PHARMACODYNAMICS

Mechanisms of action
– specific and non-specific drug effects

.

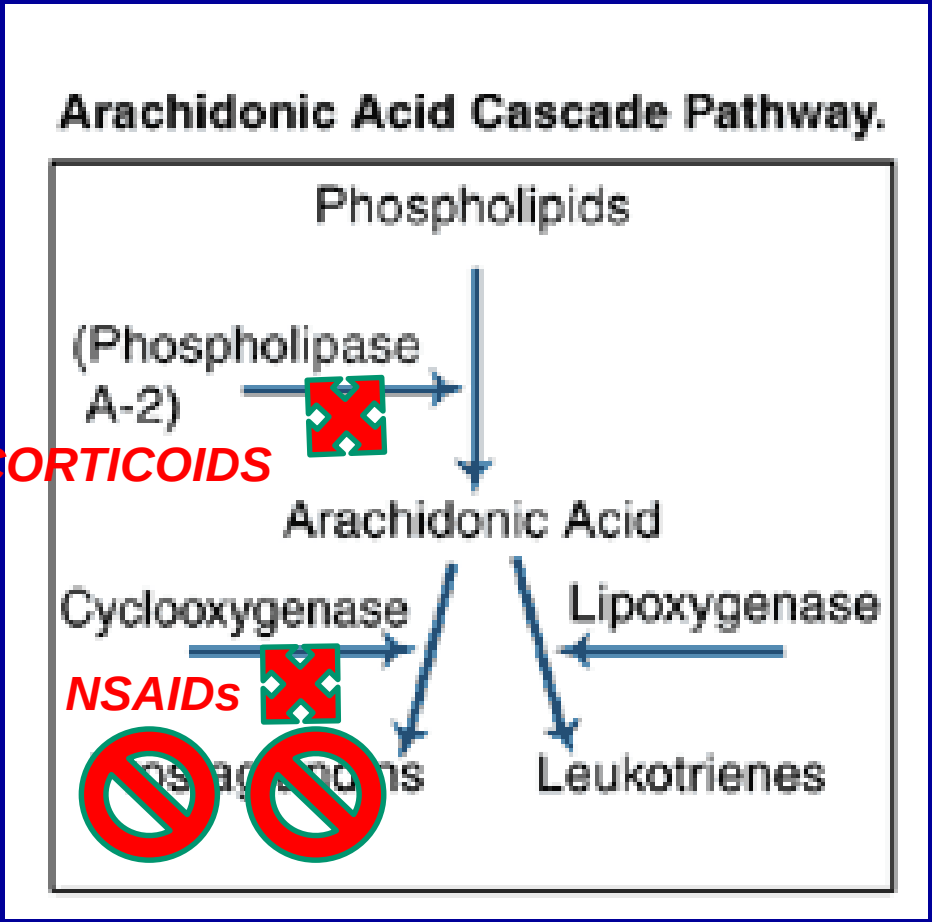
PHARMACODYNAMICS

studies drugs effects and their mechanisms

„what a drug is doing with organism”

Drugs effects *take place at the subcellular level.*

The response of organism (change in function) is described as ***action of drug***


Arachidonic Acid Cascade Pathway.
Phospholipids
(Phospholipase A-2)
GLUCOCORTICOIDS
Arachidonic Acid
Cyclooxygenase
Lipoxygenase
NSAIDs
Leukotrienes

MECHANISMS OF DRUG ACTIONS

I. Non-specific effect

Conditioned by the general physical-chemical properties of substances - no specific chemical and structural configuration of drugs is needed (eg. general anesthetics - soluble in fats)

II. Specific effects (mediated by specific target molecules)

effect depends on the specific molecules configuration

The concentration of the active substance in the receptor - an effective concentration.

I. Non-specific effect

Osmotic effects

Affecting pH

Oxidation or reduction

Mechanical protection of surface

Binding of drugs to a large surface

Detergent effect

Non-specific mechanisms of action (examples)

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 (examples)

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 (examples)

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 (examples)

Adsorbents

substances with large surface binding (adsorbing) other substances, toxins, etc. - charcoal

Non-specific mechanisms of action (examples)

Surfactants, detergents

affect surface tension of cell membranes; they are used as disinfectants and antiseptics (e.g. soaps, benzyl dodecinium bromide, carbethopendecinium bromide)

Non-specific mechanisms of action (examples)

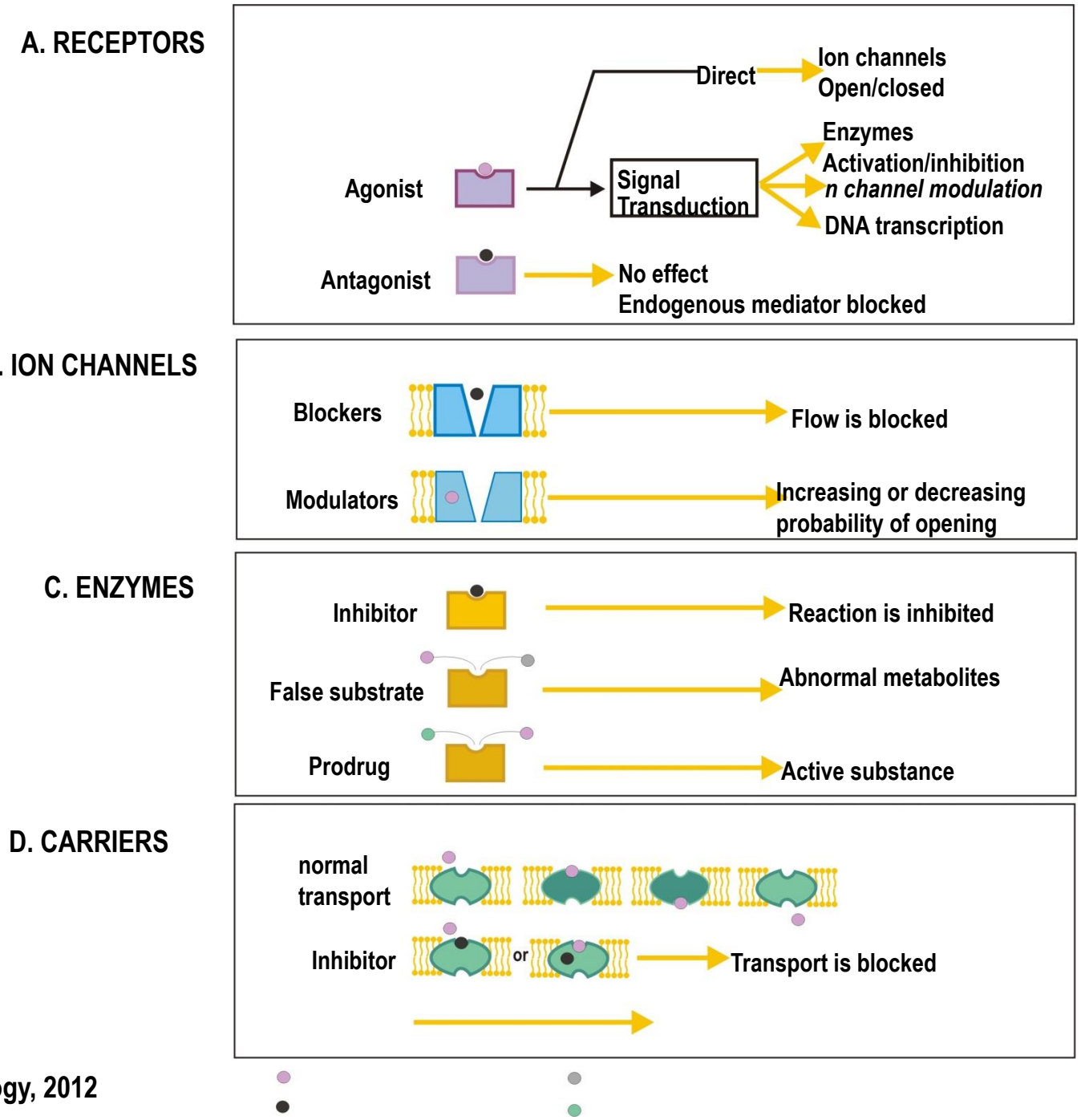
General anesthetics

according to the lipid theory of Overton and Meyer (1899-1901), the effect of general anesthetics is based on their liposolubility

II. Specific action

Targeted structures:

1. Receptors
2. Ion channels
3. Enzymes
4. Transport carriers



Rang and Dale Pharmacology, 2012

II. Specific action

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

The molecule of the active substance binds to the receptor to form a receptor complex

Ligand (pharmacon) - receptor complex.

Two main properties of the substance (drug)

1. **Affinity**
2. **Intrinsic activity**

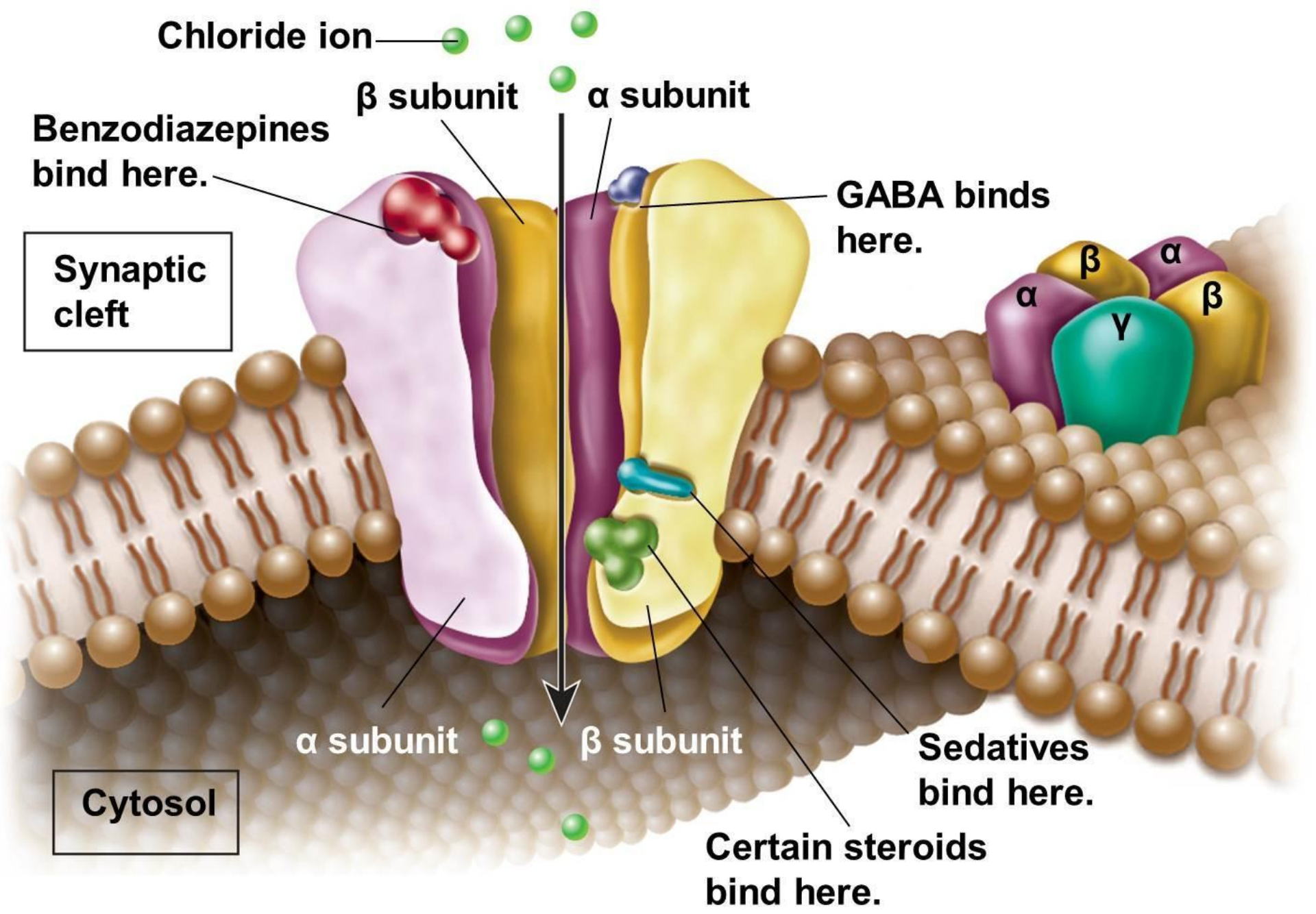
- The binding alone is useless without signal transduction
- Signal transduction by receptors can be done by four major principles :

  - Ion channels
  - G-protein coupled receptors
  - Receptor tyrosine kinases
  - Intracellular receptors

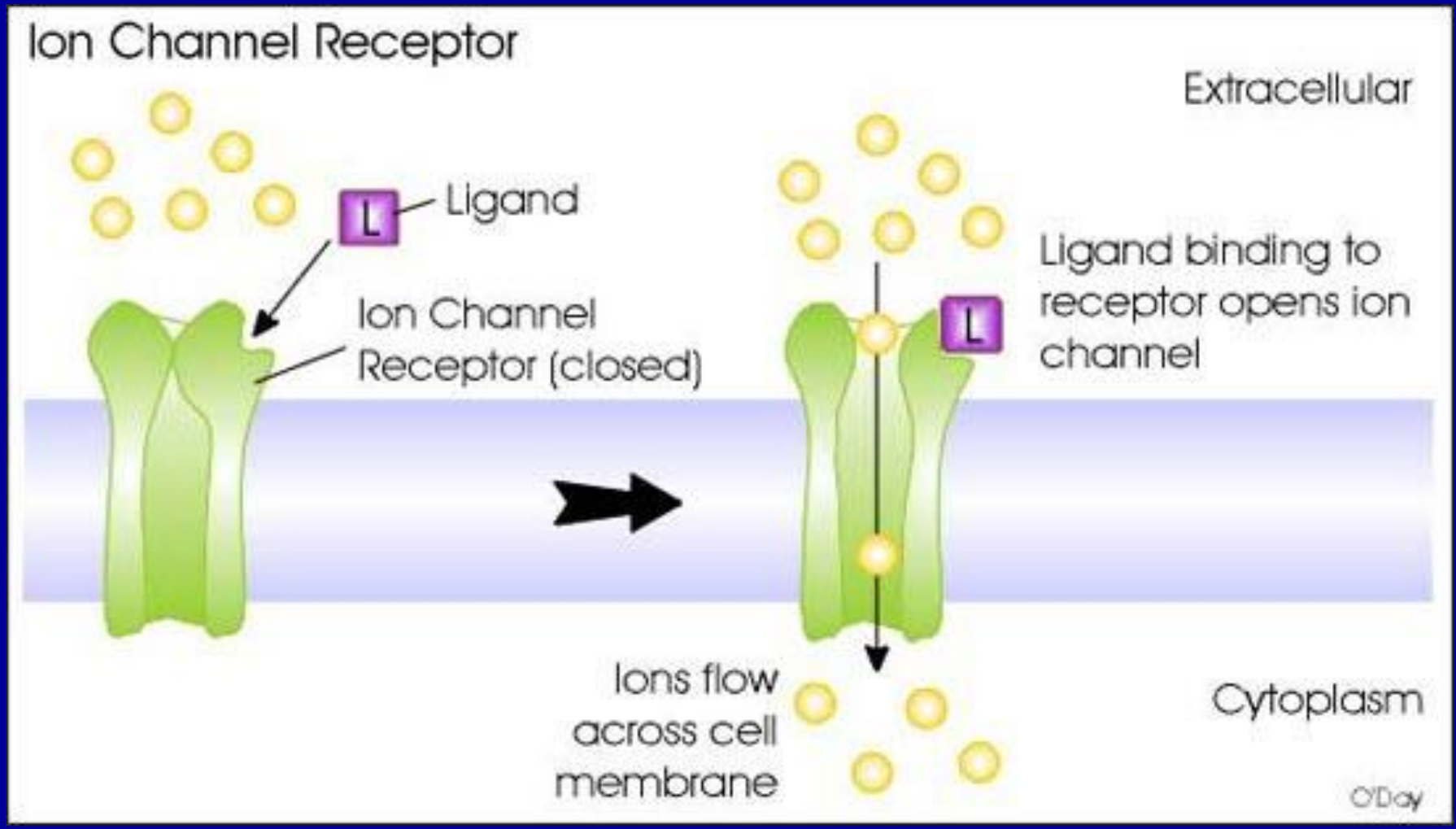
4 main type of receptors

	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.

Ligand-gated ion channels



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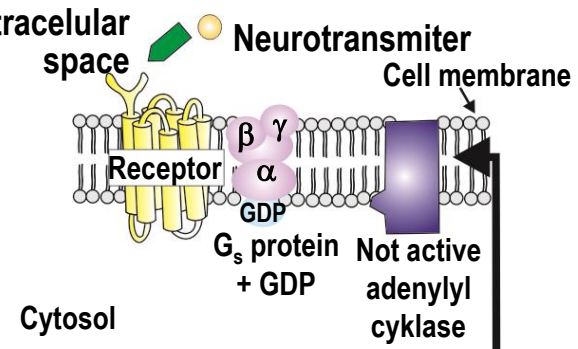
G-protein coupled receptor (metabotropic)

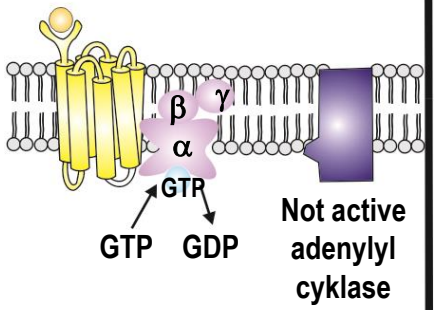
- inserted into the plasma membrane in a serpentine fashion that results in seven transmembrane domains (heptahelical structure)
- more subtypes - Gs Gi Go Gq
- 3 subunits (α β γ)
  - α-subunit has GTPase activity

- Examples: muskarim – cholinergic receptor, adrenoceptors, opioid receptors….

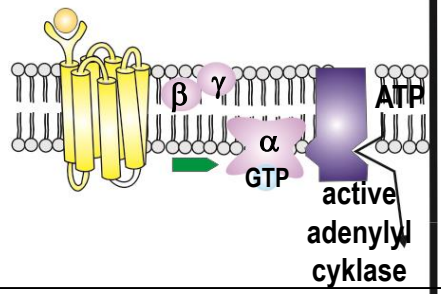
1 – innactive state - no interaction with G_s protein



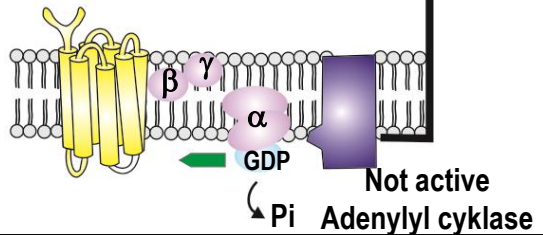
2 – active receptor – structural change + interaction with G_s protein. G_s protein releasing GDP and bind GTP.



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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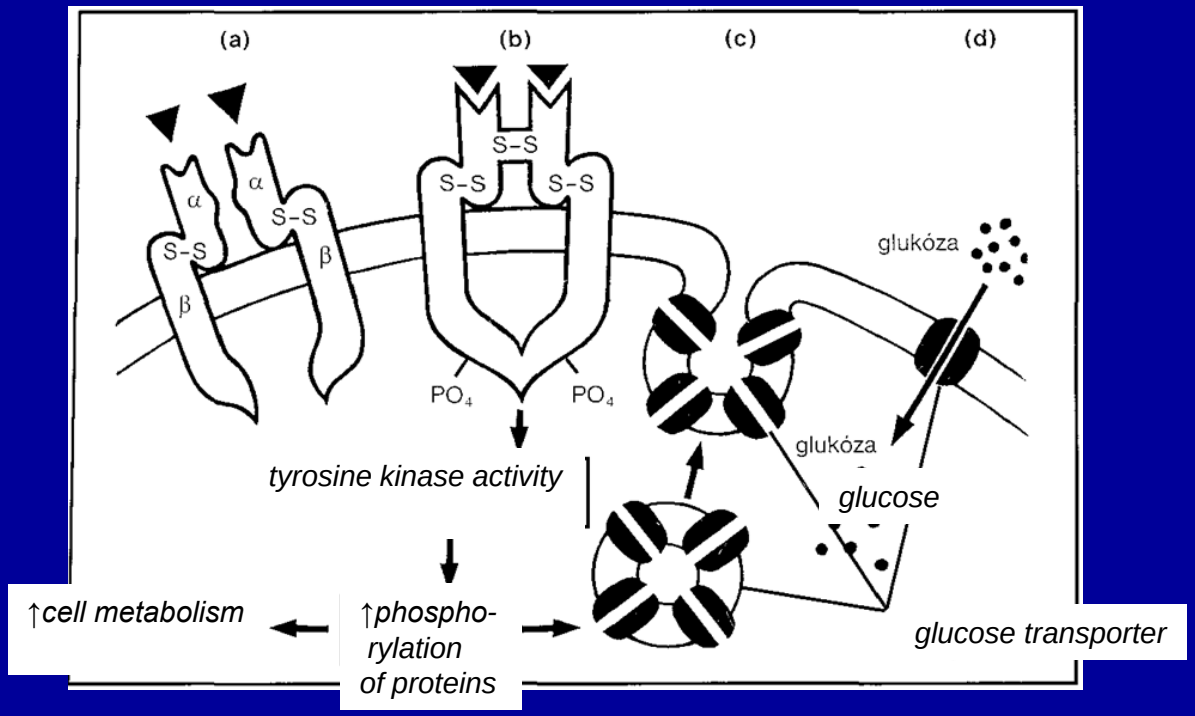
Rang and Dale Pharmacology, 2012

Receptor Tyrosine Kinases (enzymes)

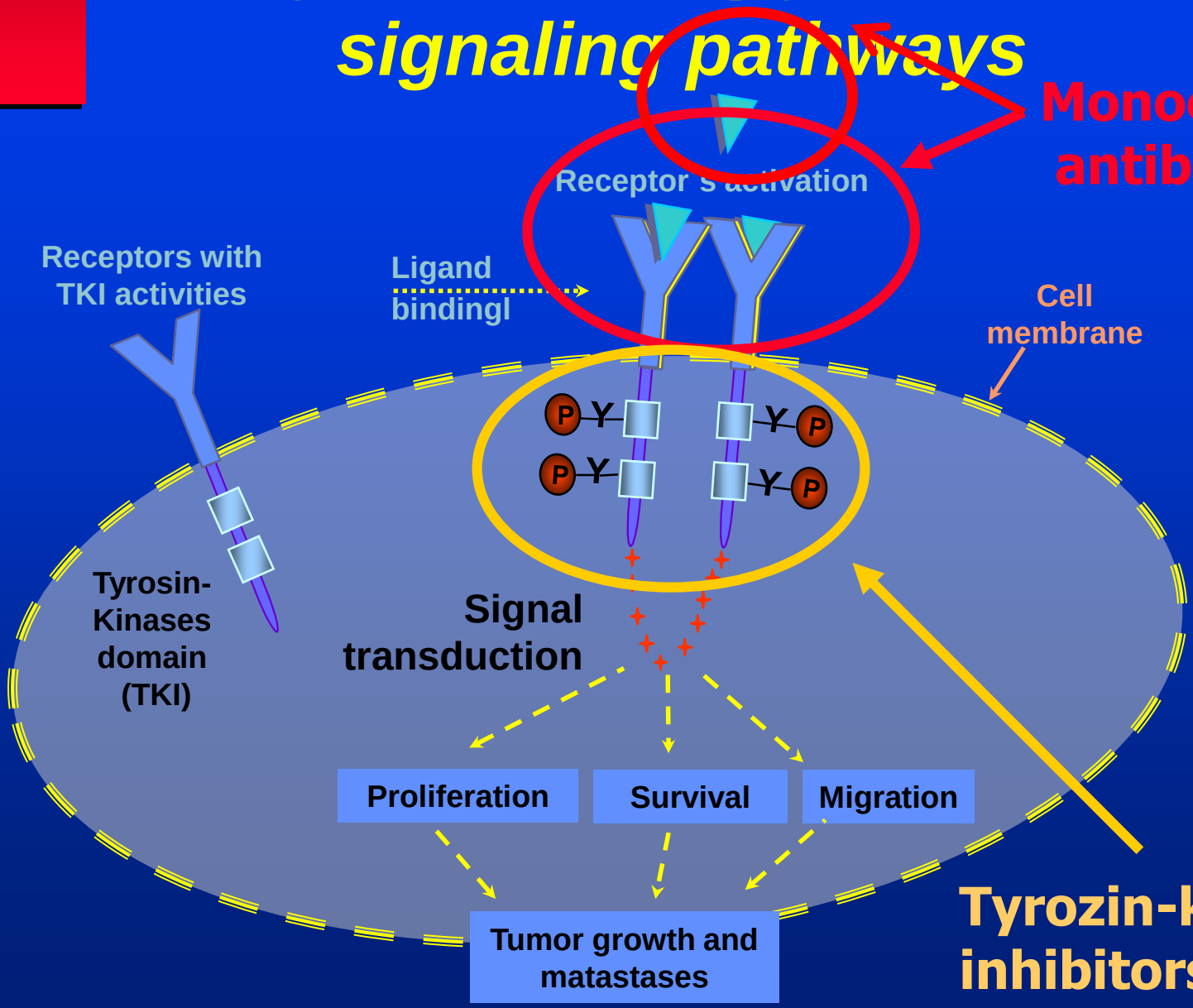
- RTKs mediate signaling by insulin and a variety of growth factors such as EGF, VEGF, PDGF..
- Importance in the regulation of oncogenes and cell growth
- Exists on the cell surface as monomers with the single transmembrane domain
- When activated, the receptors dimerize and transfer phosphate to hydroxyl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

Kinase-linked receptors

Insulin receptor



Targeted therapy – receptor signaling pathways



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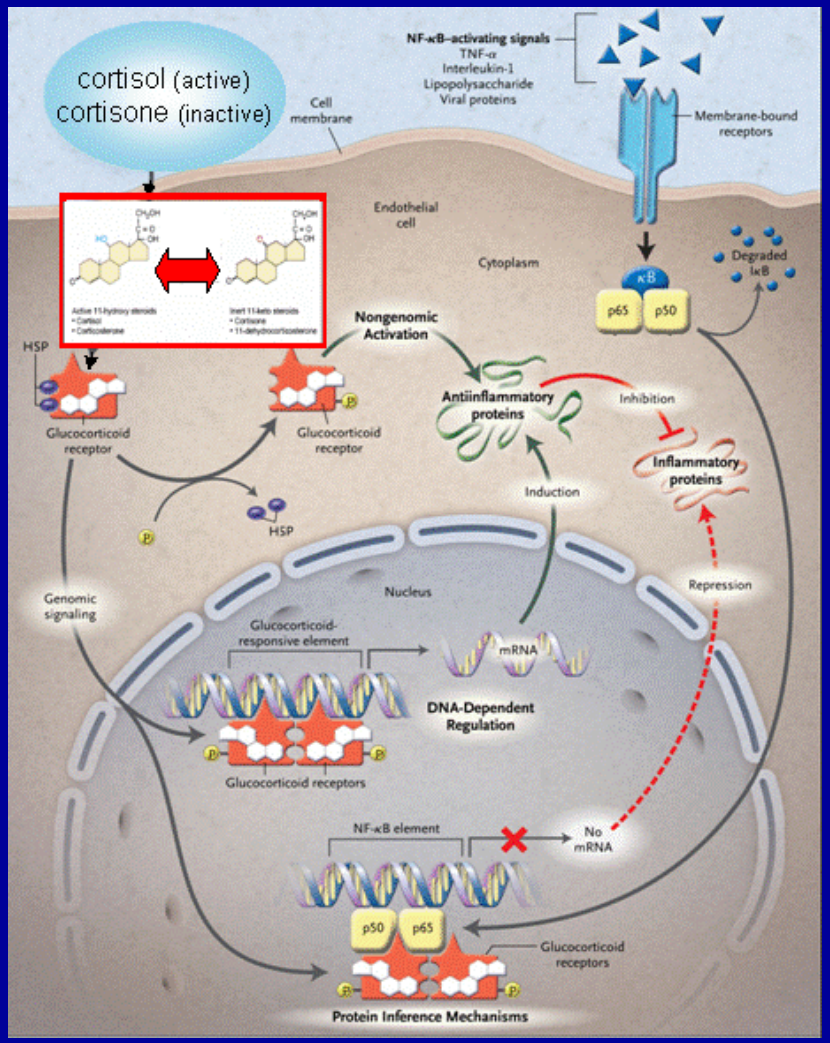
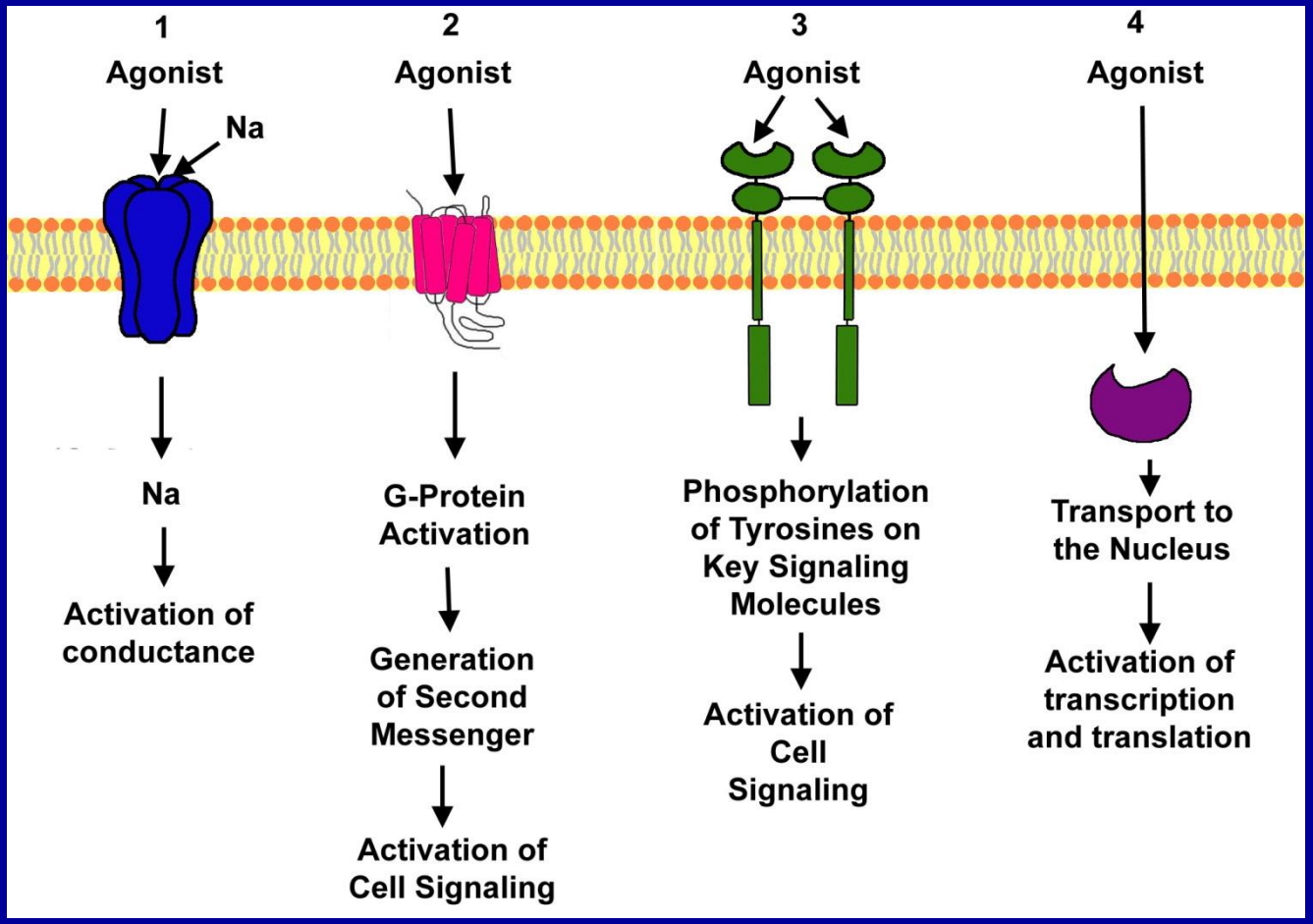
Rang and Dale Pharmacology, 2012

Intracellular receptors

Activated receptor proteins form dimer and move to the promoter region of the DNA, altering transcription processes (and thereby changing protein synthesis)




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

HETERORECEPTOR x AUTORECEPTOR

Heteroreceptor *= receptor regulating synthesis and/or release of other mediators than its own ligand.*

Heteroreceptors are presynaptic receptors, that response to neurotransmiters, neuromodulators or neurohormons released from nearby neurons or cells.

They are opposites of autoreceptors, that are sensitive only to neurotransmiters or hormones released by cell in which they are embedded.

HETERORECEPTOR x AUTORECEPTOR

***Autoreceptor** = receptor located on presynaptic nerve cell membranes and serves as a part of a feedback loop in signal transduction.*

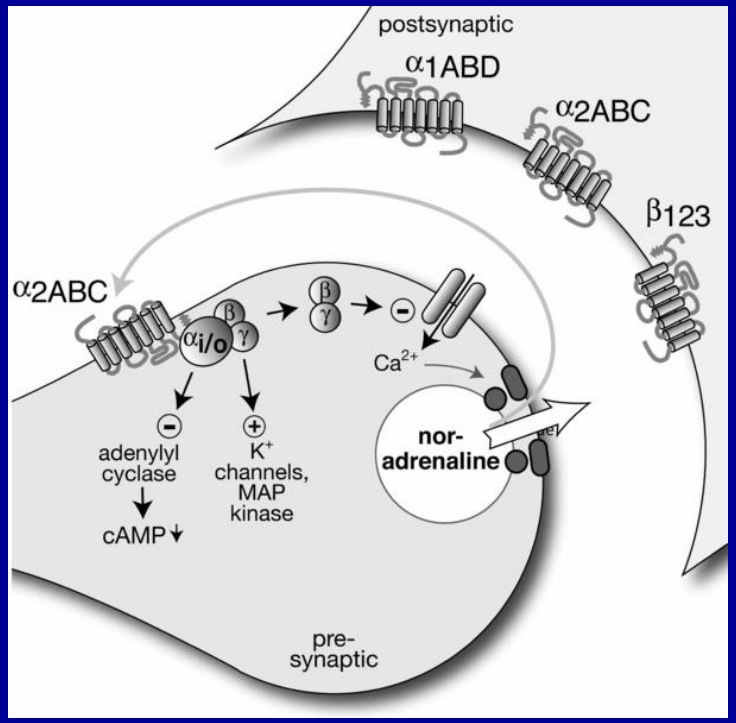
It is sensitive only to those neurotransmitters or hormones that are released by the neuron in whose membrane the autoreceptor sits.

Presynaptic neuron releases the neurotransmitter across a synaptic cleft to be detected by the receptors on a postsynaptic neuron.

Autoreceptors on the presynaptic neuron will also detect this neurotransmitter and often function to control internal cell processes, typically inhibiting further release or synthesis of the neurotransmitter.

Thus, release of neurotransmitter is regulated by negative feedback

HETERORECEPTOR x AUTORECEPTOR

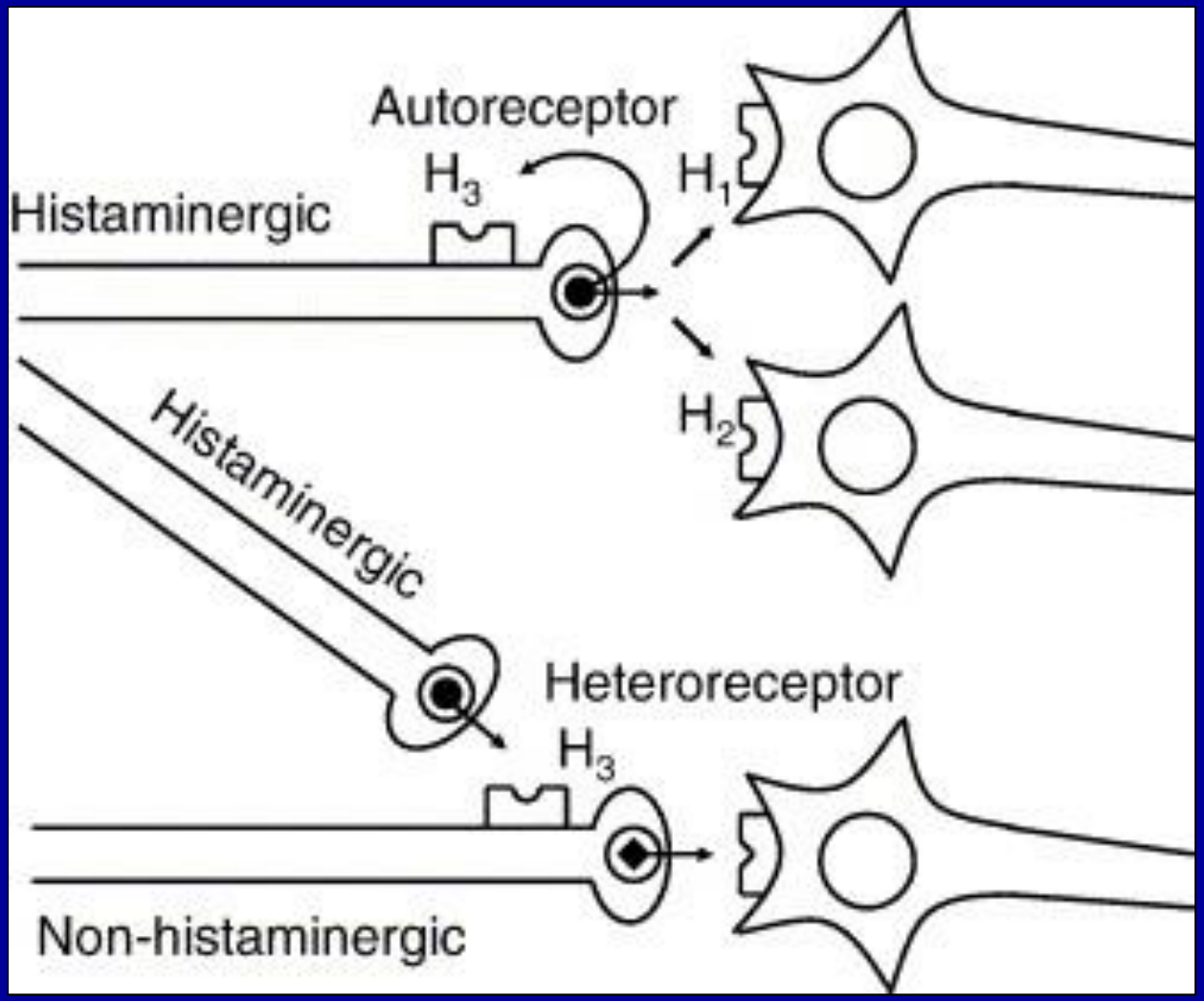


A pre-synaptic neuron releases a neurotransmitter, here nor-adrenaline (norepinephrine), into the synaptic cleft.

There the transmitter acts on the receptors of the post-synaptic neuron, but also on autoreceptors of the pre-synaptic neuron.

Activation of these autoreceptors typically inhibits further release of the neurotransmitter

HETERORECEPTOR x AUTORECEPTOR



Evaluation of efficacy : DOSE – RESPONSE CURVE (DRC)

1. During the preclinical development

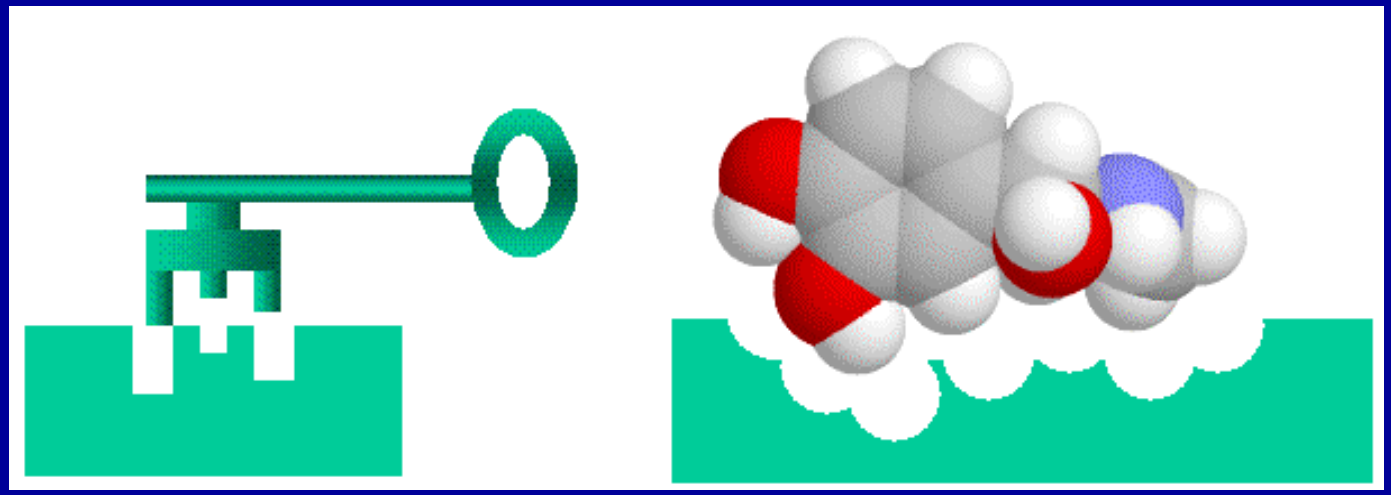
2. Confirmation during the clinical trials

3. Real-life pharmacotherapy

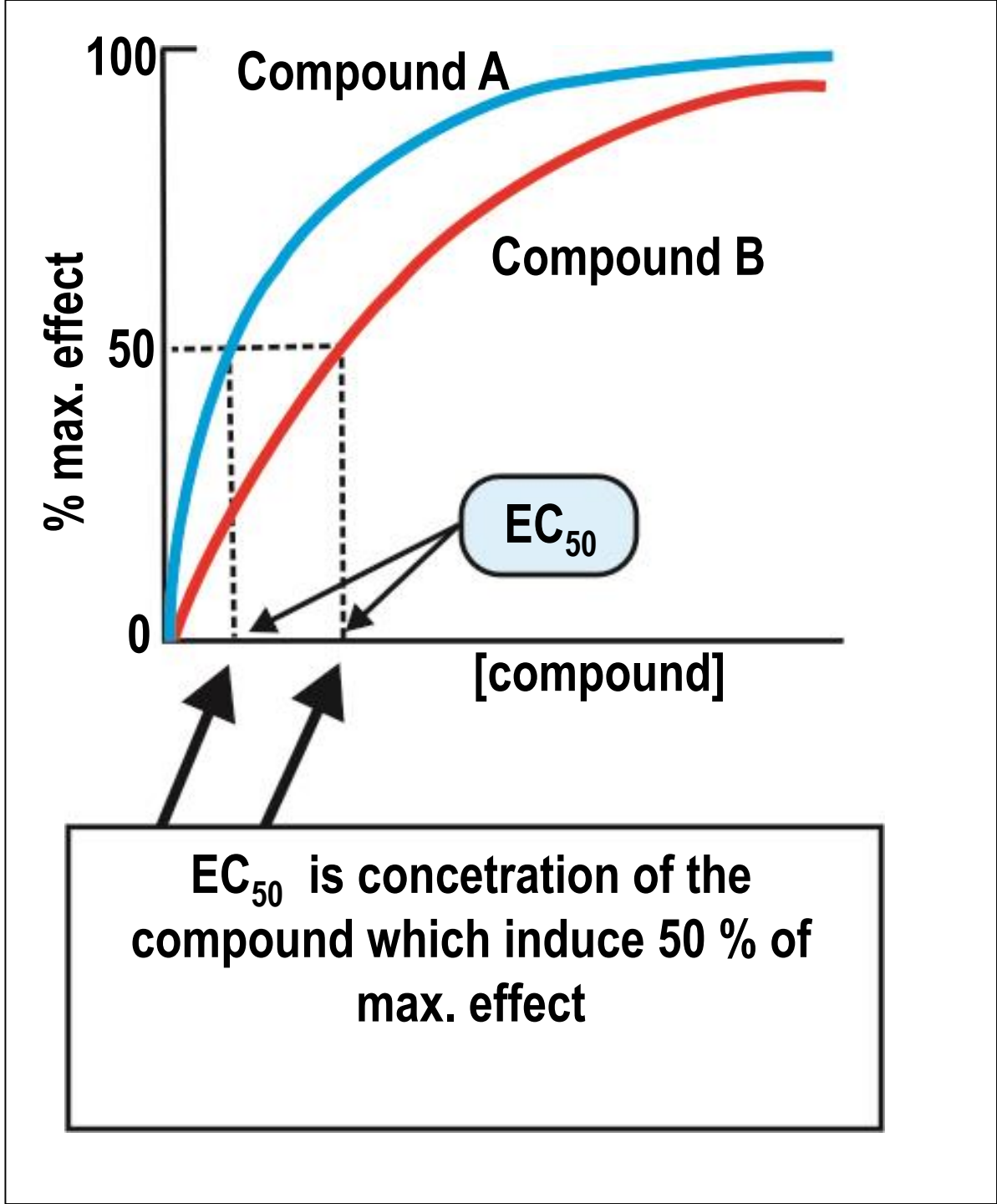
Ligand

a f f i n i t y *= ability of a drug to bind to a certain receptor.*
We evaluate it as concentration that leads to the half effect of the possible maximum - ED_{50}

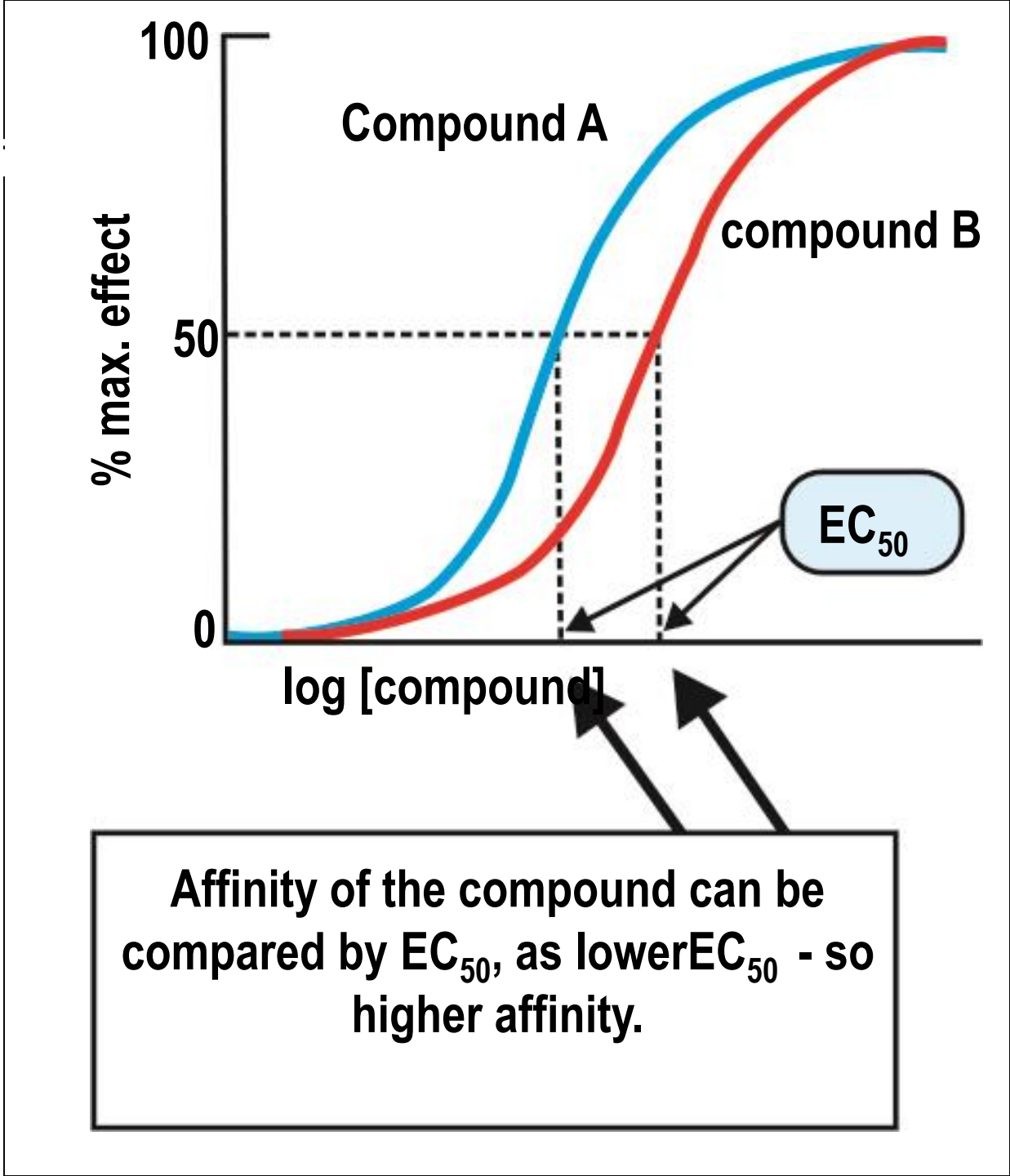
i n t r i n s i c a c t i v i t y *= ability of a drug to provoke after binding to a receptor such changes in its configuration (conformational change), that will lead to a signal and affecting of effector.*

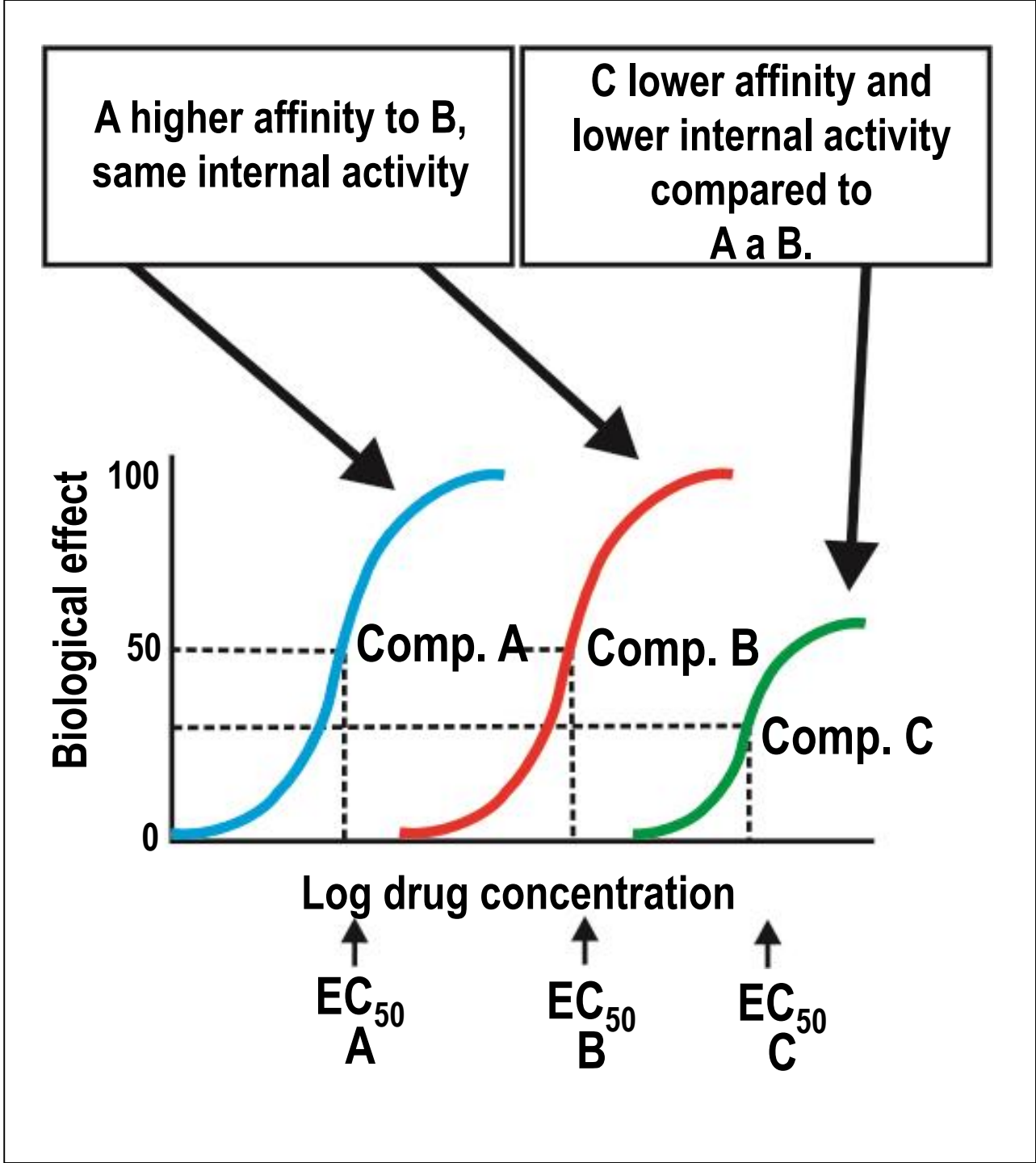


DRC – linear curve



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

AGONISM – ANTAGONISM

Agonist: the drug binds to the receptor (affinity) causing activation of the receptor (efficacy = 1)

eg. **phenylephrin** – agonist on α_1 adrenoceptors (similar response like adrenalin)

The types of agonist :

FULL AGONIST– can elicit a maximal efficacy (response)

PARTIAL AGONIST – drug with intermediate level of of efficacy, such that even when 100% of the receptors are occupied t he tissue response is submaximal (>0 and < 1)

INVERSE AGONIST shows selectivity for the resting state of the receptor, this being of significance only in unusual situations where the receptors show constitutive activity.

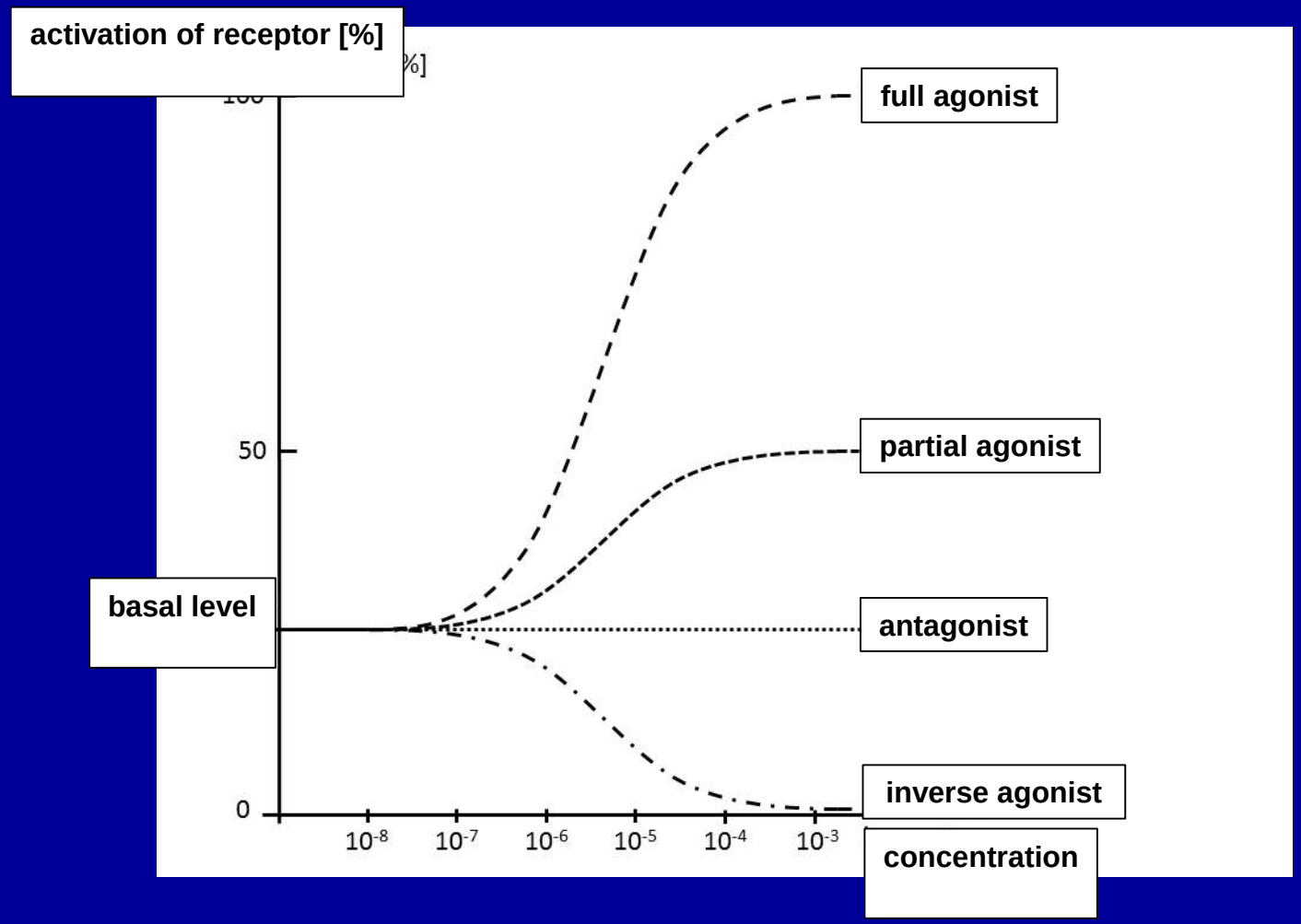
inverse agonists

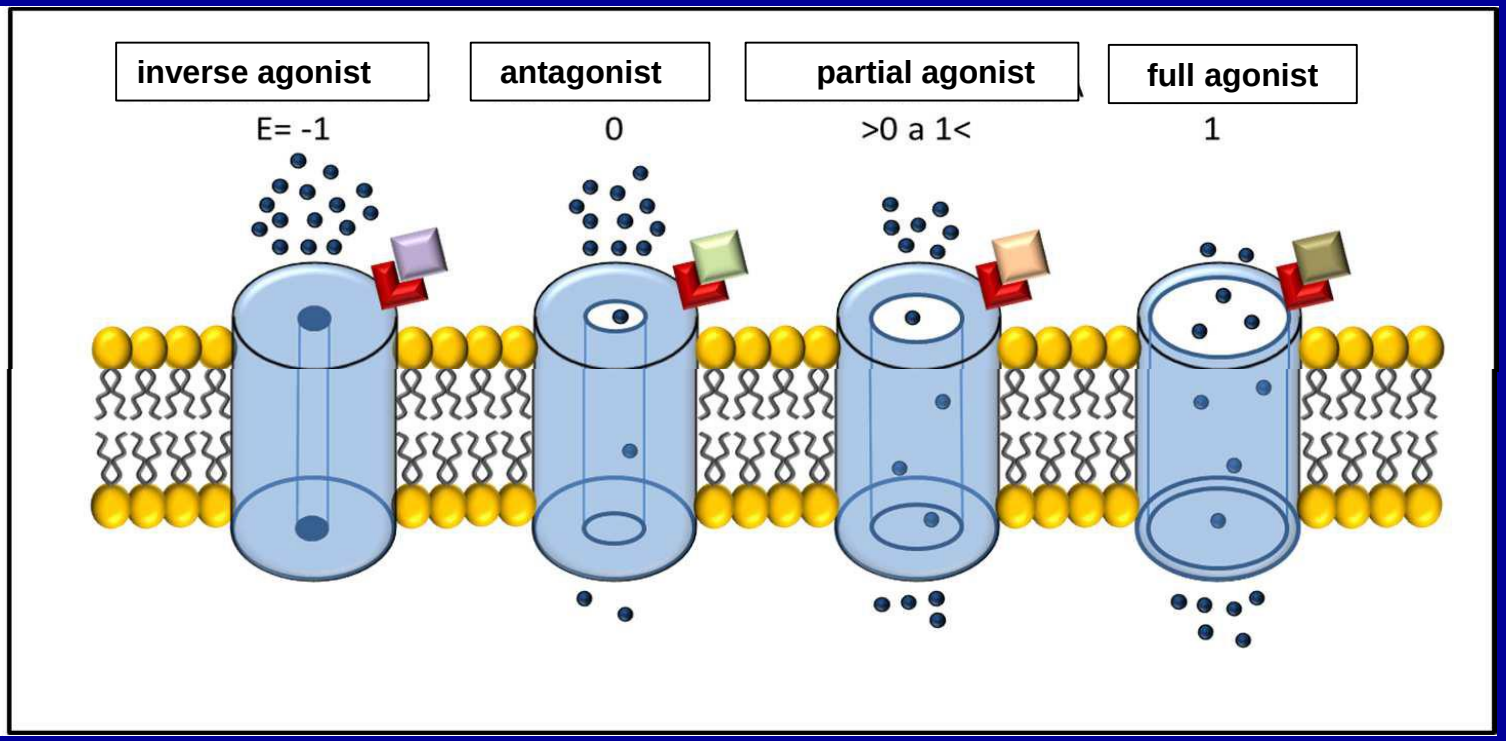
an inverse agonist is an agent that binds to the same receptor as an agonist but induces a pharmacological response opposite to that agonist.

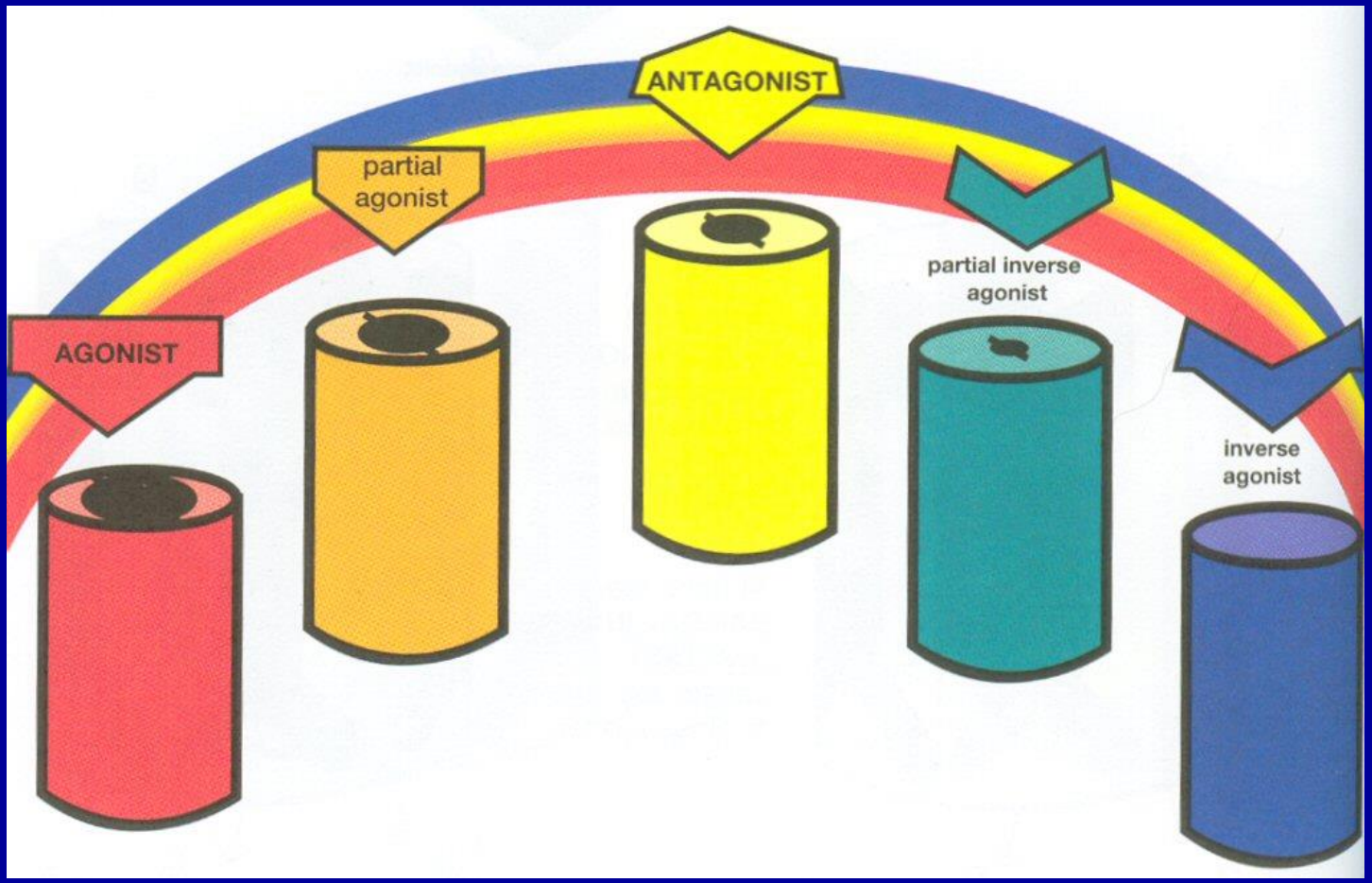
A prerequisite for an inverse agonist response is that the receptor must have a constitutive (also known as basal) level activity in the absence of any ligand.

An agonist increases the activity of a receptor above its basal level while an inverse agonist decreases the activity below the basal level.

A neutral antagonists has no activity in the absence of an agonist or inverse agonist but can block the activity of either.


activation of receptor [%]
full agonist
partial agonist
basal level
antagonist
inverse agonist
50
0
10^{-8}
10^{-7}
10^{-6}
10^{-5}
10^{-4}
10^{-3}
concentration


inverse agonist
antagonist
partial agonist
full agonist
E= -1
0
>0 a 1<
1


ANTAGONIST
partial agonist
partial inverse agonist
AGONIST
inverse agonist

ANTAGONISM

- frequently, the effect of one drug is diminished or completely abolished in the presence of another

/1/ ANTAGONISM by receptor block

a) Competitive, reversible antagonism:

The two drugs compete with each other, on the same binding site on receptor.

Affinity = 1, efficacy = 0

competitive antagonist prevent the binding of the agonist

ANTAGONISM

b) Non – competitive antagonism :

- **allosteric antagonism**

  antagonist binds on different binding site of the receptor, allosteric inhibitoin

- **irreversible antagonism**

  the drug forms covalent bonds to the receptor , eg. phenoxybenzamine (non-selective, irreversible alpha blocker)

Antagonism of substances – pharmacological at the receptor level

a) competitive

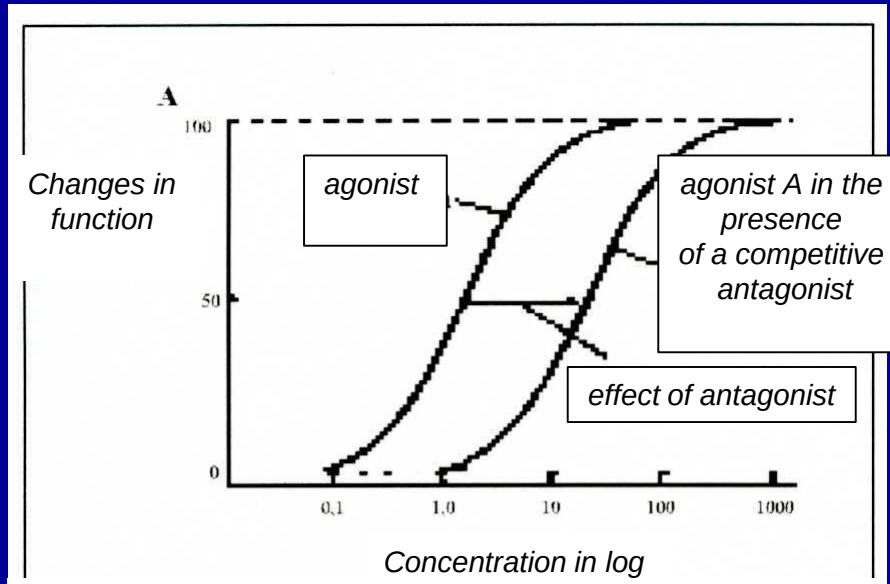
Substance A (agonist) has certain affinity (ED_{50} = 1 mg) and certain intrinsic activity (α = 1) – the left curve.

Agonist is in the presence of antagonist displaced from the bond to the receptor R.

*It is necessary for the **same effect** of agonist A to increase its dose 10 times (ED_{50} is higher 10 times).*

The curve of agonist moves to the right (the higher concentration of antagonist and the higher its affinity to the receptor – the larger the shift of the curve.

Antagonist has certain affinity, but its intrinsic activity β = 0.



Atropine = competitive antagonist of M receptors

Antagonism of substances – pharmacological at the receptor level

b) non-competitive

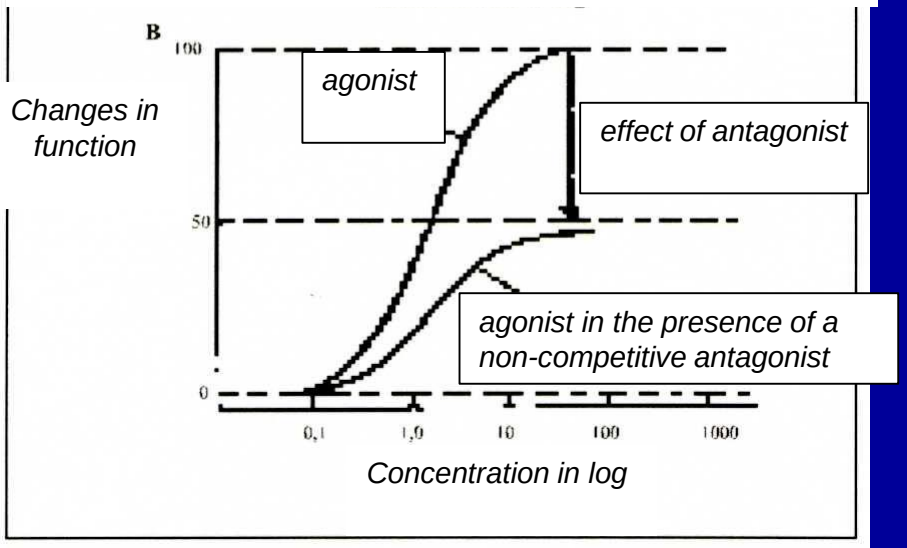
Decrease of agonist effect in another way than competition for the same binding site at a receptor R.

It is not possible to displace the antagonist using high concentrations of agonist.

It is explained on the subcellular level by blockade of another receptive site (RX).

Binding of agonist to R is not affected, however there is not present full activation of receptor R by agonist.

Valsartan = non-competitive antagonist of AT1 receptor



ANTAGONISM

/2/ Chemical antagonism

Chemical antagonism refers to the uncommon situation where the two substances combine in solution; as a result, the effect of the active drug is lost.

Examples include the use of chelating agents (e.g. dimercaprol) that bind to heavy metals and thus reduce their toxicity.

ANTAGONISM

/3/ Pharmacokinetic antagonism

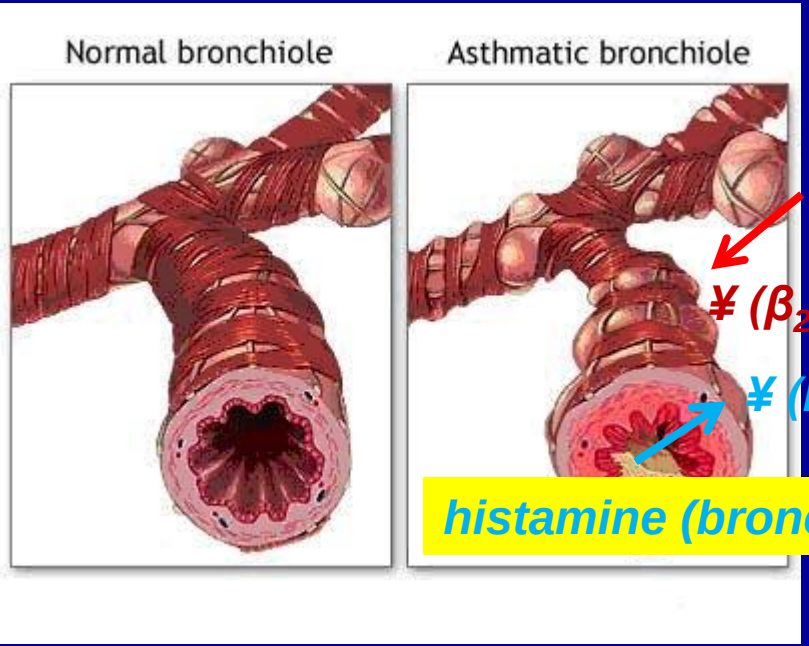
„Antagonist" effectively reduces the concentration of the active drug at its site of action (interaction warfarin – phenobarbital)

ANTAGONISM
/4/ Physiological antagonism

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

Histamine x norepinephrine (affecting of vessels).

Affecting of bronchioles.



Regulation of receptors

Receptors are dynamic systems, that can adapt and balance in this way e.g. changes in neuromediators availability.

Some receptors have very short halftime of existence, e.g. benzodiazepine receptors only few hours.

Two types of receptor regulation can be distinguished:

1. ***regulation by a change in receptor number** – decrease (downregulation), or increase (upregulation) in the number of binding sites for agonists as response to physiological stimulation of receptors*

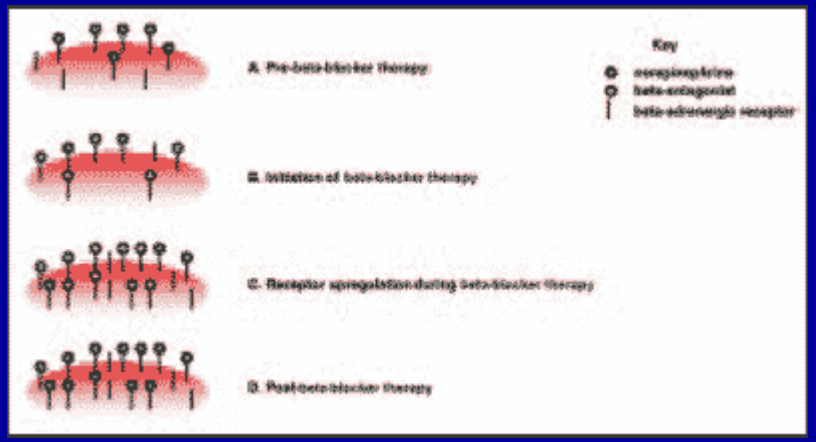
2. ***regulation by receptor properties**, i.e. response to receptor stimulation, that can be affected by mutual relationship among different receptors.*

Generally, however the differentiation of these two regulation types is artificial; e.g. desensitization can be caused by both mechanisms.

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.

II. Specific action

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

2. Ion channels

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

II. Specific action

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

3. Enzymes

- *Competitive or non-competitive enzyme inhibitors*
  - reversible
    - *acetylcholinesteraze*– physostigmine
    - *phosphodiaserase* – methylxantine
  - irreversible:
    - *cyklooxygenaze* – ASA (aspirin)
    - *MAO-B* – selegilin
    - *aldehyddehydrogenaze*– disulfiram

Effect on enzymes

Acetylcholinesterase inhibitors (rivastigmine, pyridostigmine):

Pyridostigmine is a parasympathomimetic drug, reversible inhibitor of acetylcholinesterase.

It prolongs the effect of acetylcholine.

Augmented neuromuscular transmission (in both skeletal and smooth muscles).

Miosis, bradycardia, increased intestinal tone, increased tone of skeletal muscles, bronchoconstriction, stimulation of salivary glands…

Effect on enzymes

Inhibitors of monoaminooxidase (moclobemide):

Antidepressant – reversible inhibition of monoaminooxidase, preferably type A.

Decrease in serotonin metabolism, norepinephrine and dopamine leading to their increased extracellular concentrations.

Effect on enzymes

Inhibitors of ACE - angiotensin converting enzyme (enalapril):

Angiotensin converting enzyme (ACE) catalyses conversion of angiotensin I to vazopressoric angiotensin II.

ACE inhibition leads to decrease in plasma concentration of angiotensin II.

II. Specific action

1. Receptors
2. Ion channels
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4. Transport„carriers“

e.g. a **proton pump** is an integral membrane protein that is capable of moving protons across a biological membrane.

Mechanisms are based on conformational changes of the protein structure

Proton pump inhibitors (PPIs) are a class (group) of drugs that work on the cells that line the stomach, reducing the production of acid.

They include: omeprazole, pantoprazole etc…. various different brand names (generics)