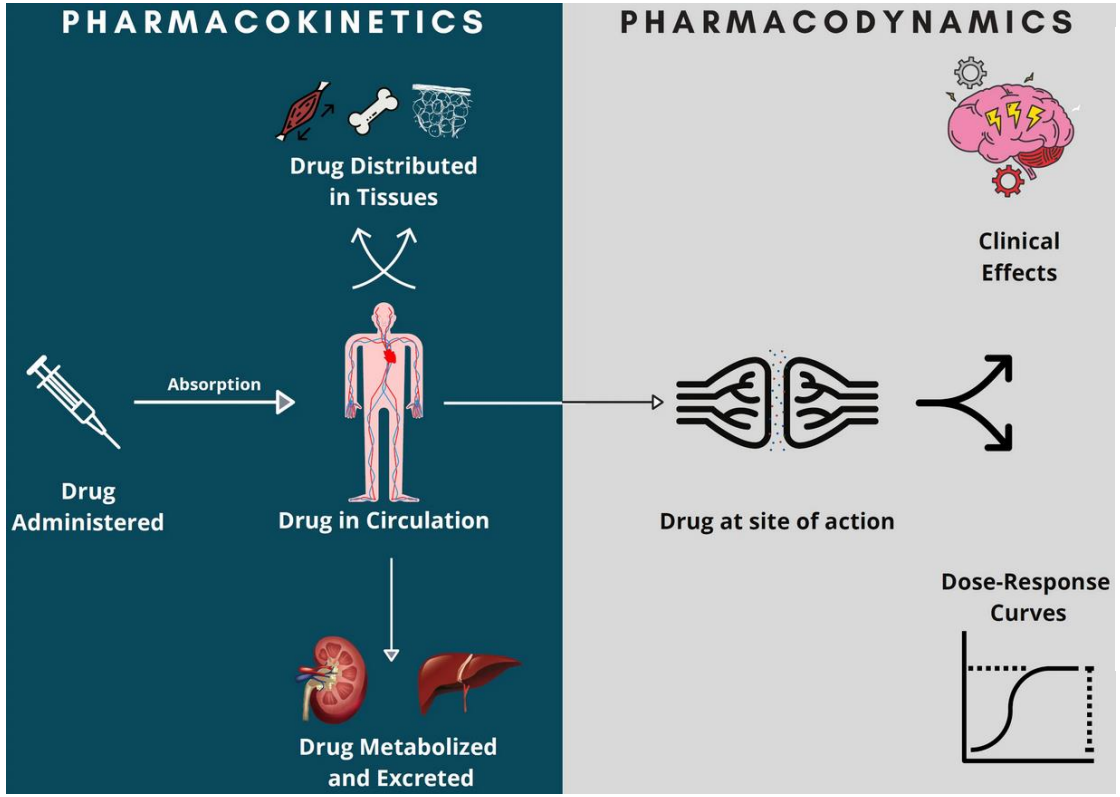
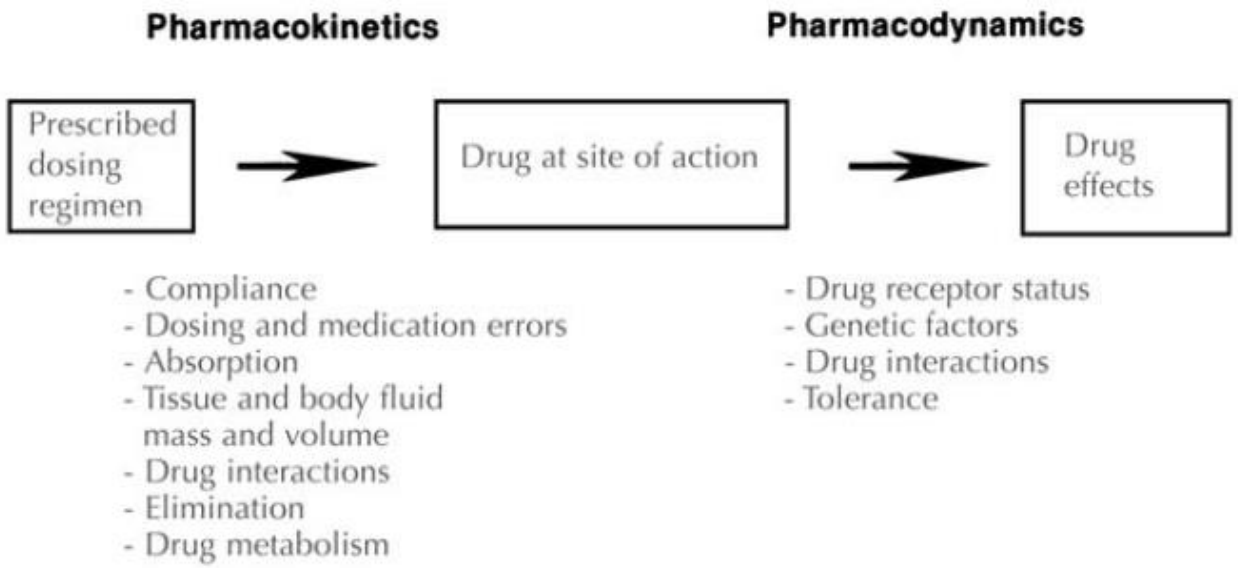
MUNI
PHARM

PHARMACODYNAMICS
DRUG RECEPTORS

Assoc. Prof. PharmDr. Peter Kollár, Ph.D.
Department of Pharmacology and Toxicology
Faculty of Pharmacy MU

Pharmacology

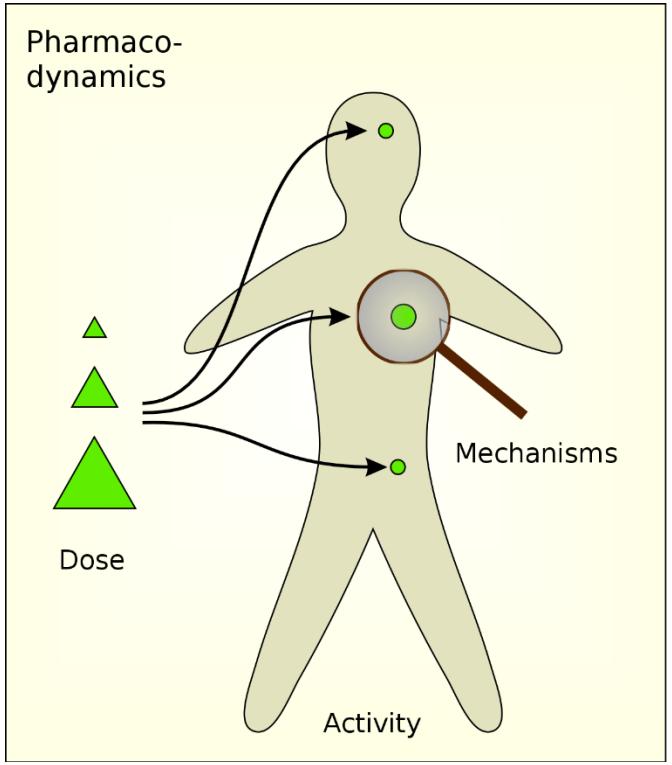




MUNI PHARM

Pharmacodynamics

- Deals with the effects of drugs on biologic systems
- It studies the drug´s mechanism of action at molecular level
- It provides basis for rational use of drugs and design of better or more effective drugs
- “What the drug does to the body”



MUNI
PHARM

Terms used in Pharmacodynamics I.

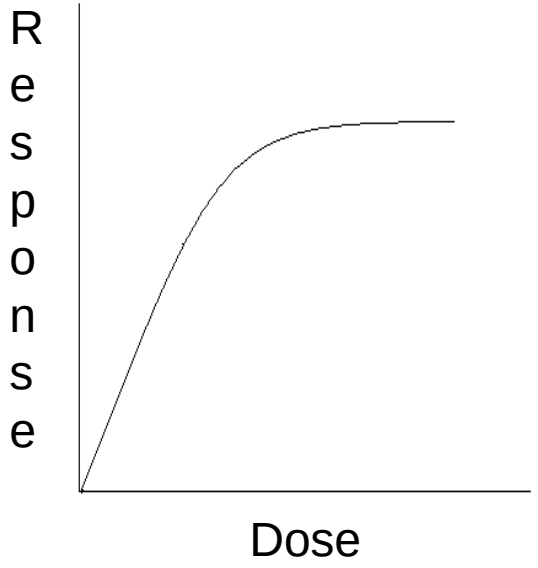
- **Receptor:**
  - Specific molecule, through which drugs (D) interact to produce changes in system function
  - Component of cell or organism that interacts with D and initiates chain of biochemical events leading to observed D's effects
- **Effector:**
  - Molecule that translate D receptor interaction into change in cellular activity (e.g. adenylyl cyclase)

MUNI PHARM

Terms used in Pharmacodynamics II.

- **Affinity:** ability of D to bind a receptor
  - determined by dissociation constant (Kd) (the lower the Kd the higher the affinity)

- **Efficacy:** ability of D-rec. complex to produce effect
  - usually dose-dependent
  - determined by graded dose-response curve

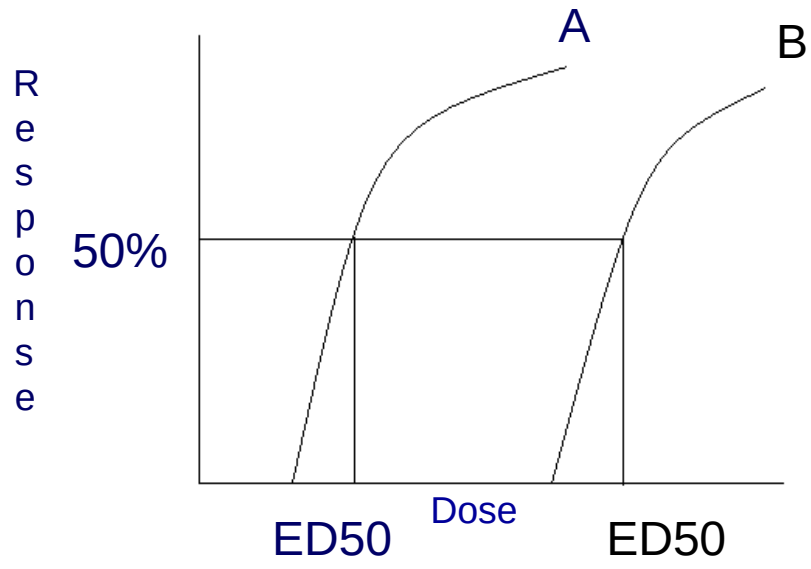


$$Drug\,(D) + \mathrm{Re}ceptor\,(R) \xleftrightarrow{Kd} D/R\,Complex \rightarrow (\mathrm{Re}sponse)$$

MUNI PHARM

Terms used in Pharmacodynamics III.

- **Potency:** it refers to the concentration (EC_{50}) or dose (ED_{50}) of D producing 50% of maximum effect
  - depends on the Kd which determines rec. affinity to bind that D
  - the lower the ED_{50}, the more potent D



drug A > drug B

MUNI PHARM

Receptor Structures

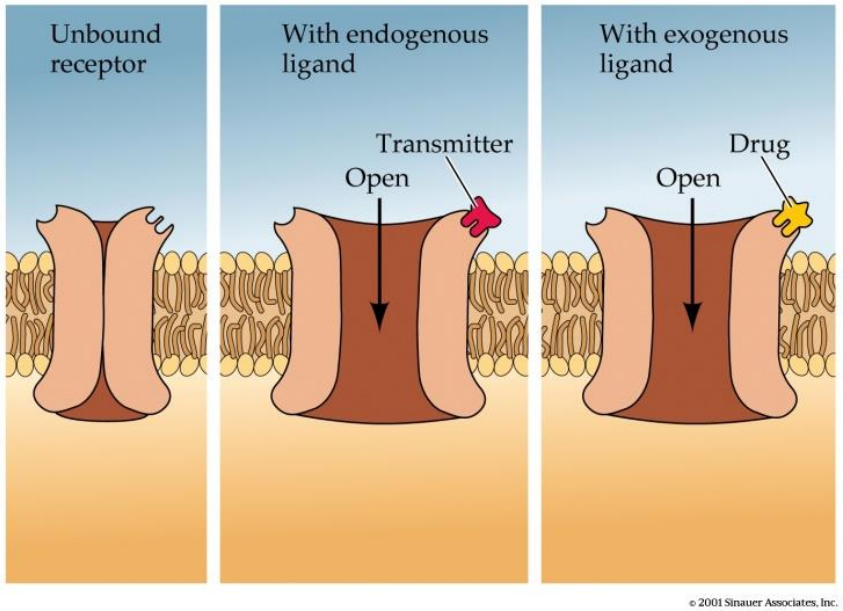
1) **Ion Channel Receptors**
2) **Carrier Proteins**
3) **G Protein-Coupled Receptors**
4) **Enzymes**

– The majority of receptors characterized to date are proteins; a few Rp are other macromolecules, such as DNA

MUNI PHARM

Receptor Agonists

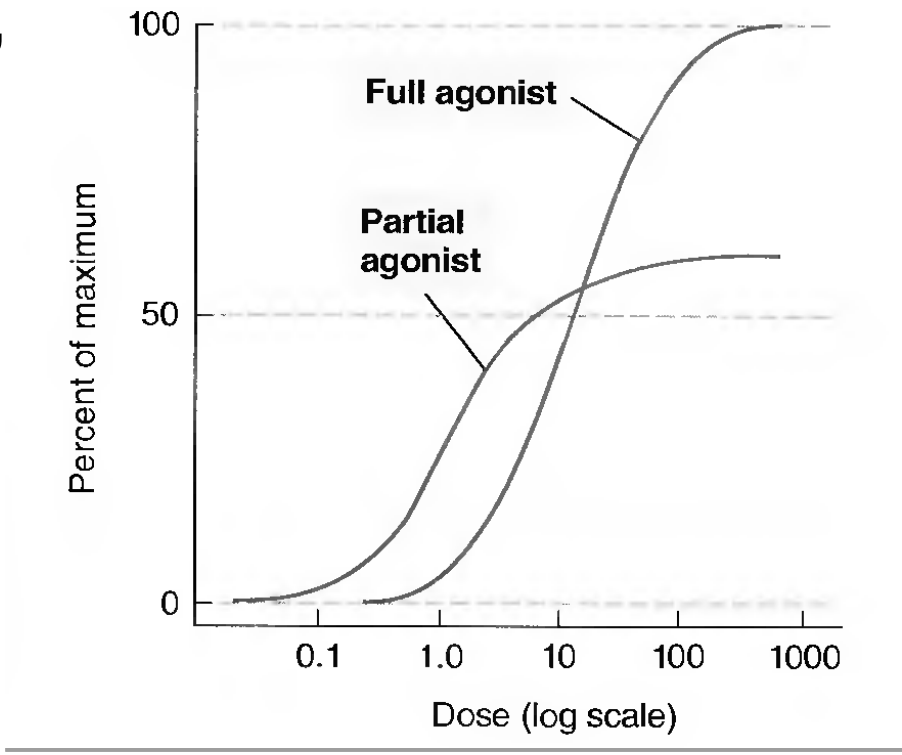
- Mimic actions of neurotransmitter at same site, or bind to nearby site and facilitate neurotransmitter binding
- Agonist is able to fully activate the effector system when it binds to the receptor



MUNI PHARM

Partial Agonists

- Partial agonist produces less than full effect, even when it has saturated the receptor
- In the presence of full agonist, partial agonist acts as inhibitor



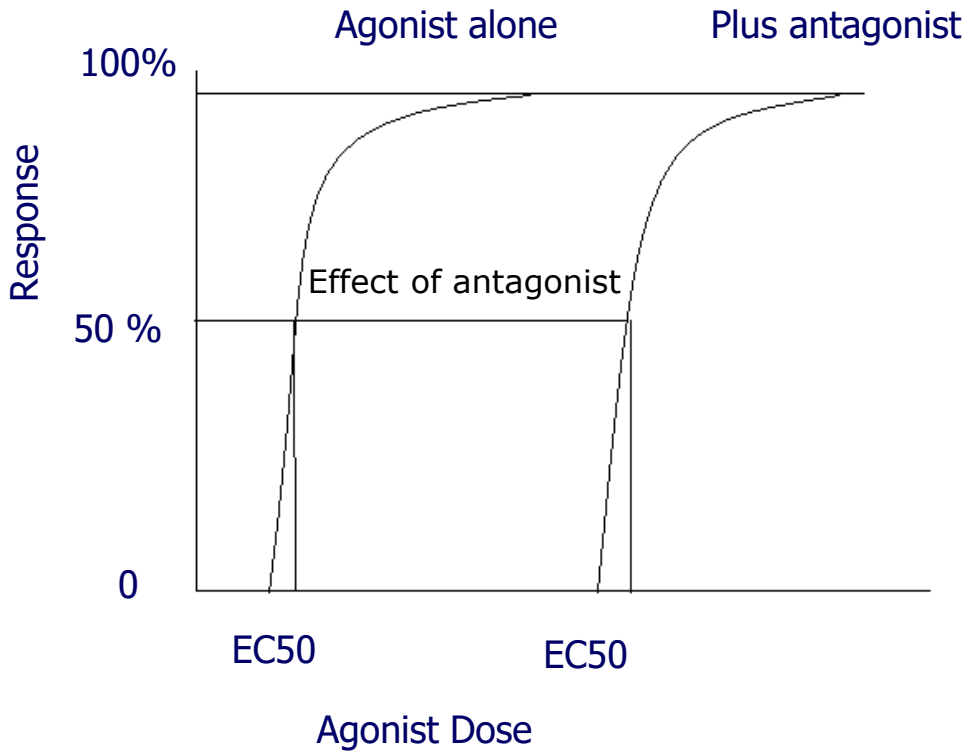
MUNI PHARM

Types of receptor Antagonists

1. Competitive Antagonist:

- Antagonist could be displaced by excessive dose of agonist
- Competitive antagonist decreases potency of agonist but doesn't alter its maximal effect
- Dose-response curve shows parallel shift to the right

- Examples:
- propranolol antagonizes adrenaline on β-receptors
- atropine antagonizes ACh on cholinergic muscarinic receptors

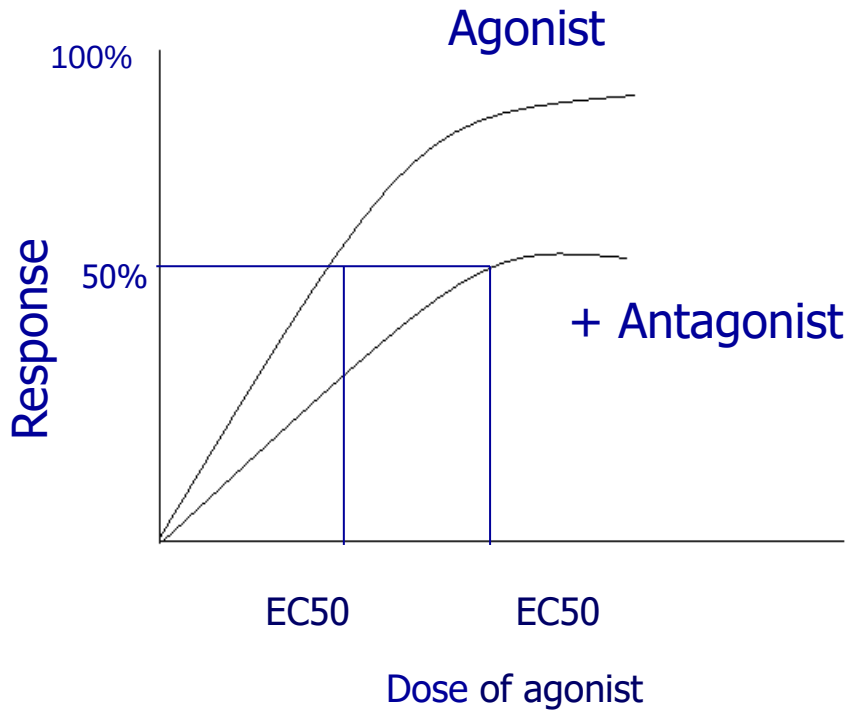


MUNI PHARM

Types of receptor Antagonists

2. Non-Competitive Antagonist:

- Antagonist is not displaced by agonist
- Antagonist decreases potency and maximal effect of agonist
- Dose-response curve shows non-parallel shift to the right



MUNI PHARM

Signaling Mechanisms

- Once agonist has bound to its receptor, various effector mechanisms are activated
- For most D-receptor interactions the drug is present in EC space, while the effector mechanism is located intracellularly and modifies some IC process

MUNI
PHARM

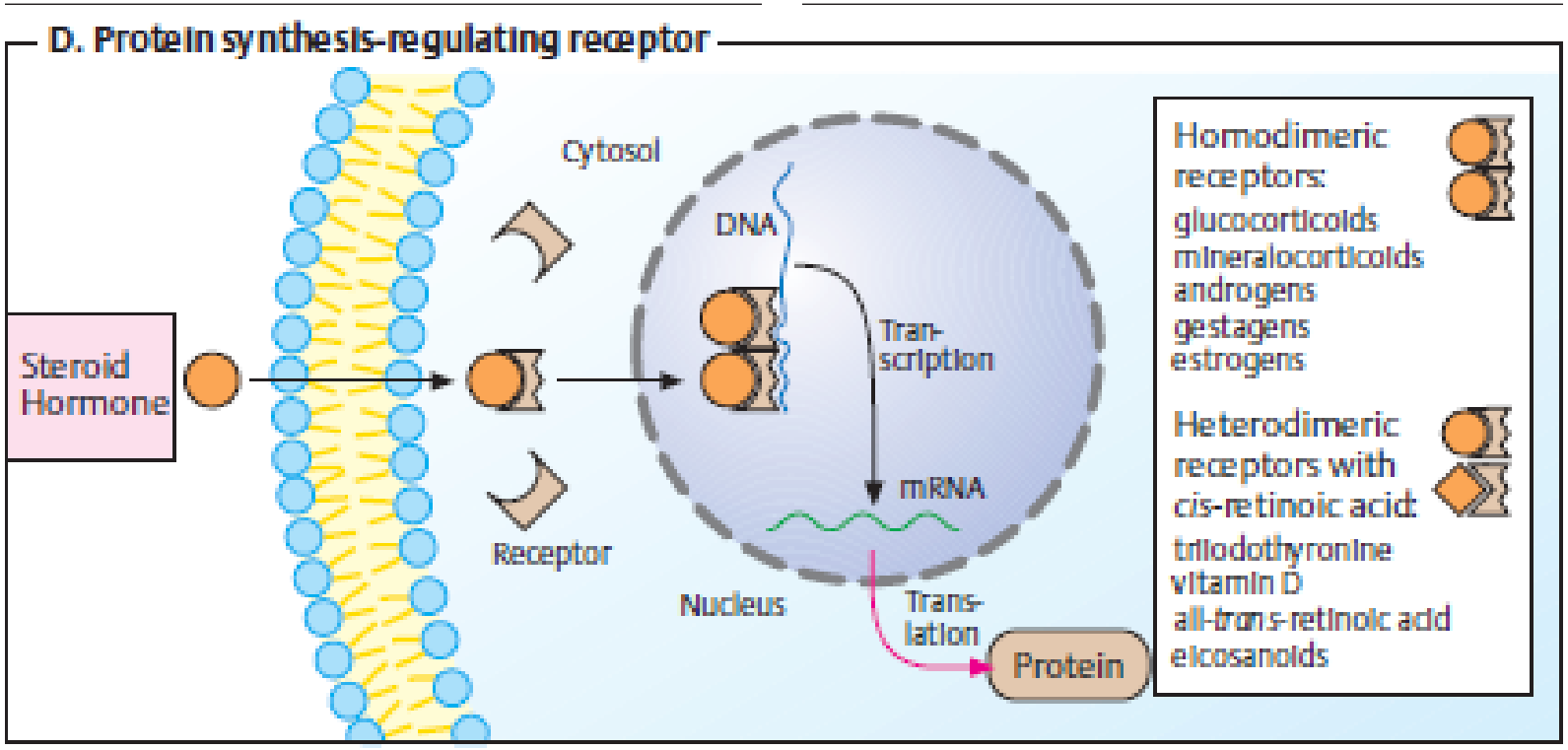
Major types of signaling mechanisms for receptor-effector systems

1) Intracellular receptors
2) Receptors located on membrane-spanning enzymes
3) Receptors located on membrane-spanning molecules that bind separate IC tyrosine kinase molecules
4) Receptors located on membrane ion channels
5) Receptors linked to effectors via G proteins

MUNI PHARM

1. Intracellular receptors

- More lipid-soluble or diffusible agents may cross membrane and combine with IC receptor, that affects an IC effector molecule
- No specialized transmembrane signaling device is required

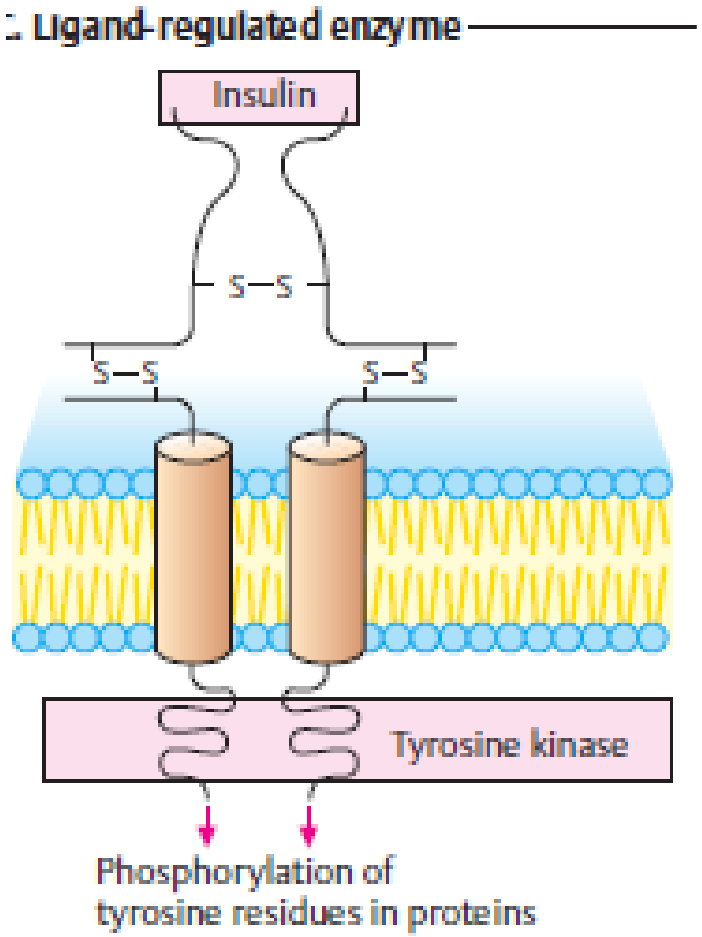


e.g.: corticosteroids, mineral corticoids, sex steroids, vitamin D, thyroid hormone

MUNI PHARM

2. Receptors located on membrane-spanning enzymes

- Drugs combine with receptors on EC part of enzymes and modify their IC activity
- e.g.: Insulin acts on a tyrosine kinase that is located in the membrane
- When activated, receptors dimerize and phosphorylate specific protein substrates



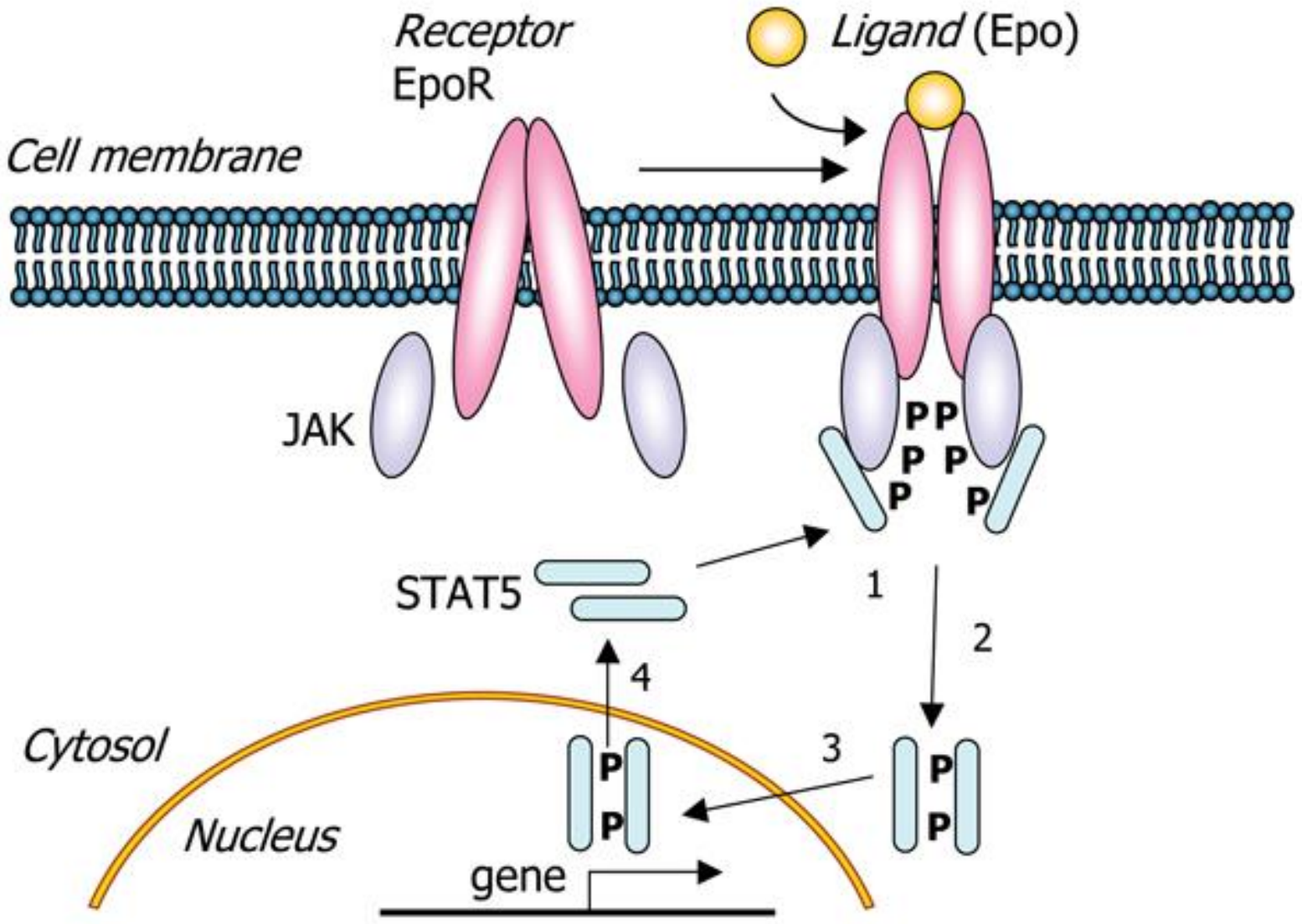
MUNI
PHARM

3. Receptors located on membrane-spanning molecules that bind separate IC tyrosine kinase molecules

- Receptors have EC and IC domains and form dimers
- After rec. activation by appropriate D, tyrosine kinase molecules (Janus kinases) are activated, resulting in phosphorylation of "STAT" molecules (**S**ignal **T**ransducers and **A**ctivators of **T**ranscription)
- STAT dimers then travel to nucleus, where they regulate transcription

MUNI PHARM

Jak-Stat pathway



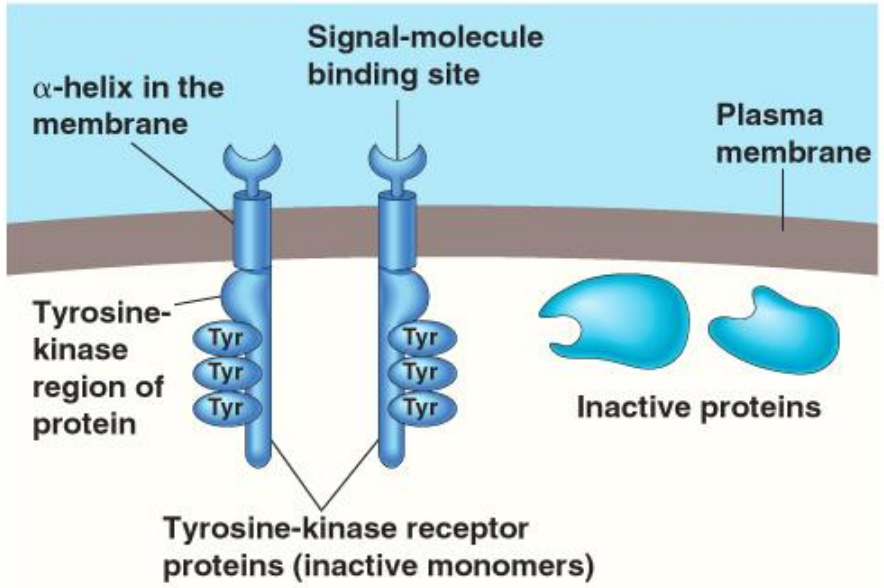
Klipp and Liebermeister BMC Neuroscience 2006 7(Suppl 1):S10

MUNI PHARM

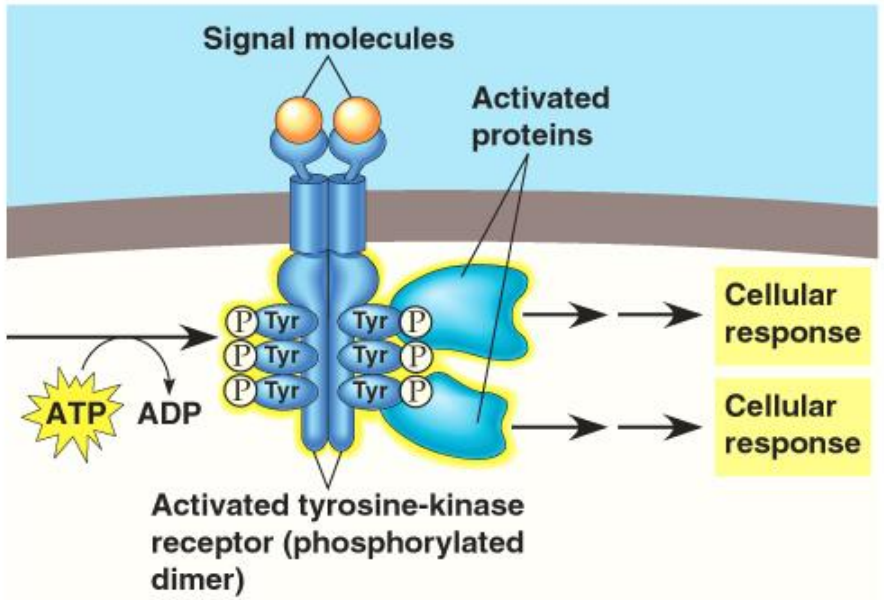
Tyrosine-kinase receptors

- Receptors exist as individual polypeptides
- Each has EC signal-binding site
- An IC tail with a number of tyrosines and a single α-helix spanning the membrane

MUNI
PHARM



(a) Inactive tyrosine-kinase receptor system



(b) Activated system

Ligands bind to both receptors

The two receptor polypeptides aggregate forming a dimer

Activates the tyrosine-kinase parts of the dimer

Each phosphorylates (using ATP) the tyrosines on the tail of the other polypeptide

Receptor proteins are now recognized by relay proteins inside the cell

Relay proteins bind to the phosphorylated tyrosines (may activate 10 or more different transduction pathways)

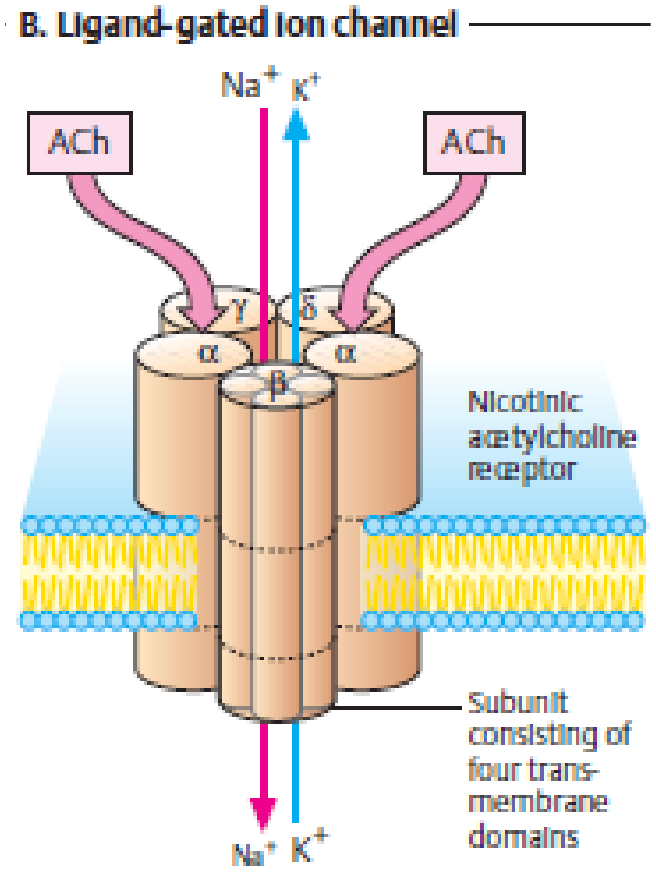
4. Receptors located on membrane ion channels

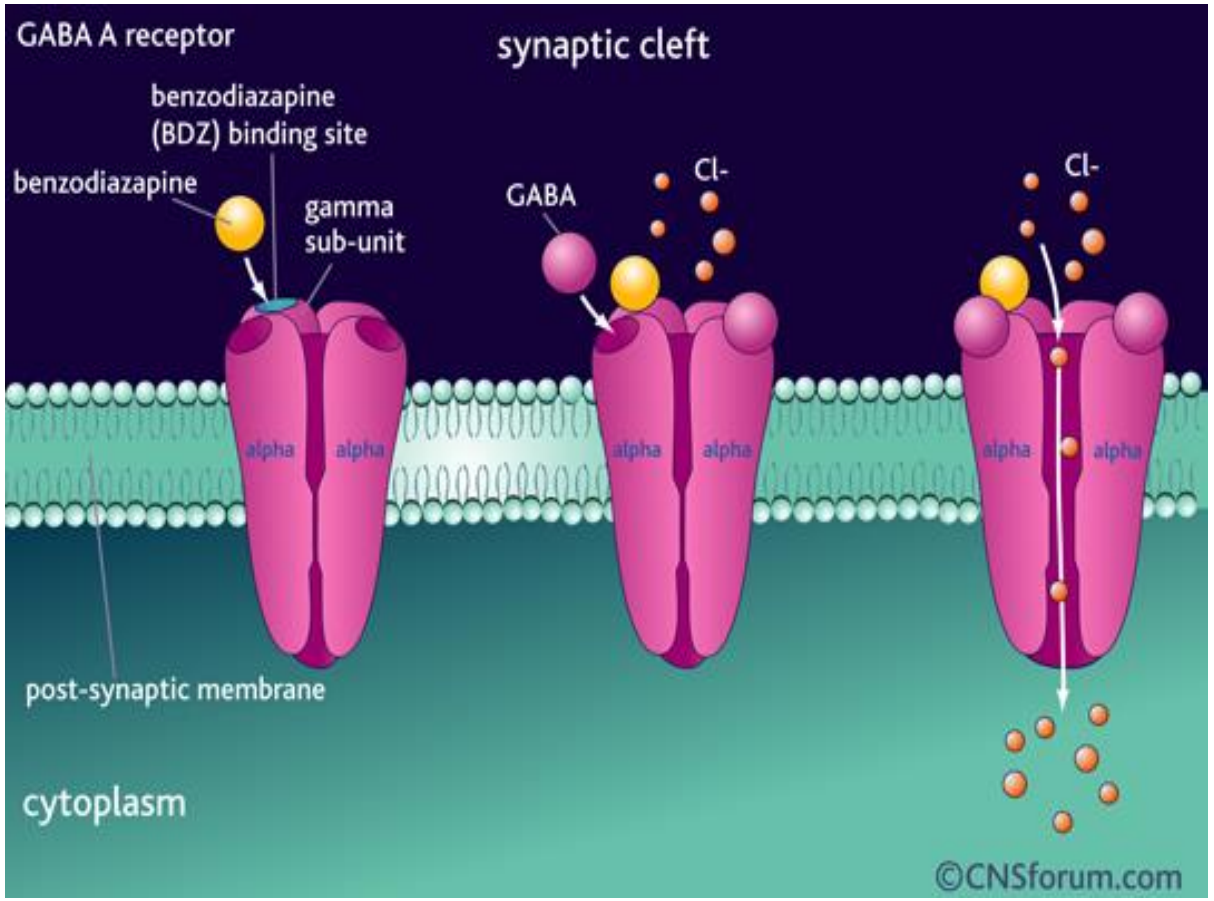
- Receptors that regulate membrane ion channels may **directly** cause the opening of an ion channel (eg, acetylcholine at the nicotinic receptor) or **modify** the ion channel's response to other agents (eg, benzodiazepines at the GABA channel)
- The result is a change in transmembrane electrical potential

MUNI PHARM

4. Receptors located on membrane ion channels

- Directly open channel
- Modify the response of channel to other substances





MUNI PHARM

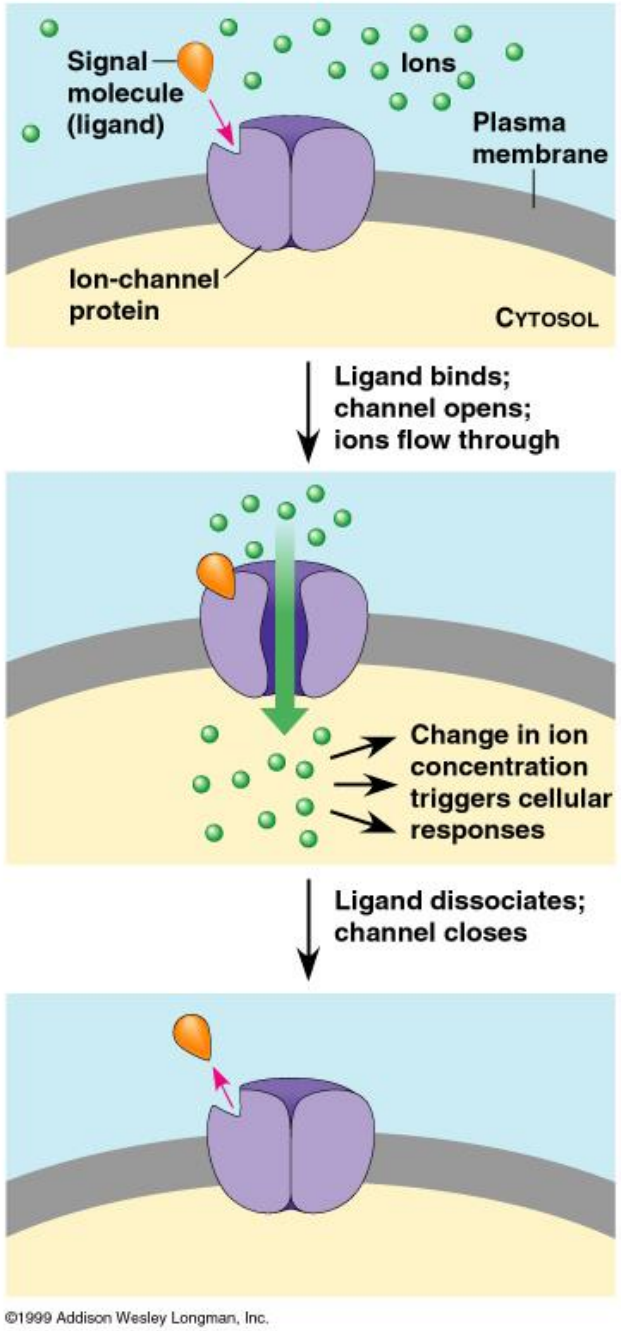
Ion channel receptor

– Structure: Protein pores in the plasma membrane

Signal molecule binds as a ligand at a specific site on the receptor

Conformational changes open the channel allowing ions to flow into the cell

The change in ion concentration within the cell triggers cellular responses



MUNI PHARM

5. Receptors linked to effectors via G proteins

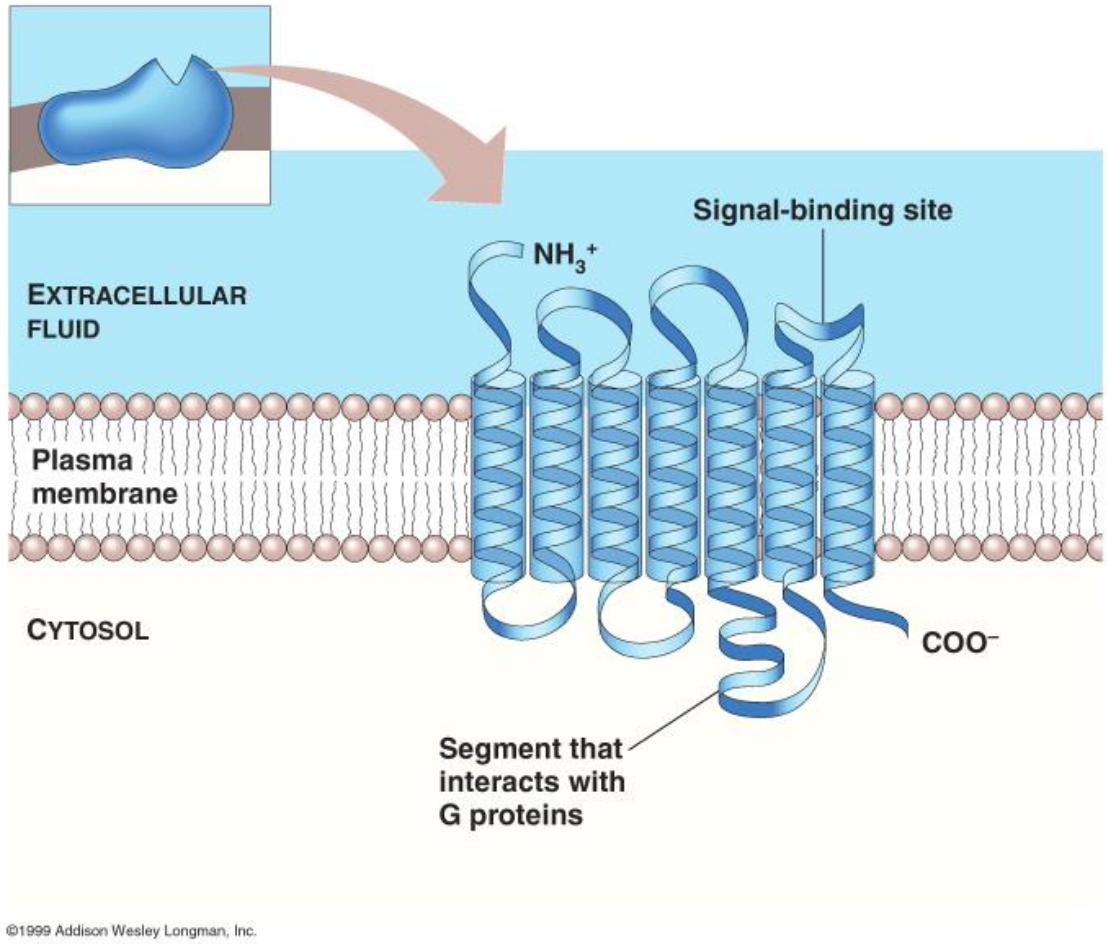
- Number of drugs bind to receptors, that are linked by coupling proteins to IC or membrane effectors
- Typical examples of this group are sympathomimetics (adrenergic drugs), which activate or inhibit adenylyl cyclase by a multistep process:
  - activation of receptor by D results in activation of G proteins that either stimulate or inhibit the cyclase

MUNI PHARM

G protein-linked receptors

Structure:

- Single polypeptide chain threaded back-and-forth, resulting in 7 transmembrane α-helices
- G protein attached to cytoplasmic side of membrane (functions as a switch)



MUNI PHARM

Chemical signal binds as a ligand to a G protein-linked receptor

G protein linked receptor changes shape and interacts with a G protein

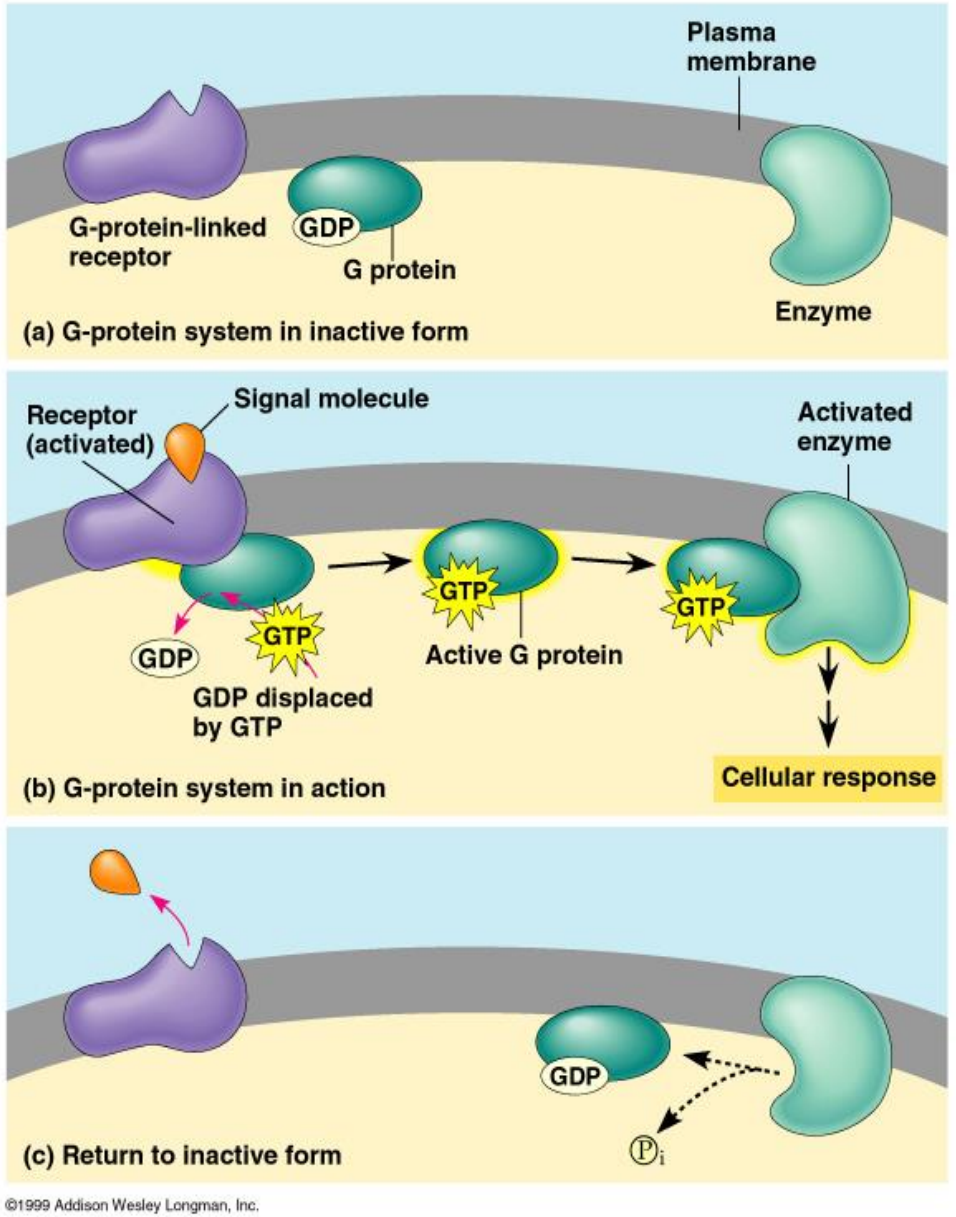
Interaction causes GDP to be displaced and GTP to be bound to the G protein

The active G protein binds to another protein, usually an enzyme

The enzyme is activated

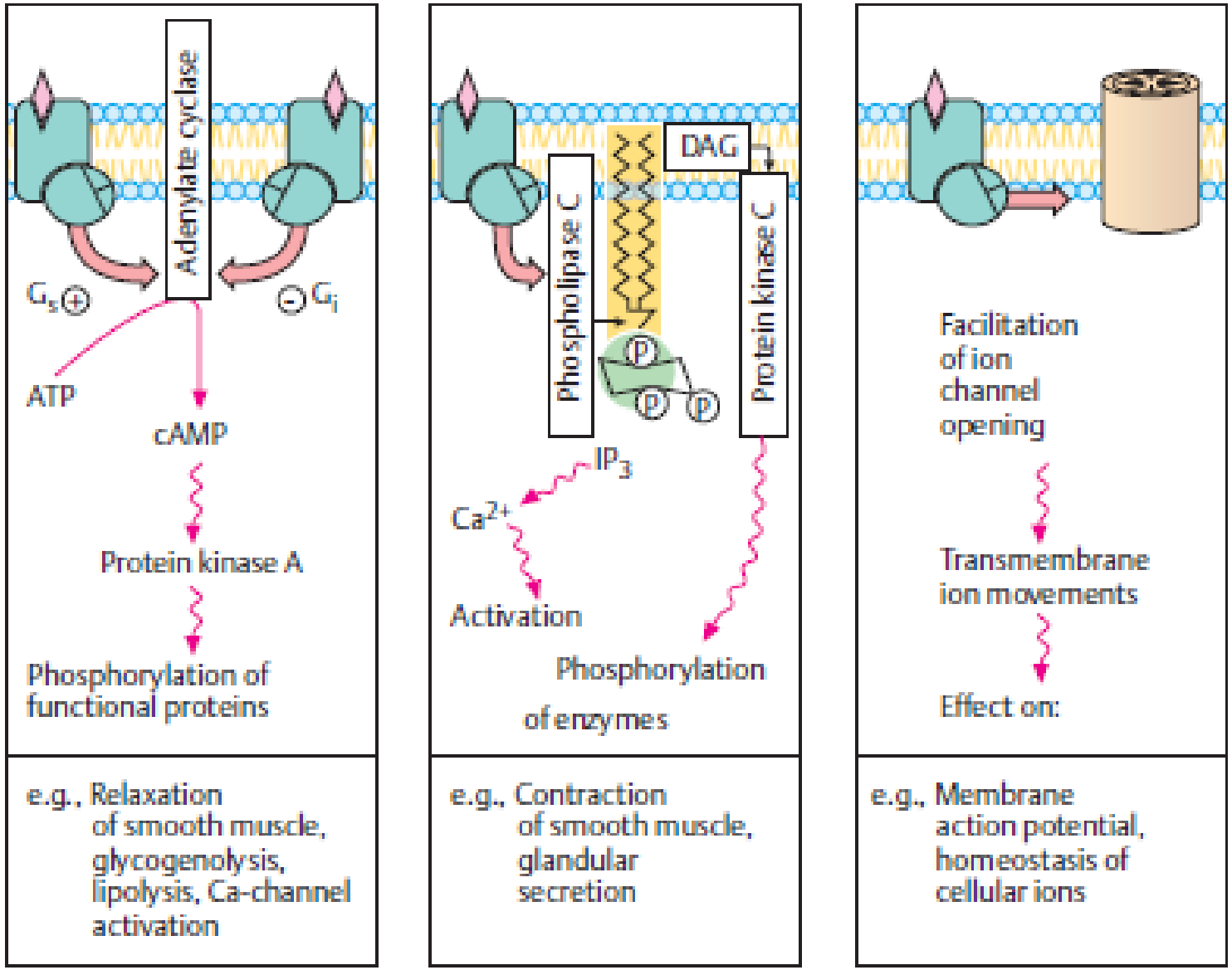
G protein hydrolyzes GTP back to GDP

G protein releases from the enzyme and the reaction stops



MUNI PHARM

B. G-Proteins, cellular messenger substances, and effects



Thank you
for your attention

MUNI PHARM