GENERAL PHARMACODYNAMICS

Receptor theory of drug action

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

Receptor-effector system

Affinity

- ✓ the ability of the ligand to bind to the receptor $1/K_d$

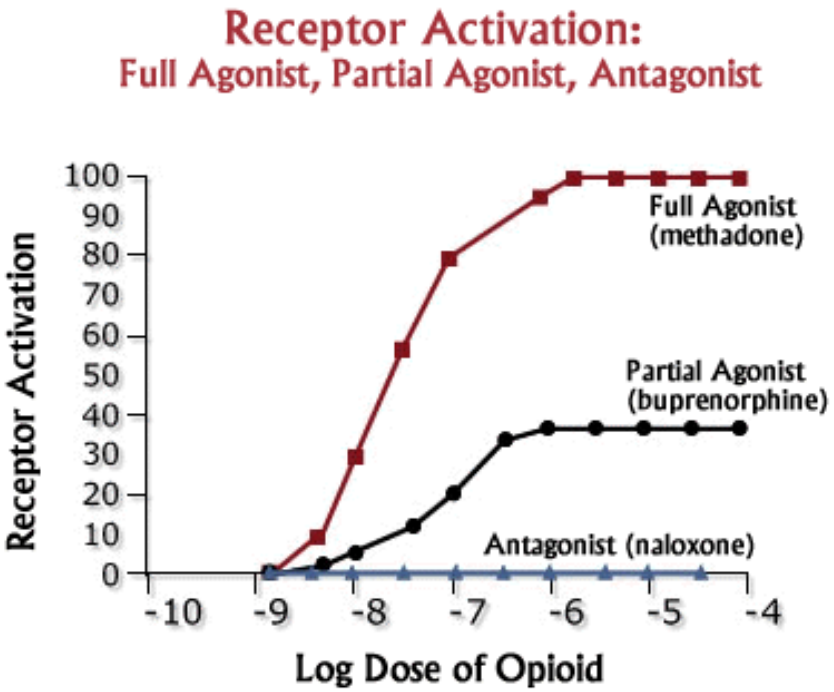
Instrinsic activity

- ✓ 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!!!

Receptor-effector system

Relation between dose and effect



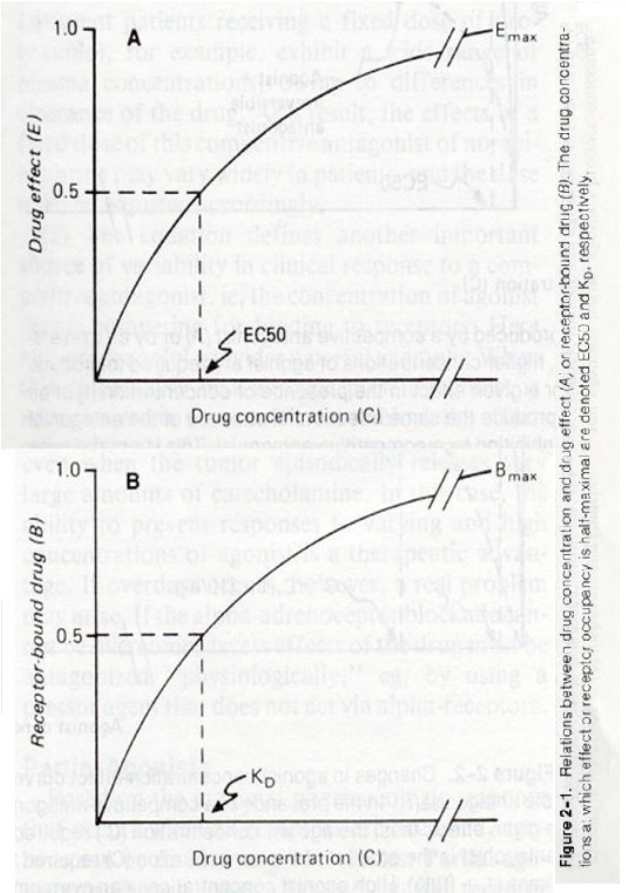


Figure 2-1. Relations between drug concentration and drug effect (A), or receptor-bound drug (B). The drug concentrations at which effect or receptor occupancy is half-maximal are denoted EC50 and K_D, respectively.

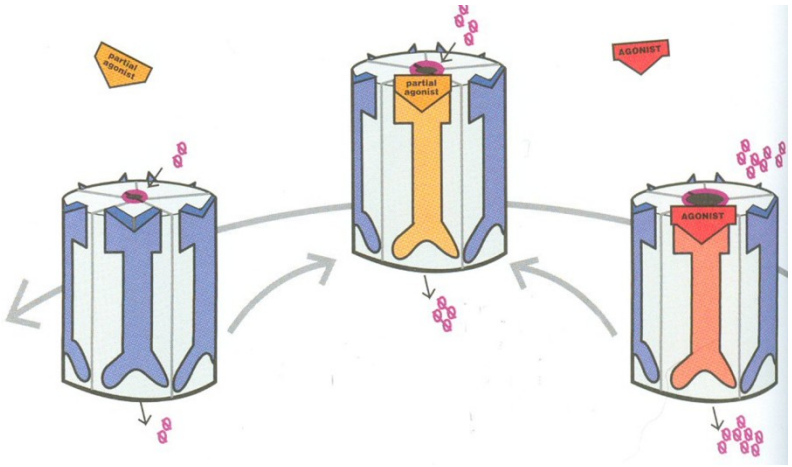
Intrinsic activity (classification of ligands)

Ligand classification

Agonist

Full agonist

- IS= 1

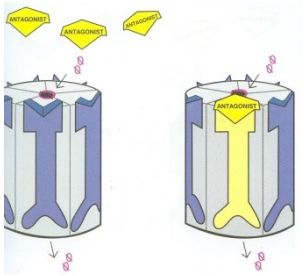


Partial agonist

- dualist
- IS in a range from 0‹ to ›1
- Acts as antagonist in the presence of full agonist

Ligand classification

Antagonist

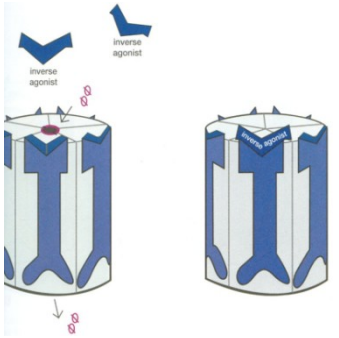


- ✓ IS = 0
- ✓ Blocks agonist binding to receptor

Inverse agonist/superantagonist

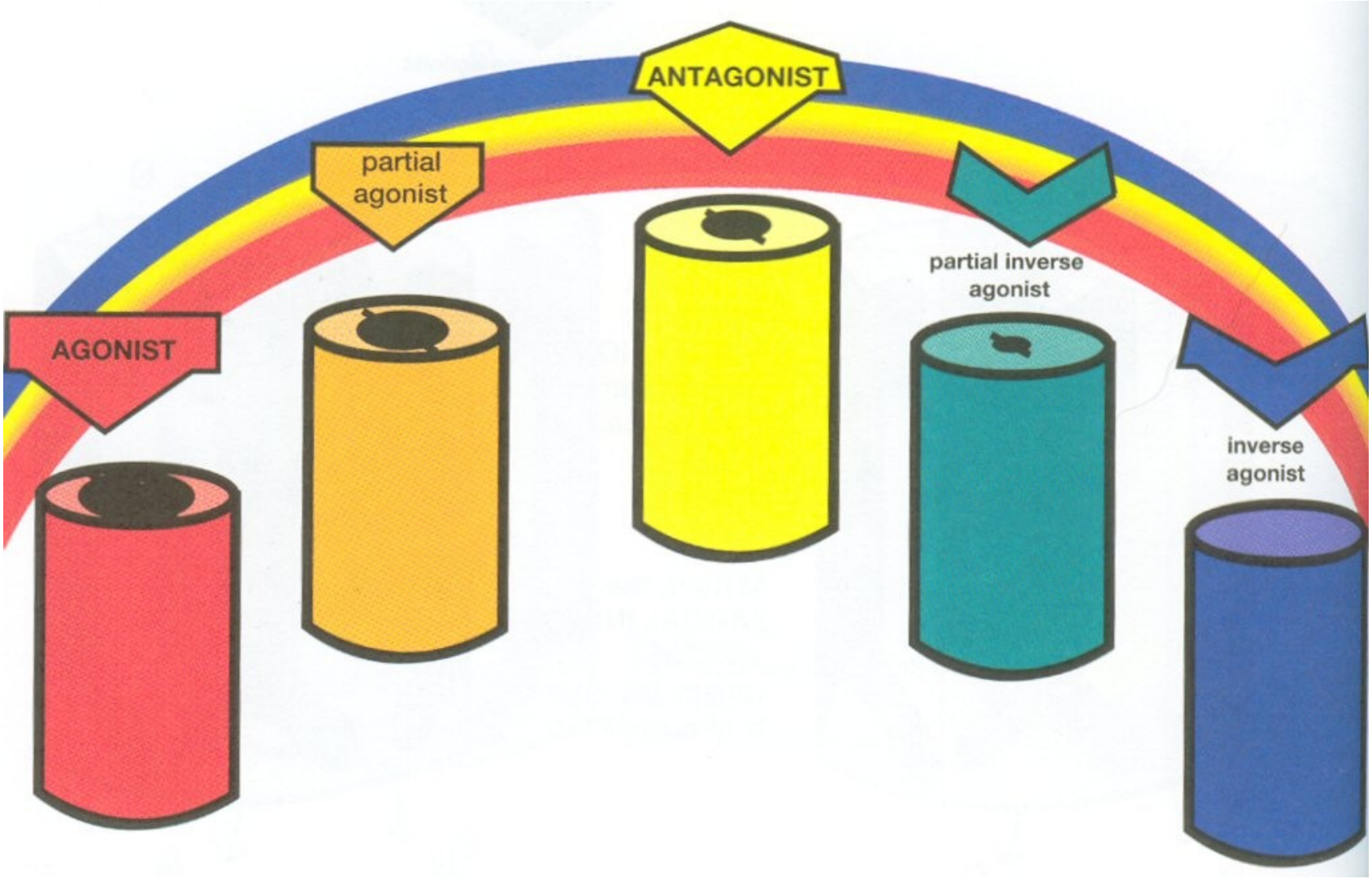
- ✓ IS = -1
- ✓ Stabilizesthe receptor in the constitutive activity

Antagonism

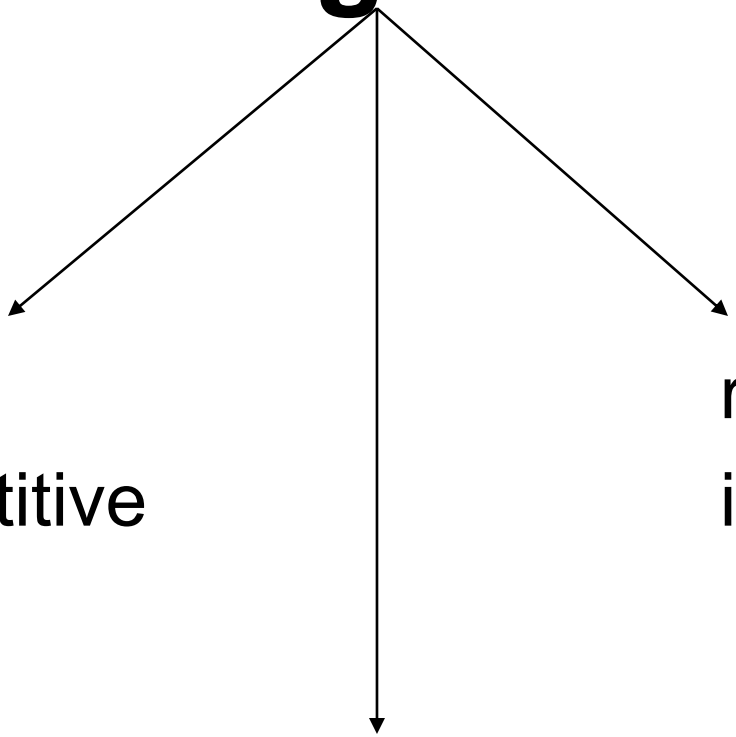


- ✓ competitive x non-competitive
- ✓ reversible x irreversible
- ✓ on the receptor level x on the level of function

Spectrum of ligands



Antagonism



competitive

non-competitive

reversible

irreversible

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

Antagonism

Chemical

- ✓ drug inactivation by forming complexes with other molecules (protamine + heparin)

Physiologic

- ✓ drug intereaction on the level of function, drugs evoking opposite effects by different mechanism (diuretics + vassopresin, nitrates + α_1 agonists)

Regulation of receptor function

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

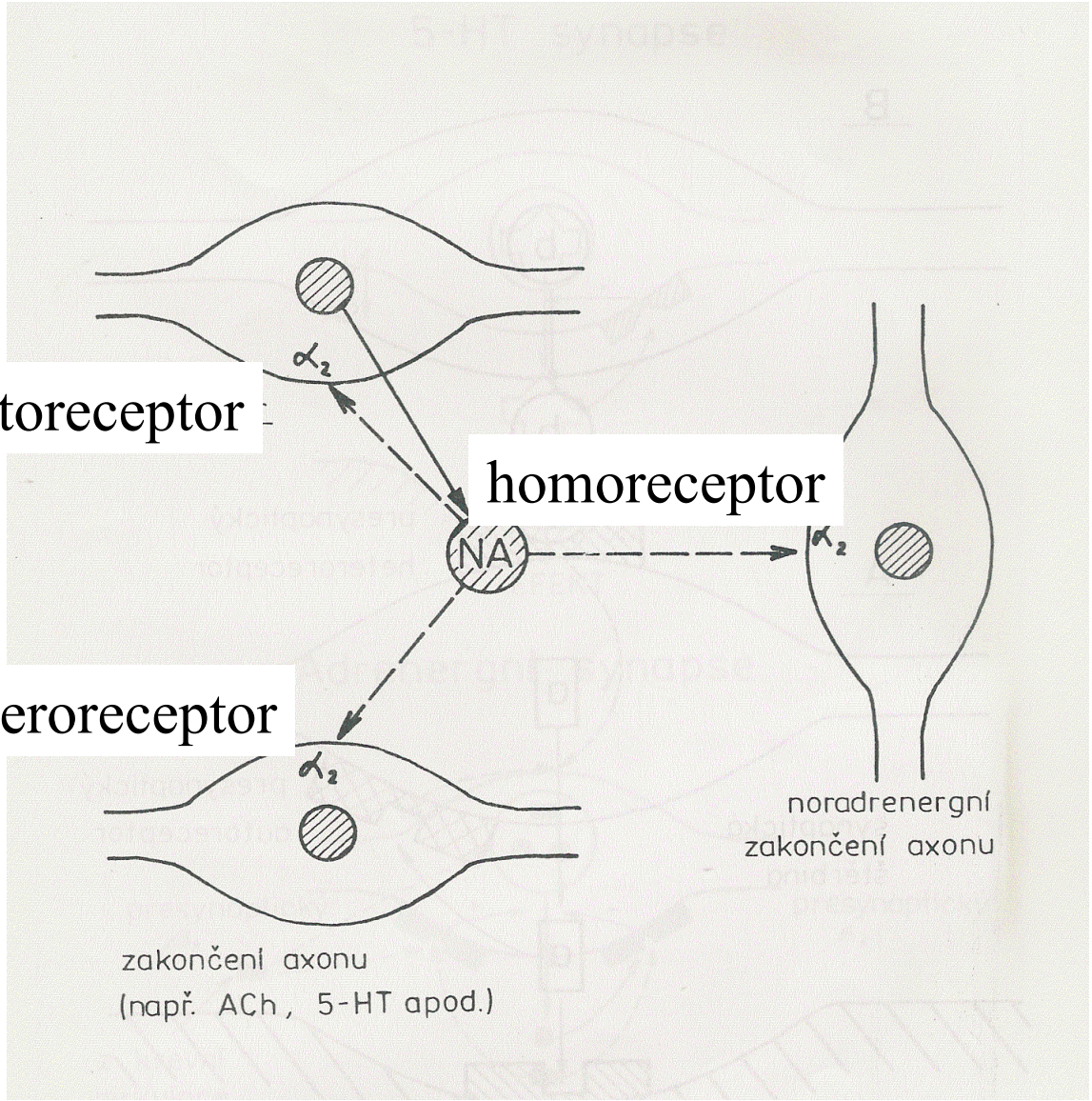
Presynaptic modulation

- Release of the primary neurotransmitter from the nerve endings is modified by:

a) autoreceptors

b) homoreceptors

c) heteroreceptors


autoreceptor
homoreceptor
heteroreceptor
α2
α2
α2
NA
noradrenergní
zakončení axonu
zakončení axonu
(např. ACh, 5-HT apod.)

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

- **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

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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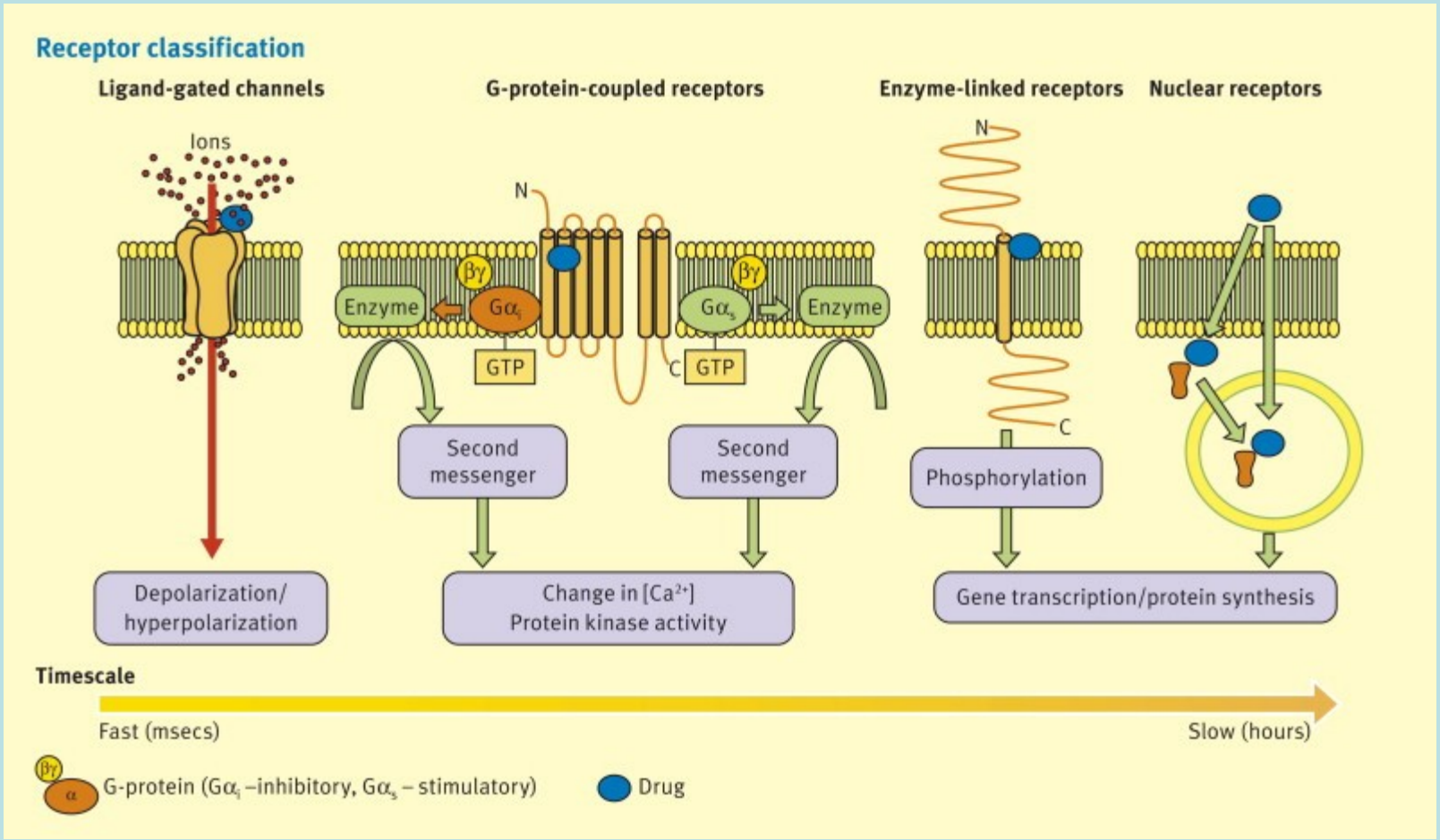

Non-receptor mechanisms of action

Based on phys.-chem. properties

- influencing pH
- oxidating and reducing agents
- protein precipitation
- creating protective layers
- adsorbentsa
- detergents
- chelating agents
- radionuclides

Non-receptor mechanisms of action

Interaction with „non-receptor“ proteins

- enzyme inhibition
- nucleoside and nucleotide analogues (cytostatics, antivirotics)
- block of transporters
- block of ionic channels (Na^+)
- binding to cellular components (ATB-ribosomes, mitotic spindle)