BASIC TERMINOLOGY. DRUG CLASSIFICATION. MECHANISMS OF DRUG EFFECTS. BASICS OF PHARMACOKINETICS.

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INTRODUCTION

PHARMACOLOGY

- THE SCIENCE THAT STUDIES THE INTERACTION (I.E. MUTUAL EFFECTS) BETWEEN A DRUG AND THE BIOLOGICAL SYSTEM (FROM THE MOLECULAR LEVEL TO THE FULL ORGANISM LEVEL)

general pharmacology **special pharmacology**

MAIN SUB-DISCIPLINES OF PHARMACOLOGY

- **PHARMACOKINETICS** – WHAT THE BODY DOES WITH THE DRUG
- **PHARMACODYNAMICS** – MECHANISMS OF EFFECTS

THERAPY

- PSYCHOTHERAPY
- PHYSIOTHERAPY
- SURGERY
- **PHARMACOTHERAPY**
  - CAUSAL(ATB)
  - SUBSTITUTION (INSULIN, T4)
  - SYMPTOMATIC (ANALGESICS, ANTIPYRETICS)
  - PATHOGENETIC (NSAIDS, ANTIPARKINSONICS, ANTIDEPRESSANTS, …)
- PLACEBO

CLASSIFICATION OF PHARMACEUTICALS

- **Pharmaceuticals** (= pharmaceutical drugs, active substances) are any substances the effects (physical or chemical) of which cause positive changes in biological functions in the organism
- **origin:**
  - Human, animal, herbal, chemical

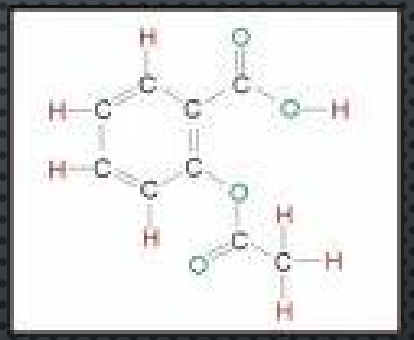
- **Auxiliary substances** are necessary for the formulation
- **medicinal products =** active and auxiliary substances which are modified into a specific **dosage form**

PRODRUGS

- PHARMACOLOGICALLY INACTIVE SUBSTANCE FROM WHICH A PHARMACOLOGICALLY ACTIVE METABOLITE ARISES ONCE IN THE BODY
- *LEVODOPA -) DOPAMIN*
- *VALACIKLOVIR -) ACIKLOVIR*
- *BROMHEXIN -) AMBROXOL*

TERMINOLOGY OF PHARMACEUTICALS

- Chemical name
  - 2-acetoxybenzoic acid
- Generic mane
  - Acetylsalicylic acid
- international non-proprietary name (INN)
  - acidum acetylsalicylicum
- Pharmacopoeial name
  - acidum acetylsalicylicum
- Trade or corporate name
  - Acylpyrin®, Aspirin ®



BASICS OF PHARMACODYNAMICS

MECHANISMS OF DRUG EFFECT

- **SPECIFIC**
  - **RECEPTOR MEDIATED**
    - ION CHANNEL
    - G-PROTEIN COUPLED
    - COUPLED WITH ENZYME AKTIVITY
    - INTRACELULAR RECEPTORS REGULATING GENE EXPRESSION
  - **NON-RECEPTOR MEDIATED** (SPECIFIC INTERACTION WITH OTHER MACROMOLECULES IN THE BODY)
- **NON-SPECIFIC**

RECEPTOR MEDIATED MECHANISMS

- **RECEPTORS** = PROTEINS WHOSE PHYSIOLOGICAL ROLE CONSISTS IN SIGNAL TRANSFER TO THE CELL FOLLOWING THEIR ACTIVATION BY AN ENDOGENOUS MOLECULE (NEUROTRANSMITTER, HORMONE).

- **LIGANDS** = SUBSTANCES THAT CAN BIND TO A RECEPTOR.

AFFINITY

- WILLINGNESS OF THE SUBSTANCE TO BIND TO THE GIVEN RECEPTOR TYPE

INTRINSIC ACTIVITY (EFFICACY)

- ABILITY OF THE LIGAND TO ACTIVATE THE RECEPTOR = TO CAUSE SIGNAL TRANSFER BY THE RECEPTOR
- REACHES VALUES OF 0 – 1, I.E. 1 = 100% OF EFFECT

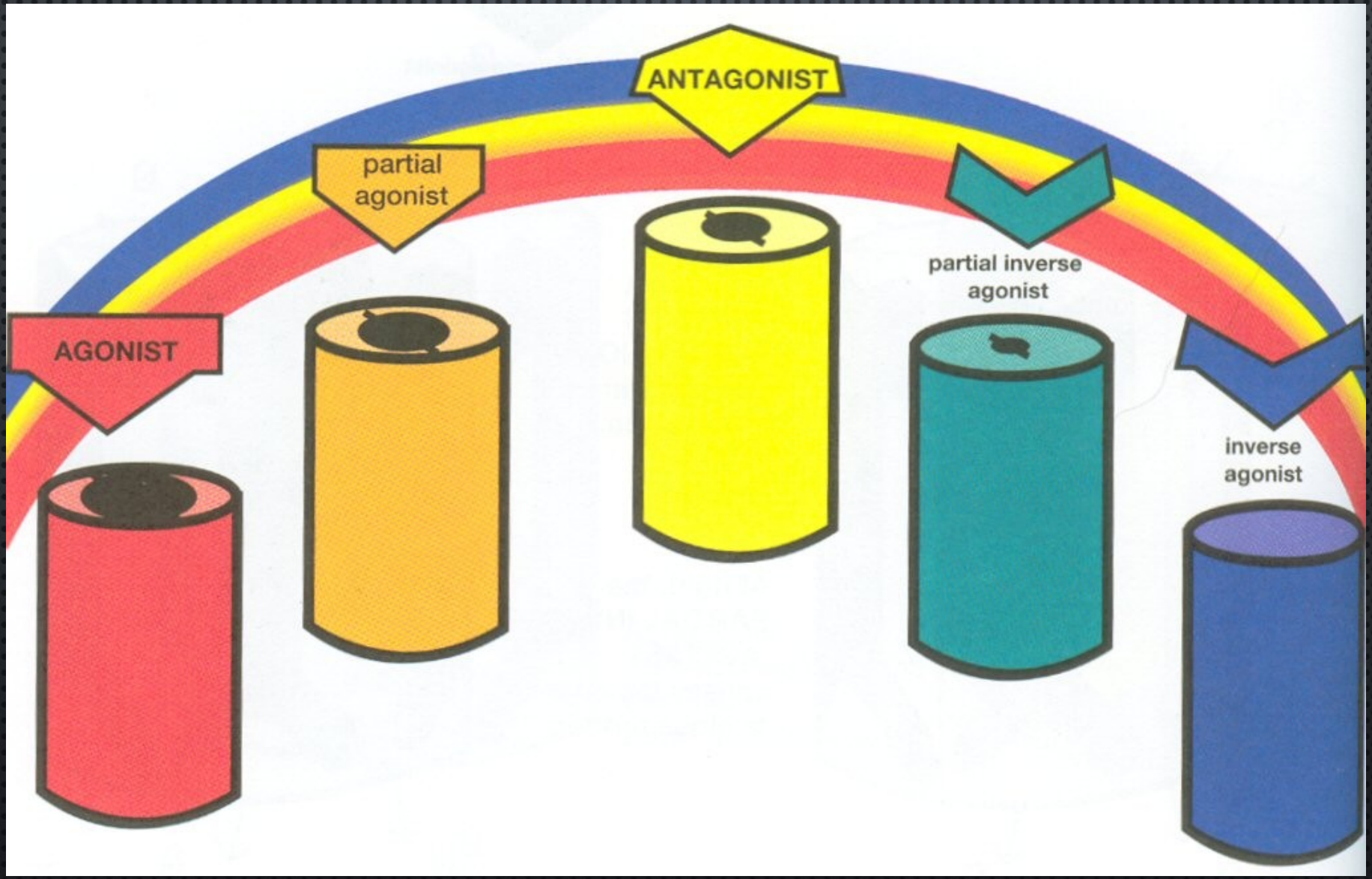
TYPES OF RECEPTOR LIGANDS

- **AGONIST**
  - Activate receptor
- **ANTAGONIST**
  - Block receptor

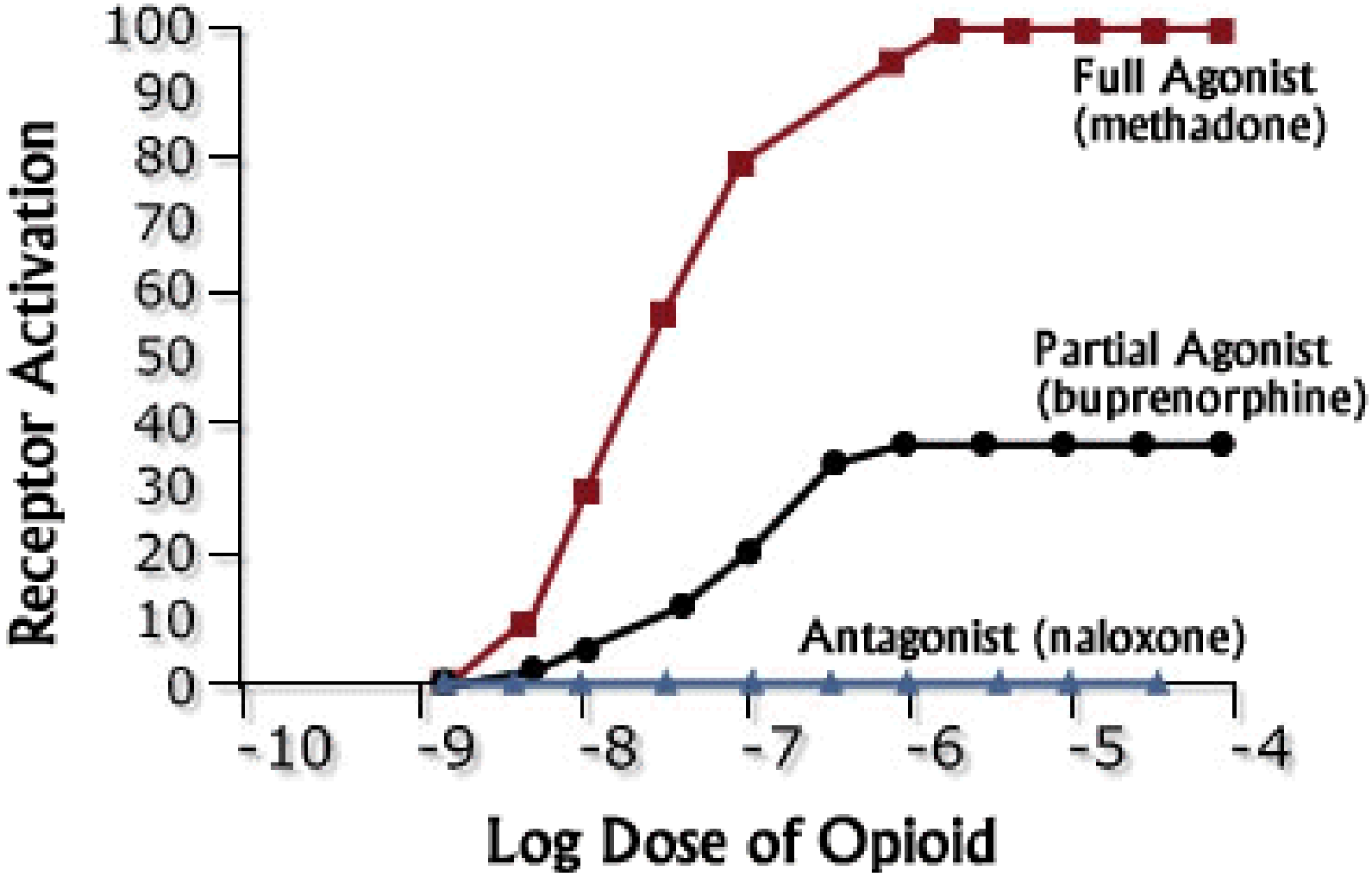
FULL AGONIST: INTRINSIC ACTIVITY ≅ 1

PARCIAL AGONIST (DUALIST): 0 < INTRINSIC ACTIVITY < 1

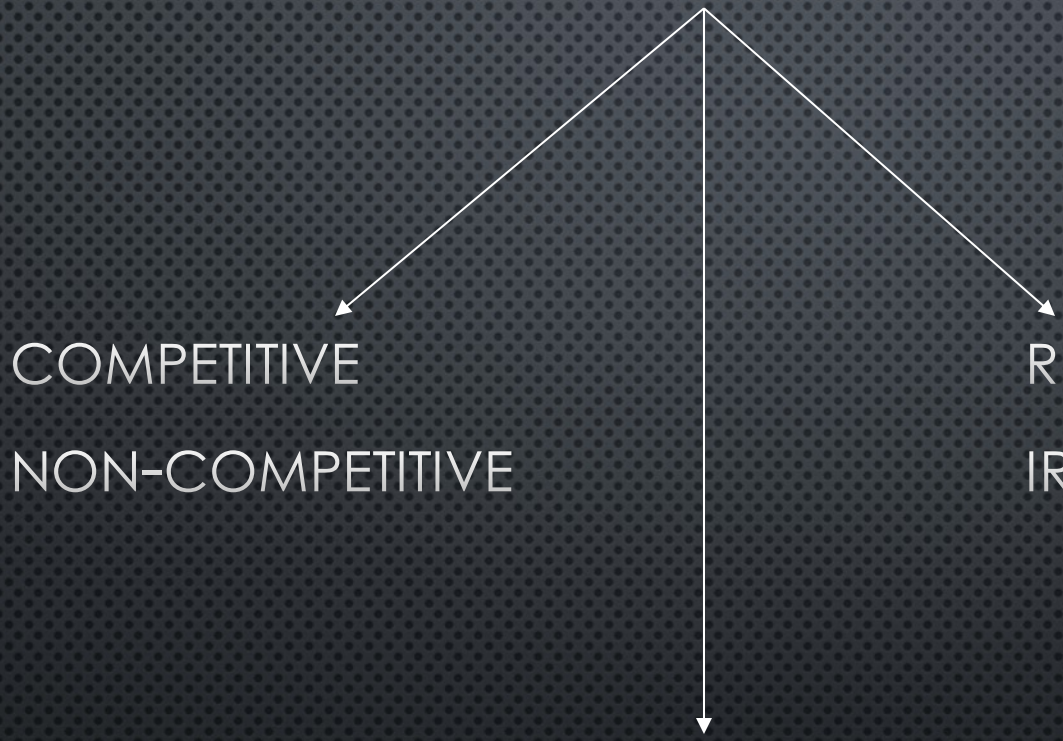
ANTAGONIST: INTRINSIC ACTIVITY ≅ 0


ANTAGONIST
partial agonist
partial inverse agonist
AGONIST
inverse agonist

Receptor Activation:
Full Agonist, Partial Agonist, Antagonist



ANTAGONISM



COMPETITIVE

NON-COMPETITIVE

REVERSIBLE

IRREVERSIBLE

AT THE RECEPTOR LEVEL

AT THE FUNCTION LEVEL

HTTPS://WWW.YOUTUBE.COM/WATCH?V=PQ2ZPN0K6XQ

Antagonism

Competitive

- ✓ ligands compete for the same binding site
- ✓ [redacted] 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
- ✓ [redacted] of agonist does not interrupt the effect of antagonist

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)

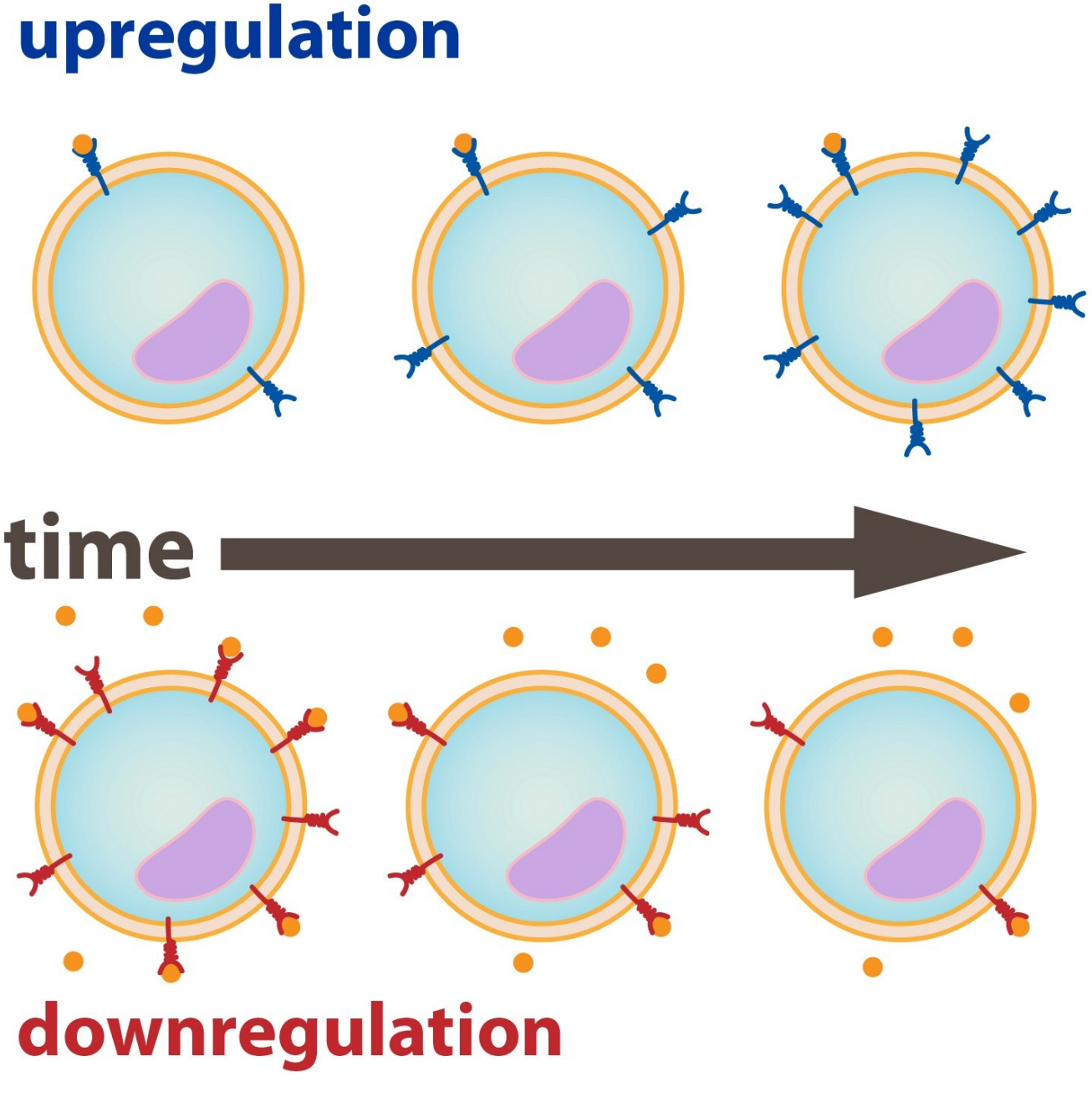
Example: chronic administration of β blockers

Regulation of receptor sensitivity and counts

- Hypersensitivity - incerase of receptor sensitivity/counts after chronic **ANTAGONIST** exposure
- **Rebound phenomenon**
- 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 b blockers

REGULATION OF RECEPTOR SENSITIVITY AND COUNTS

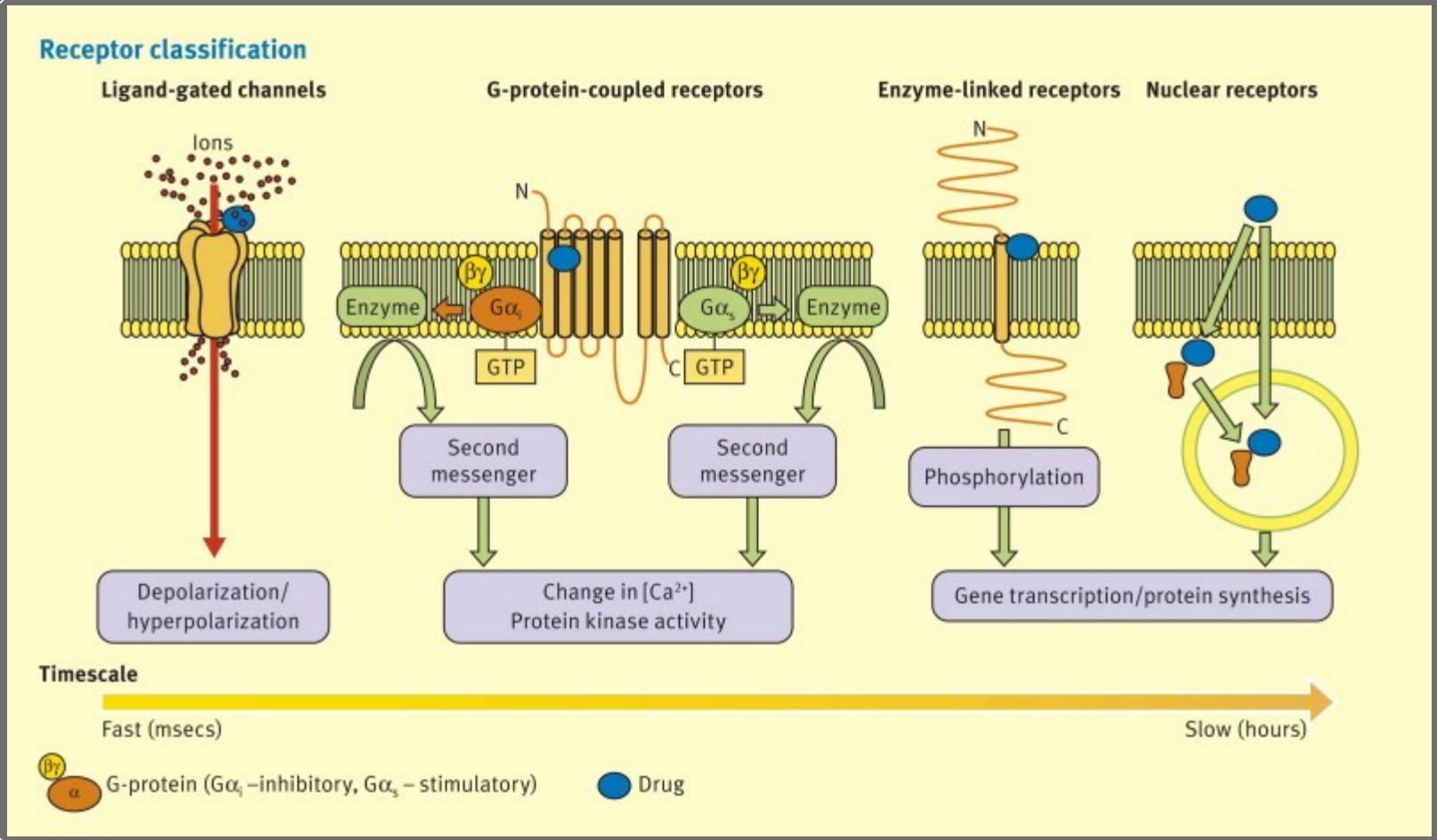
- DESENSITIZATION – REDUCED RECEPTOR SENSITIVITY/COUNTS AFTER CHRONIC **AGONIST** EXPOSURE
- **TOLERANCE** – REDUCED SENSITIVITY TO THE ACTIVE SUBSTANCE, ARISING FROM THE REPEATED ADMINISTRATION OF THE DRUG (DAYS – WEEKS) → DOWN-REGULATION
  - EFFECT REQUIRES INCREASINGLY HIGHER DOSES
  - THE ORIGINAL REACTIVITY RETURNS A CERTAIN PERIOD OF TIME AFTER DISCONTINUATION OF THE DRUG
  - EX. OF TOLERANCE – OPIOIDS ADMINISTRATION


upregulation
time
downregulation

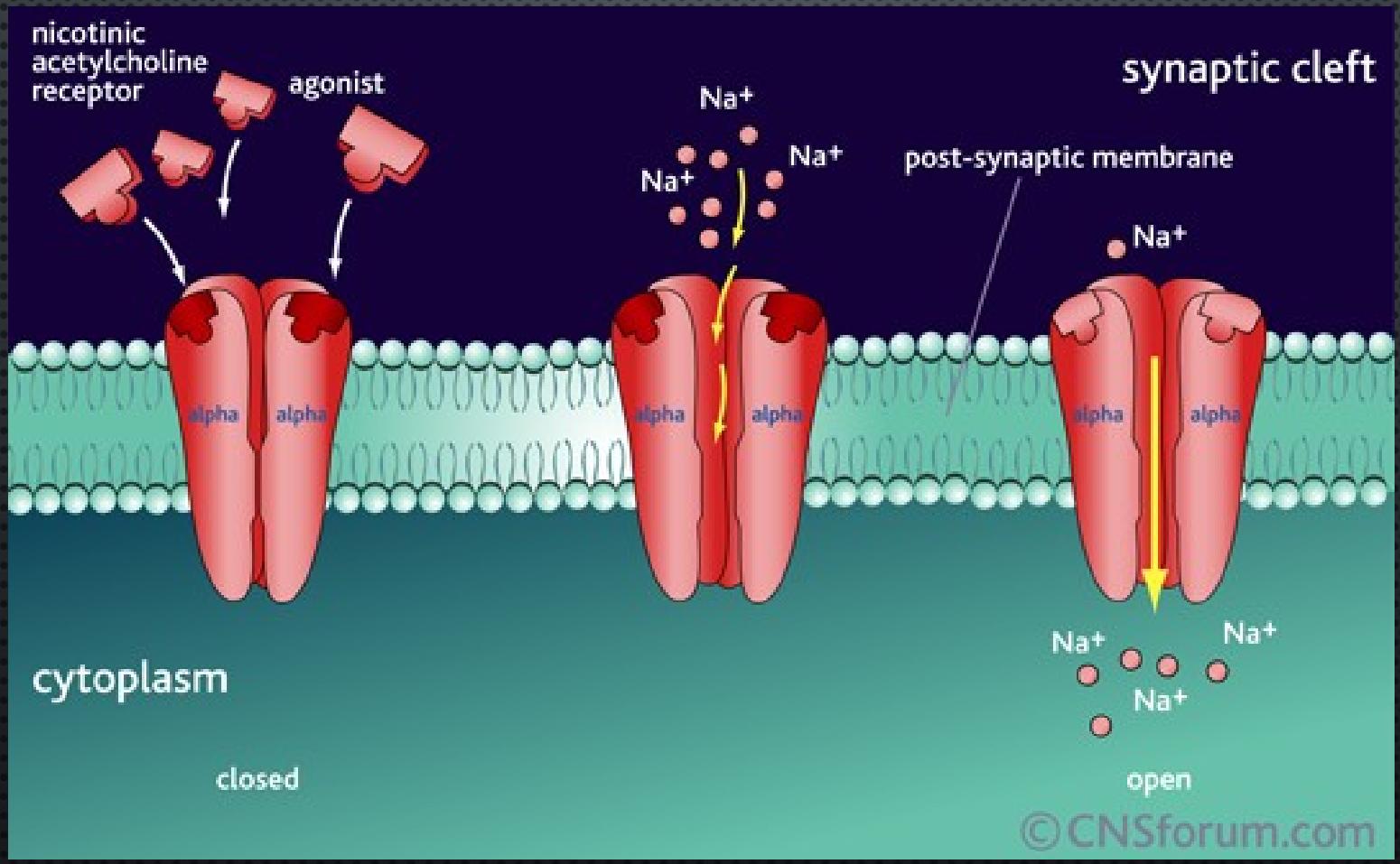
RECEPTOR DESENSITIZATION

- **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
  - EX. OF TACHYPHYLAXIS – NITRATES ADMINISTRATION

Receptor classification



NICOTINIC RECEPTOR

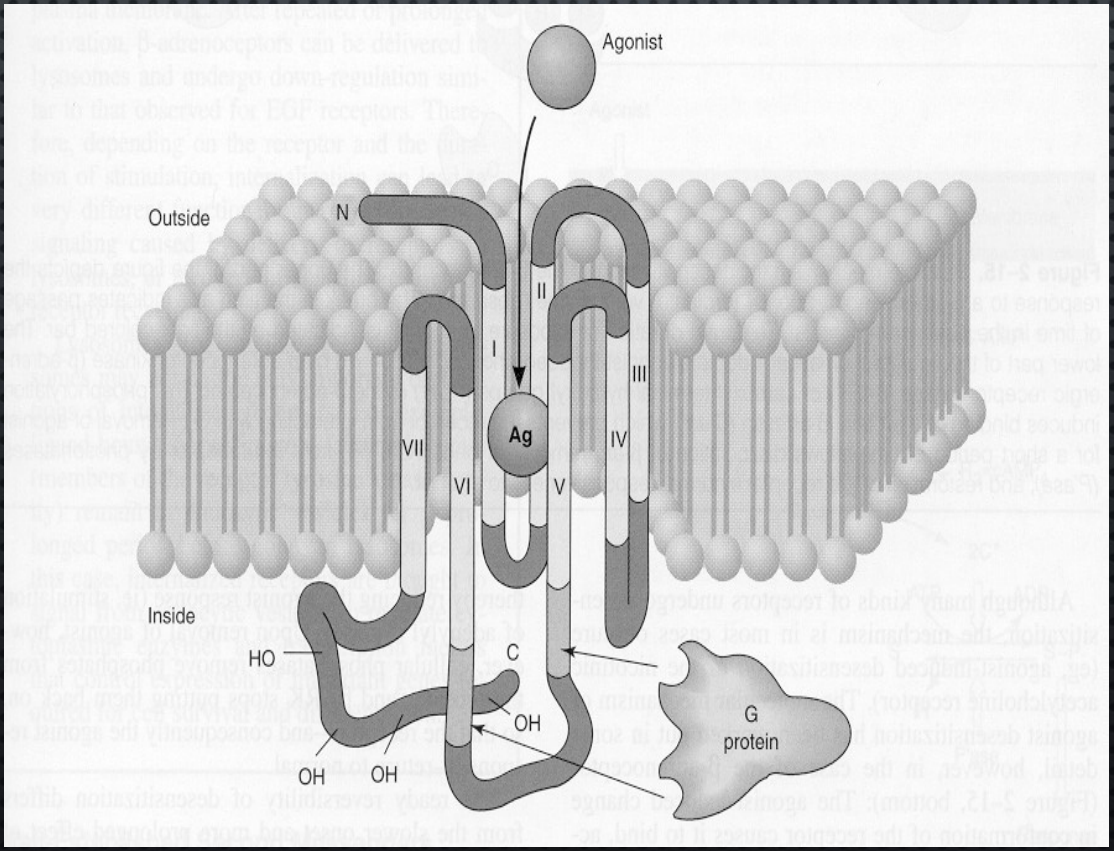


Katzung BG, 2001

METABOTROPIC RECEPTORS

= G-PROTEIN COUPLED RECEPTORS

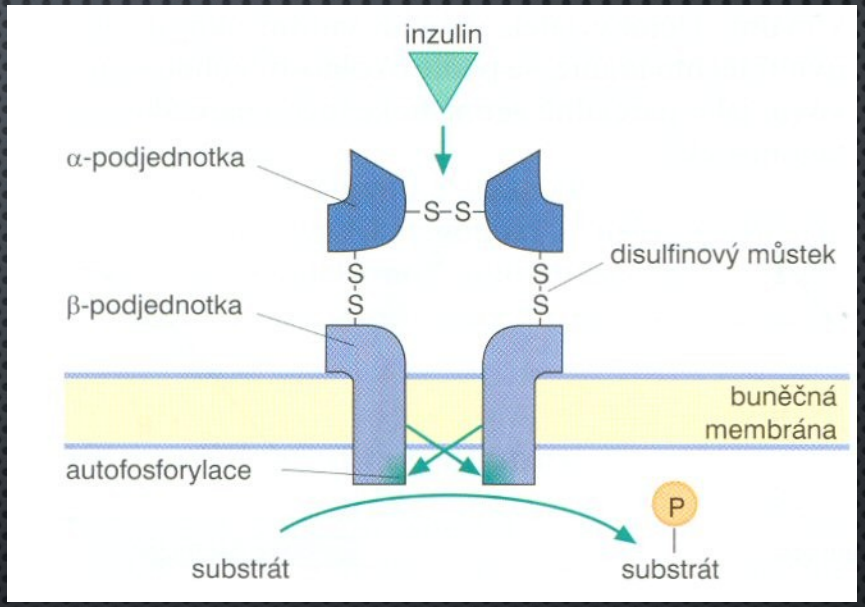
- MUSCARINIC, ADRENERGIC, DOPAMINERGIC, GABA-B…

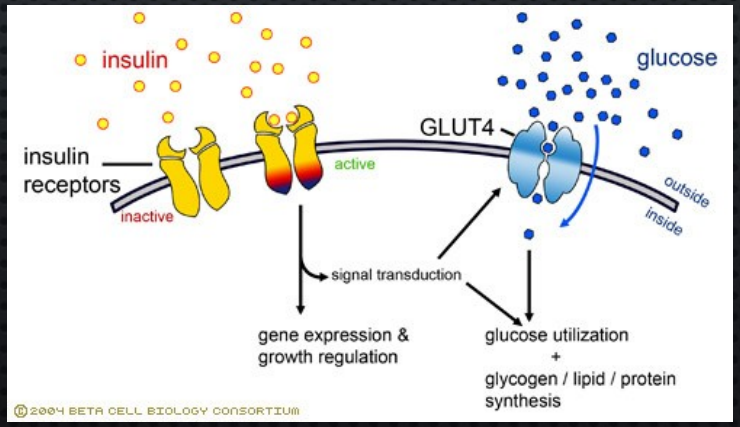


ENZYME-LINKED RECEPTORS

INSULIN RC

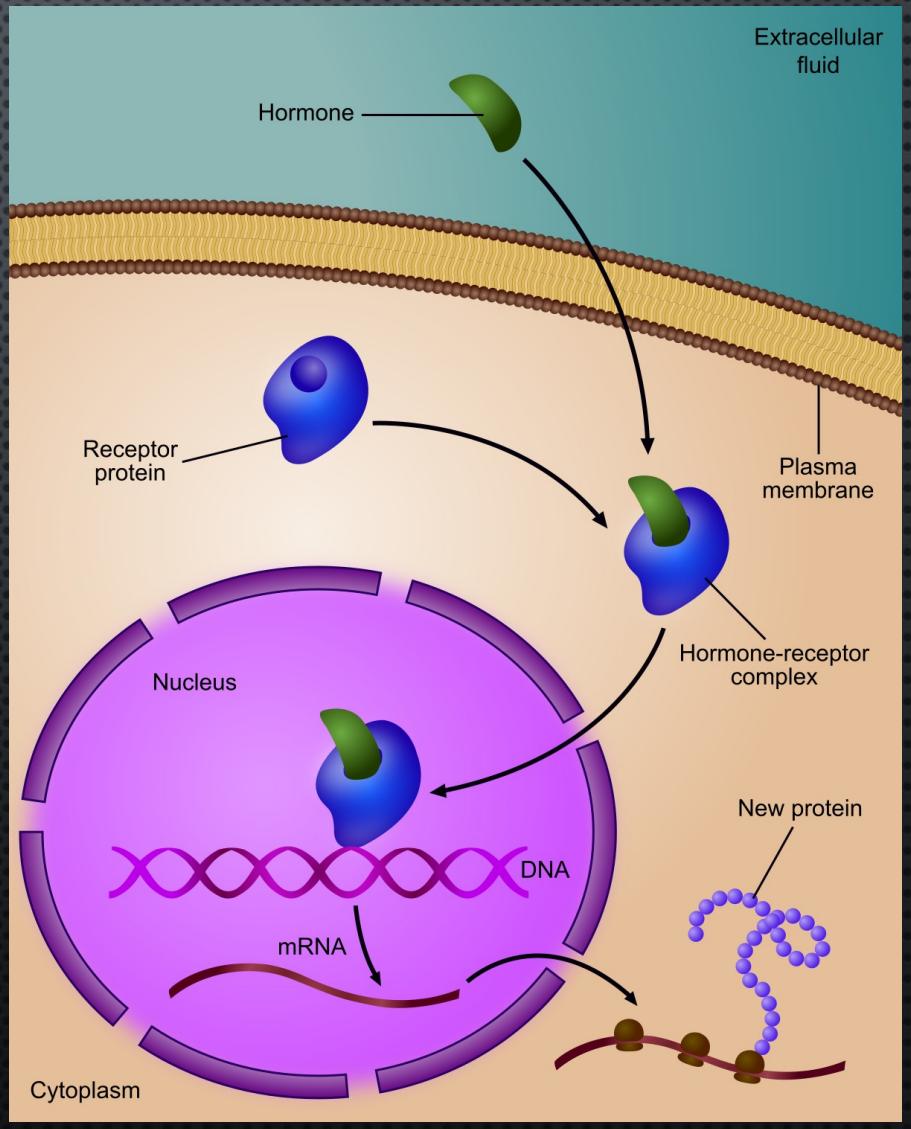
- ACTIVATION OF THYROSINKINASE, ↑ SYNTHESIS AND ↓ DEGREDATION OF GLYCOGEN





RECEPTORS REGULATING PROTEOSYNTHESIS

- LIPOPHILIC STEROID HORMONES
- GLUCOCORTICOIDS, T_3, T_4, VIT. D, RETINOIDY
- EFFECT REQUIRES HOURS-DAYS



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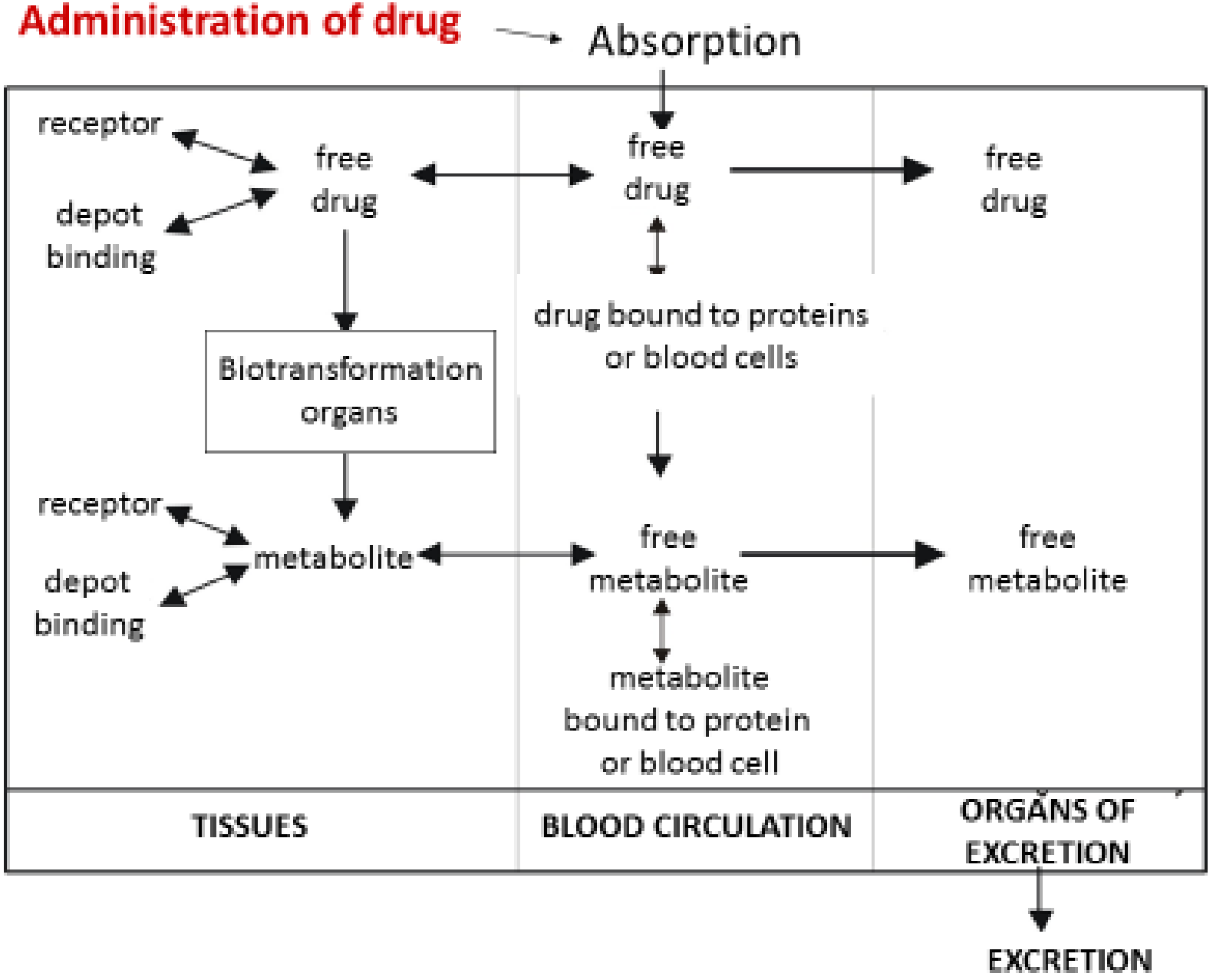
BASICS OF PHARMACOKINETICS

PHARMACOKINETICS = ADME

= ABSORPTION, DISTRIBUTION, METABOLISM, EXCRETION

- Primary pharmacokinetic parameters
  - bioavaliability
  - Volume of distribution
  - clearance
  - Elimination halflife


Administration of drug
Absorption
receptor
depot
binding
free
drug
free
drug
free
drug
drug bound to proteins
or blood cells
Biotransformation
organs
receptor
depot
binding
metabolite
free
metabolite
free
metabolite
metabolite
bound to protein
or blood cell
TISSUES
BLOOD CIRCULATION
ORGANS OF
EXCRETION
EXCRETION

ABSORPTION

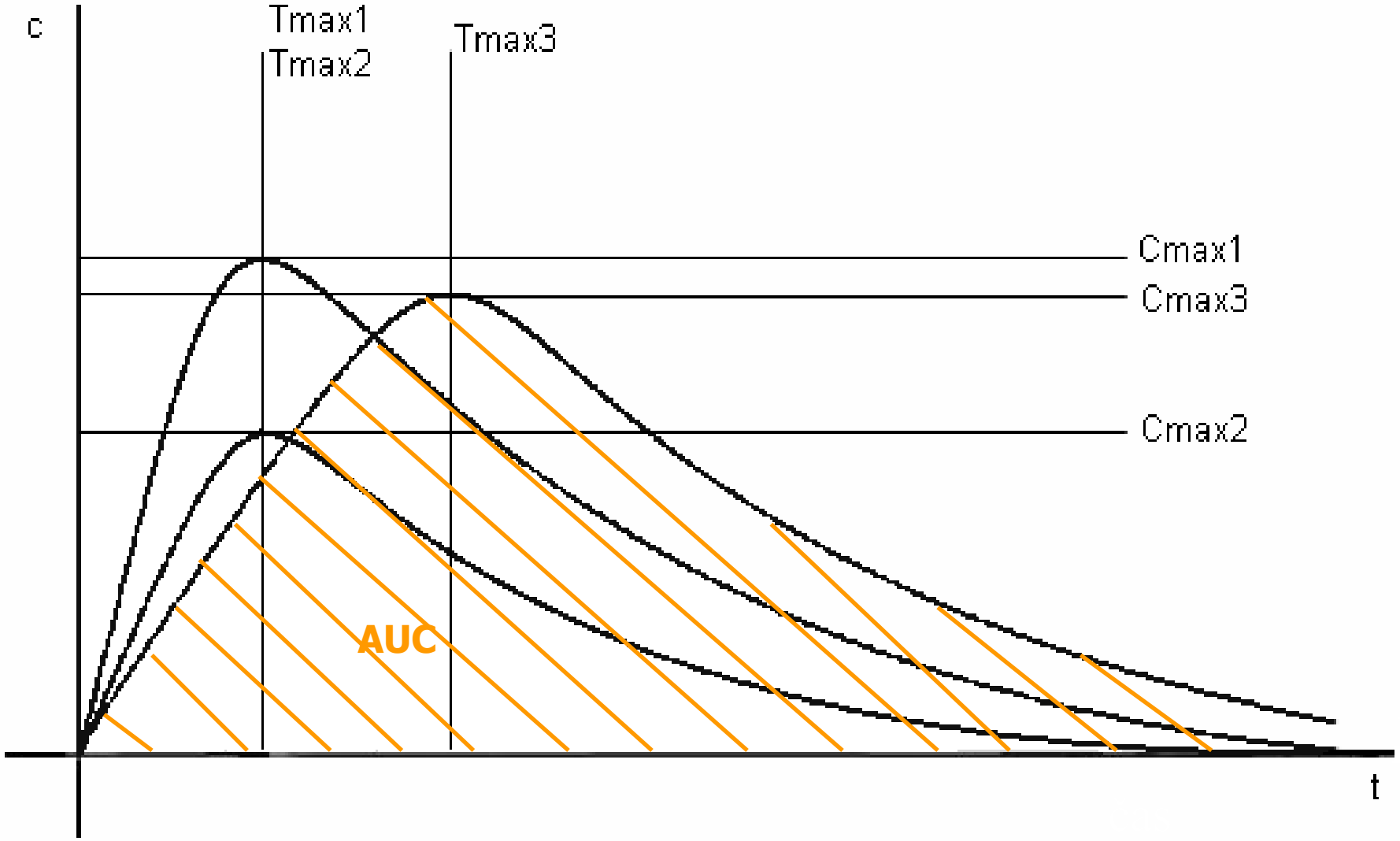
- PENETRATION OF DISSOLVED DRUG FROM THE SITE OF ADMINISTRATION TO BLOOD (SYSTEMIC CIRCULATION) – NECESSARY FOR GENERAL EFFECT– **SYSTEMIC EFFECT**
- **LOCAL EFFECT:**
  - ON SKIN, MUCOSAS OR VENTRICLES
  - ABSORPTION IS UNDESIRABLE – POSSIBLE AE
  - IE. LOCAL CORTICOIDS, LOCAL ANESTHETICS

ABSORPTION

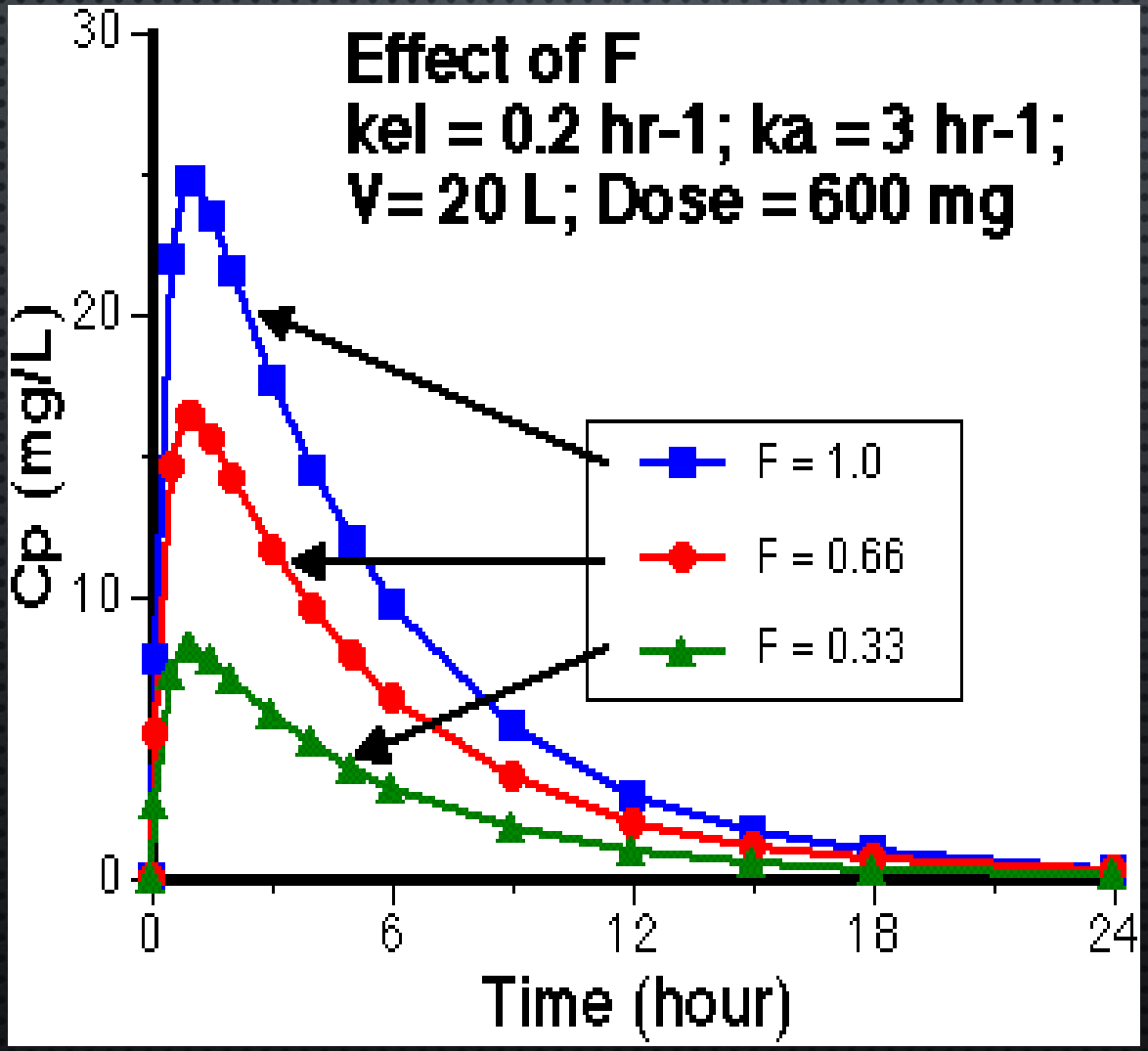
RYCHLOST A ROZSAH ABSORPCE

- **C_{MAX}**- MAX. CONCENTRATION OF DRUG IN PLASMA AFTER SINGLE DOSE
- **T_{MAX}**- TIME, WHEN DRUG REACH C_{MAX} (SPEED)
- **F** - BIOAVAILABILITY (EXTENT)
  - FRACTION WHICH GETS TO THE BLOODSTREAM
  - EXTRAVASCULAR ADMINISTRATION: 0-100% (RESP. 0-1)
  - INRTAVENOUS: 100% = 1

Oral administration

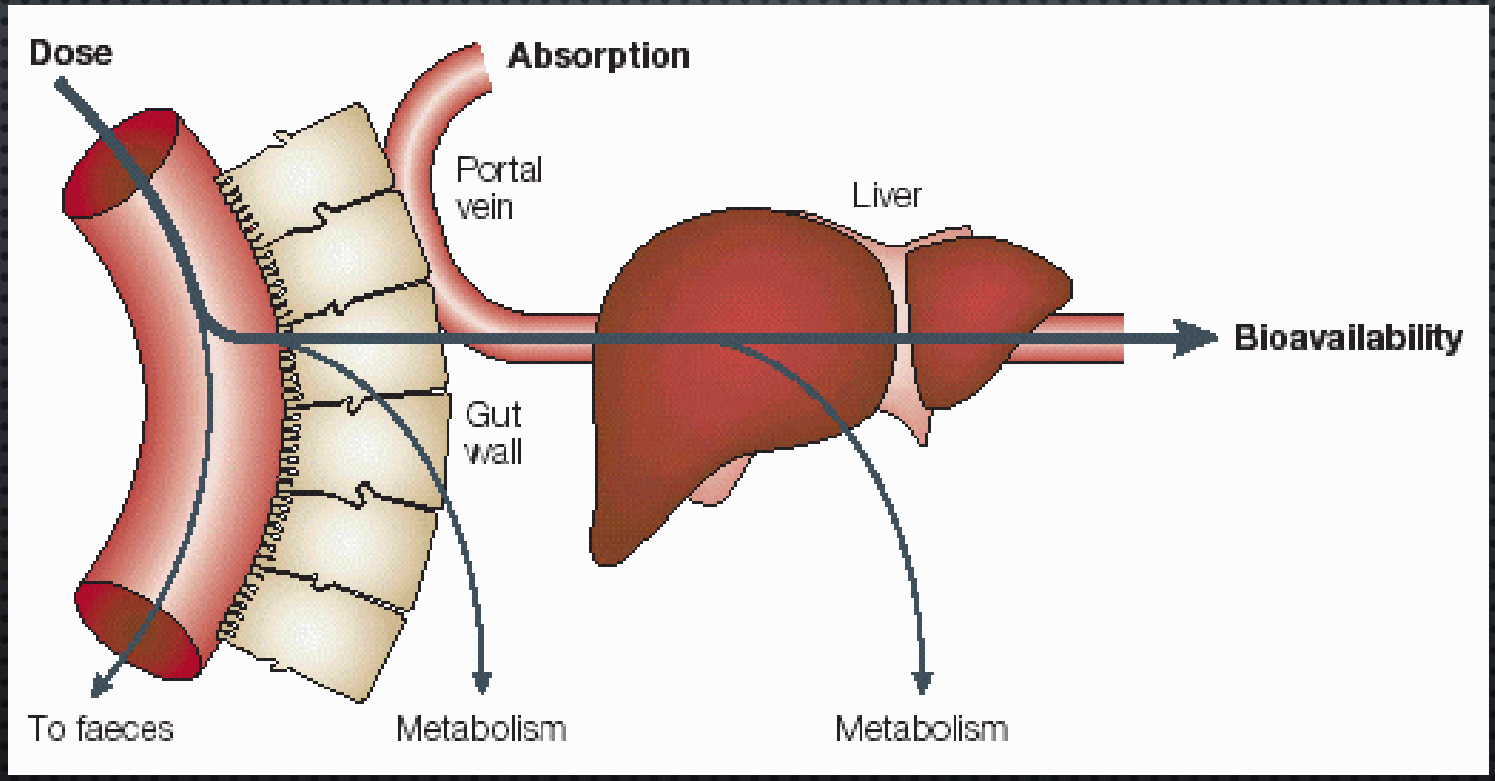


Effects of different bioavailability (F) on the pharmacokinetics



Presystemic elimination

First pass effect

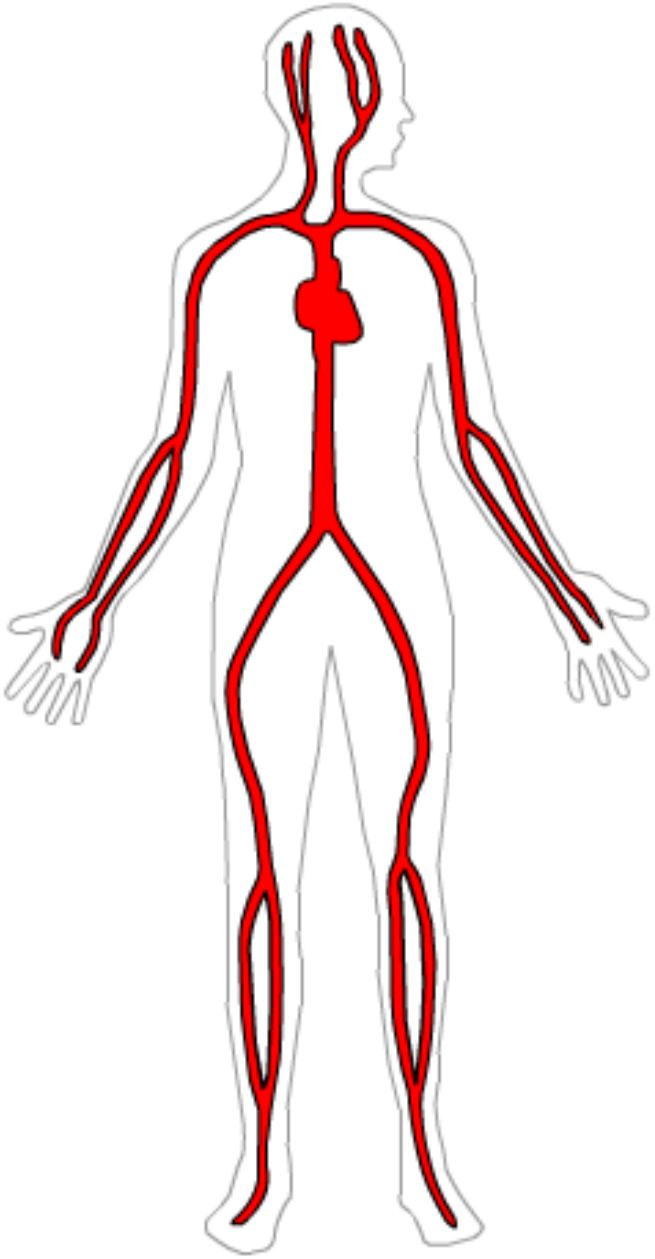


http://icp.org.nz/icp_t6.html

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

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



Vd

5 L

10,000 L

Drug concentrated in blood stream

Drug in blood and extracellular space

Drug equally distributed in blood and tissues

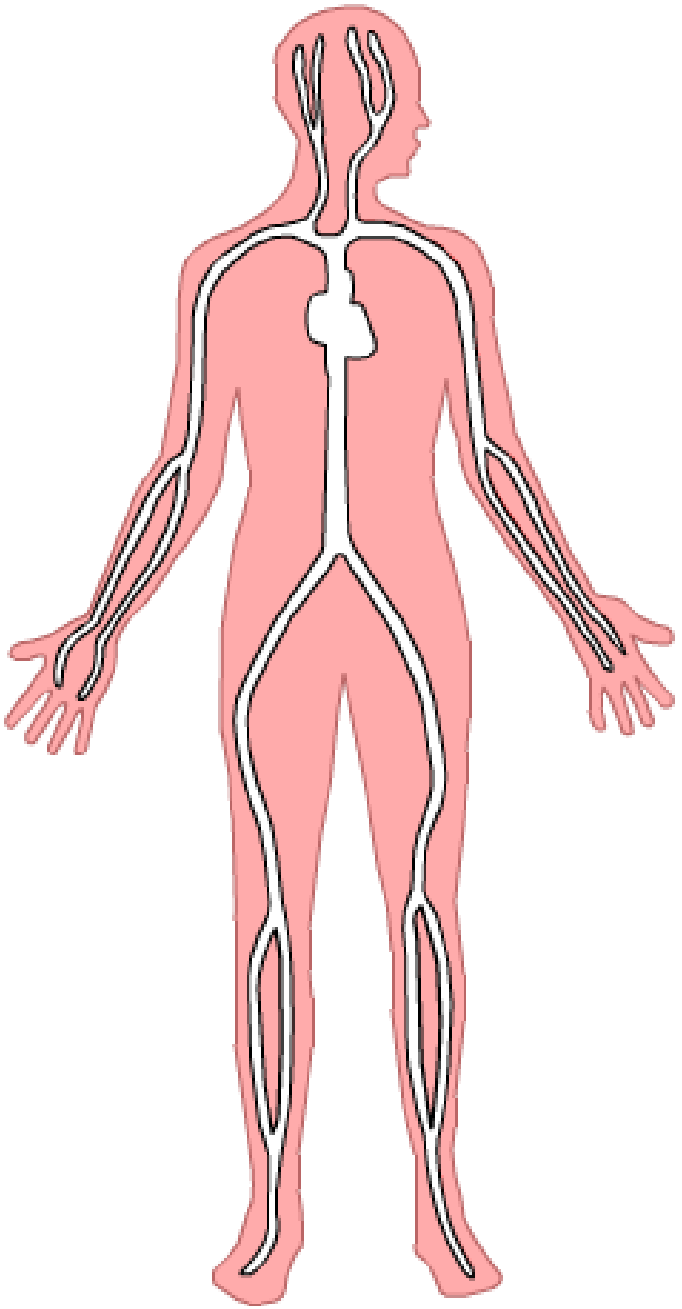
Drug moderately concentrated in tissues

Drug highly concentrated in tissues (usually adipose)

Amount in body = Vd x plasma concentration

$$Ab = Vd \times Cp$$

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



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Drug moderately concentrated in tissues

Drug highly concentrated in tissues (usually adipose)

10,000 L

Amount in body = Vd x plasma concentration

$$Ab = Vd \times Cp$$

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

ELIMINATION

- **BIOTRANSFORMATION - METABOLISM**
  - **BIODEGRADATION**
  - **BIOACTIVATION (PRODRUG:** BROMHEXIN – AMBROXOL)

- **EXCRETION**
  - KIDNEY, LIVER, LUNGS, SKIN, BREASTMILK…

http://icp.org.nz/icp_t2.html

BIOTRANSFORMATION

- **PHASE I** OXIDATION
  REDUCTION
  HYDROLYSIS

  } More hydrophilic compounds, sometimes active metabolites

- **PHASE II** **CONJUGATION** – INACTIVATION (GLUCURONIC ACID)

EXCRETION - CLEARANCE (CL)

CL = ABILITY OF THE ORGANISM TO EXCRETE THE DRUG

= THE VOLUME OF PLASMA FROM WHICH A SUBSTANCE IS COMPLETELY REMOVED PER UNIT TIME

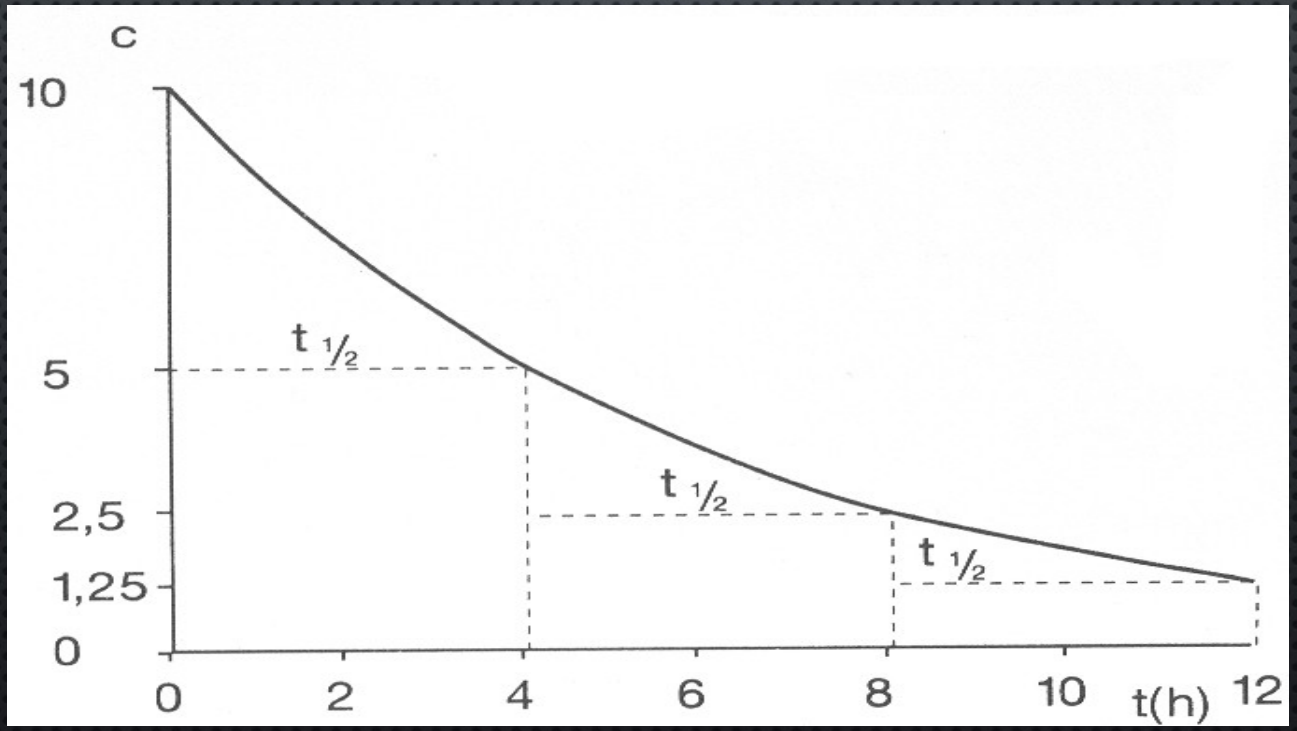
- TOTAL = RENAL + HEPATAL + LUNG…

http://icp.org.nz/icp_t1.html

ELIMINATION HALF-LIFE ($T_{1/2}$)

= TIME TO ELIMINATE HALF OF THE DRUG FROM THE BLOOD

- DRUG IS CONSIDERED TO BE ELIMINATED AFTER 4-5 HALF-LIVES



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