BASIC OF PHARMACOLOGY

LECTURE 1

CONTENT OF THE LECTURES

1. **LECTURE** (17. 9.)

BASIC PHARMACOLOGICAL TERMINOLOGY.

DRUG CLASSIFICATION.

MECHANISMS OF DRUG EFFECTS.

BASICS OF PHARMACOKINETICS.

CONTENT OF THE LECTURES

2. LECTURE (1. 10.)

FACTORS INFLUENCING DRUG EFFECTS.

ADVERSE DRUG EFFECTS.

DRUG INTERACTION.

DEVELOPMENT OF NEW DRUGS, DRUG LIFE-CYCLE.

CONTENT OF THE LECTURES

3. LECTURE (8. 10.)

PHARMACOLOGY OF VEGETATIVE NERVOUS SYSTEM.

ADRENERGIC AND CHOLINERGIC RECEPTORS AND THEIR AGONISTS AND ANTAGONISTS.

CONTENT OF THE LECTURES

4. LECTURE (29. 10.)

GLUCOCORTICOIDS AND IMMUNOSUPPRESSANT THERAPY.

PHARMACOLOGY OF ALLERGIC REACTIONS – ANTIHISTAMINES.

CONTENT OF THE PRACTICALS

1. PRACTICAL LESSON (24. 9.)

DRUG FORMS AND ROUTES OF ADMINISTRATION.

DRUGS DATABASES AND HANBOOKS (SÚKL/EMA DATABASES, AISLP, ETC.,

LEGISLATION OF DRUGS PRESCRIPTION,

PRESCRIPTION OF NARCOTIC AND PSYCHOTROPIC AGENTS.

CONTENT OF THE PRACTICALS

2. PRACTICAL LESSON (15. 10.)

THERAPY OF PARKINSON DISEASE, MENIER DISEASE

MYASTHENIA GRAVIS

SPASMS AND DYSKINESIA.

CONTENT OF THE PRACTICALS

3. PRACTICAL LESSON (22. 10.)

NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

THERAPY OF RHEUMATIC DISEASES

ANTIURATICS, ANODYNES.

CONTENT OF THE PRACTICALS

4. PRACTICAL LESSON (5. 11.)

MYORELAXANTS

LOCAL ANAESTHETICS

CREDITS

ORGANISATION OF COLLOQUIUM TERM.

RECOMMENDED LITERATURE

PHARMACOLOGY. EDITED BY MICHELLE ALEXIA CLARK. 5TH ED. BALTIMORE: WOLTERS KLUWER HEALTH/LIPPINCOTT WILLIAMS & WILKINS, 2012. XII, 612. ISBN 9781451113143

TEXTBOOK ON SPECIAL PHARMACOLOGY

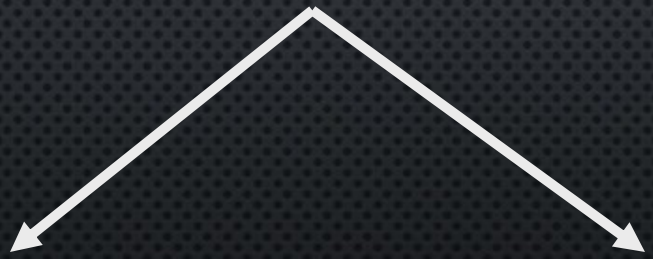
PRESENTATIONS

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

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, glucocorticoids)
  - 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

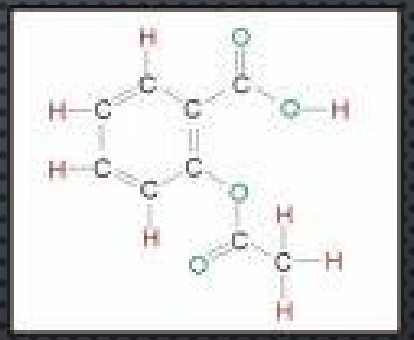
- **Auxiliary substances** are necessary for the formulation
- **medicinal products =** active and auxiliary substances which are modified into a specific **dosage form**

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

- NON-SPECIFIC
- 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 MECHANISMS OF ACTION

SUBSTANCES ACTING BY MEANS OF OSMOTIC PROPERTIES

THESE SUBSTANCES DO NOT CROSS CELL MEMBRANE, THIS IS HOWEVER PERMEABLE FOR WATER.

WATER MOVES FROM MORE DILUTED SITE TO SITE WITH HIGHER CONCENTRATION OF SOLUTION – UNTIL OSMOTIC BALANCE IS REACHED.

SALINE LAXATIVES (MAGNESIUM SULPHATE)

OSMOTIC DIURETICS (MANNITOL)

NON-SPECIFIC MECHANISMS OF ACTION

SUBSTANCES AFFECTING ACID – BASE BALANCE

- ANTACIDS, SUBSTANCES CHANGING pH OF URINE (E.G. ACIDIFYING SALT – AMMONIUM CHLORIDE – TREATMENT OF AMPHETHAMINE INTOXICATION)

- SUBSTANCES USED FOR REGULATION OF SYSTEMIC ACID – BASE BALANCE DISORDERS (E.G. SODIUM BICARBONATE FOR METABOLIC ACIDOSIS, SODIUM CITRATE, POTASSIUM CITRATE)

NON-SPECIFIC MECHANISMS OF ACTION

SUBSTANCES CAUSING OXIDATION OR REDUCTION

- SOME DISINFECTANTS (E.G. 3% HYDROGEN PEROXIDE) ACT AS OXIDIZING AGENT
- METHYLENE BLUE IS USED FOR ITS REDUCING PROPERTIES FOR METHEMOGLOBINEMIA TREATMENT

NON-SPECIFIC MECHANISMS OF ACTION

ADSORBENTS

SUBSTANCES WITH LARGE SURFACE BINDING (ADSORBING) OTHER SUBSTANCES, TOXINS, ETC. - CHARCOAL

NON-SPECIFIC MECHANISMS OF ACTION

SURFACTANTS, DETERGENTS

AFFECT SURFACE TENSION OF CELL MEMBRANES; THEY ARE USED AS DISINFECTANTS AND ANTISEPTICS (E.G. SOAPS, BENZYL DODECINIUM BROMIDE, CARBETHOPENDECINIUM BROMIDE)

Specific mechanisms of action

1. Receptors
2. Ion channels
3. Enzymes
4. Carriers

RECEPTOR MEDIATED MECHANISMS

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

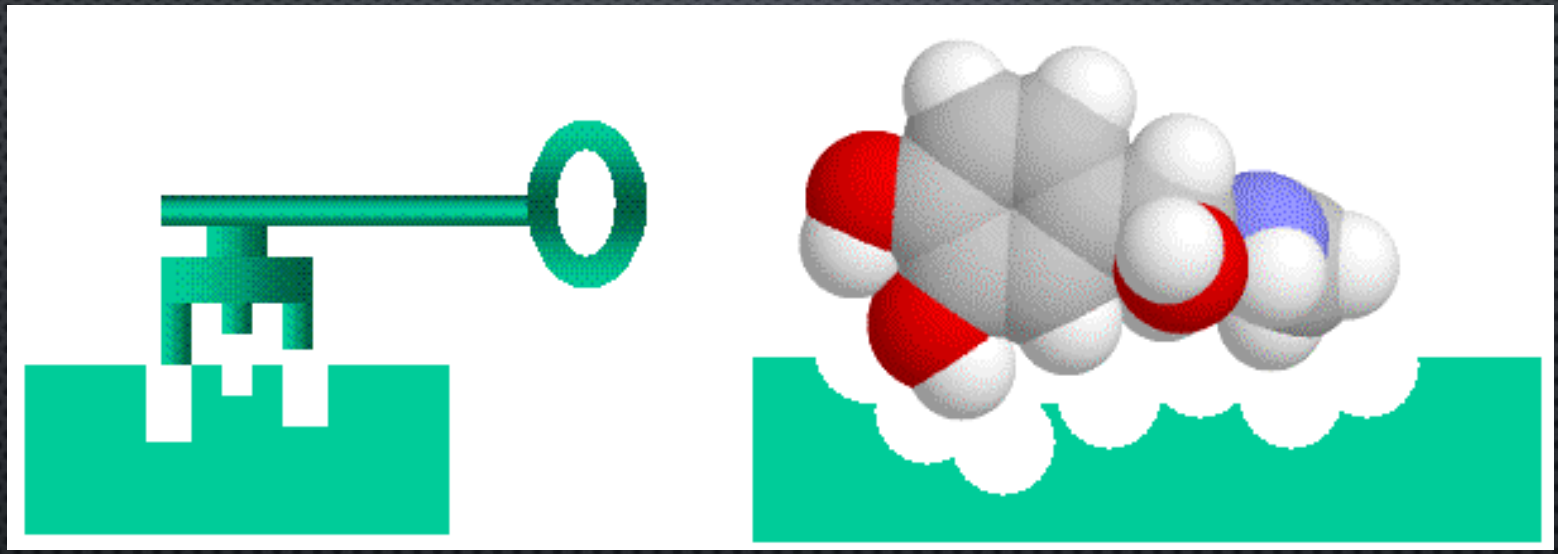
- **LIGANDS** = SUBSTANCES THAT CAN BIND TO A RECEPTOR.

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



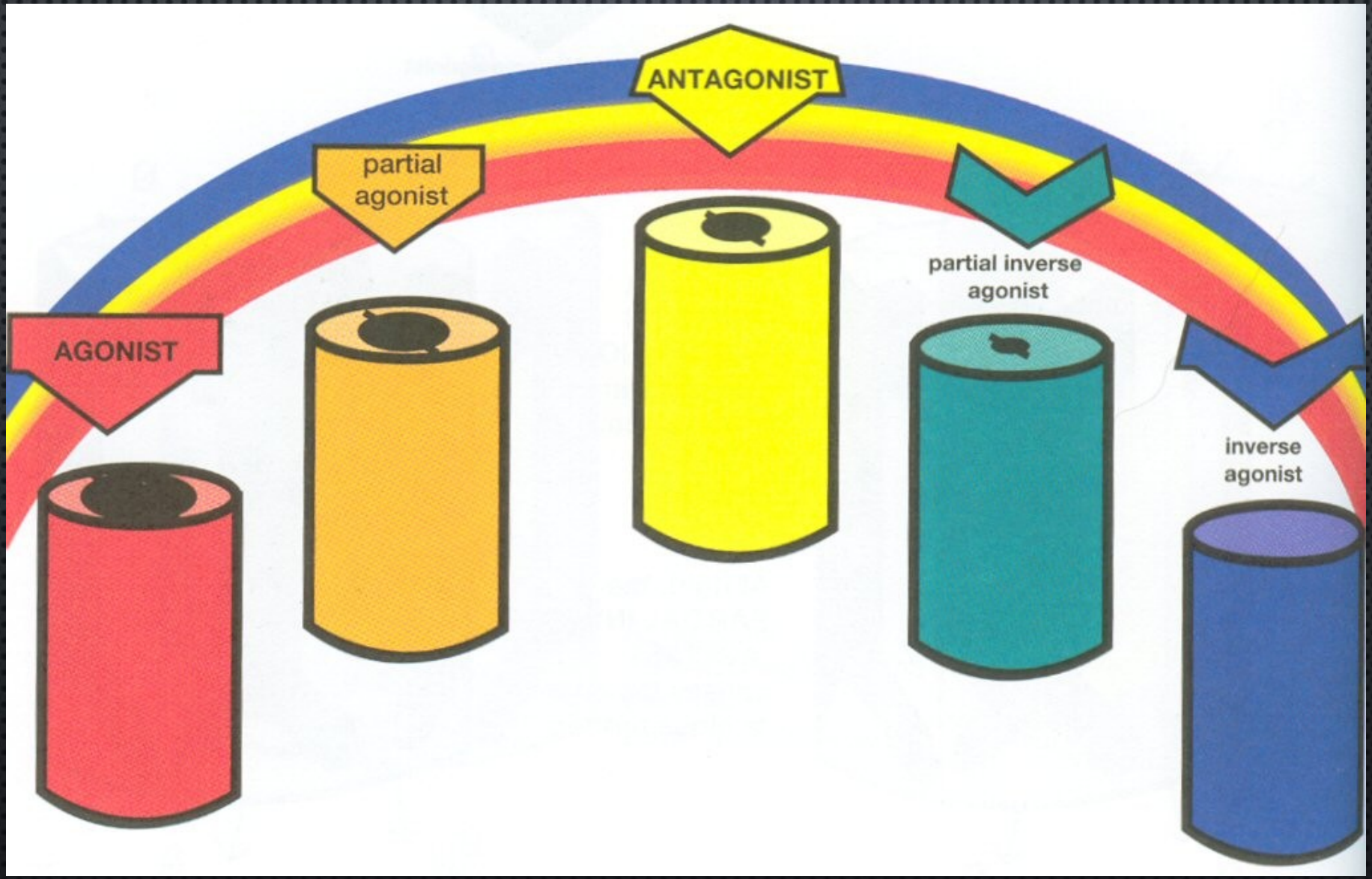
TYPES OF RECEPTOR LIGANDS

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

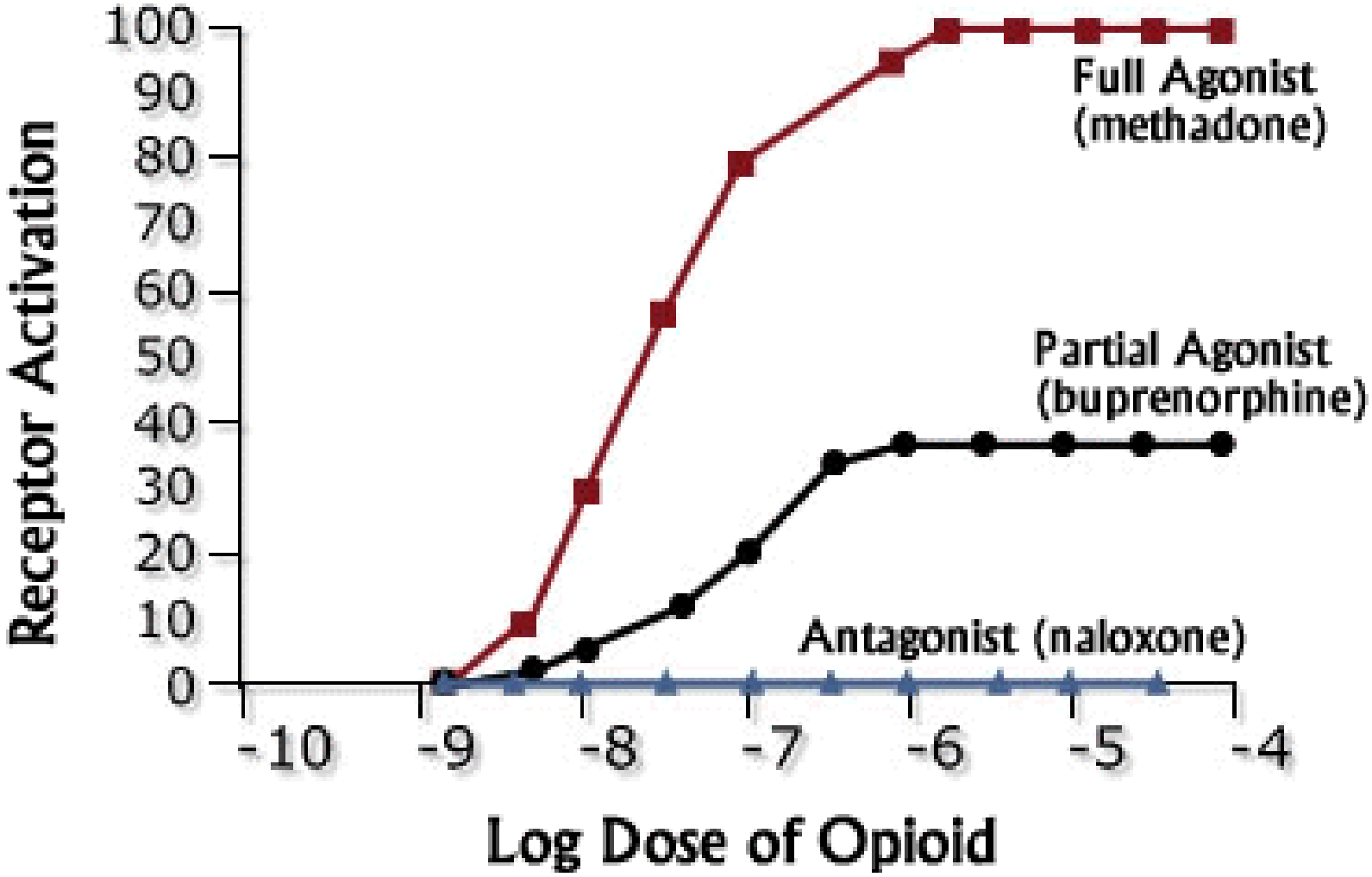
FULL AGONIST: INTRINSIC ACTIVITY ≅ 1

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

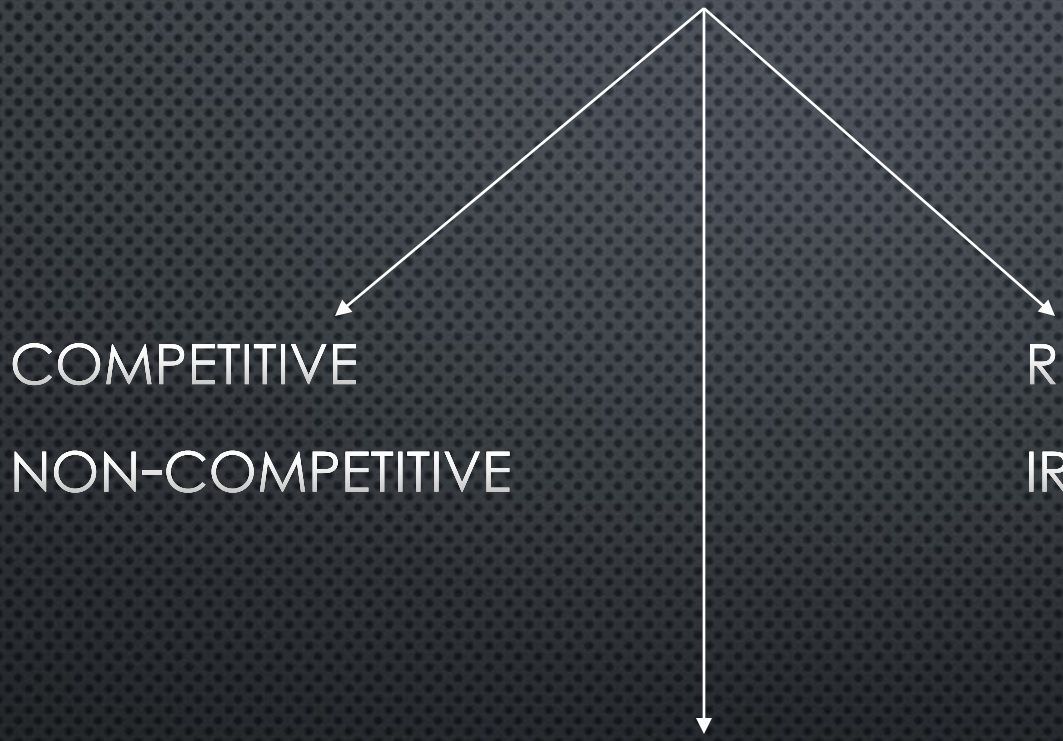
ANTAGONIST: INTRINSIC ACTIVITY ≅ 0


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]c of antagonist decreases agonist effect and inversely
- ✓ the presence of antagonist incerases the amounts of agonist needed to evoke the effect

Non-competitive

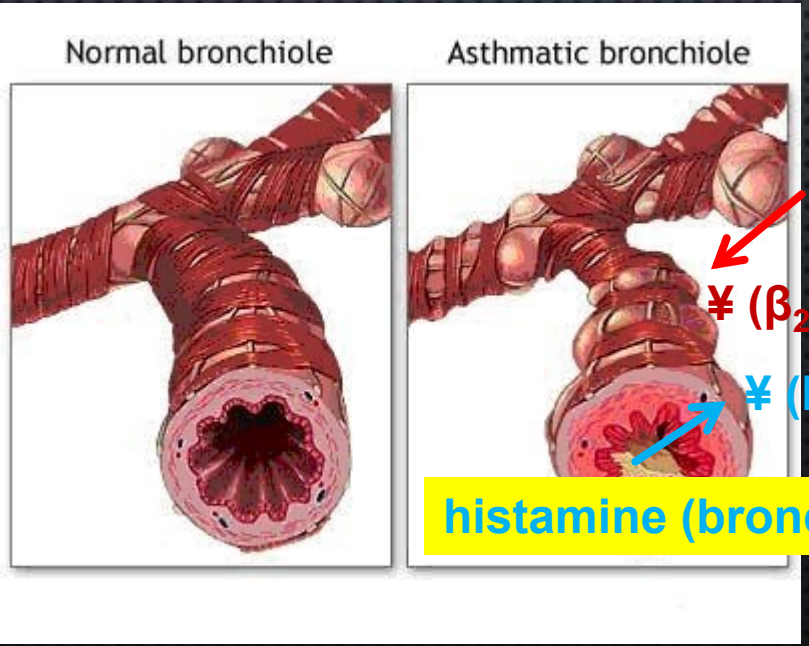
- ✓ allosteric antagonism
- ✓ irreverzible bounds
- ✓ [redacted]c of agonist does not interrupt the effect of antagonist

ANTAGONISM
Physiological antagonism

Two different ligands act on different target structures and their opposite effects occur in the same organ.

Histamine x norepinephrine (affecting of vessels).

Affecting of bronchioles.



REGULATION OF RECEPTOR SENSITIVITY AND COUNTS

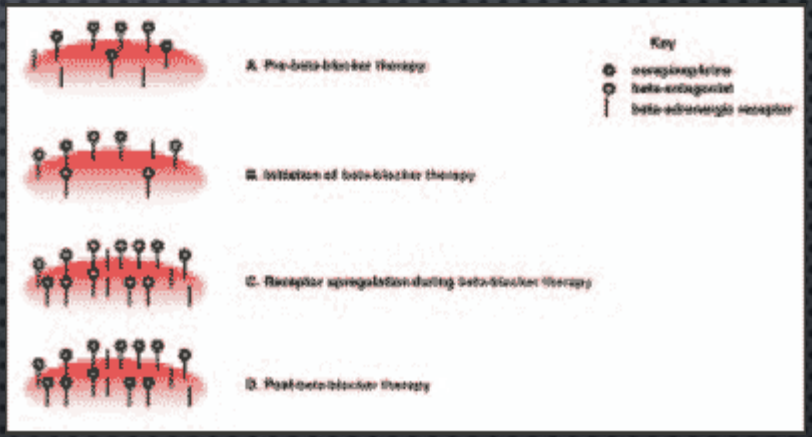
- HYPERSENSITIVITY - INCERASE OF RECEPTOR SENSITIVITY/COUNTS AFTER CHRONIC **ANTAGONIST** EXPOSURE

- **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

Up regulation of β-receptors following long-term therapy

- abrupt cessation of therapy may lead to excessive stimulation of β-receptors thereby exacerbating the symptoms

rebound phenomenon !



A. Representation of beta-receptor density on cardiac myocyte prior to initiation of beta-antagonist therapy.

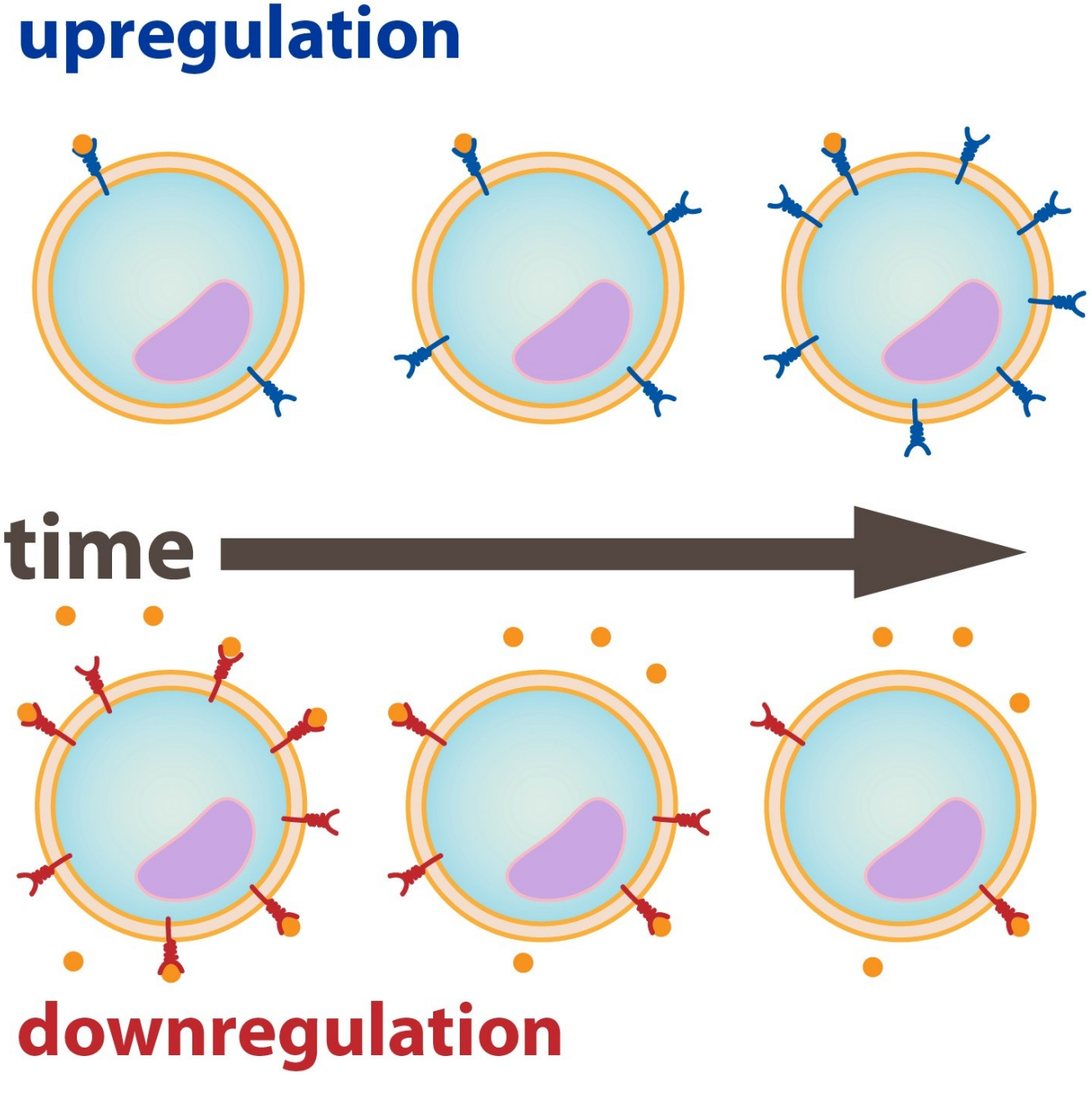
B. Reduction in beta-receptor stimulation after initiation of beta antagonist.

C. Receptor upregulation as a result of chronic beta-receptor blockade.

D. Supersensitivity of cardiac myocyte following abrupt withdrawal of beta-antagonist therapy.

REGULATION OF RECEPTOR SENSITIVITY AND COUNTS

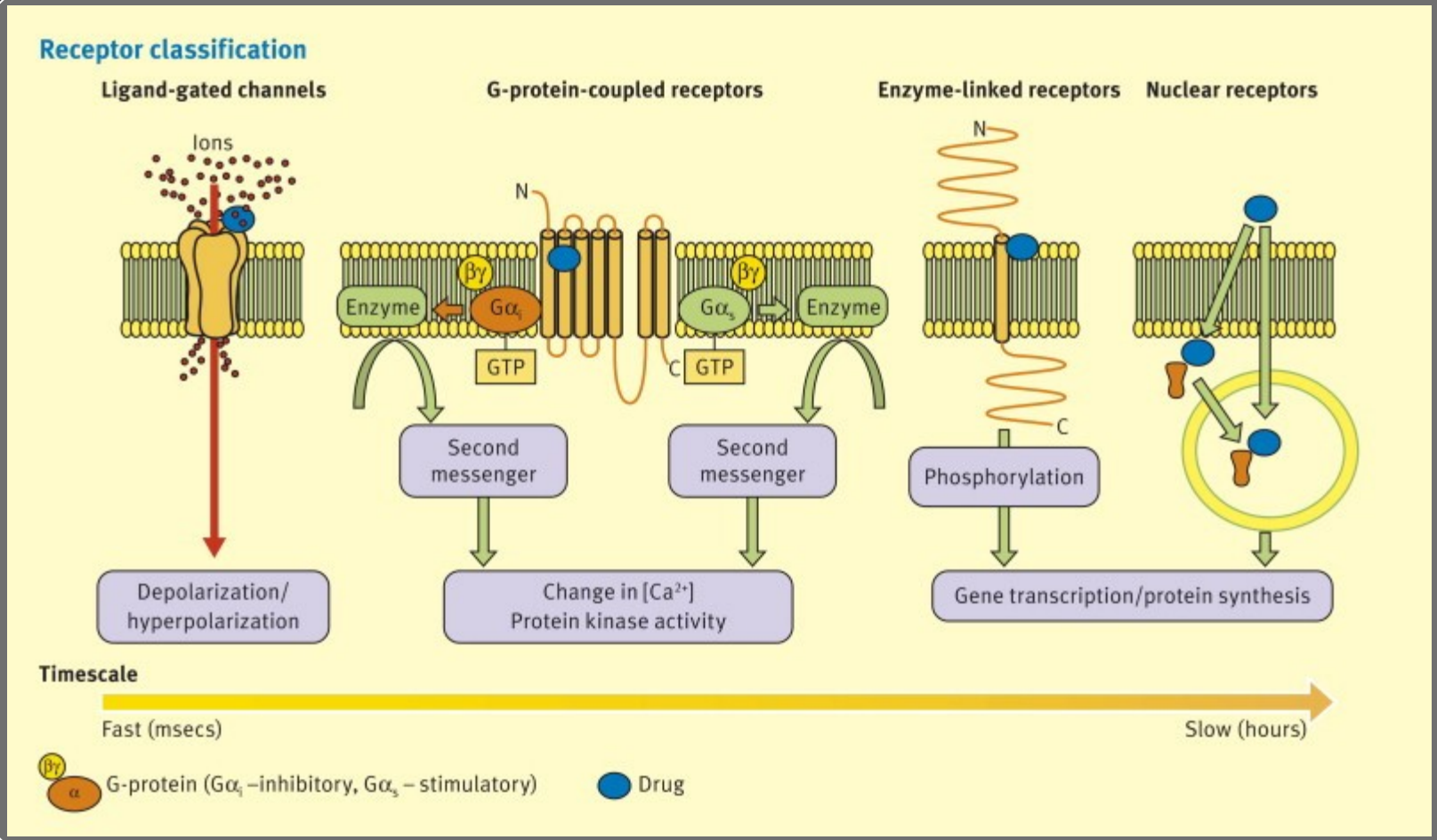
- DESENSITIZATION – REDUCED RECEPTOR SENSITIVITY/COUNTS AFTER CHRONIC **AGONIST** EXPOSURE
- **TOLERANCE** – REDUCED SENSITIVITY TO THE ACTIVE SUBSTANCE, ARISING FROM THE REPEATED ADMINISTRATION OF THE DRUG (DAYS – WEEKS) → DOWN-REGULATION
  - EFFECT REQUIRES INCREASINGLY HIGHER DOSES
  - THE ORIGINAL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


upregulation
time
downregulation

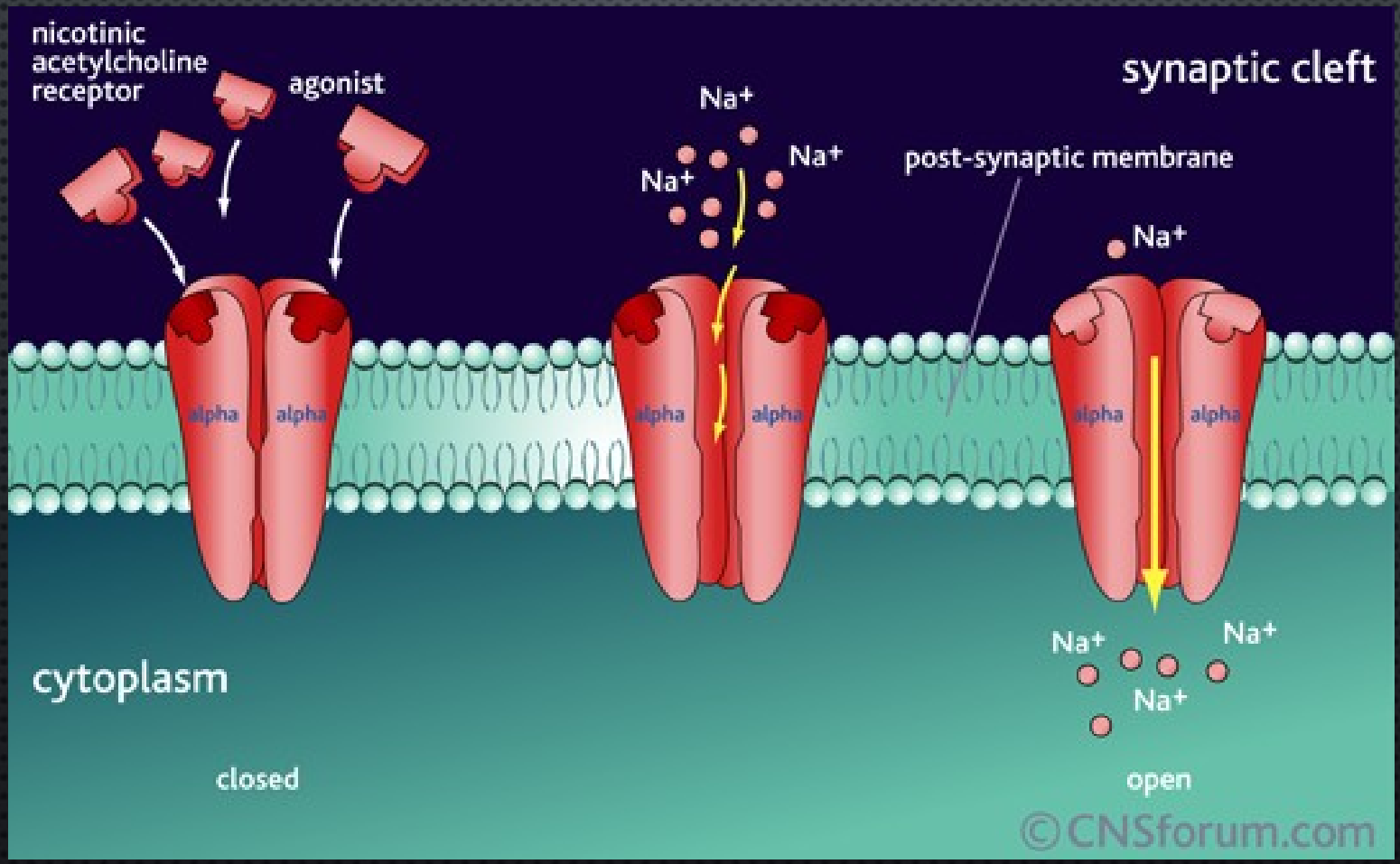
RECEPTOR DESENSITIZATION

- **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 – EPINEPHRINE ADMINISTRATION

Receptor clasification



NICOTINIC RECEPTOR

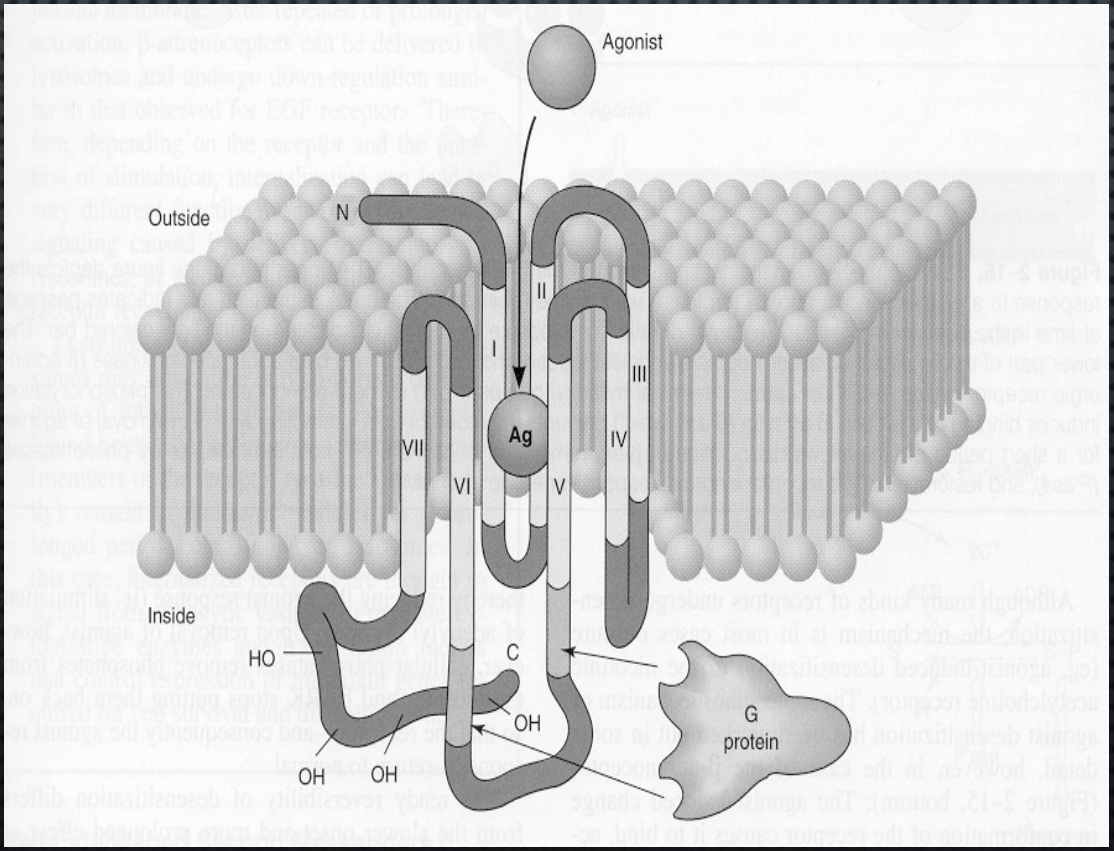


Katzung BG, 2001

METABOTROPIC RECEPTORS

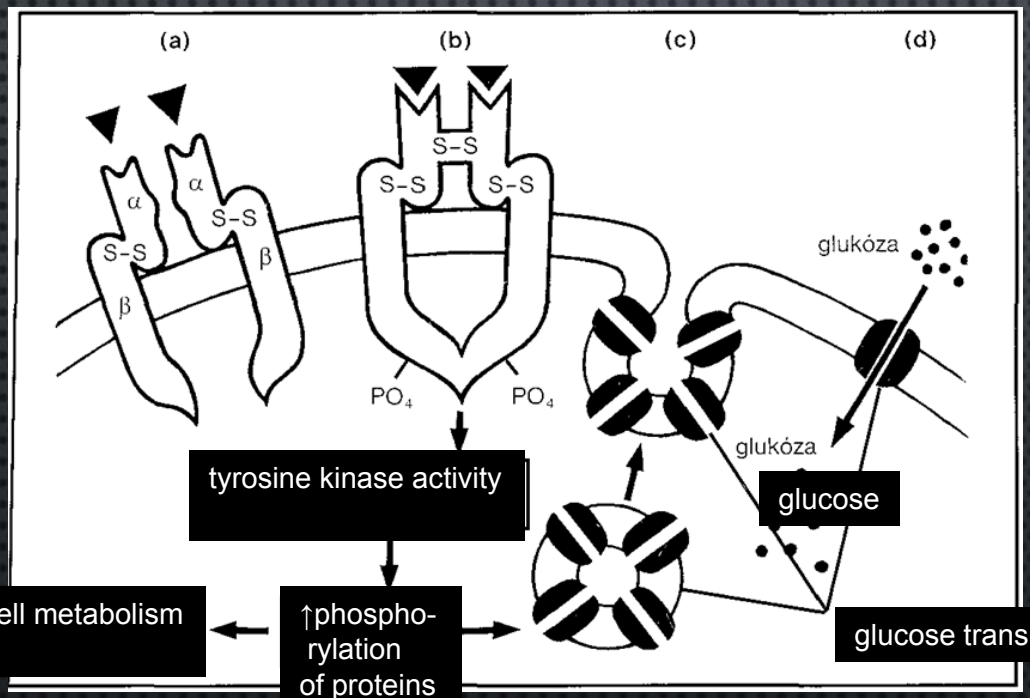
= G-PROTEIN COUPLED RECEPTORS

- MUSCARINIC, ADRENERGIC, DOPAMINERGIC, GABA-B…



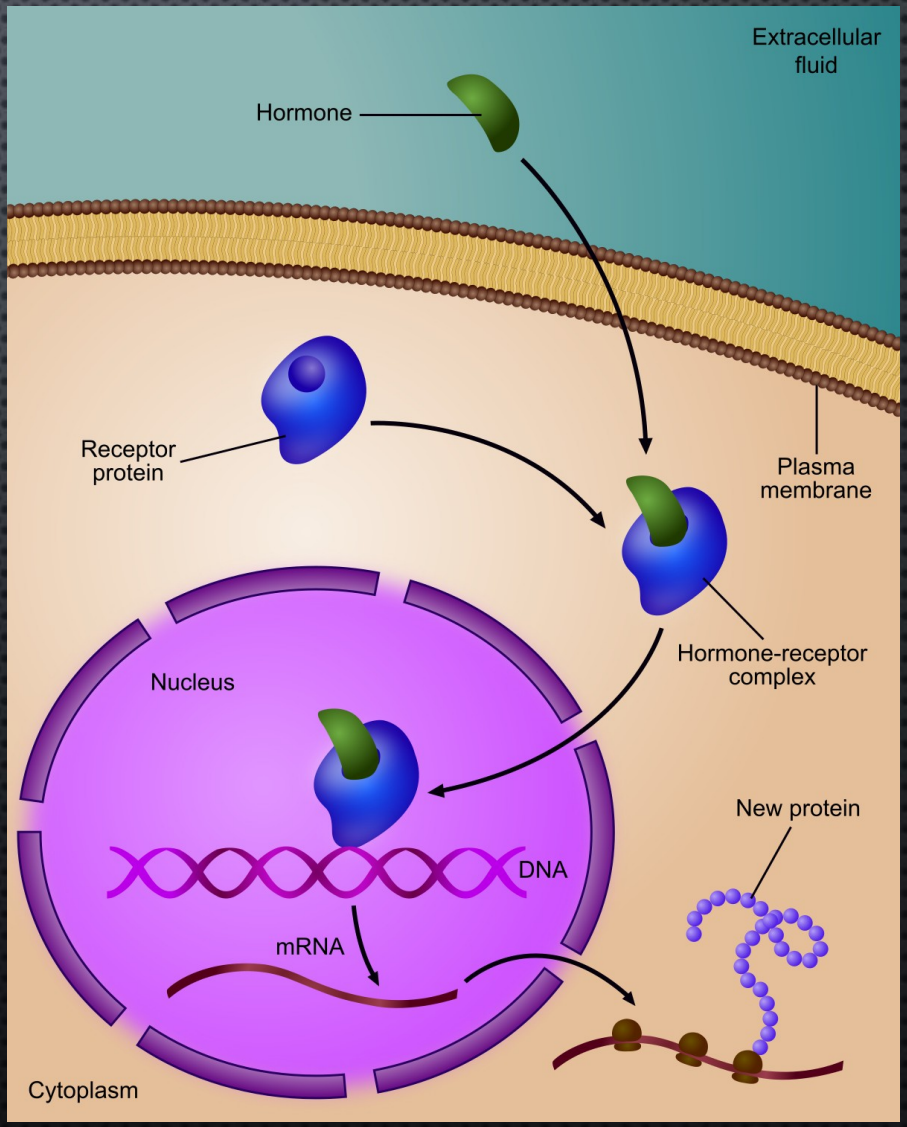
Kinase-linked receptors

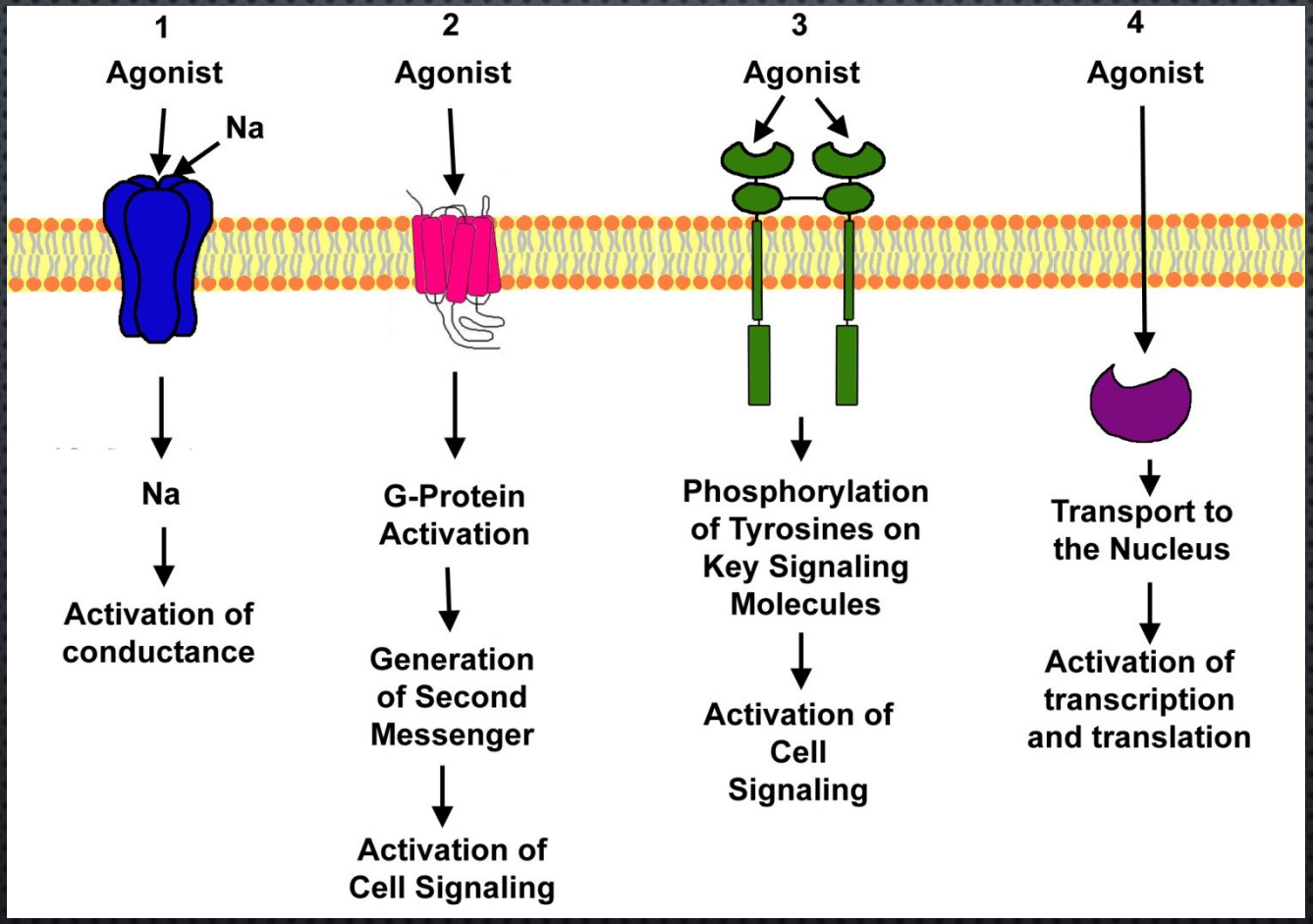
Insulin receptor



RECEPTORS REGULATING PROTEOSYNTHESIS

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



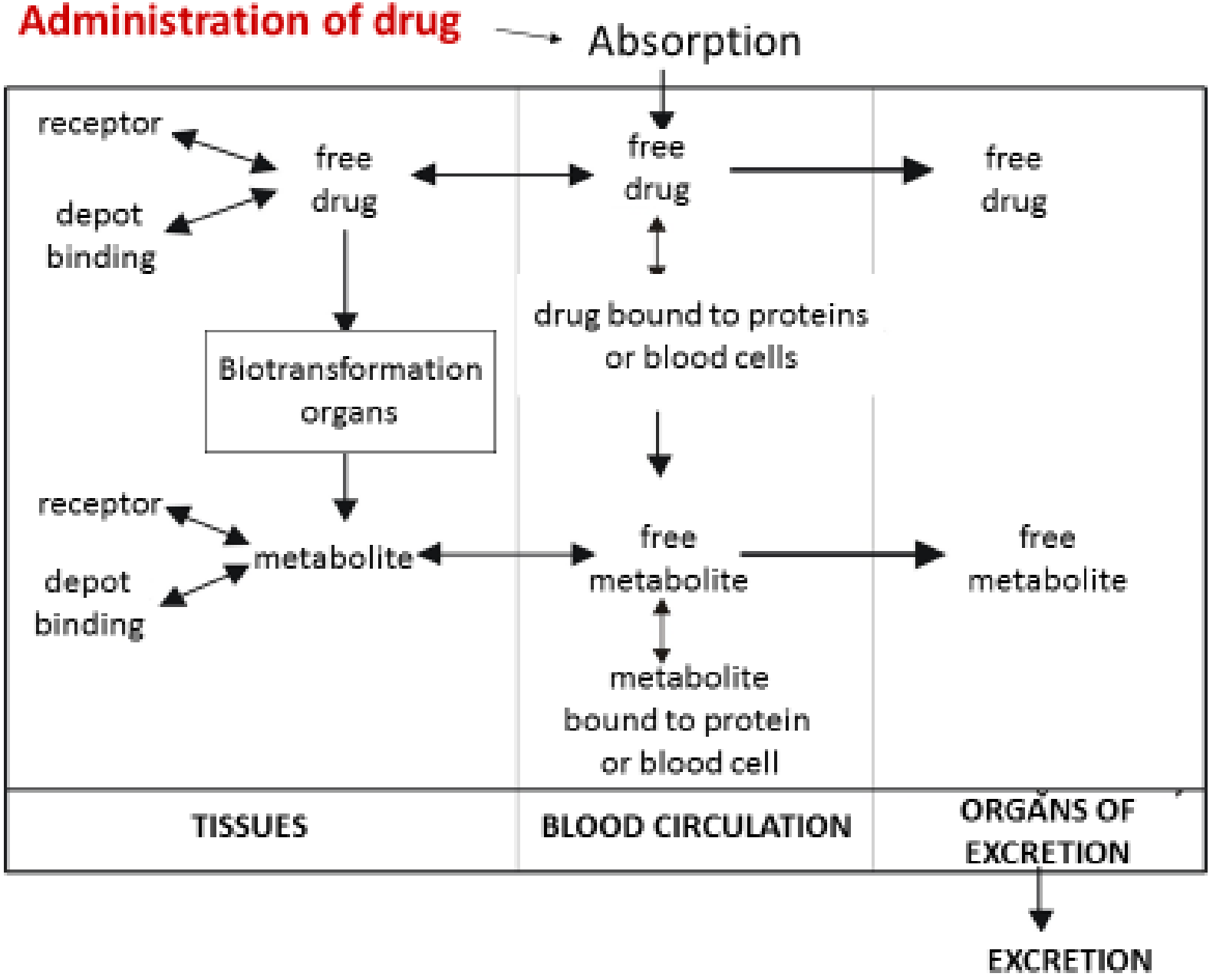

1
Agonist
Na
Na
Activation of conductance
2
Agonist
G-Protein Activation
Generation of Second Messenger
Activation of Cell Signaling
3
Agonist
Phosphorylation of Tyrosines on Key Signaling Molecules
Activation of Cell Signaling
4
Agonist
Transport to the Nucleus
Activation of transcription and translation

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

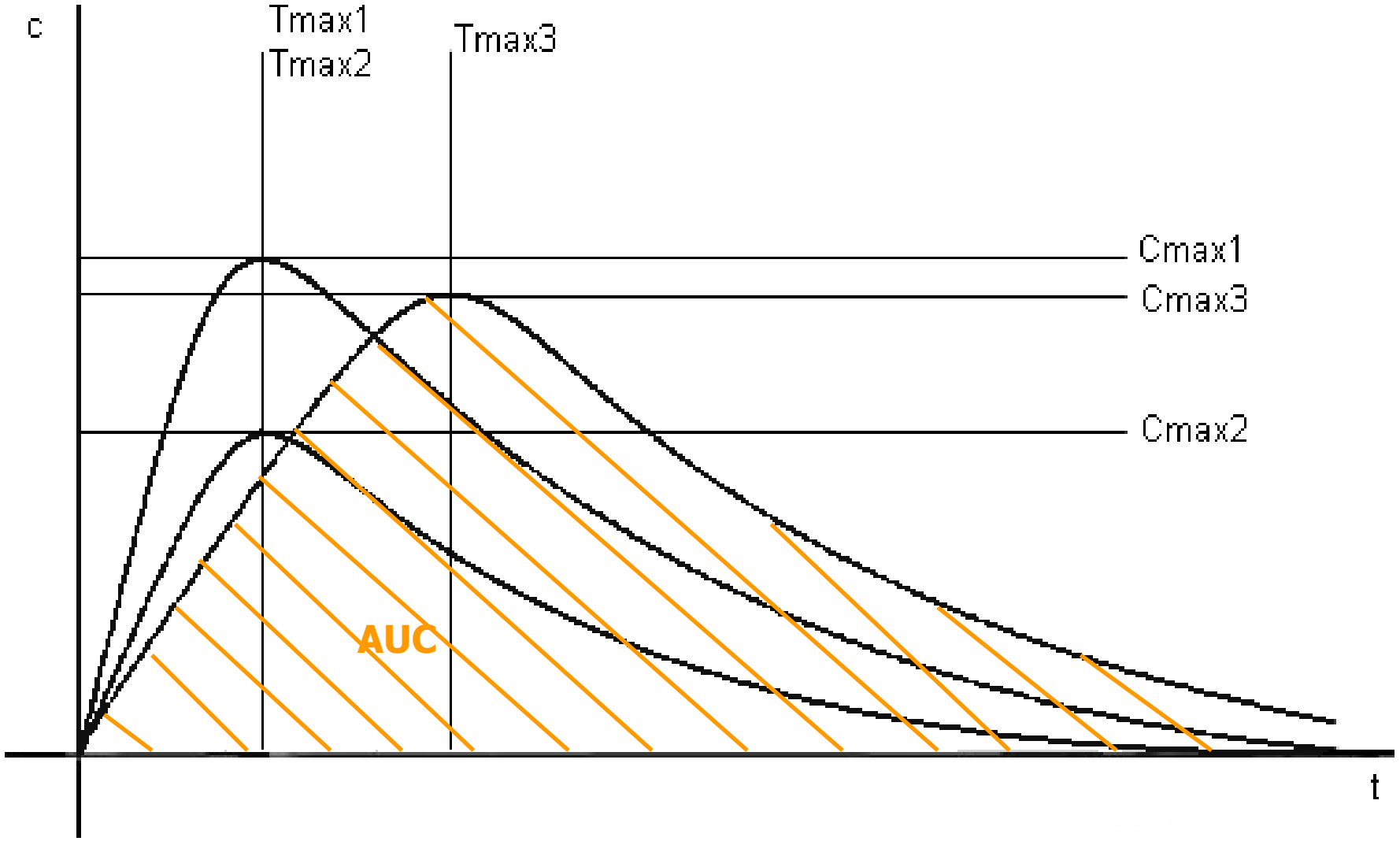
SPEED AND EXTENT OF ABSORPTION

- **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

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

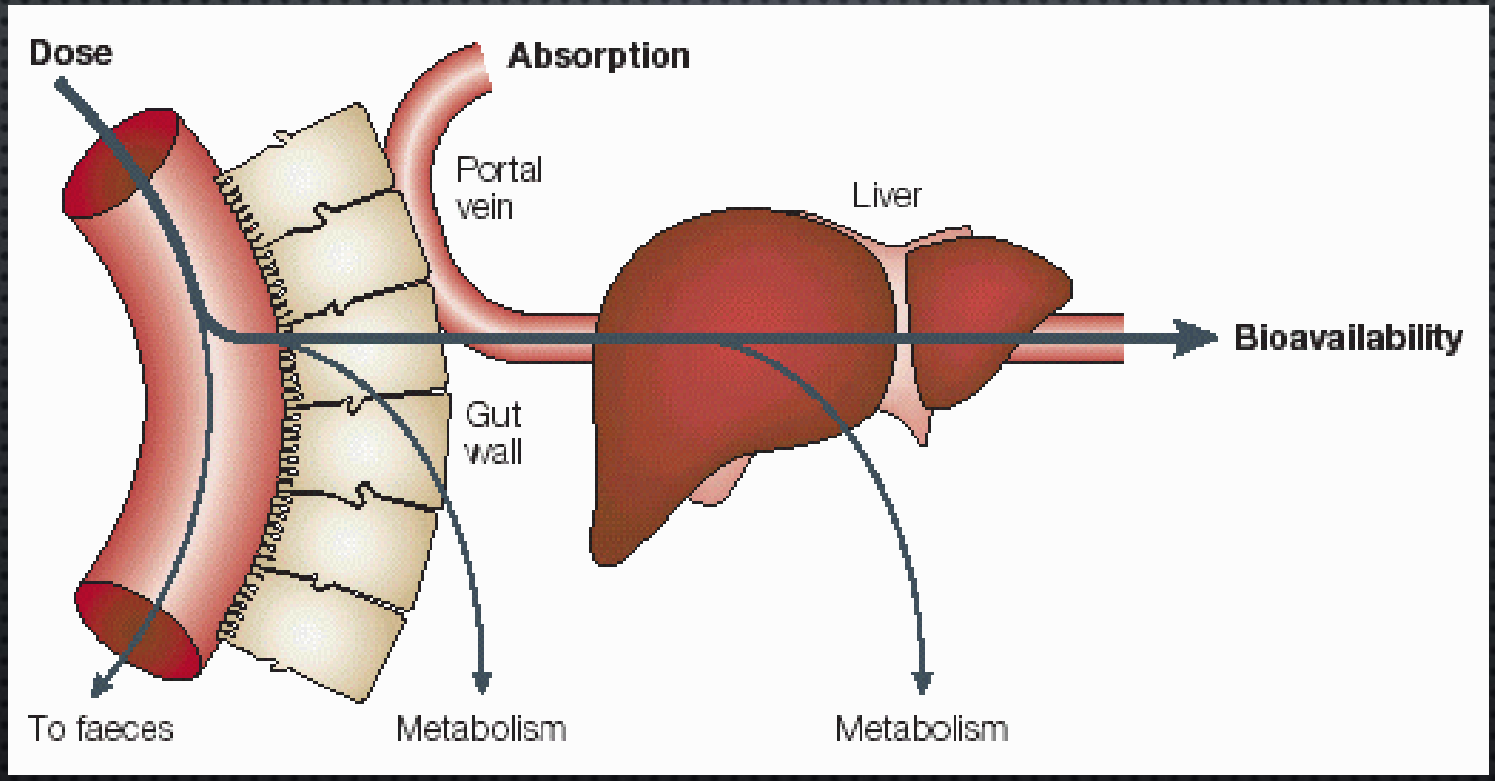
http://icp.org.nz/icp_t6.html?htmlCond=1

Oral administration



Presystemic elimination

First pass effect



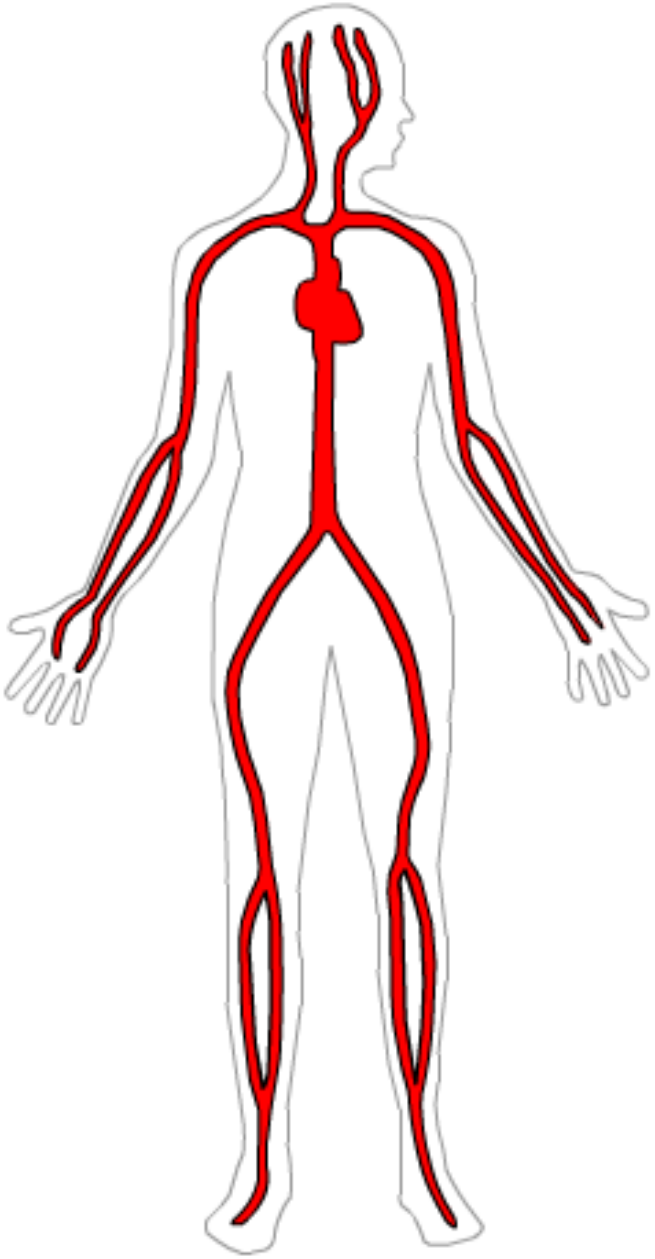
http://icp.org.nz/icp_t6.html

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

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

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



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

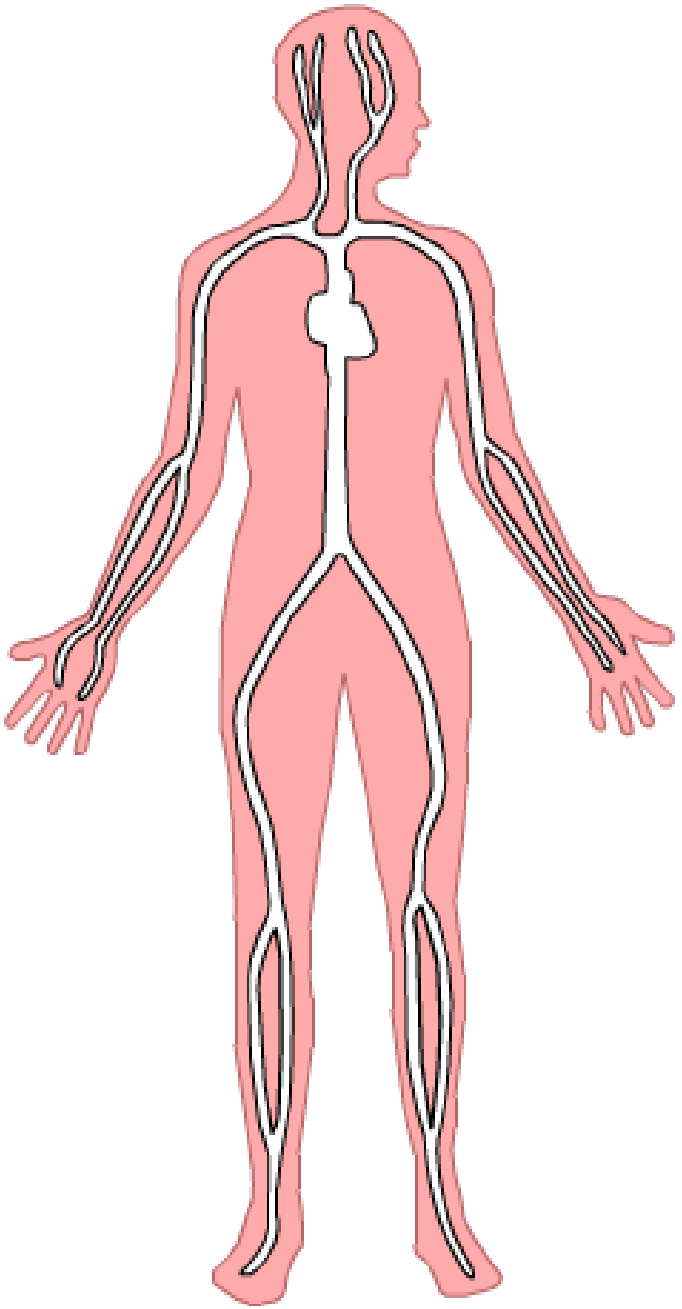
Drug highly concentrated
in tissues
(usually adipose)

10,000 L

Amount in body = Vd x plasma concentration

$$Ab = Vd \times Cp$$

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



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

$$Ab = Vd \times Cp$$

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

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

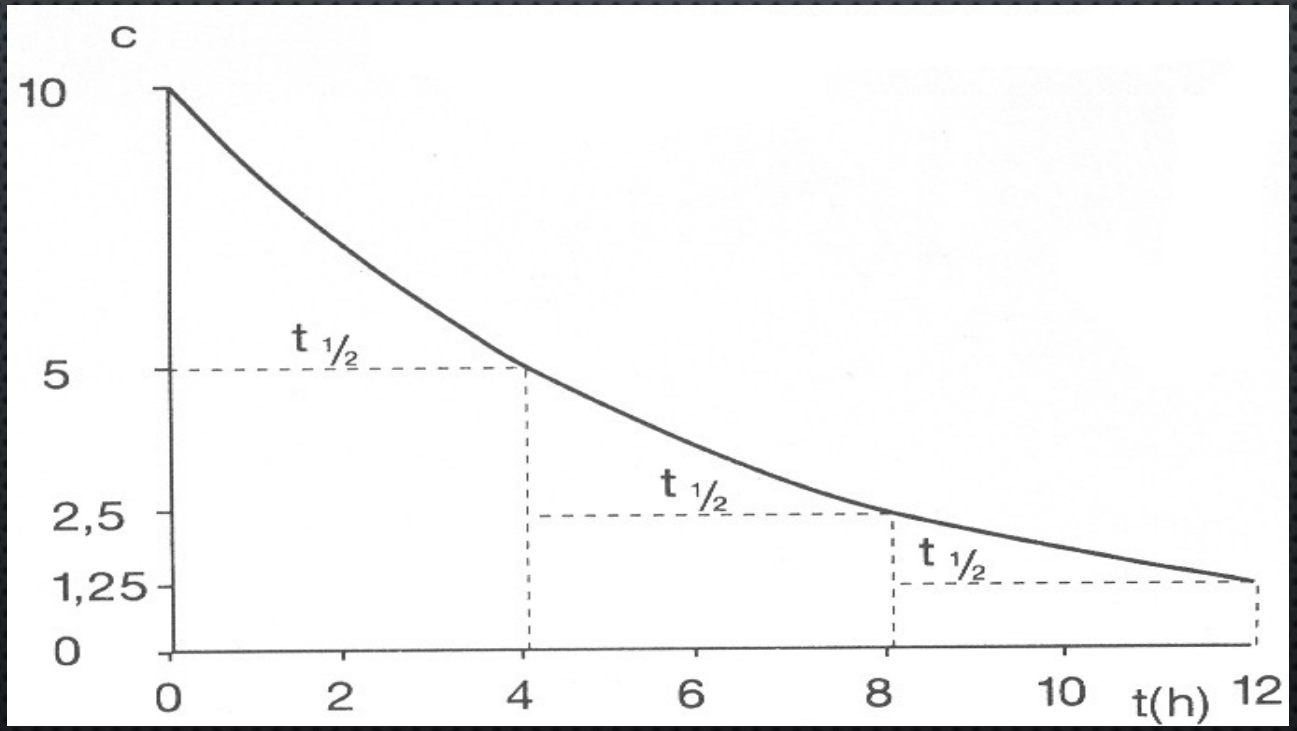
- TOTAL = RENAL + HEPATAL + LUNG…

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



http://icp.org.nz/icp_t4.html