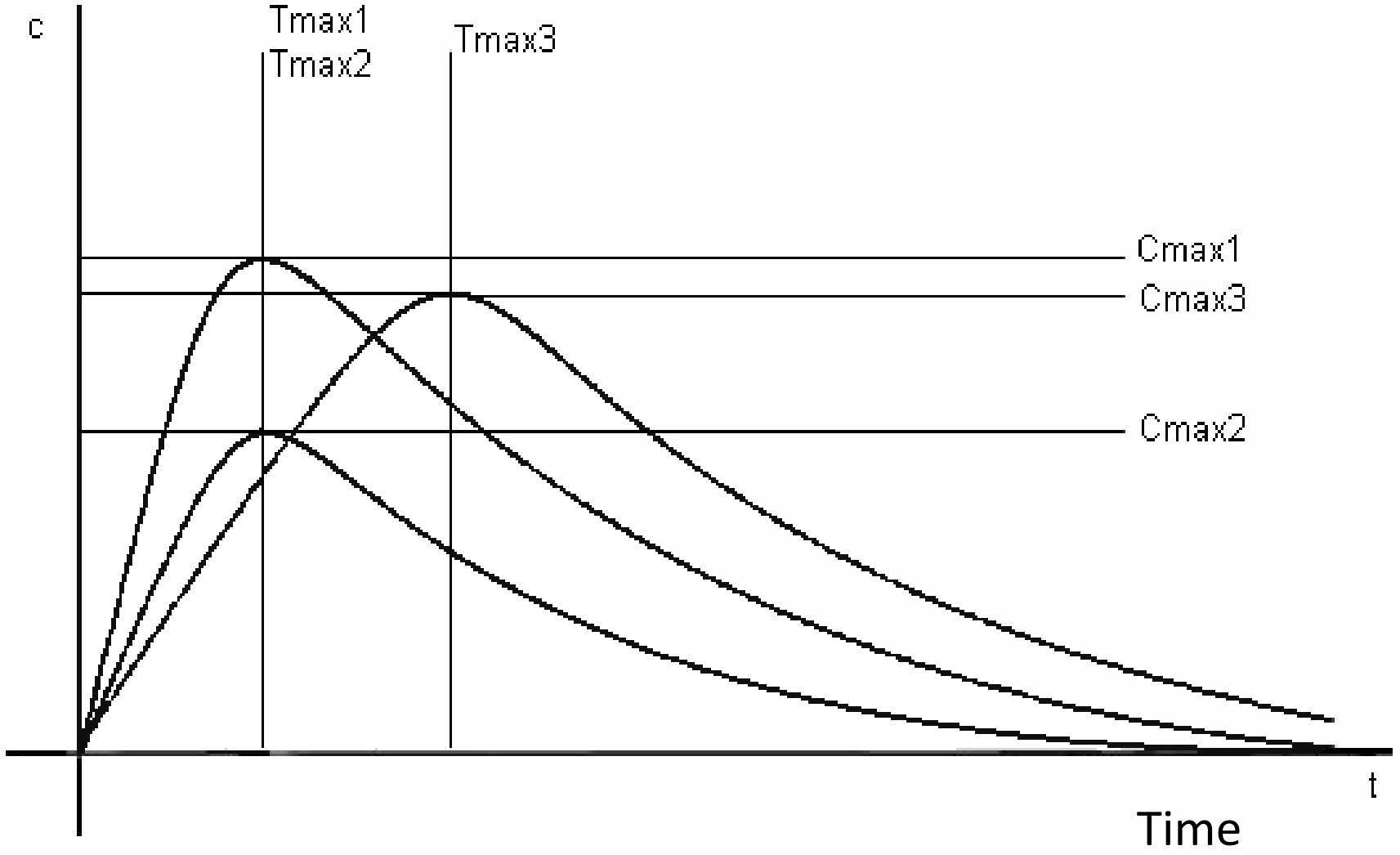
Concentration of drug



Bioavailability- F

how much from the administered dose get to circulation

extravascular administration - 0-100% (resp. 0-1)

intravenous (intravascular) - 100% = 1

- if F is < 20 % = 0 - 0,2 – it not worth to administer the drug by this way

  (some of them are administered through that - SET, bisfosfonates)

- the measure of bioavailability is the **area under the curve** (AUC)

http://icp.org.nz/icp_t6.html

$$F = \frac{AUC_{po}}{AUC_{iv}}$$

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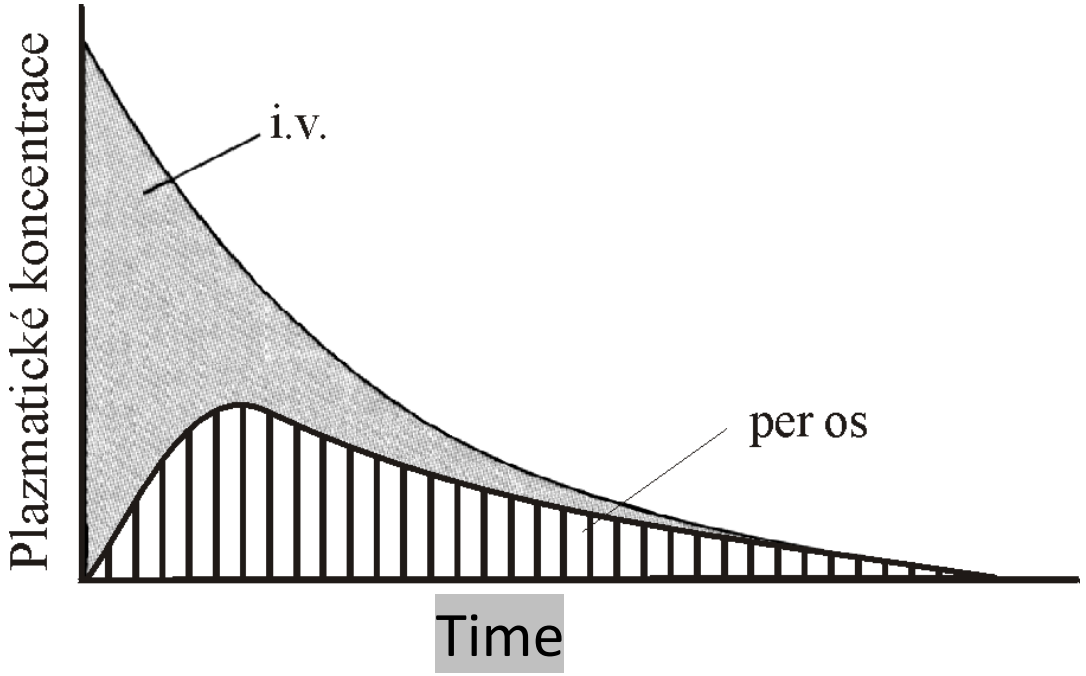
AUC – area under the curve



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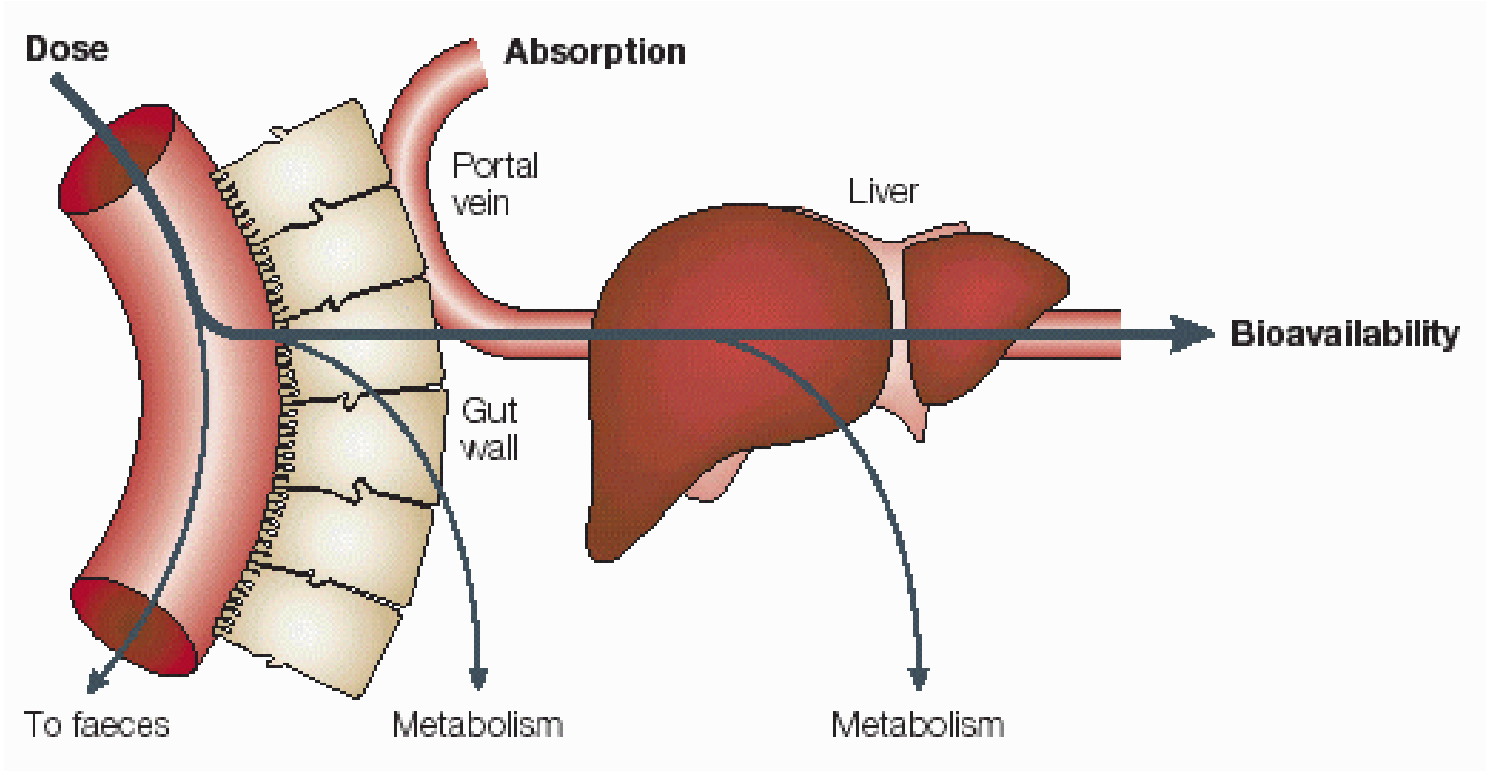
Presystemic elimination

First pass effect



http://icp.org.nz/icp_t6.html?htmlCond=1

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Other factors influencing drug absorption

- gender, weight, plasmatic volume, speed of gastric discharging
- age - pH, bile, enzymes
- pathophysiological defect – diseases of liver, inflammation ...
- body constitution (BW/LBM)
- diet

  - acceleration/ decceleration
  - chemical incompatibilities
  - GIT functionality

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Distribution

- Penetration of drug from blood to tissues, dynamic proces where we are interested in:

  speed of distribution- depends on:

  bindings

  membrane penetration

  organ perfusion

Volume of distribution V_d

- hypothetic, theoretical volume
- rate between amount of drug in organism and plastmatic concentration

$$Vd = \frac{D \,.\, F}{C_0}\,[l]$$

http://icp.org.nz/icp_t3.html?htmlCond=0

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The apparent volume of distribution, *V*d, is defined as the volume that would contain the total body content of the drug at a concentration equal to that present in the plasma

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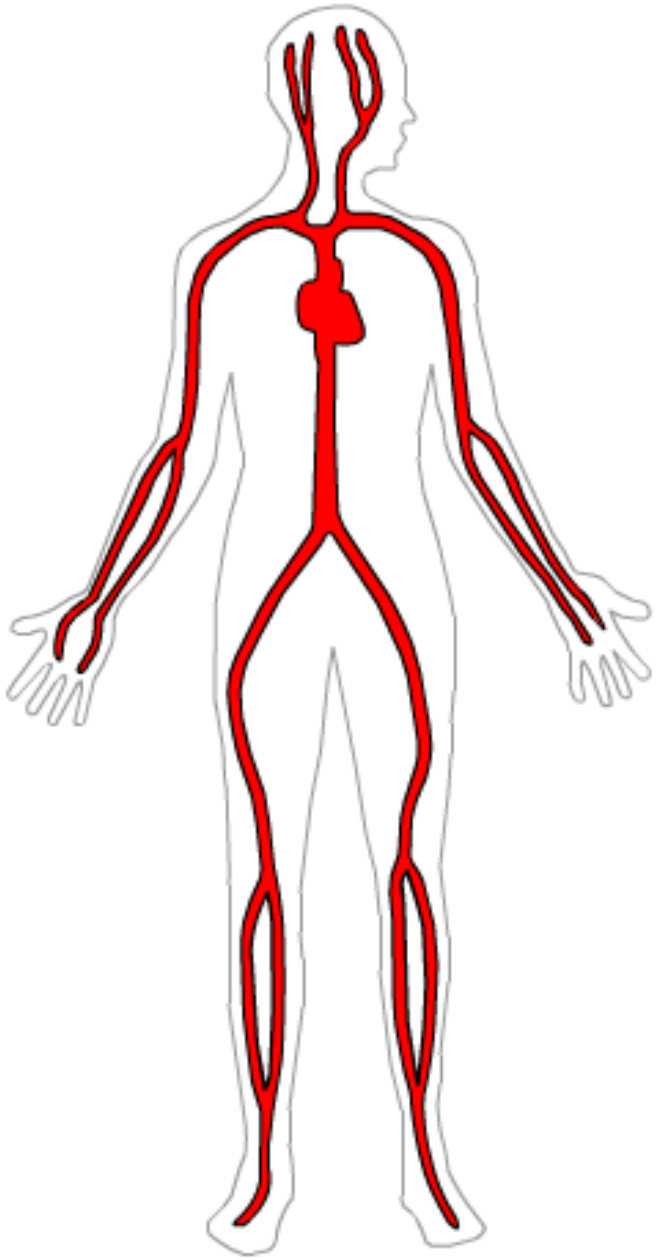

Drug concentrated in blood stream

Drug in blood and extracellular space

Drug equally distributed in blood and tissues

Drug moderately concentrated in tissues

Drug highly concentrated in tissues (usually adipose)

Amount in body = Vd x plasma concentration

$$Ab = Vd \times Cp$$

$$Vd = \frac{Ab}{Cp}$$

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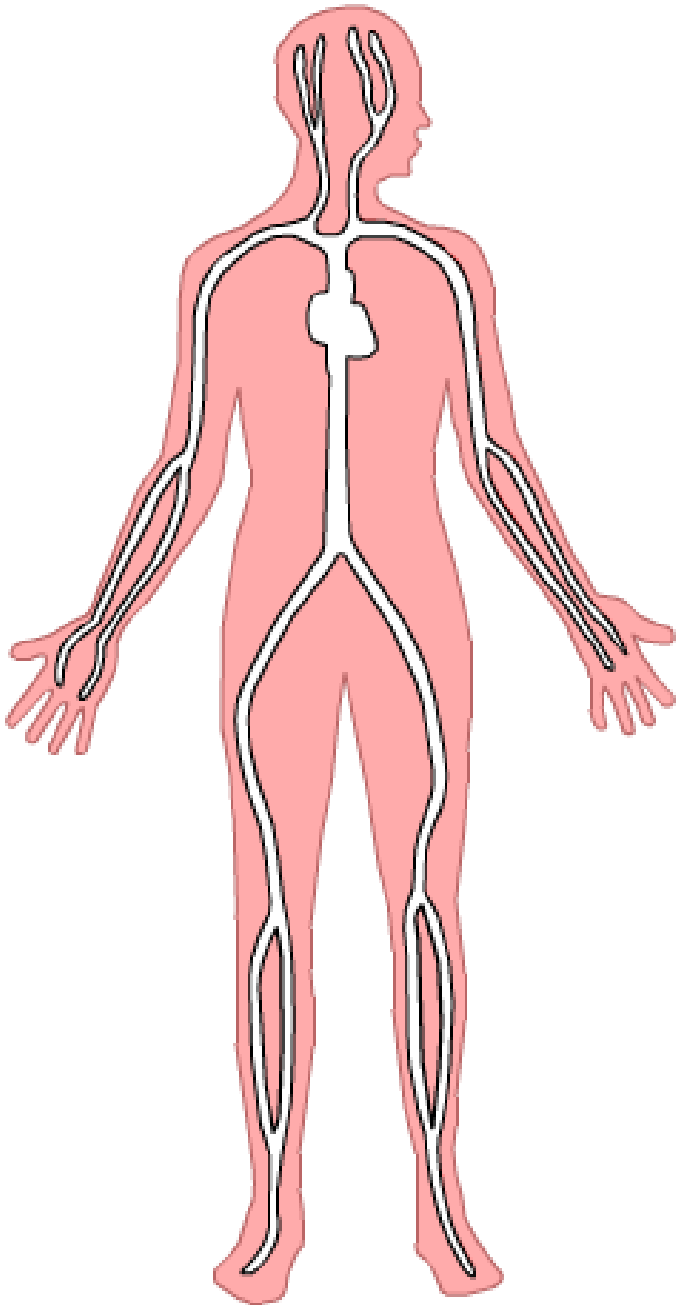

Vd

5 L

Drug concentrated in blood stream

Drug in blood and extracellular space

Drug equally distributed in blood and tissues

Drug moderately concentrated in tissues

Drug highly concentrated in tissues (usually adipose)

10,000 L

Amount in body = Vd x plasma concentration

$$Ab = Vd \times Cp$$

$$Vd = \frac{Ab}{Cp}$$

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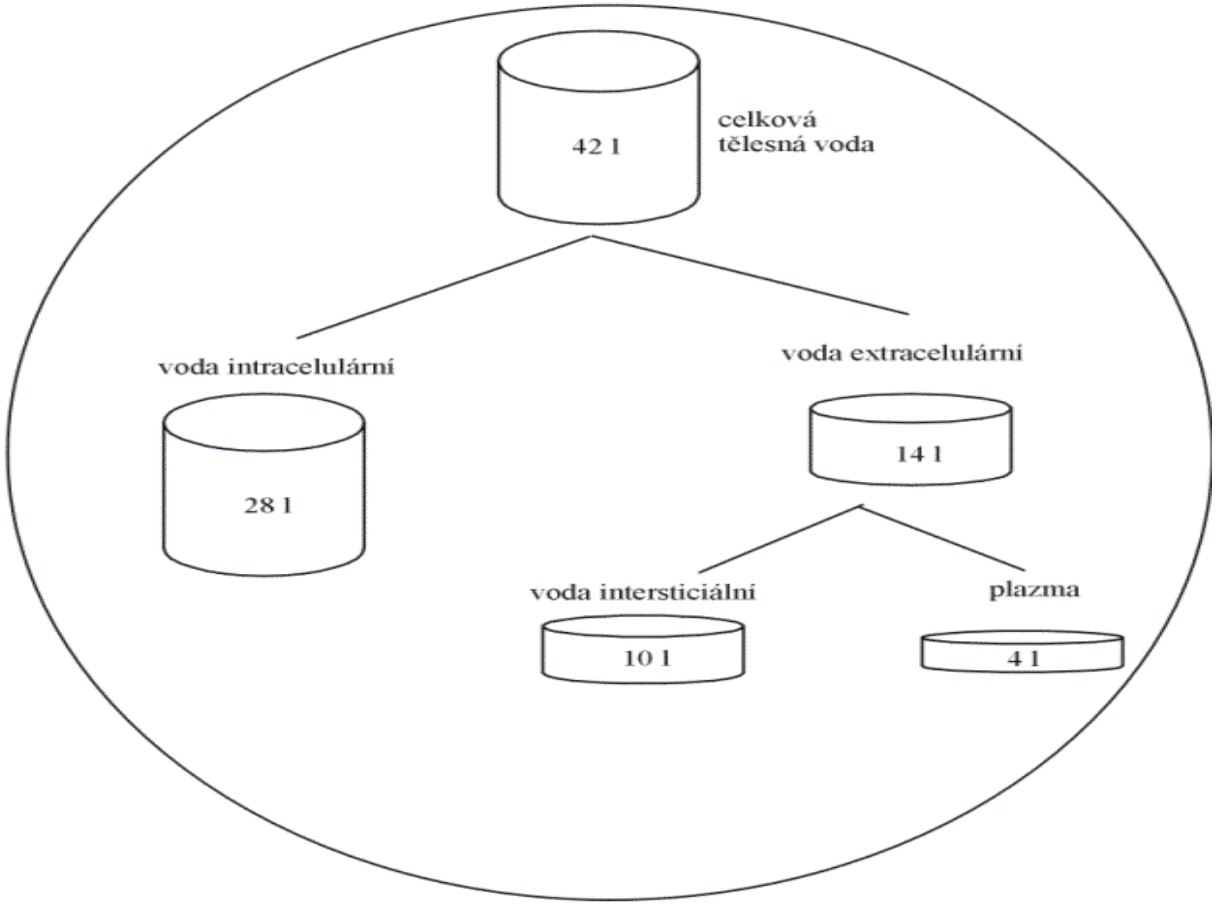
Vd = **hypothetical volume**,

Final value of Vd can be even 50000 liters (antimalarial drugs).
What does this value tell us:

We can assess distribution of the drug in the body.



Distribution

Assessment of the effect of hemodialysis and hemoperfusion

- drugs with higher Vd can not be eliminate from the body by these technics

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Biotransformation - metabolism

- Predominantly in liver, but also in other organs and parts of body

Enzymatic processes

- **bioactivation (prodrug**)

  cyclophosphamide – phosphoramide

- **biodegradation**

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Biotransformation - metabolism

1. **Phase:**
   - oxidation, hydrolysis → drug is still partly lipophilic
   - cytochromes P450, dehydrogenases
2. **Phase:**
   - conjugation → molecules becomes hydrophilic

Metabolites

- effective („more/less“)
- ineffective
- toxic

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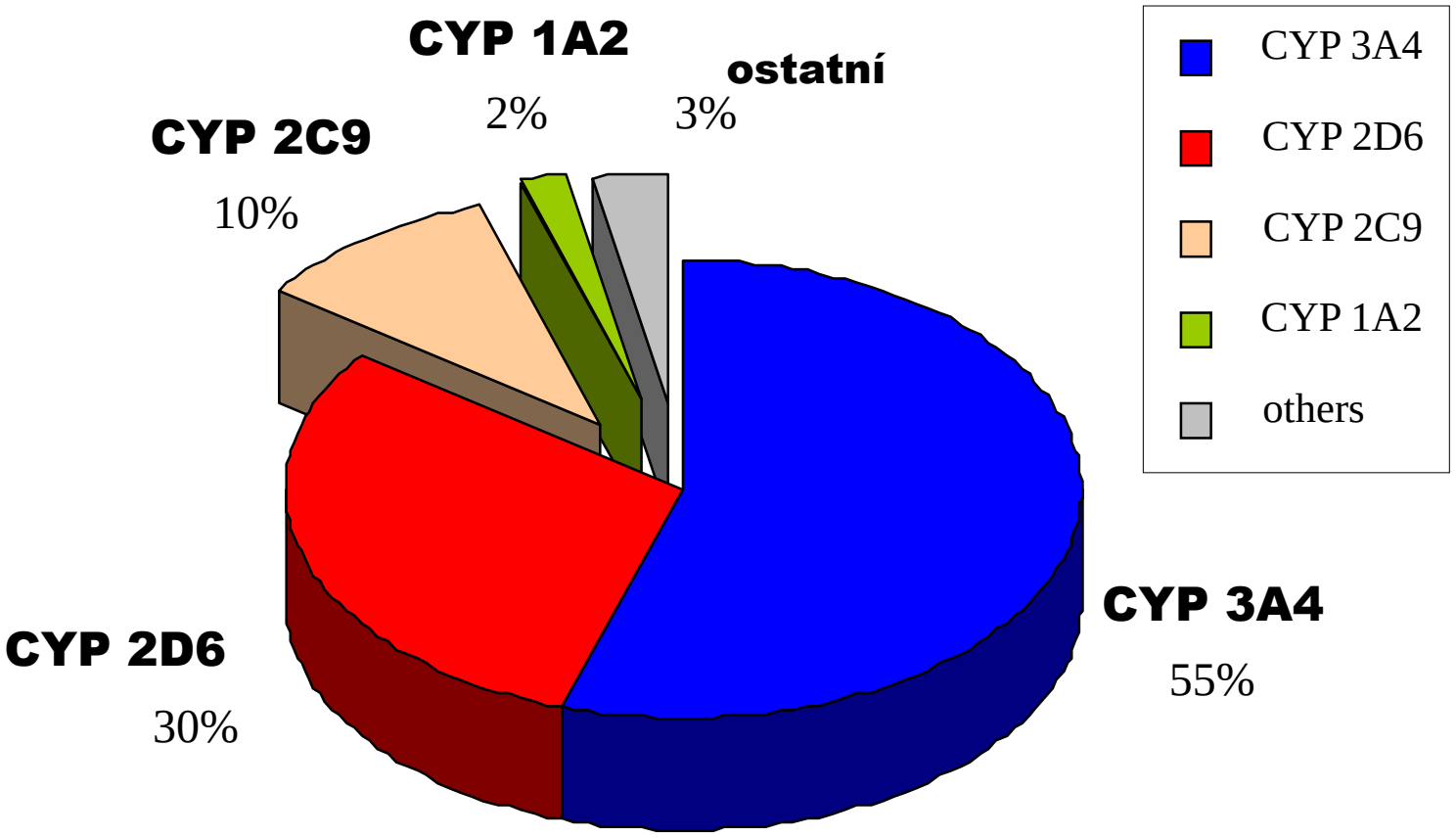
CYP 1A2
2%
ostatní
3%
CYP 2C9
10%
CYP 3A4
55%
CYP 2D6
30%
CYP 3A4
CYP 2D6
CYP 2C9
CYP 1A2
others

Inducers of CYP450

- **dexametazon**
- **fenobarbital**
- **rifampicine**
- **fenytoin**
- **St. John´s worth (Hypericum *perforatum)***
- **Maidenhair Tree *(Ginkgo biloba)***

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Inhibitors of CYP450

- antidepressants (fluoxetin, fluvoxamin, paroxetin)
- chinin, chinidin
- chloramphenicol, erytromycine
- ketokonazol, itrakonazol
- grapefruit juice

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Excretion

kidneys

bile

lungs

Saliva, skin, hair, milk…

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Excretion by kidney

- MW < 60.000 D (MW of albumin = 68.000 D)
- glomerular filtration
- tubular secretion
  - organic acids
    - furosemide
    - thiazide diuretics
    - penicilins
    - glukuronids
  - organic bases
    - morfin
- tubular reabsorption
  - diazepam

alkalization

natrium hydrogencarbonate

acidification

ammonium chloride

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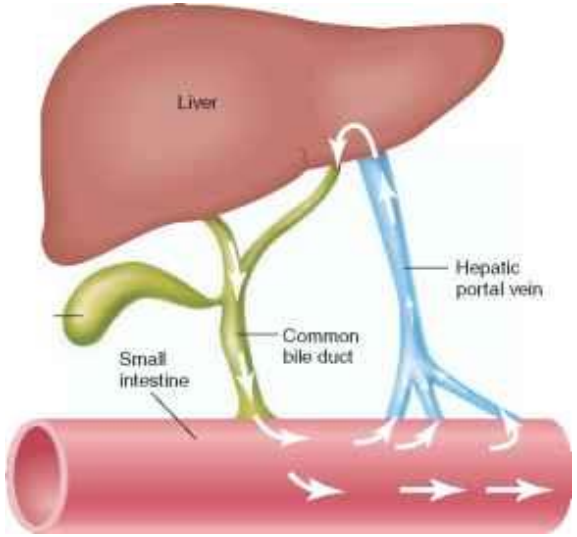
Excretion by liver

- Substances permeate through 2 membranes of hepatocytes – basolateral and apical (canalicular)
- Metabolites are excreted primary by **pasive diffusion**, further by **active transport** (glucuronides, bile acids, penicillins, tetracyclines, etc.)
- Metabolites can be deconjugated by bacterial enzymes in intestine → release of lipophilic molecule → **re-absorption**

= ENTEROHEPATIC CIRCULATION



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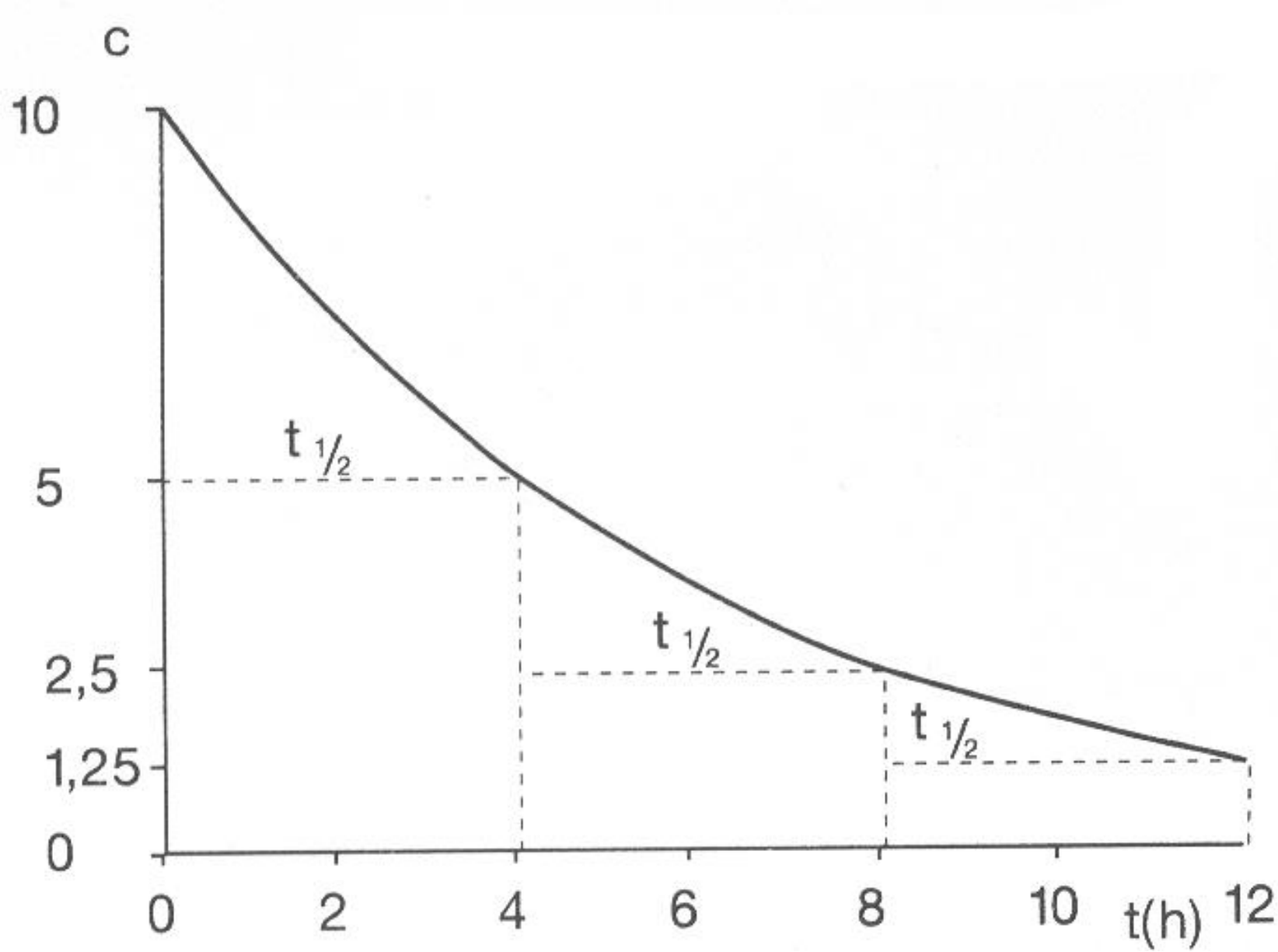

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Basics of pharmacodynamics (mechanisms of drug actions)

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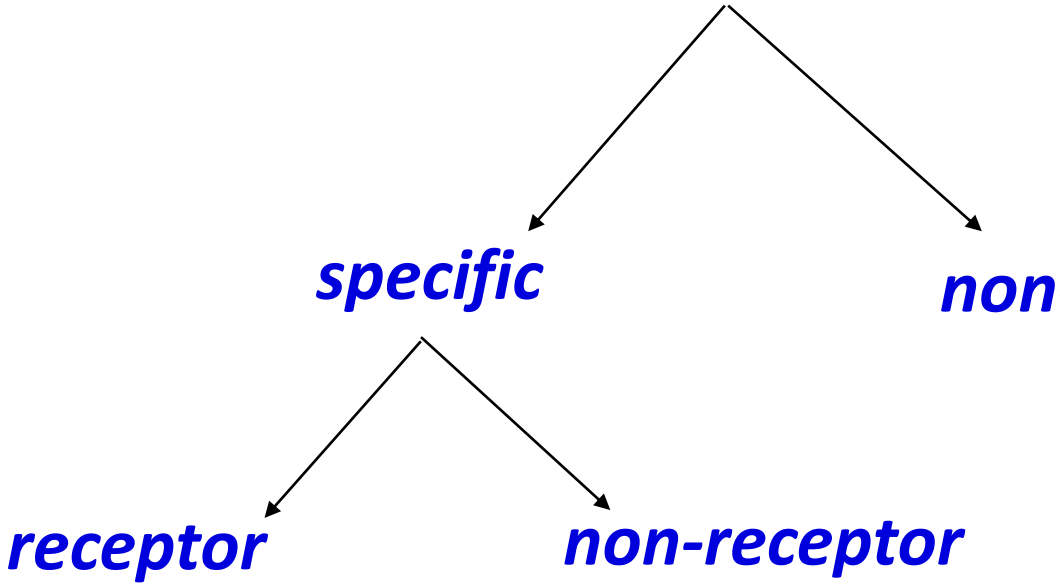
Mechanism of drug actions



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I. Non-specific drug effects

…through by the general physical-chemical properties of substances - no specific chemical and structural configuration of drugs is needed

- influencing pH
- oxidating and reducing agents
- protein precipitation
- adsorbents / detergents
- chelating agents

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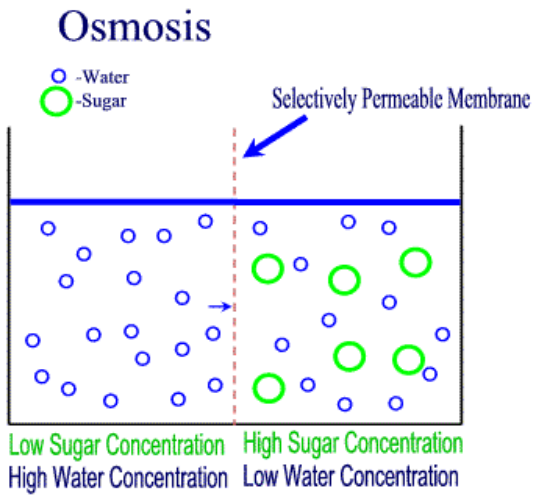
a. based on osmotic properties -

- e.g. salinic laxatives (magnesium sulphate, lactulosa)
- osmotic diuretics (mannitol)



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b. influencing acid-base balance

- Antacids
  - aluminium hydroxide
  - magnesium carbonate
  - calcium carbonate
  - sodium bicarbonate

- pH modifiers (blood, urine)
  - Sodium bicarbonate, ammonium chloride

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c. based on oxido – reducing properties

- e.g. 3% hydrogen peroxide, boric acid, fenols
- chlorhexidine act as antiseptics

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d. chelates (chelating agents)

- ethylenediaminetetraacetic acid (EDTA) is a chelating agent,

  it can form bonds with a metal ion

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II. Specific drug effects

- binding to receptors
- affecting ion channels
- affecting enzymes
- affecting transporters

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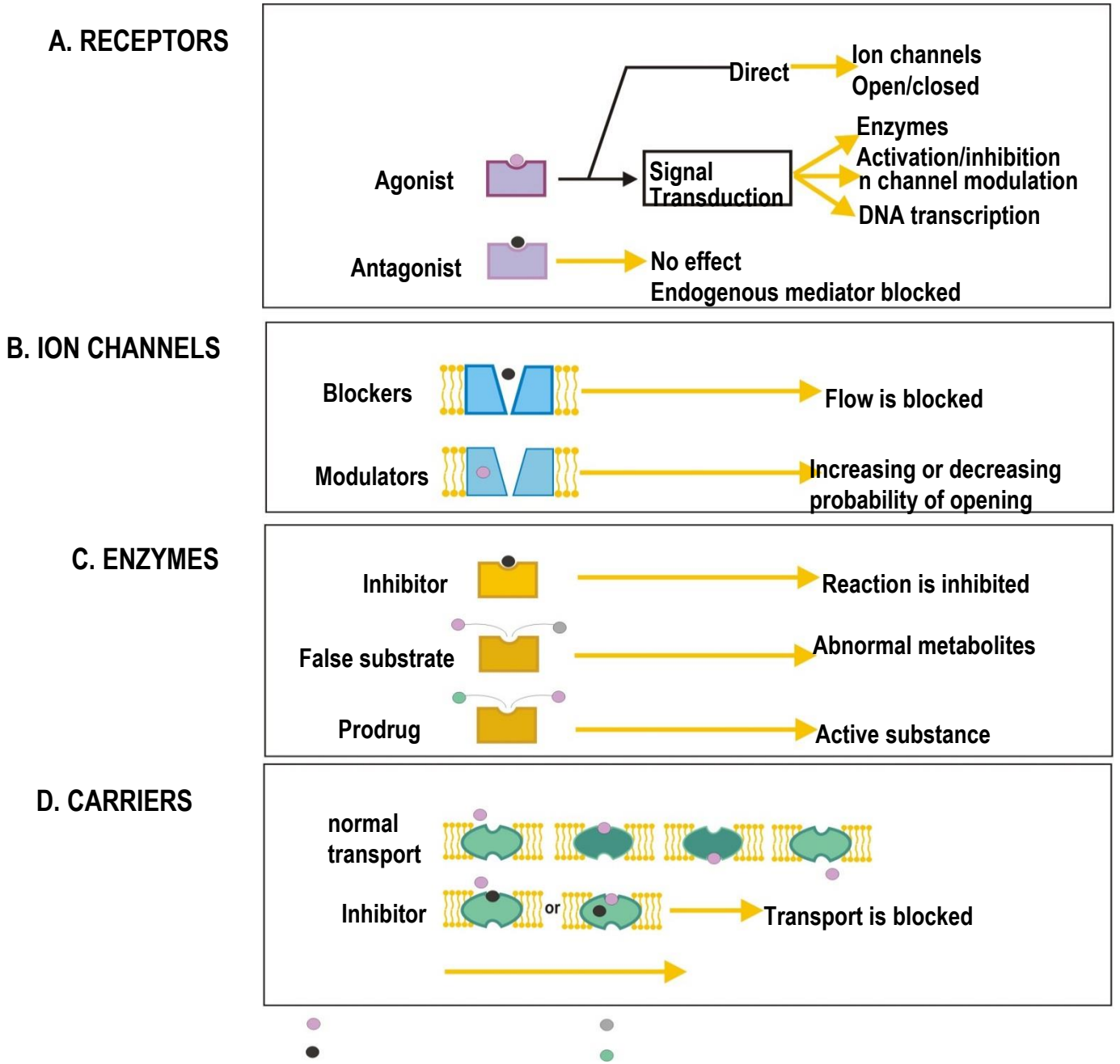

Rang and Dale Pharmacology, 2017

A. Receptor – effector system

= complex of processes

extracelullar signal ----------> intracell. signal cascade--------> effector (own effect)

- ✓ **receptor** = protein, which interacts ligands
  - involved in signal transduction
- ✓ **effector** = enzyme, ionic channel etc. change in the activity leads to the effect of drug
- ✓ **ligand** (signal molecule) = molecule able to bind to specific receptor
  - **endogenous** - neurotransmitters, hormones
  - **exogenous** - xenobiotics, drugs

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Receptor – effector system

- **Affinity**

✓ the ability of the ligand to bind to the receptor

- **Instrinsic activity**

✓ ability to evoke an effect after binding to receptor

  - !!!the presence of sufficient number of receptor for the induction of pharmacological effect is essential as well as sufficient amounts of receptor ligand!!!

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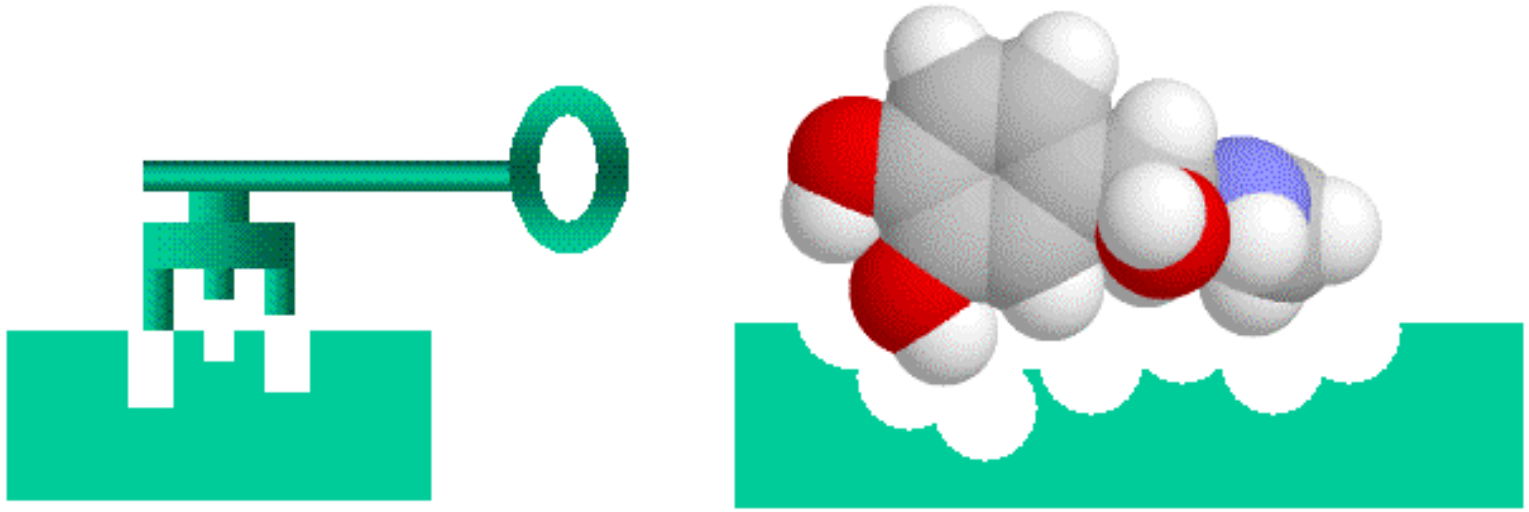
Receptor – effector system



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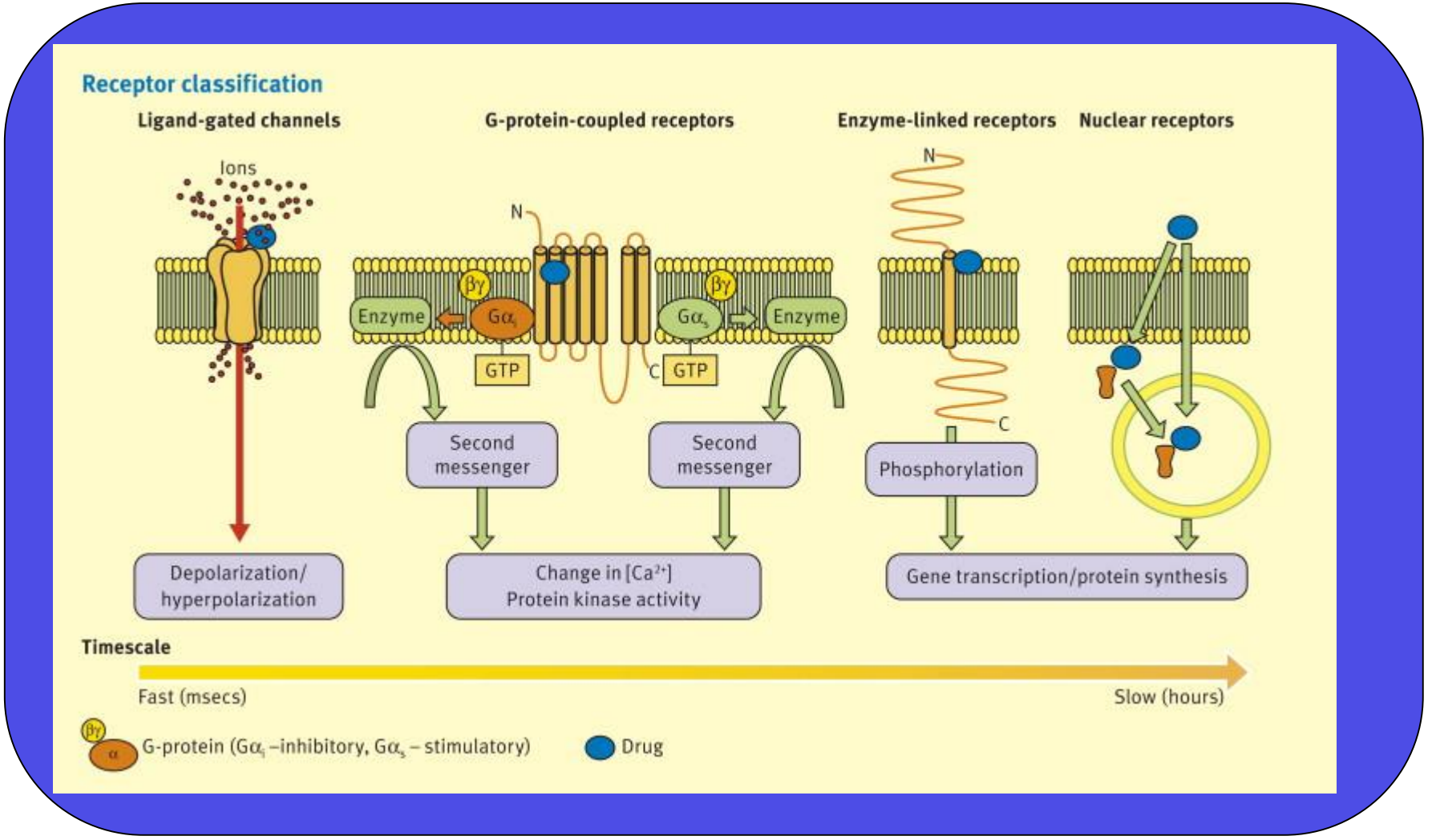
Receptor classification



4 main type of receptors

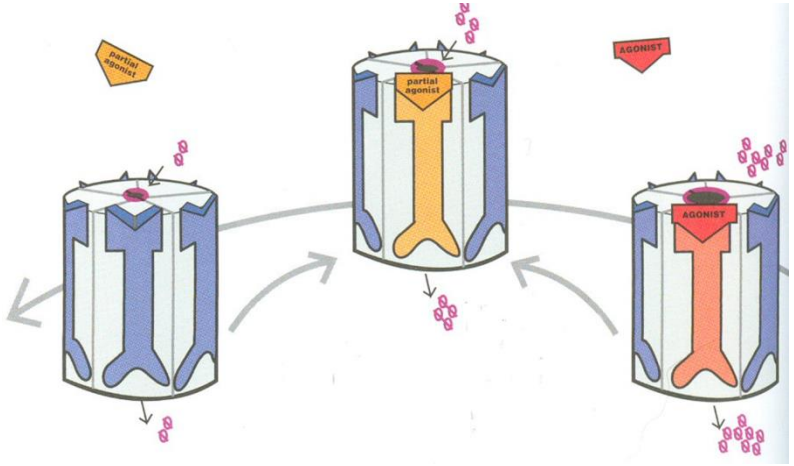
	Type 1 Receptors connected with ion channels	Type 2 G-protein coupled receptor	Type 3 Receptor tyrosin kinases	Type 4 Intracellular (nuclear) receptors
Place	Membrane	Membrane	Membrane	Intracellular
Efector	Ion channel	Channel or enzyme	Enzyme	Gene transcription
Binding	direct	G-protein	direct	DNA mediated
Examples	Nicotin-cholinergic receptor, GABA receptor	Muscarin-cholinergic adrenoreceptors	Inzulin, growth factor, cytokin receptor	Steroids, thyroid hormon receptors
Structure	Oligomer composed by subunits surrounding center of the channel	Monomer (or dimer) containing 7 transmembrane helical domains.	Single transmembrane helical domain interconencted with extracelular kinase	Monomer structure with separate receptor and DNA binding domain

Rang and Dale Pharmacology, 2012

Ligand classification (intrinsic activity) AGONISTS

Full agonist

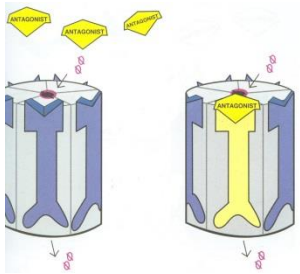
- IA = 1



Partial agonist

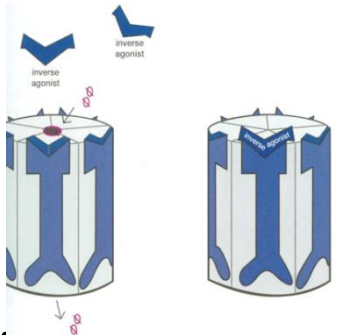
- dualist
- IA in a range from 0‹ to ›1

Ligand classification



Antagonists

- ✓ IA = 0
- ✓ Blocks agonist binding to receptor

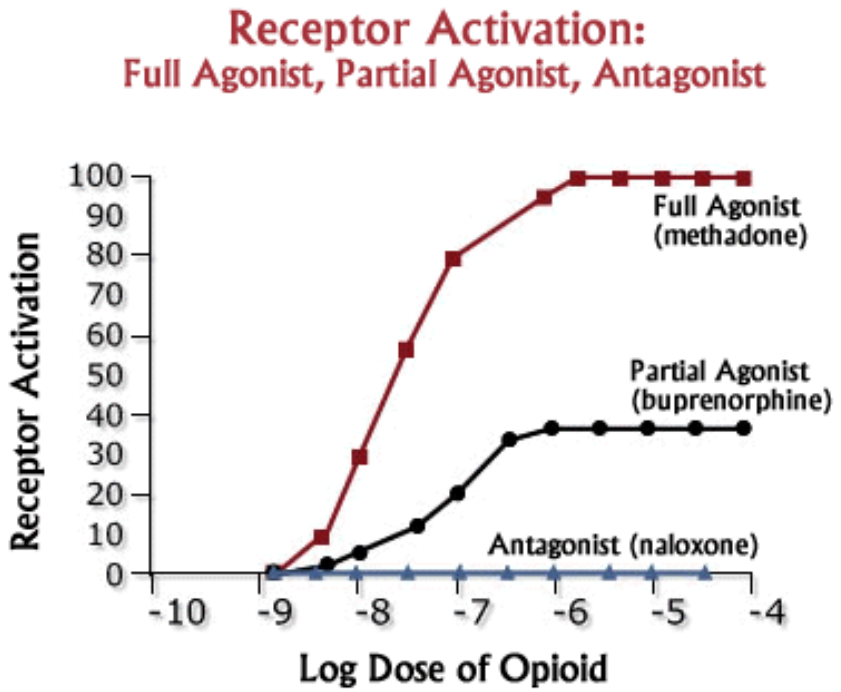


Inverse agonist

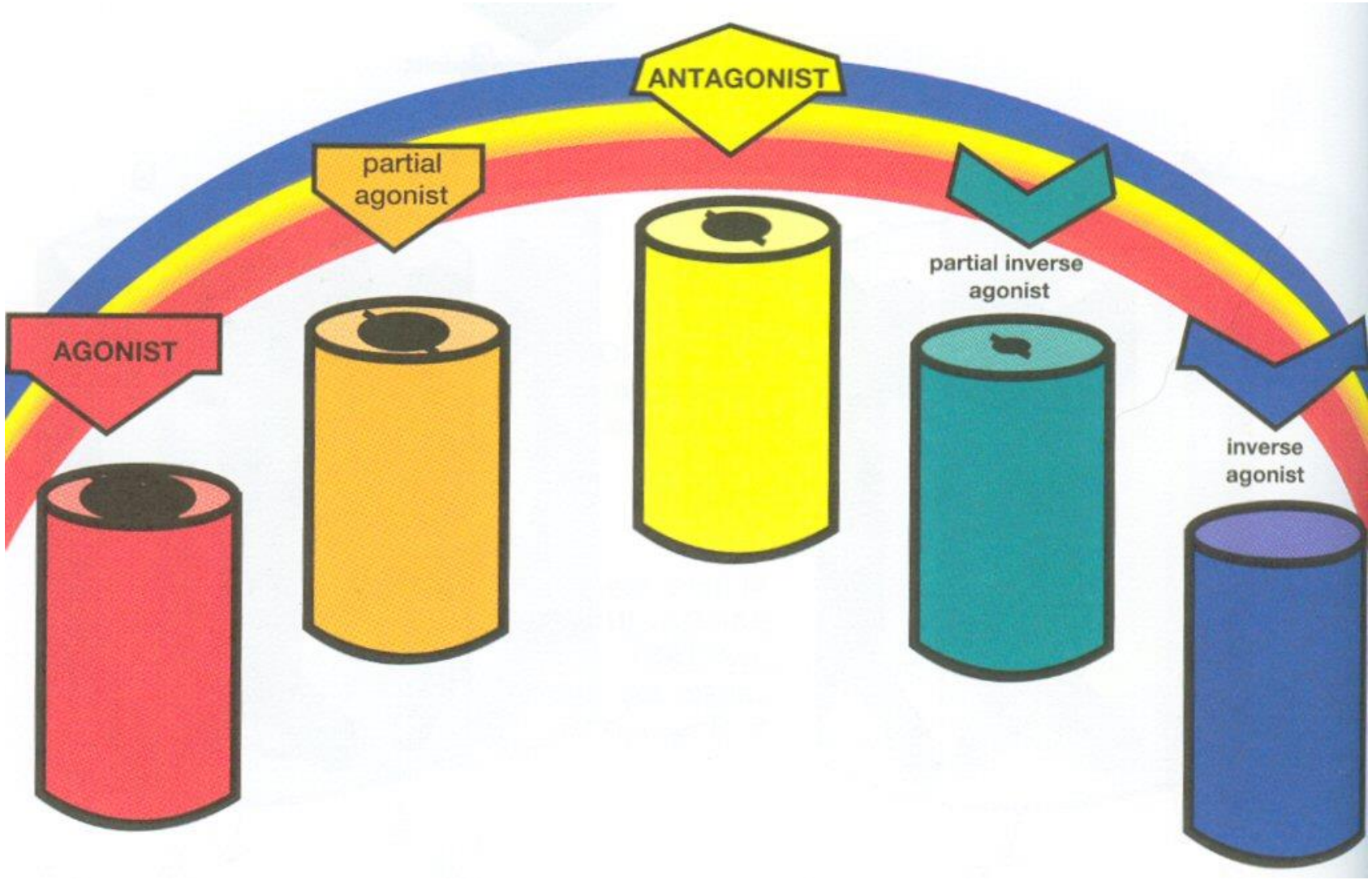
- ✓ IA = -1
- ✓ Stabilizesthe receptor in the constitutive activity

Receptor-effector system

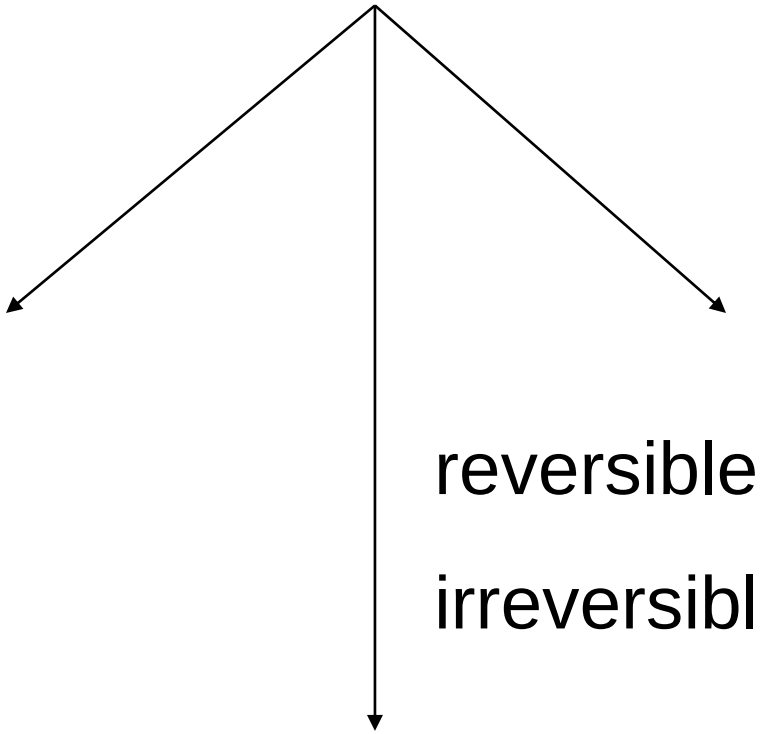
Relation between dose and effect



Spectrum of ligands



Antagonism



competitive

non-competitive

reversible

irreversible

at the receptor level
at the function level

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Antagonism

Competitive

- ✓ ligands compete for the same binding site
- ✓ ↑ c of antagonist decreases agonist effect and inversely
- ✓ the presence of antagonist incerases the amounts of agonist needed to evoke the effect

Non-competitive

- ✓ allosteric antagonism
- ✓ irreverzible bounds
- ✓ ↑ c of agonist does not interrupt the effect of antagonist

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Regulation of receptor function

Regulation of receptor sensitivity and counts

Receptor desensitization

- reducing the sensitivity of the receptors after repeated agonist exposure

- **Tachyphylaxis** – acute drug „tolerance“
  - reduced sensitivity to the active substance evolving quickly (minutes) → distortion of the signal cascade
  - the reactivity of the organism returns to the original intensity after the elimination of the substance
  - Example of tachyphylaxis – ephedrine

- **Tolerance** – reduced sensitivity to the active substance, arising from the repeated administration of the drug (days – weeks) → down-regulation, internalization of the receptors
  - to achieve the original effect required increasingly higher doses of drug
  - the original reactivity of the organism returns to a certain period of time after discontinuation of the drug
  - Example of tolerance – opioids administration

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Regulation of receptor sensitivity and counts

Hypersensitivity

✓incerase of receptor sensitivity/counts after **chronic**

anatagonist exposure

Rebound phenomenom

after discontinuation of long-term administered drugs return to its original state or ↑ intensity of the original condition (hypersensitivity of receptors to endogenous ligands → up-regulation)

Example: chronic administration of β blockers

B. Non-receptor mechanism of action

Interaction with „non-receptor“ proteins

- 1. enzyme inhibition
- 2. block of ion channels
- 3. block of transporters

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1. Enzyme inhibition

- reversible
  - acetylcholinesteraze– physostigmine
- irreversible:
  - cyklooxygenase – ASA (aspirin)
  - aldehyddehydrogenaze– disulfiram

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2. Ion channels

- Calcium channel blockers (nifedipin, isradipin…)
- Natrium channel blockers – local anesthetics

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3. “Carriers“

- Proton pump inhibitors (PPIs) – omeprazol