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PHARMACODYNAMICS

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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“

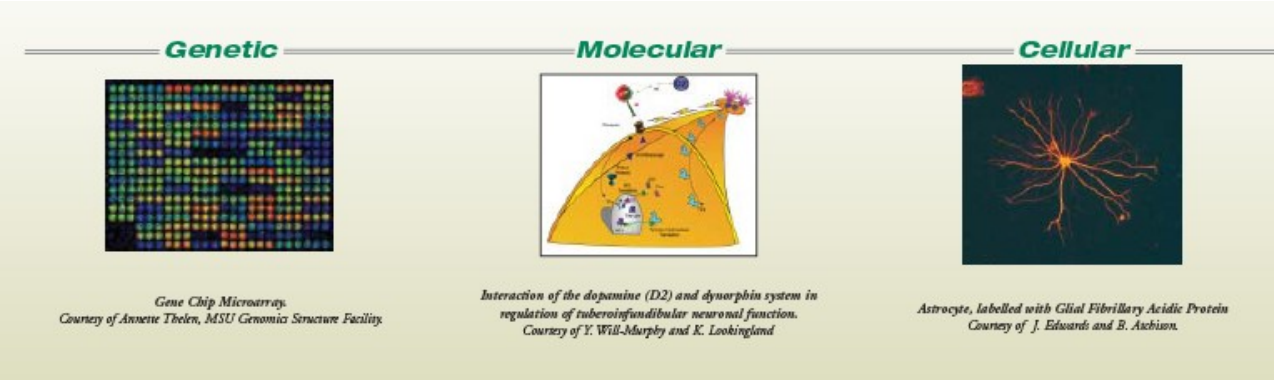
Pharmacodynamics

(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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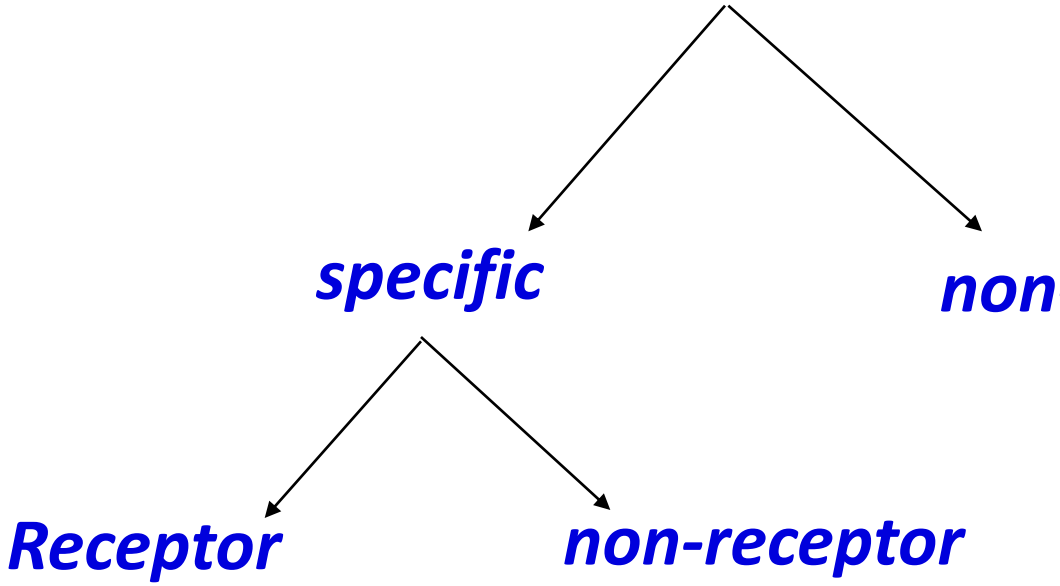
Mechanism of drug actions



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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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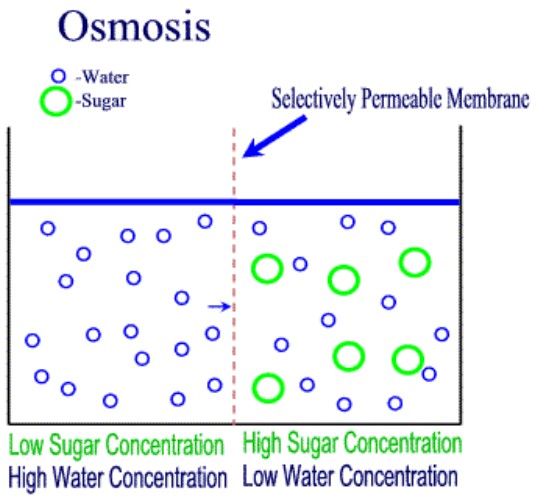
a. based on osmotic properties

- 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. drugs with a large adsorption area

- intestinal adsorbents - Carbo adsorbens (activated charcoal)
- diosmectite (treatment of diarrhoea)

- bind other substances and toxins to themselves

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e. surfactants and detergents

- surface active agents: carbethopendecinium bromide (and other quarternary ammonium salts) used primarily as antiseptics.

- some antibiotics (e.g. polymyxins - basic peptides) act as cationic detergents and disrupt phospholipids in bacterial membranes.

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f. 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

- **….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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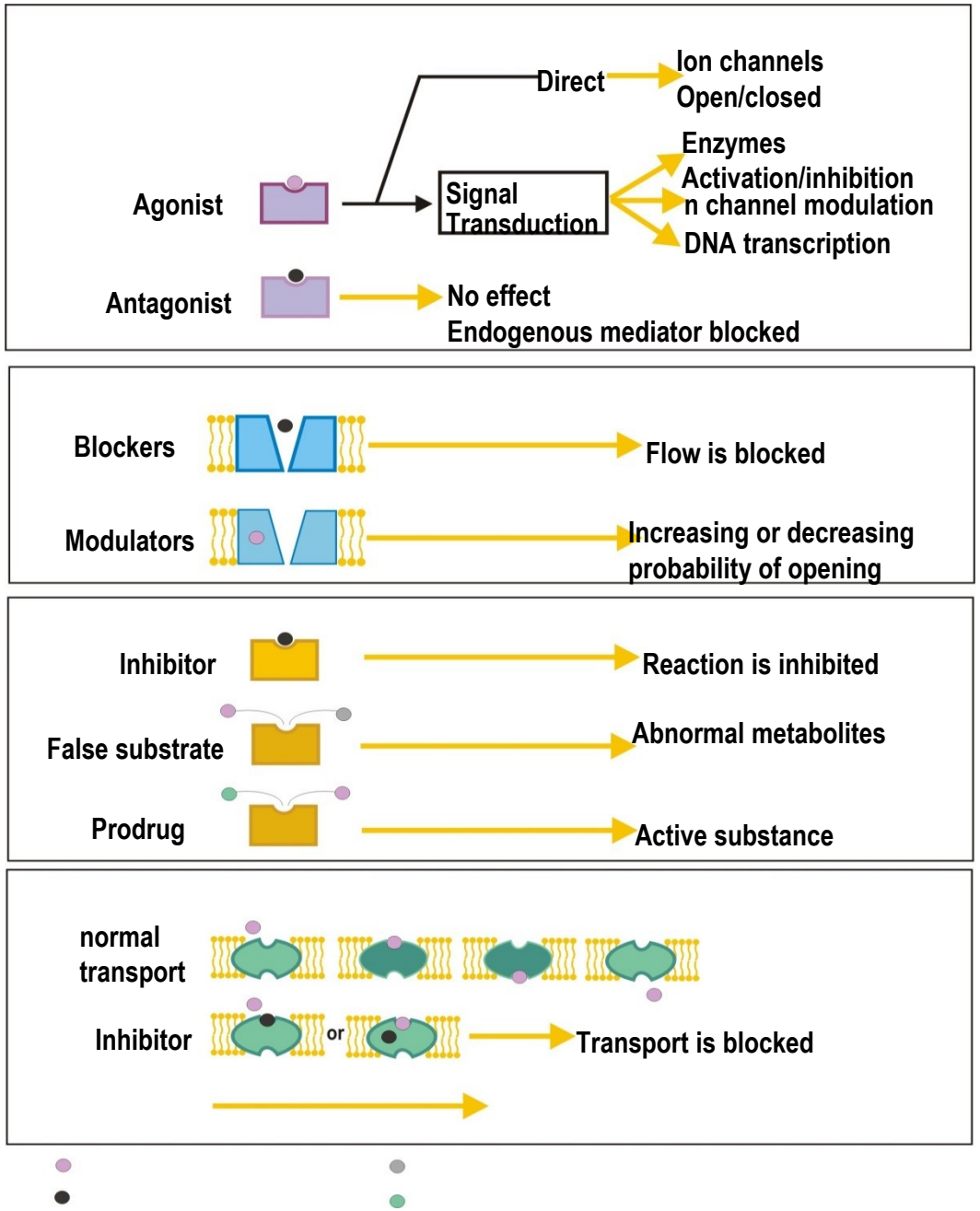

Rang and Dale Pharmacology, 2017

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

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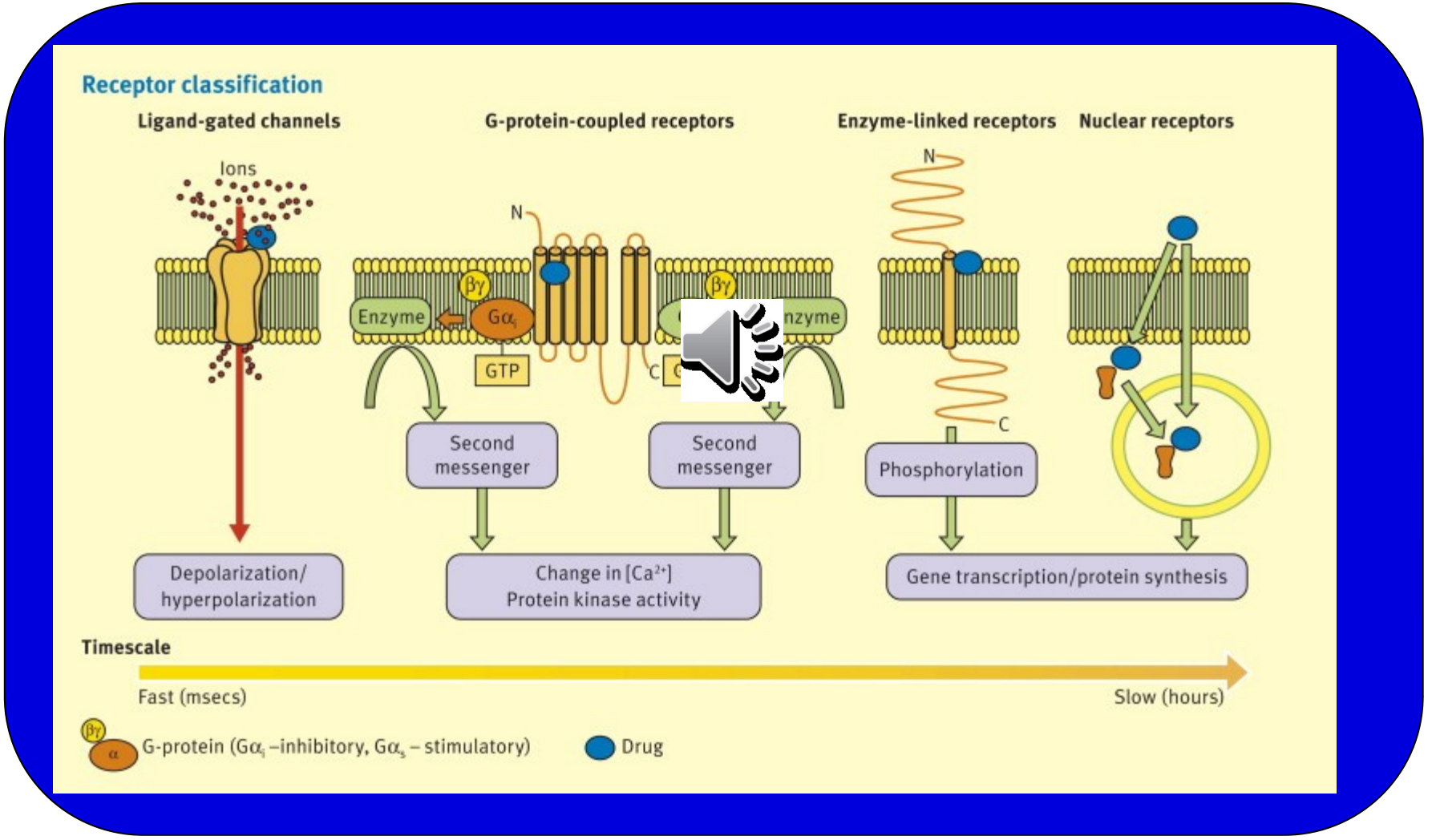
Receptor classification



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

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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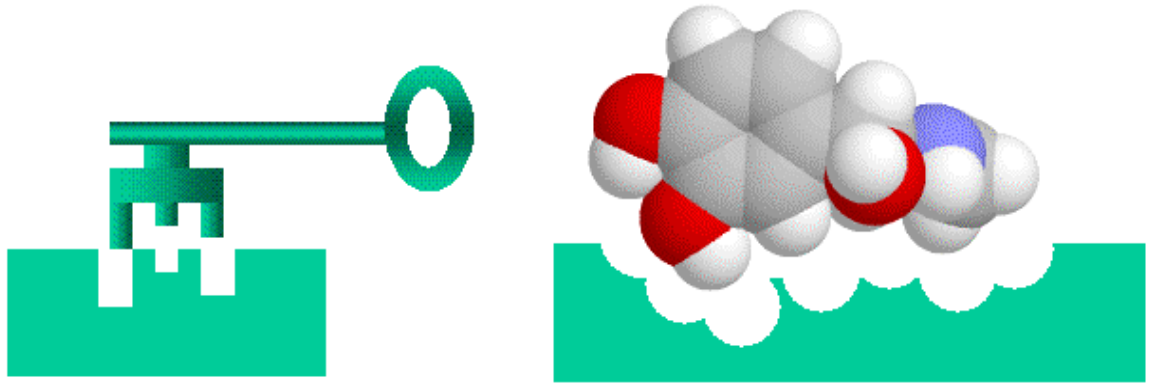
Receptor – effector system



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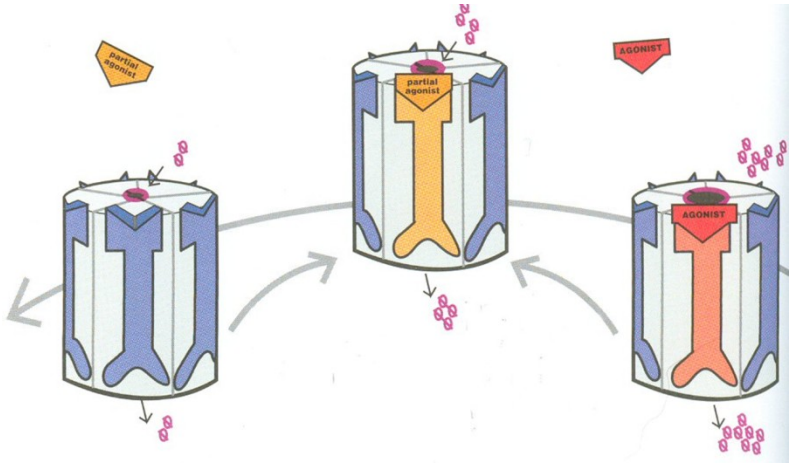
Ligand classification (intrinsic activity) AGONISTS

Full agonist

- IA = 1



Partial agonist

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

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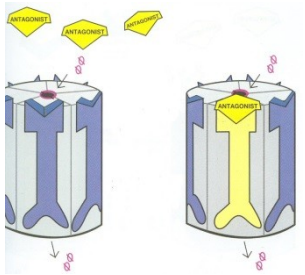
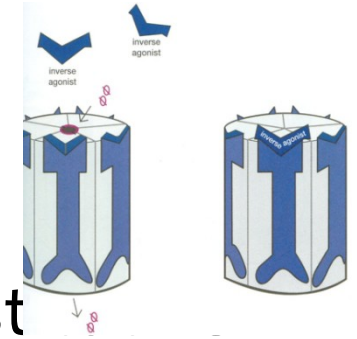
Ligand classification



Antagonists

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

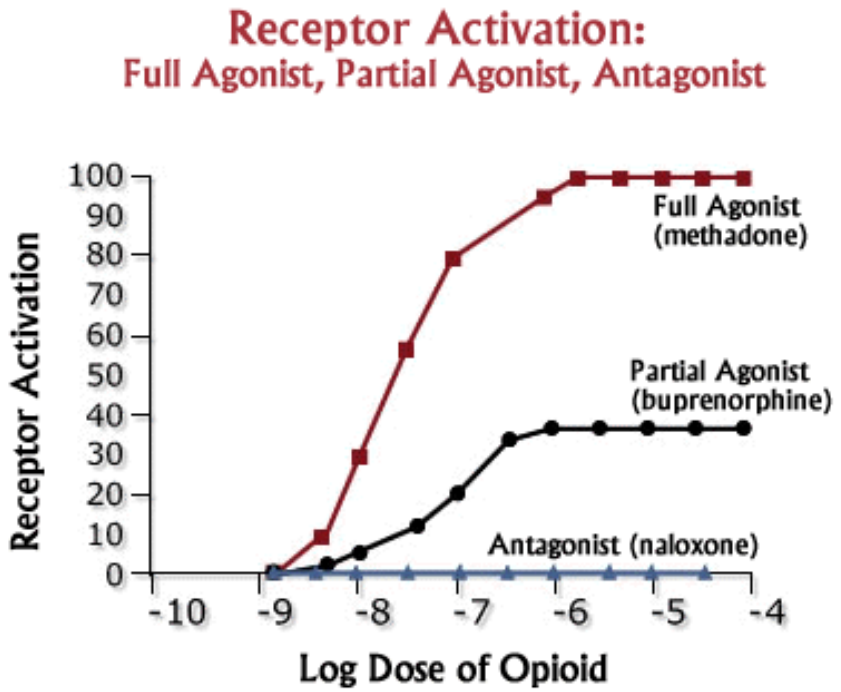


Inverse agonist

- ✓ IA = -1
- ✓ Stabilizes the receptor in the const activity

Receptor-effector system

Relation between dose and effect



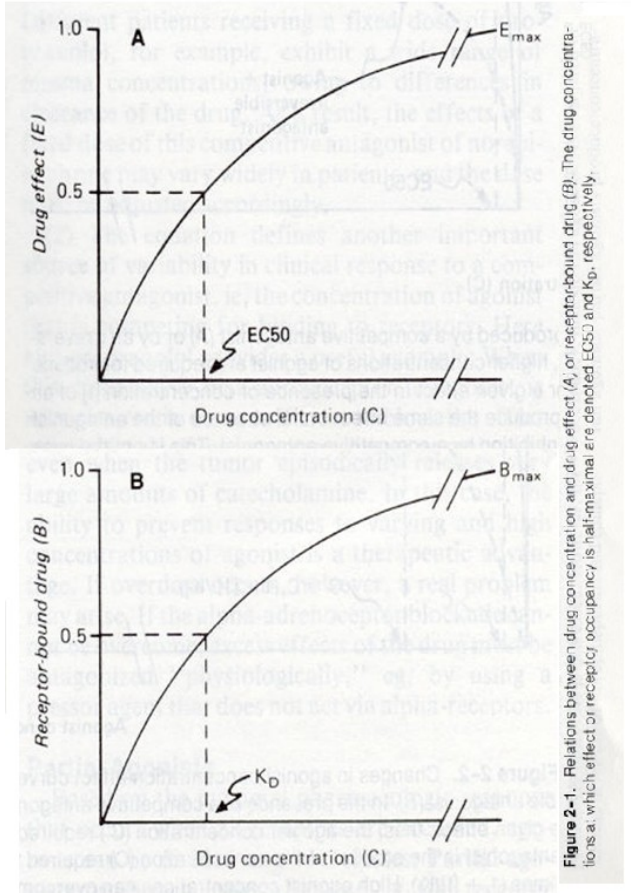
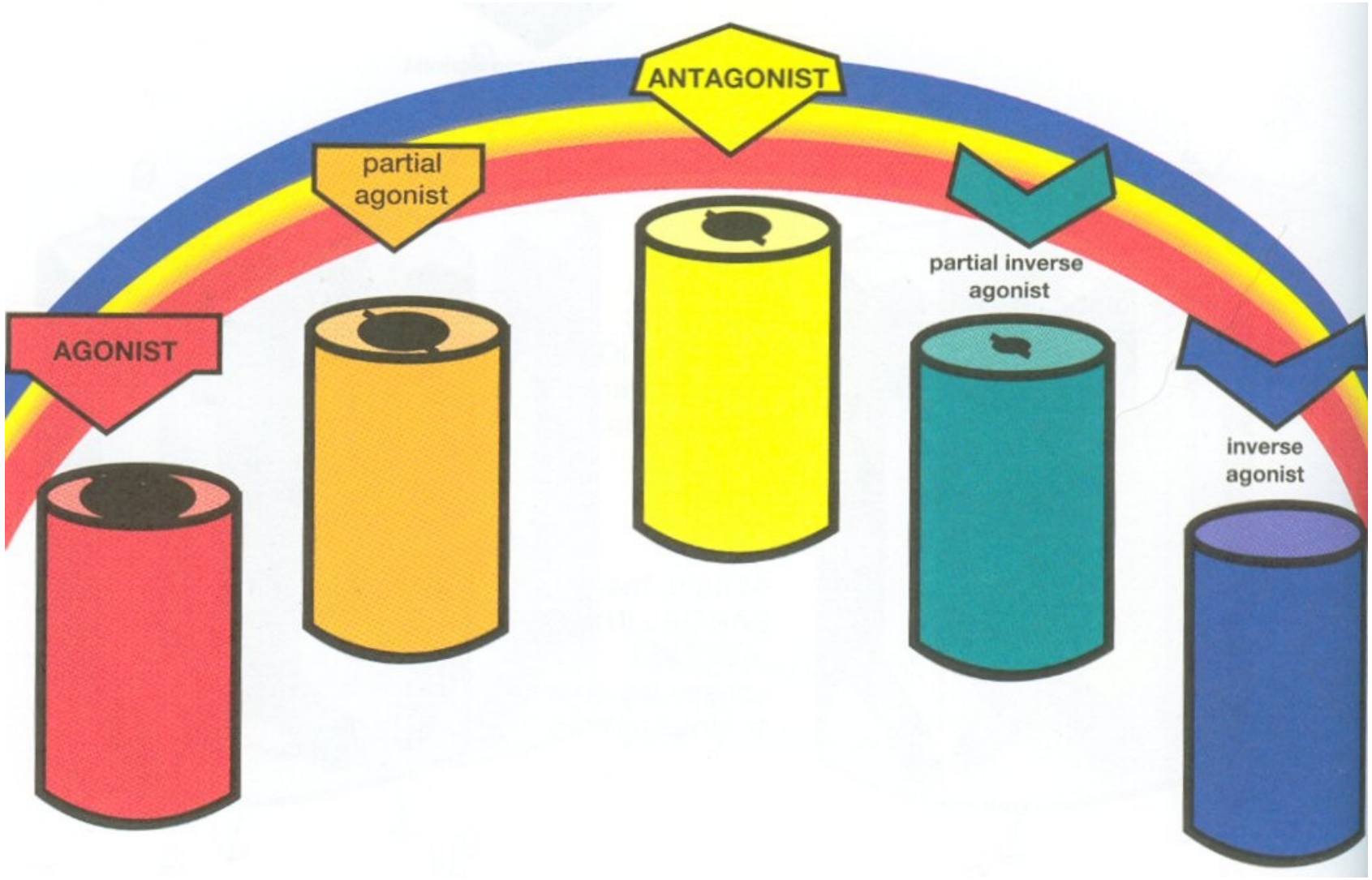
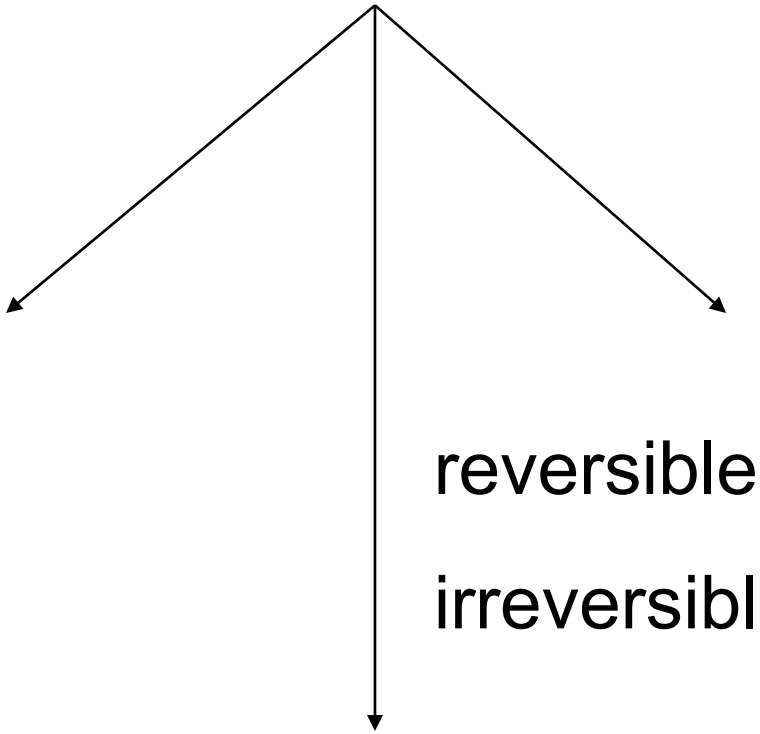


Figure 2-1. Relations between drug concentration and drug effect (*A*), or receptor-bound drug (*B*). The drug concentrations at which effect or receptor occupancy is half-maximal are denoted EC50 and K_D, respectively.

Spectrum of ligands



Antagonism



competitive

non-competitive

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
  - 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

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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

„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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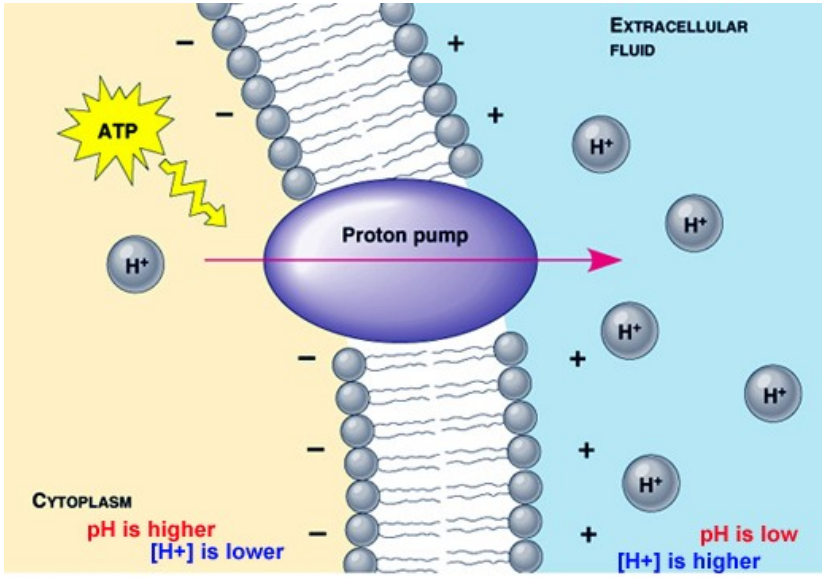
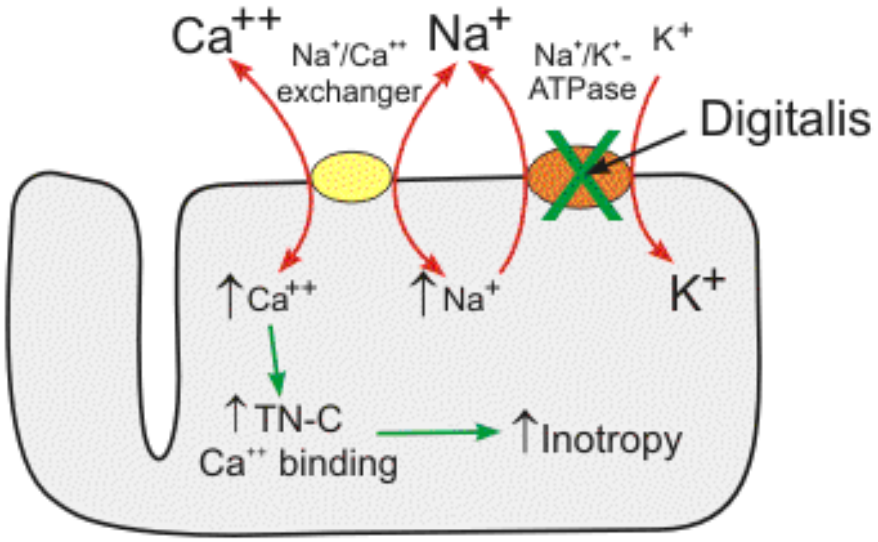
3. “Carriers“

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





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