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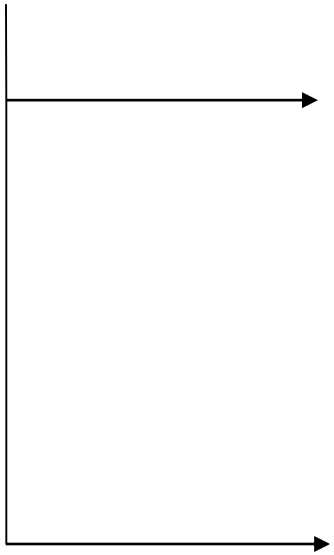
PHARMACODYNAMICS

Pharmacology Lecture

PHARMACOLOGY



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“

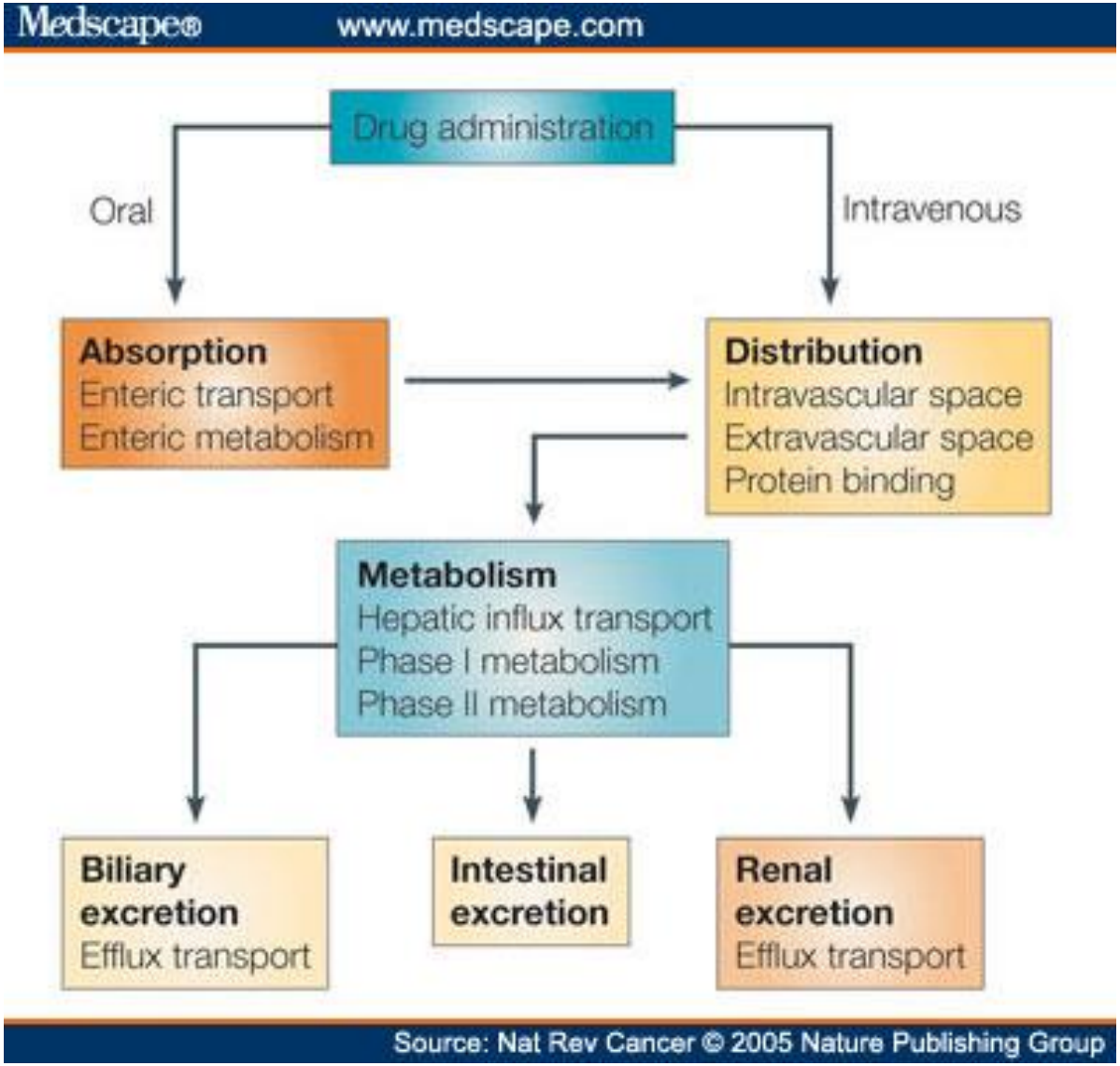
…“ADME“

Pharmacodynamics (PD)

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

„How does it work“

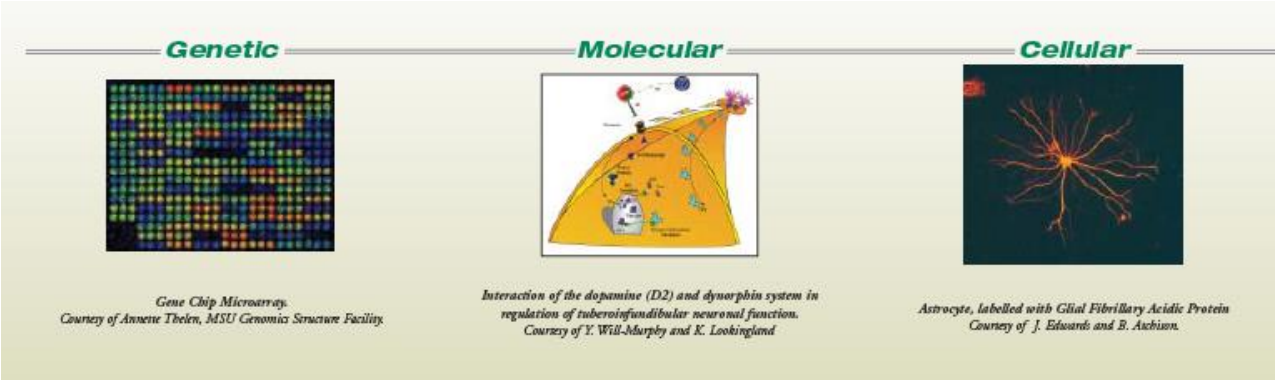
Pharmacokinetics



Pharmacodynamics
(how drugs work on the body)

- The action of a drug on the body, including receptor interactions, dose-response phenomena, and mechanisms of therapeutic and toxic action

- Main targets – cellular, molecular, genetic level…
  - Therapeutic effects
  - Adverse effects



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History of the Pharmacology

Founders of specific drug effects - physiologist **Newport Langley (1852–1925)** and immunologist **Paul Ehrlich (1854 – 1915).**

- 1905 - John Newport Langley – pharmacology of vegetative nervous system and hormonal regulations (nicotin as receptive substance)
- 1906 – Paul Ehrlich – salvarsan - selective binding to the „chemoreceptros“

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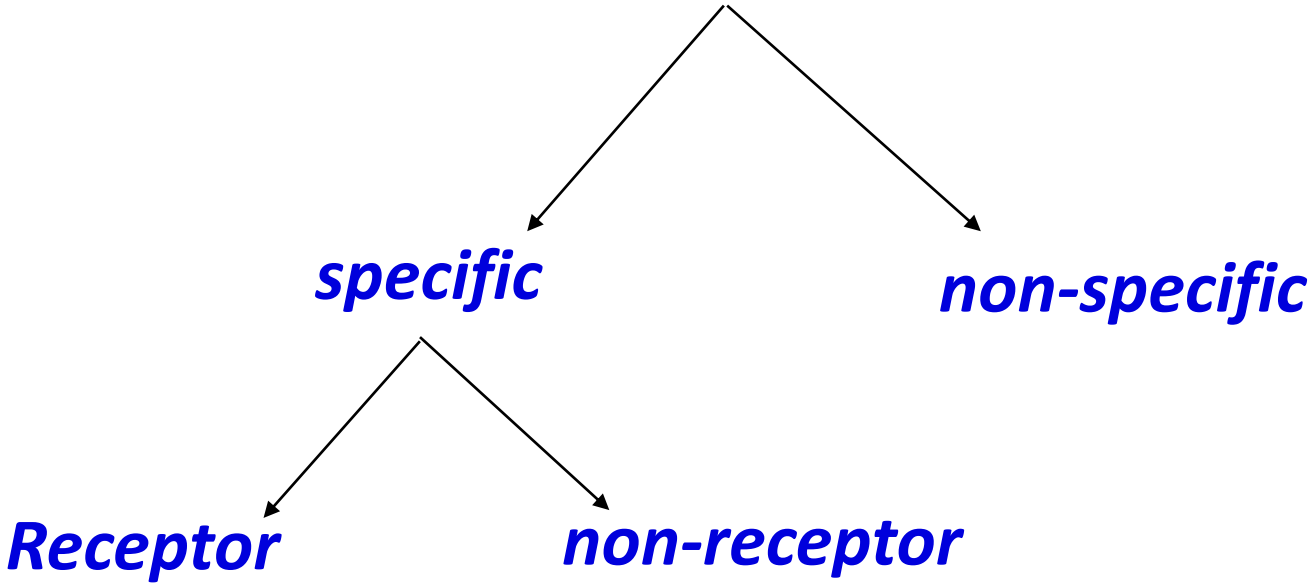
Mechanism of drug actions



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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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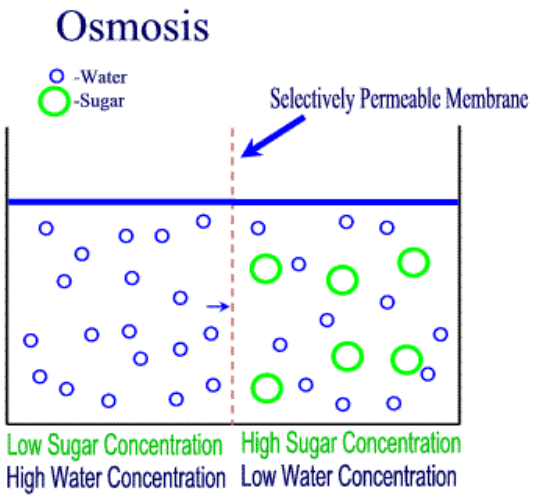
a. based on osmotic properties -

- 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
- dexrazoxane - a cyclic analog of EDTA administered with anthracyclines to prevent cardiotoxicity → Fe2 + ions)

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II. Specific drug effects

effect depends on the specific molecules configuration

- **most drugs act (bind) on receptors**
  - in or on cells
  - form tight bonds with the ligand
  - exacting requirements (size, shape, stereospecificity)

- **….on ion channels or carriers**

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Specific drug effects

- **many drugs inhibit enzymes**
  - A very common mode of action of many drugs
    - **in the patient (ACE inhibitors)**
    - **in microbes (sulfas, penicillins)**
    - **in cancer cells (5-FU, 6-MP)**
- **some drugs bind to:**
    - **proteins (in patient, or microbes)**
    - **DNA (cyclophosphamide)**
    - **microtubules (vincristine)**

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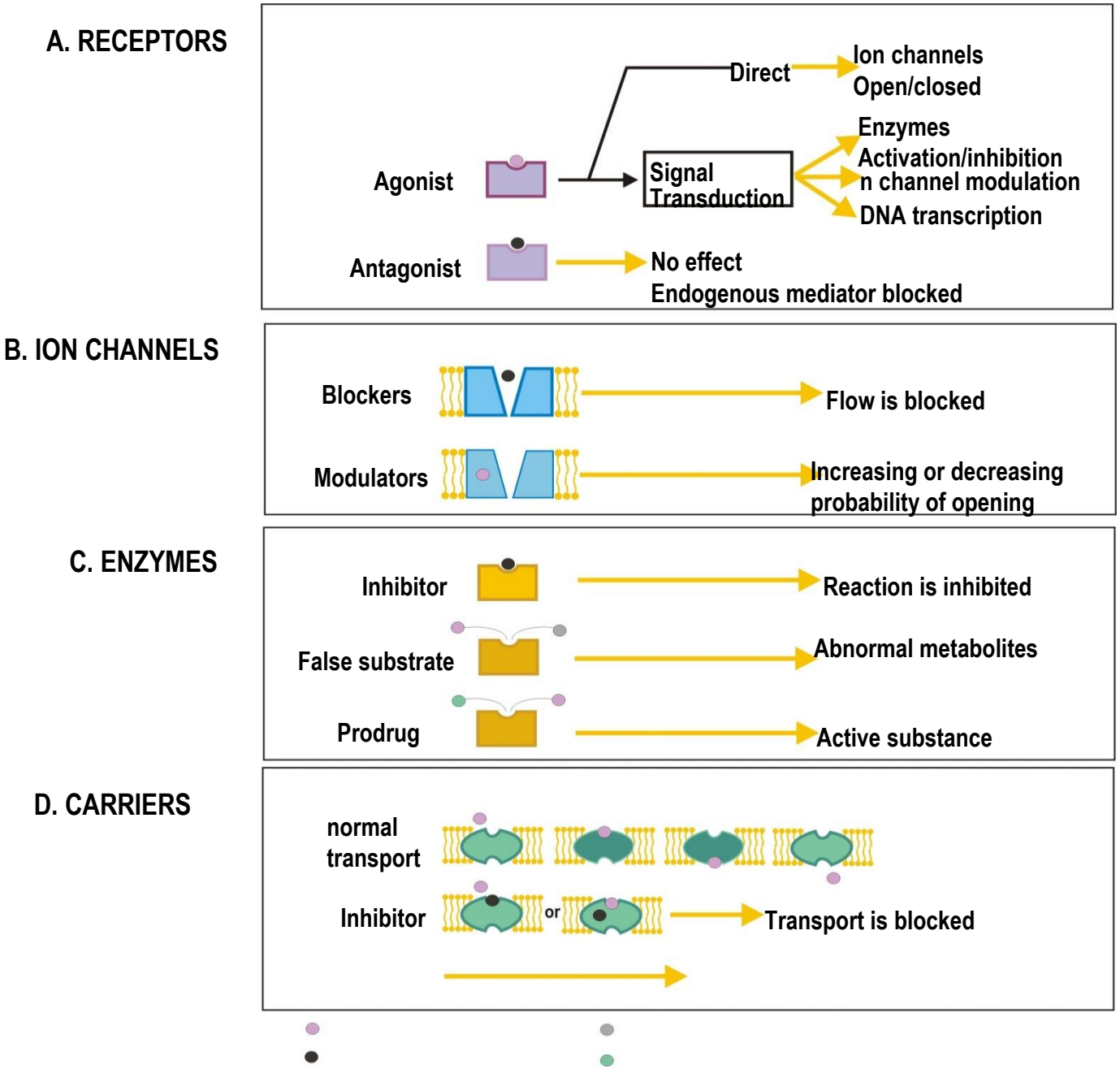

Rang and Dale Pharmacology, 2017

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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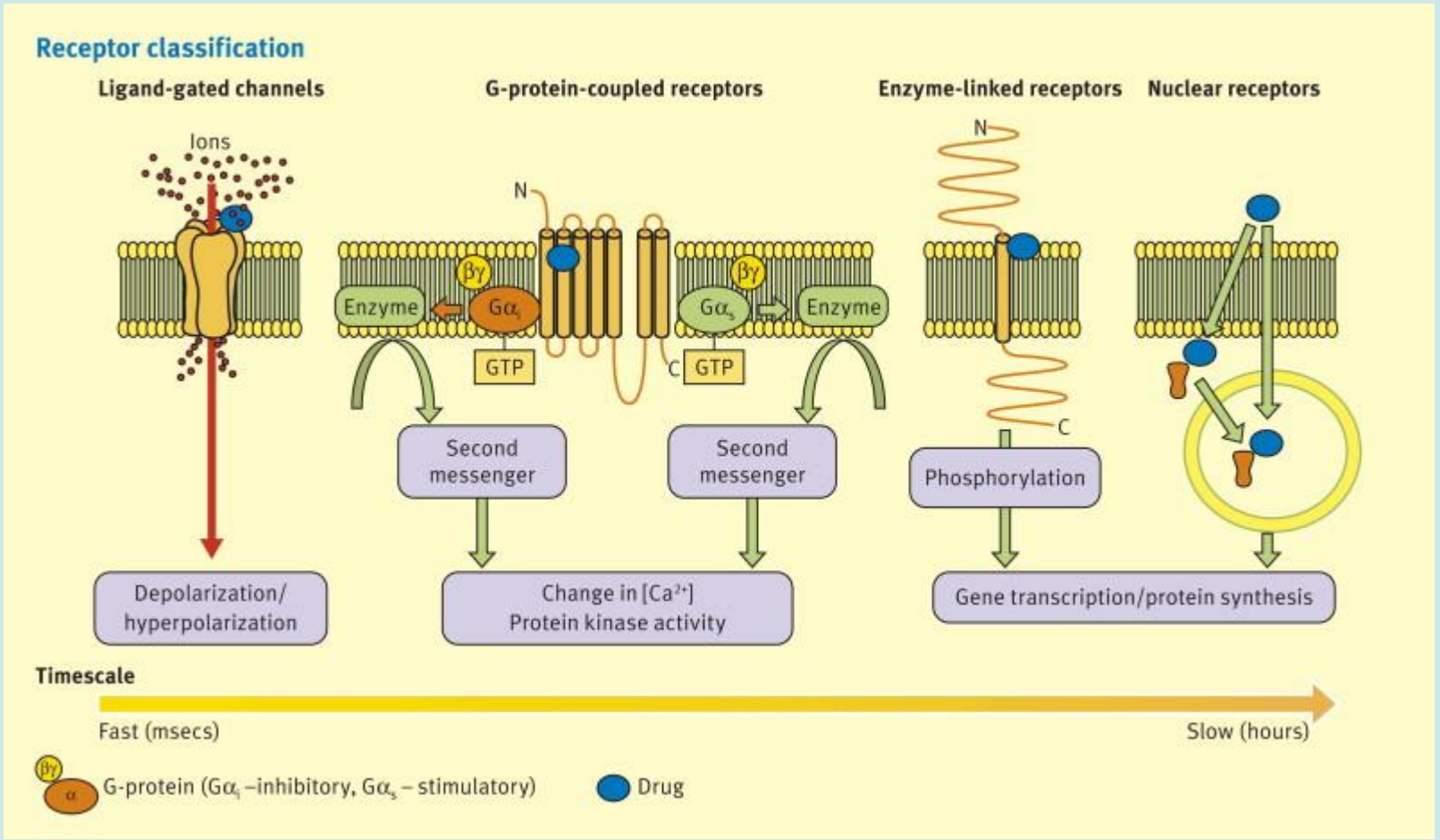
Receptor classification

Localization	Transduction	Ligands
✓ membrane	✓ metabotropic	✓ Achol
✓ cytoplasm	✓ ion. channels	✓ amines
✓ organels	✓ kinase	✓ AMA
✓ auto/heterore ceptors	✓ DNA regulating	✓ peptides

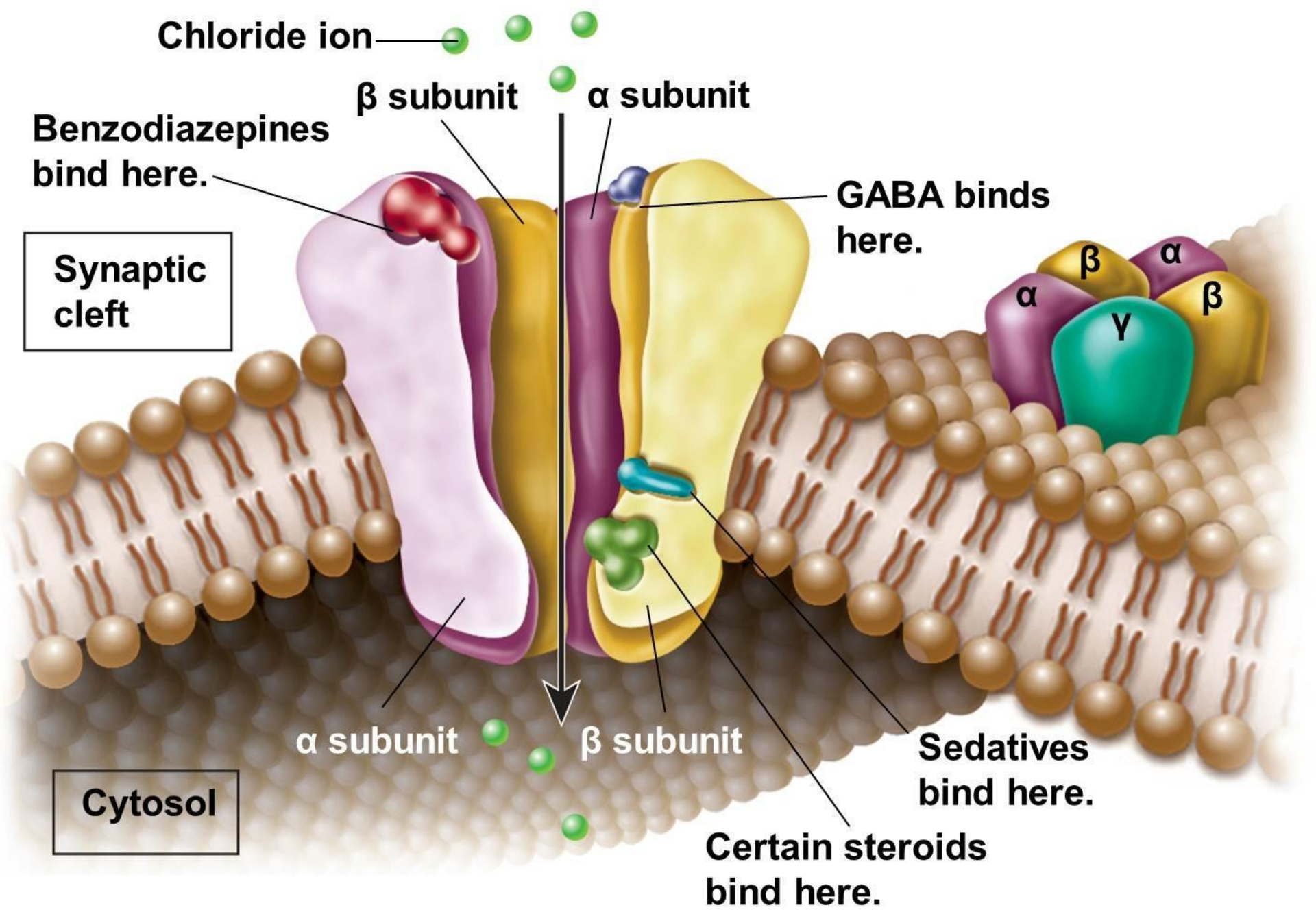
Receptor classification



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


Chloride ion
β subunit
α subunit
Benzodiazepines bind here.
GABA binds here.
Synaptic cleft
α
β
α
β
γ
α subunit
β subunit
Sedatives bind here.
Cytosol
Certain steroids bind here.

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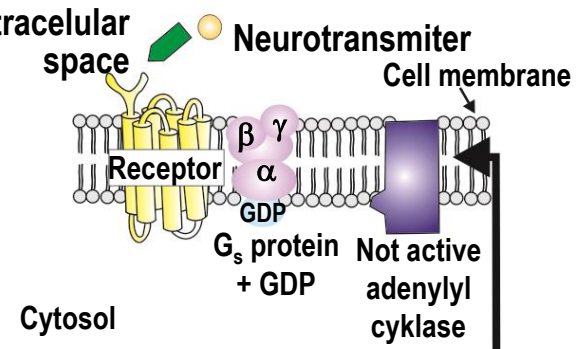
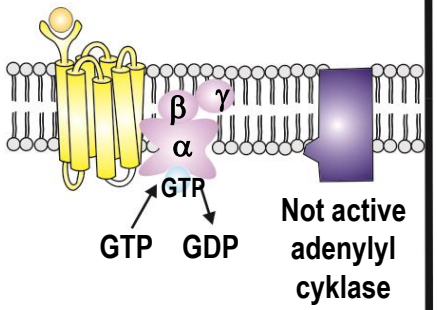
Rang and Dale Pharmacology, 2012

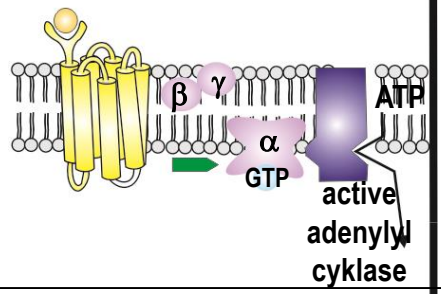
1 – innactive state - no interaction with G_s protein



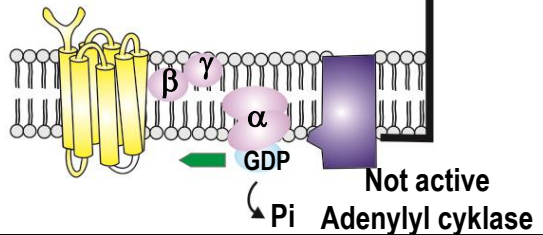
2 – active receptor – structural change + interaction with G_s protein. G_s protein releasing GDP and bind GTP.



3 – α subunit G_s protein is released – activating of adenylylcyklase



4 while neurotransmiter is not present, receptor returning to steady state. GTP on α subunit is hydrolysed to GDP and adenylylcyklase is inactivated



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Rang and Dale Pharmacology, 2012

Receptor Tyrosin Kinases (RTK)

- RTKs mediate signaling by insulin and a variety of growth factors such as EGF, VEGF, PDGF..
- Importance in the regulation of oncogenes and cell growth
- Exists on the cell surface as monomers with the single transmembrane domain
- When activated, the receptors dimerize and transfer phosphate to hydroxyl groups on tyrosines of target proteins
- Time to response : minutes to hours

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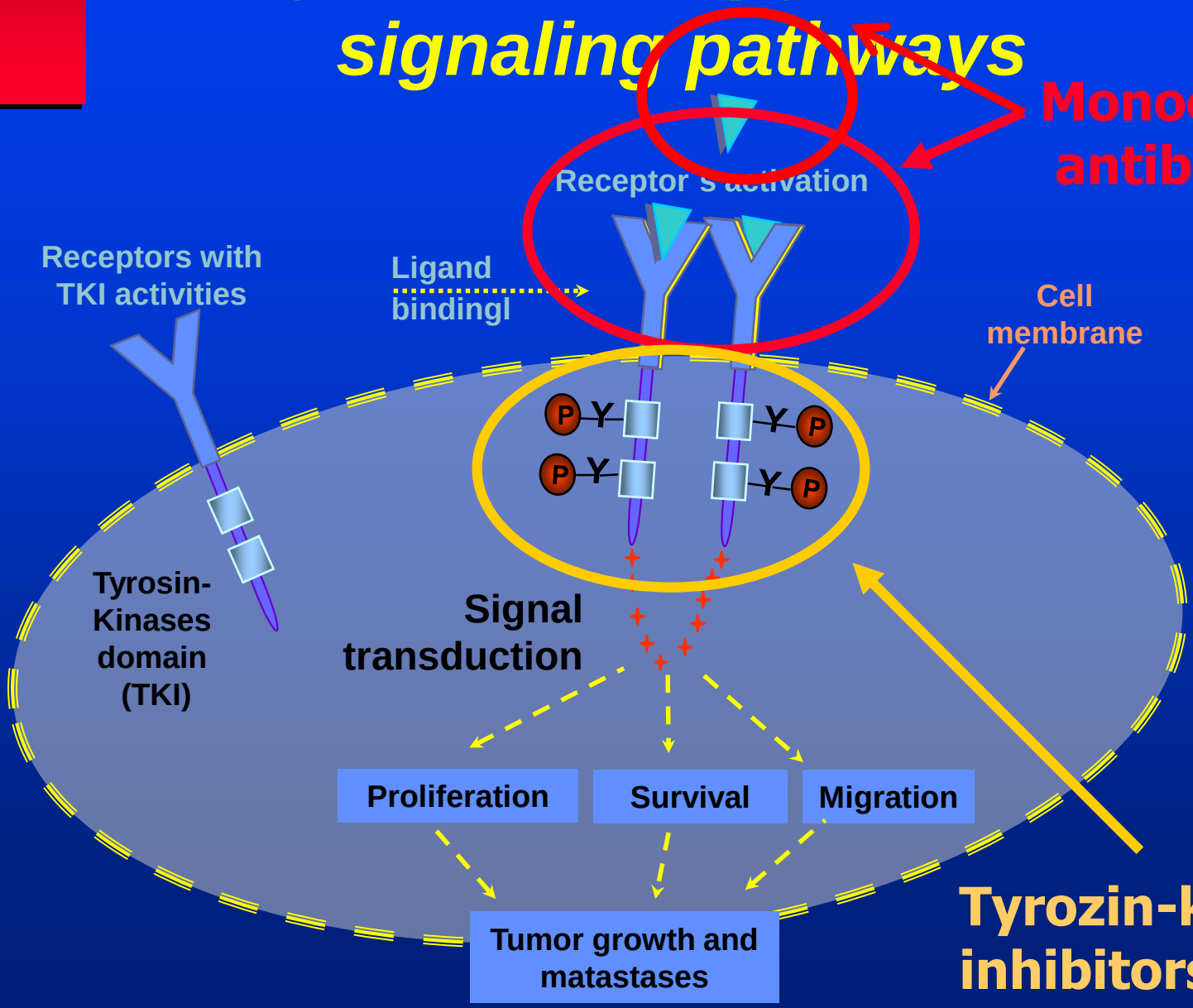
Targeted therapy – receptor signaling pathways



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Rang and Dale Pharmacology, 2012

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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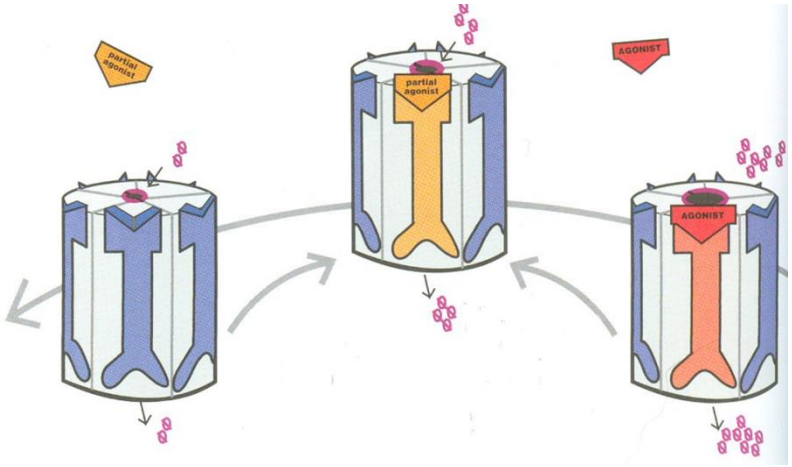
Ligand classification (intrinsic activity) AGONISTS

Full agonist

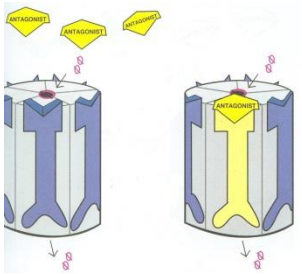
- IA = 1



Partial agonist

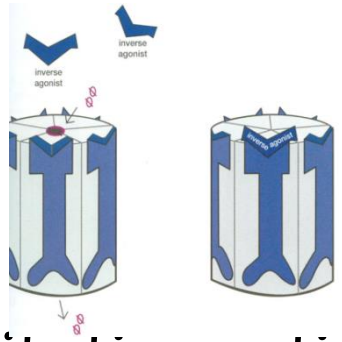
- dualist
- IA in a range from 0‹ to ›1

Ligand classification



Antagonists

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



Inverse agonist

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

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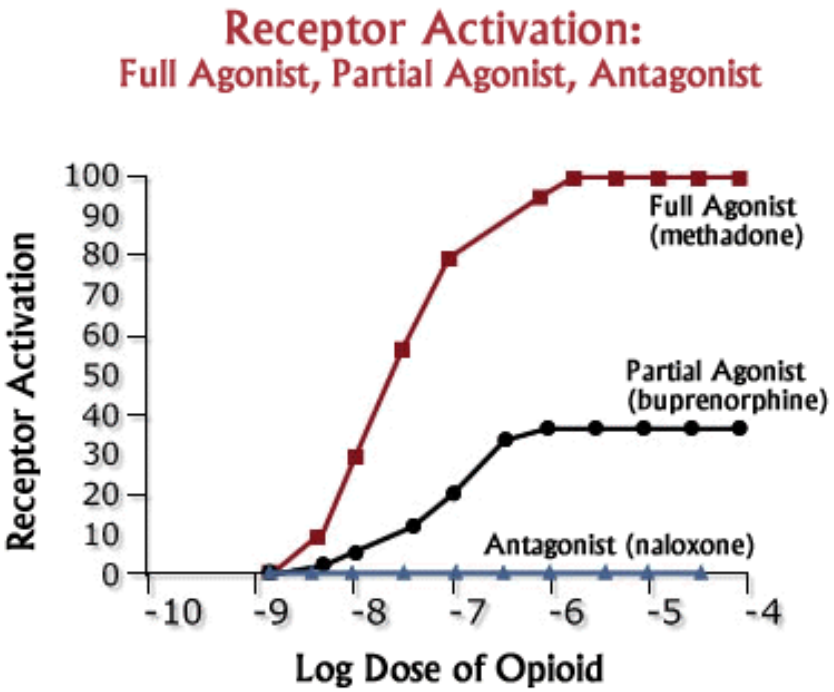
Receptor-effector system

Relation between dose and effect



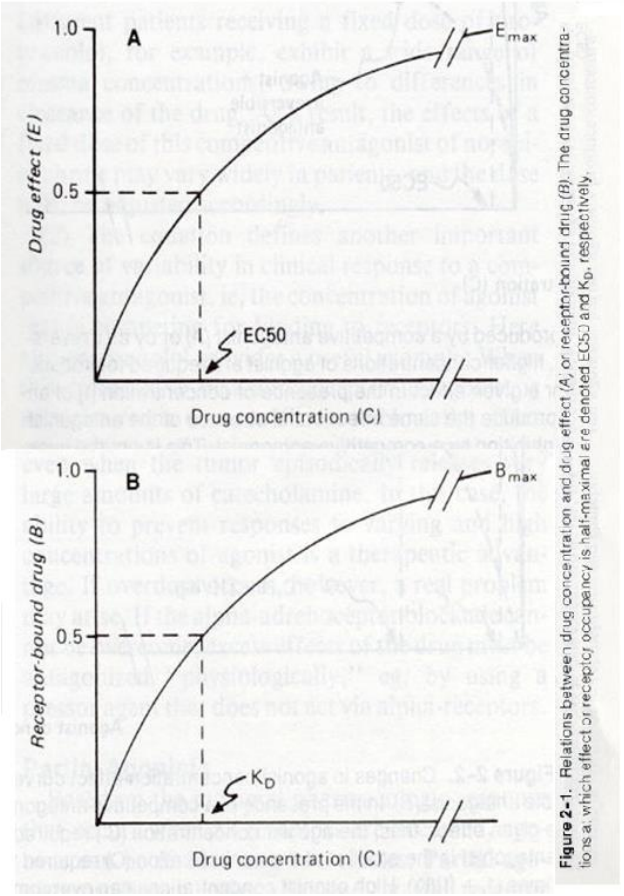
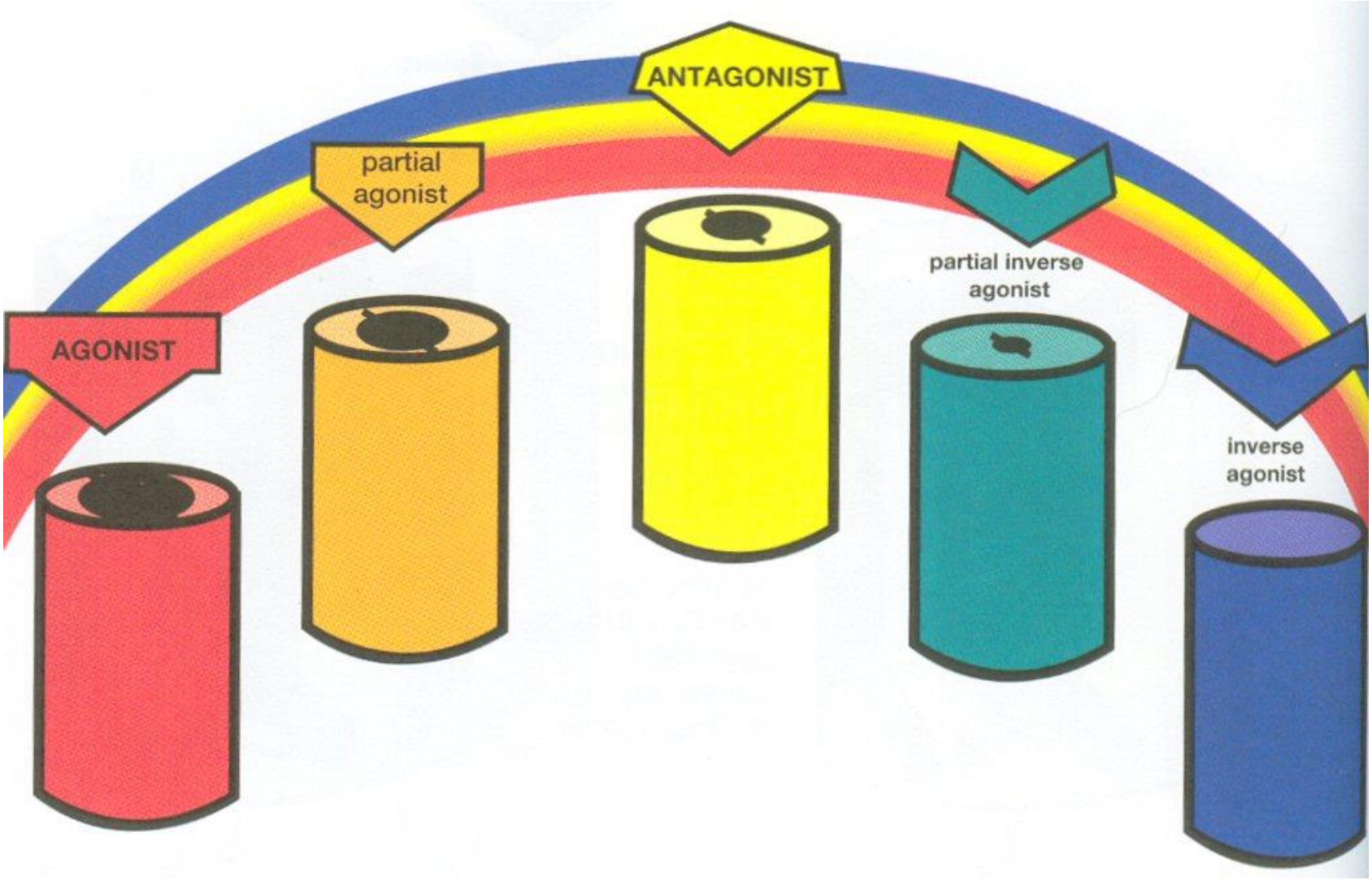
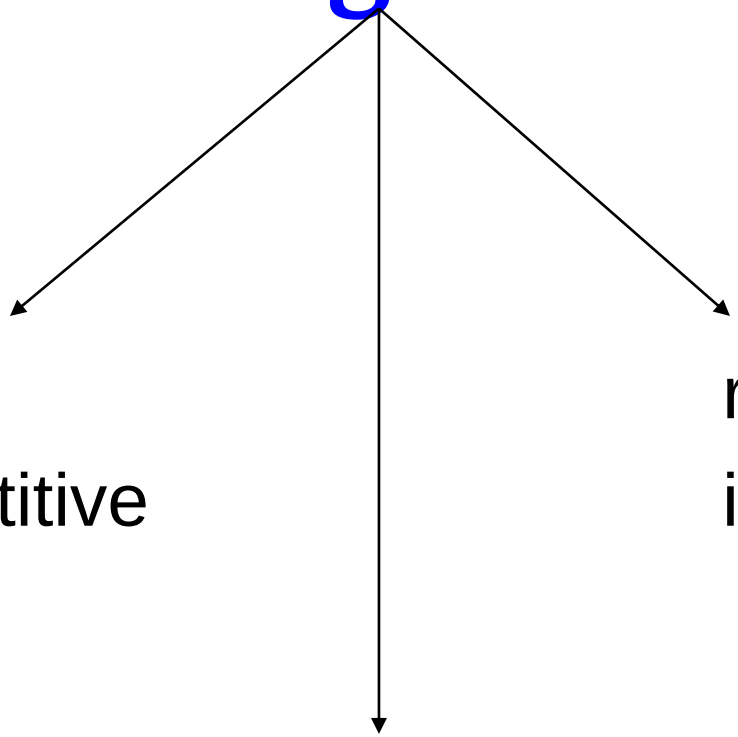


Figure 2-1. Relations between drug concentration and drug effect (A), or receptor-bound drug (B). The drug concentrations at which effect or receptor occupancy is half-maximal are denoted EC50 and K_D, respectively.

Spectrum of ligands



Antagonism



competitive

non-competitive

reverzible

irreverzible

at the receptor level

at the function level

Antagonism

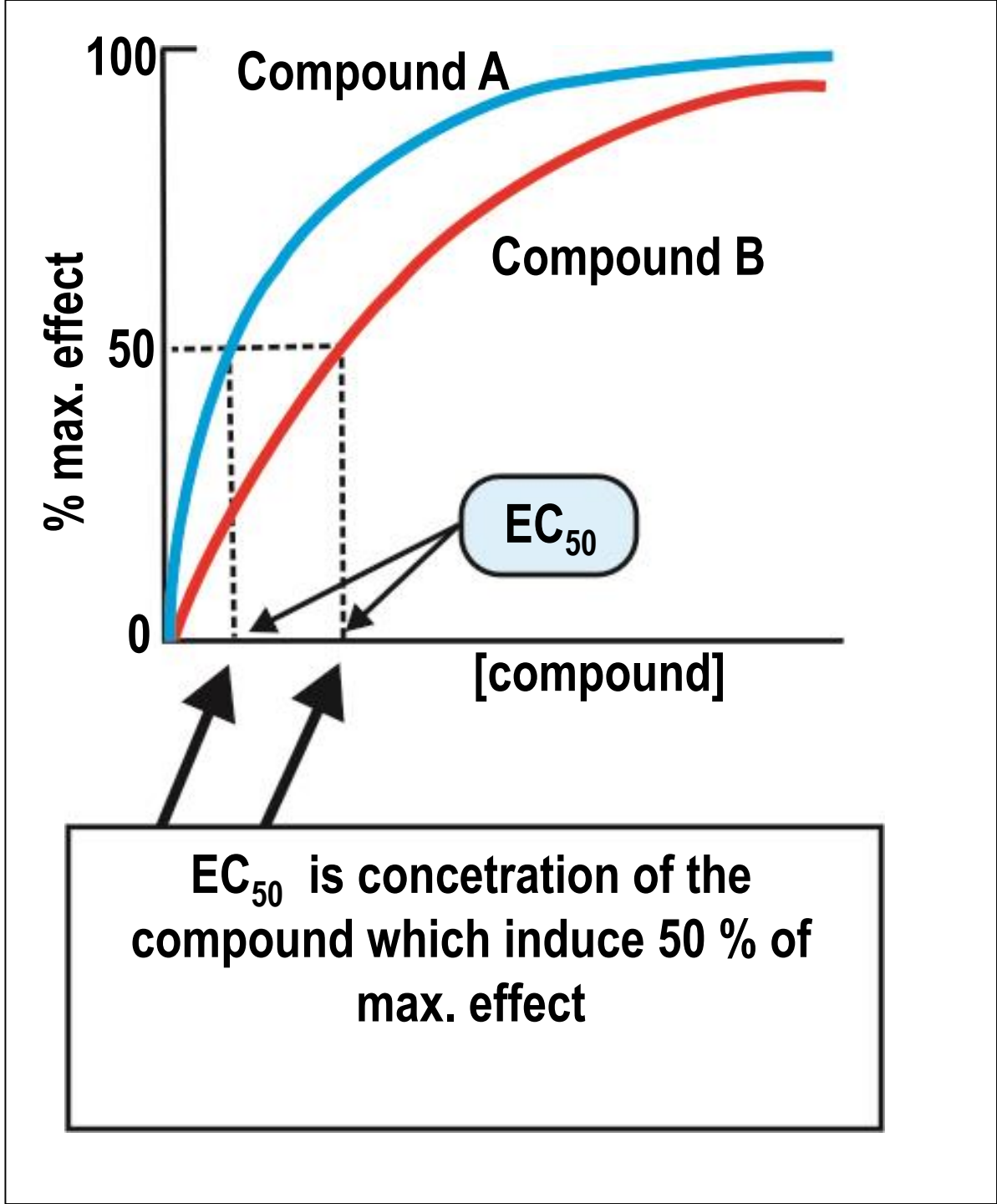
Competitive

- ✓ 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

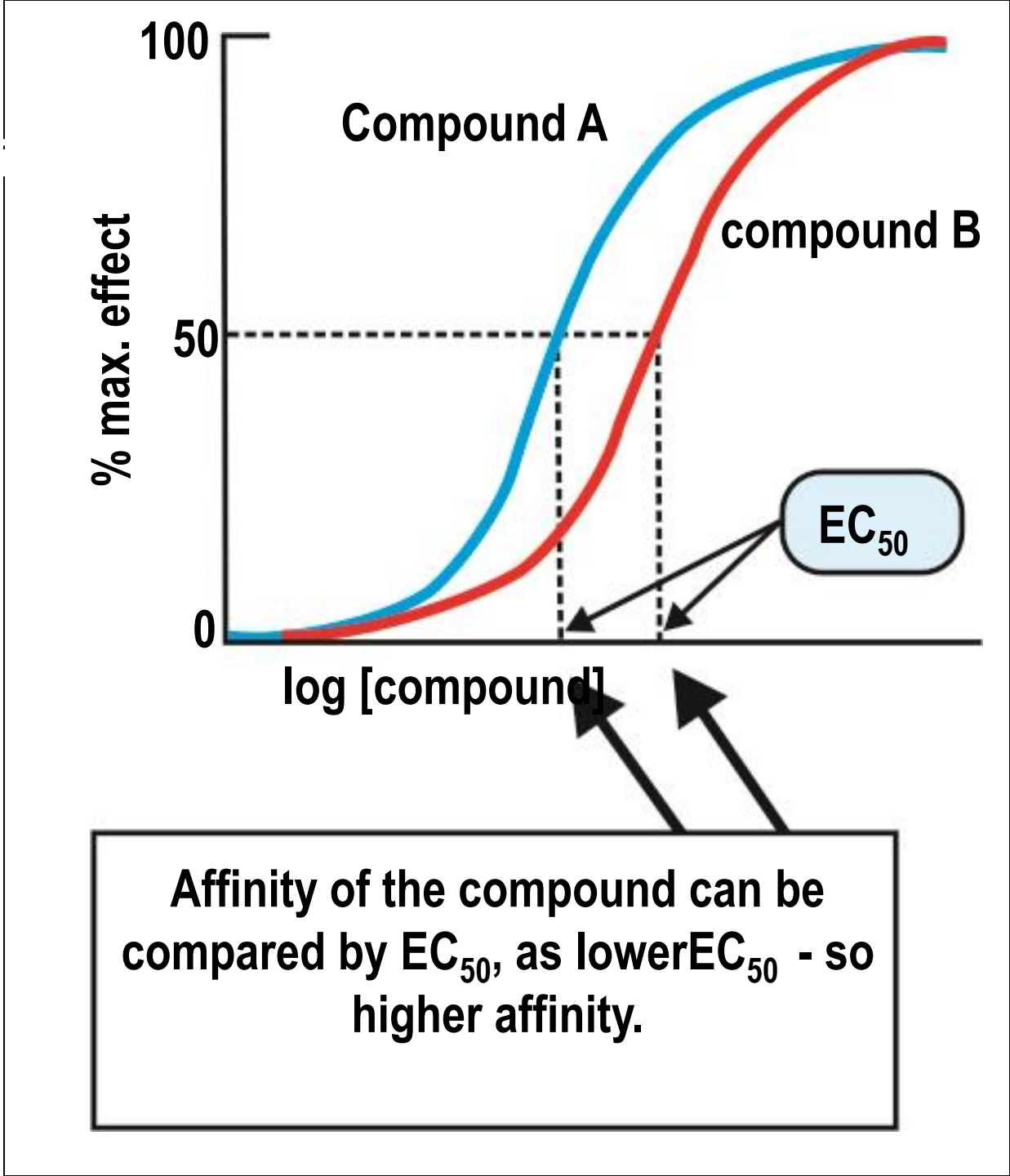
Non-competitive

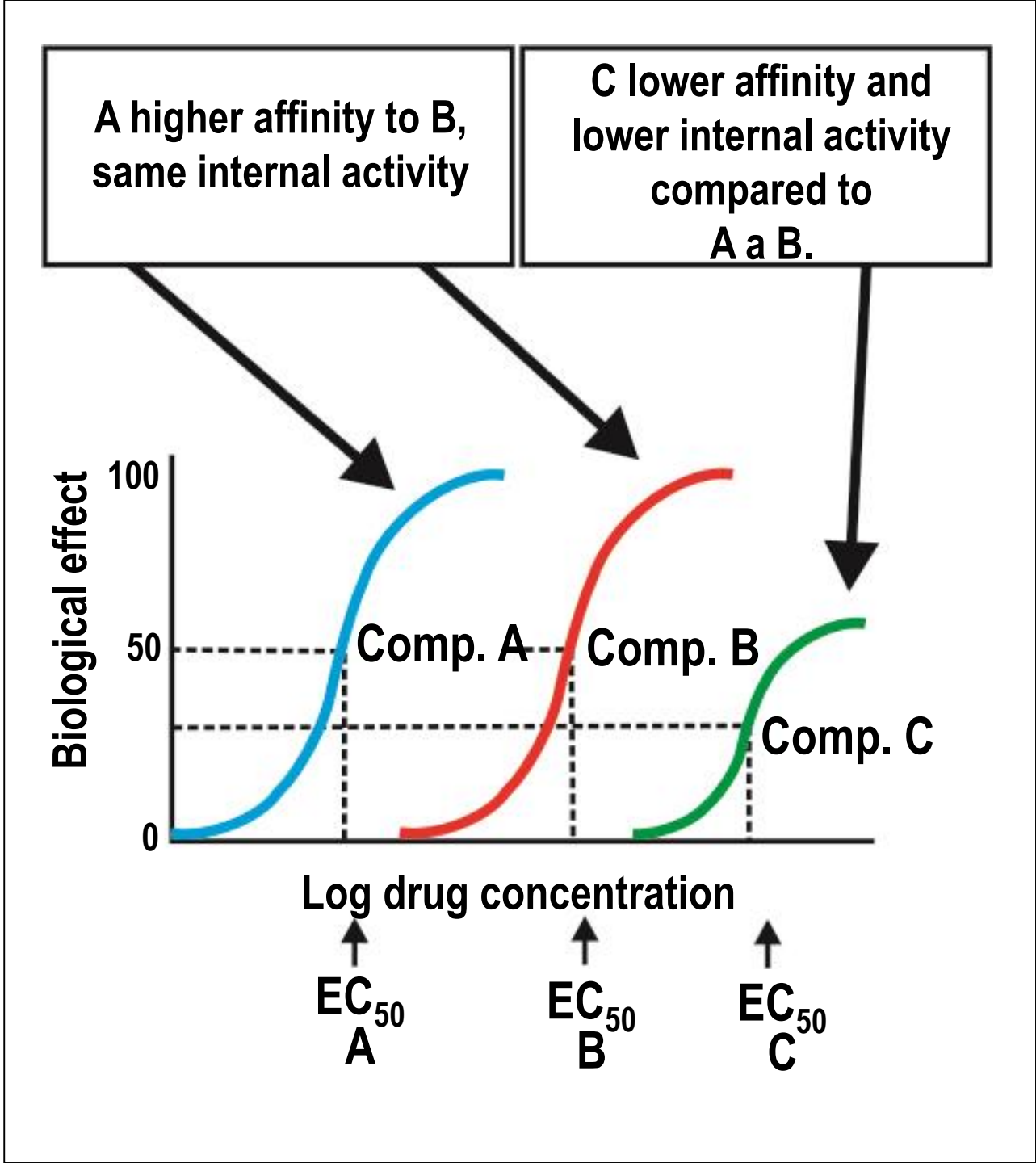
- ✓ allosteric antagonism
- ✓ irreverzible bounds
- ✓ ↑ c of agonist does not interrupt the effect of antagonist

DRC – linear curve



DRC – semilogaritmic




A higher affinity to B, same internal activity
C lower affinity and lower internal activity compared to A a B.
Biological effect
100
50
0
Comp. A
Comp. B
Comp. C
Log drug concentration
EC50 A
EC50 B
EC50 C

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
  - Ex. of tachyphylaxis – nitrates administration, 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
  - Ex. of tolerance – opioids administration

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

„non-proteins“

- binding to cellular components (ATB-ribosomes, hydroxyapatit, tubulin etc.)

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1. Enzyme inhibition

Competitive or non-competitive enzyme inhibitors

- reversible
  - acetylcholinesteraze– physostigmine
  - phosphodiesteraze – methylxantine
- irreversible:
  - Cyklooxygenaze – ASA (aspirin)
  - MAO-B – selegilin
  - aldehyddehydrogenaze– disulfiram

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2. Ion channels

- Calcium channel blockers (nifedipin, isradipin…)
- Potassium channel blockers (flupirtin – selective neuronal potassium channel modulator, oral antidiabetics…)
- Natrium channel blockers – local anesthetics

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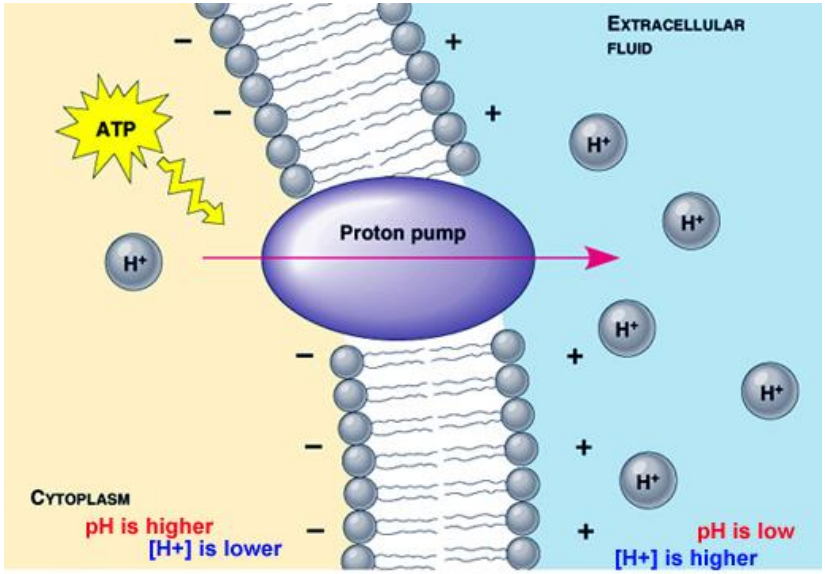
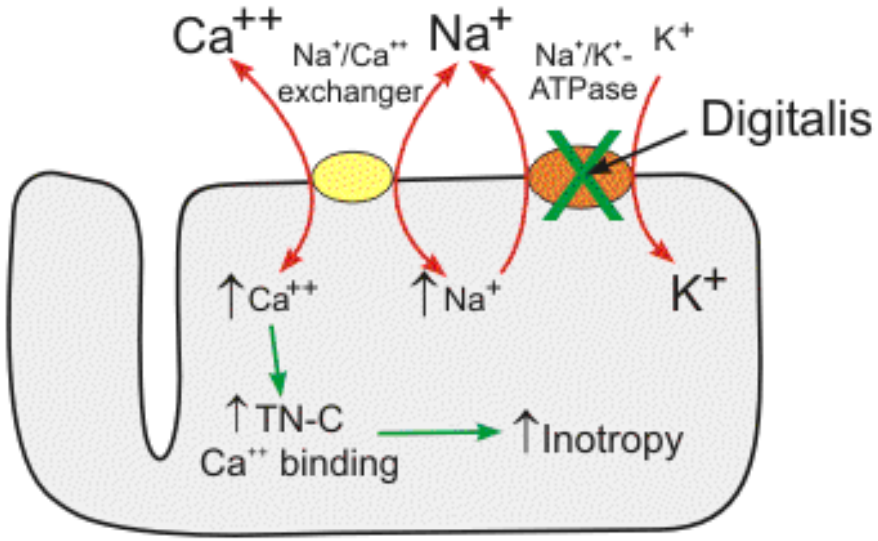
3. “Carriers“

- Proton pump inhibitors (PPIs) – omeprazol
- Na^+/K^+ ATPasa inhibitors – digoxin





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Next lecture

29.10.2019 - Adverse effects, pharmacovigilance

Thank you for your attention

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