Principles of regulation of metabolic pathways

2nd week

Regulation of metabolic processes

- the activity of the metabolic pathways must be constantly monitored and regulated in order to fulfill the physiological state of the organism

- control of anabolism/catabolism according to the needs of the cell and the whole organism

Regulation of metabolic processes

Regulation of metabolic processes is controled on 2 levels:

1. **At the level of the cell**
   - compartmentalization of metabolisms
   - by availability of substrates and products of metabolic pathways
   - by change of enzyme activity
   - by covalent modification of enzymes
   - by change of enzyme amounts

2. **At the level of whole organism**
   - coordination of the functions of specialized organs
   - regulatory mechanisms at the level of the organism:
     - endocrine system (hormones)
     - nervous system (neurotransmitters)

Regulation at the cell level

Compartmentation of metabolic processes

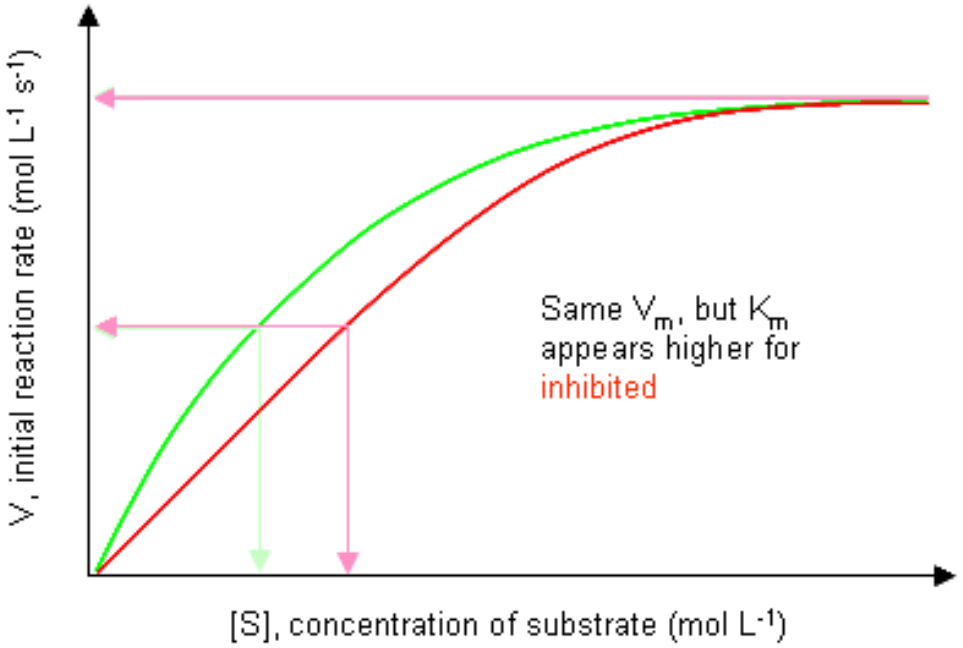
- compartmentalization of metabolic processes: semipermeable membranes ensure a chemically diverse environment in individual organelles
- organelles are distinguished by membrane transporters, enzymatic equipment, environmental properties, distribution of substrates and products
- various metabolic pathways take place in the cytoplasm, mitochondria, nucleus, ER, GA...

Regulation at the cell level

Modifying enzyme acitivity

Competitive inhibition

- inhibitor structurally similar to the substrate
- binds to active center
- **increases K_m** (↓ affinity of enzyme to substrate)
- can be removed by high substrate concentration
- inhibition is **reversible**

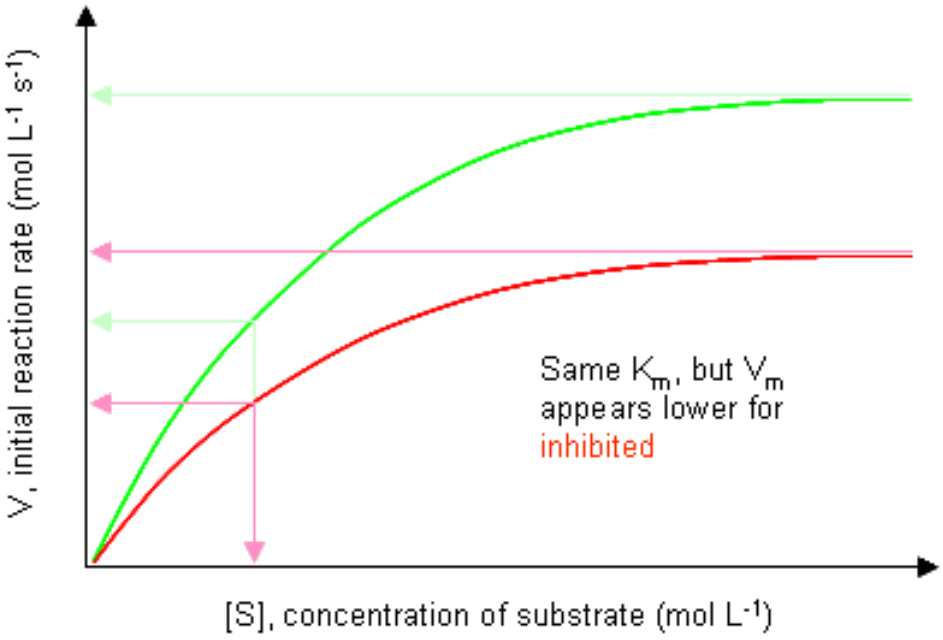


Regulation at the cell level

Modifying enzyme acitivity

Non-competitive inhibition

- inhibitor binds at different allosteric site separate from the active site of substrate binding
- **cannot be removed by high substrate concentration**
- V_{max} decreases
- reversible only when inhibitor **does not bind to active center by covalent bond**

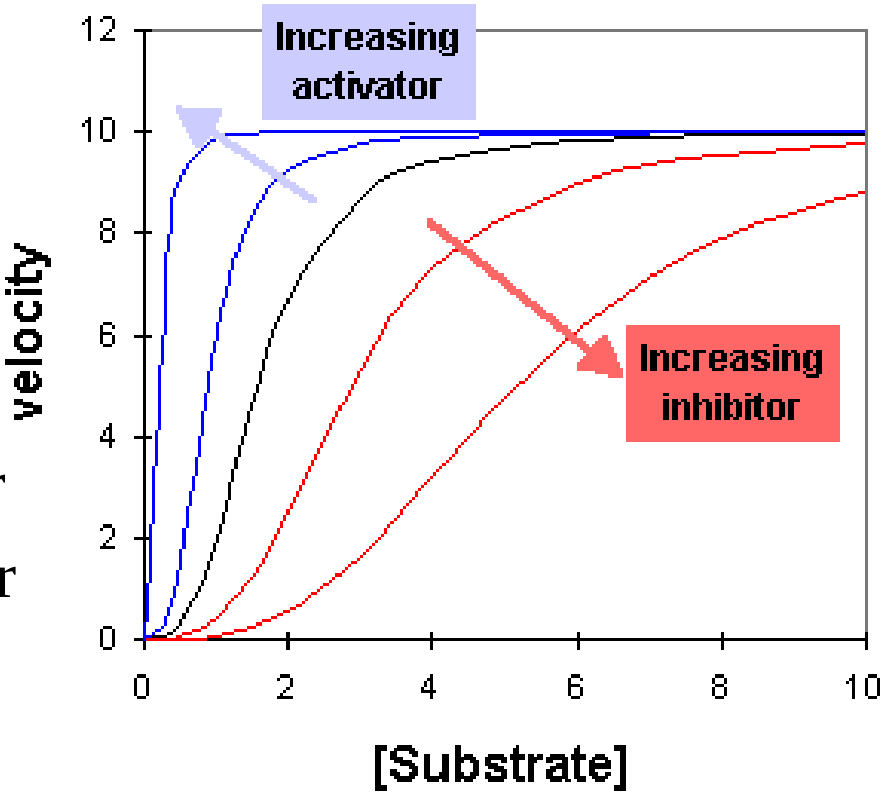


Regulation at the cell level

Modifying enzyme acitivity

Allosteric enzymes

- sigmoidal kinetics
- enzymes are more sensitive to changes in substrate concentration



- **activator** is a positive modulator
- **inhibitor** is a negative modulator

- allosteric enzymes are present in important regulatory reactions in metabolism

Regulation at the cell level

Substrates and products of metabolic pathways

Inhibition (activation) in regulation of metabolic processes:

- inhibition by product – **feed back**
- activation by substrate **- feed forward** – an intermediate product (substrate) produced early in metabolic pathway affects the activity of the following enzyme that catalyze a reaction further down the pathway

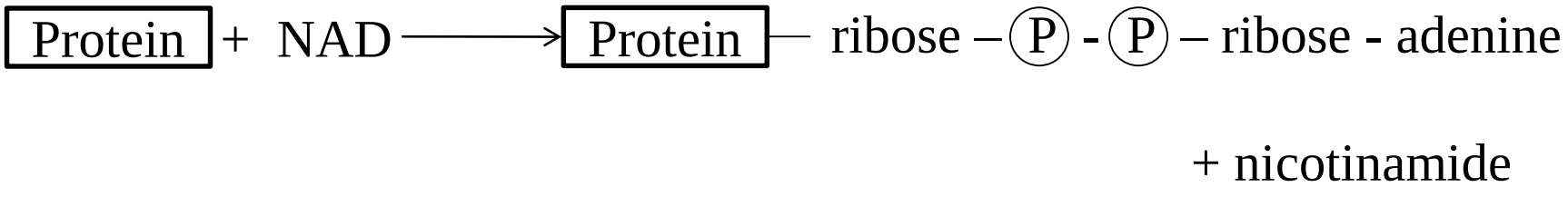
Regulation at the cell level

Covalent modfication of enzymes

1. Adenylation
2. ADP-ribosylation
3. Phosphorylation/dephosphorylation
4. Proteolysis
5. Other ways – prenylation, acylation....

Adenylation:

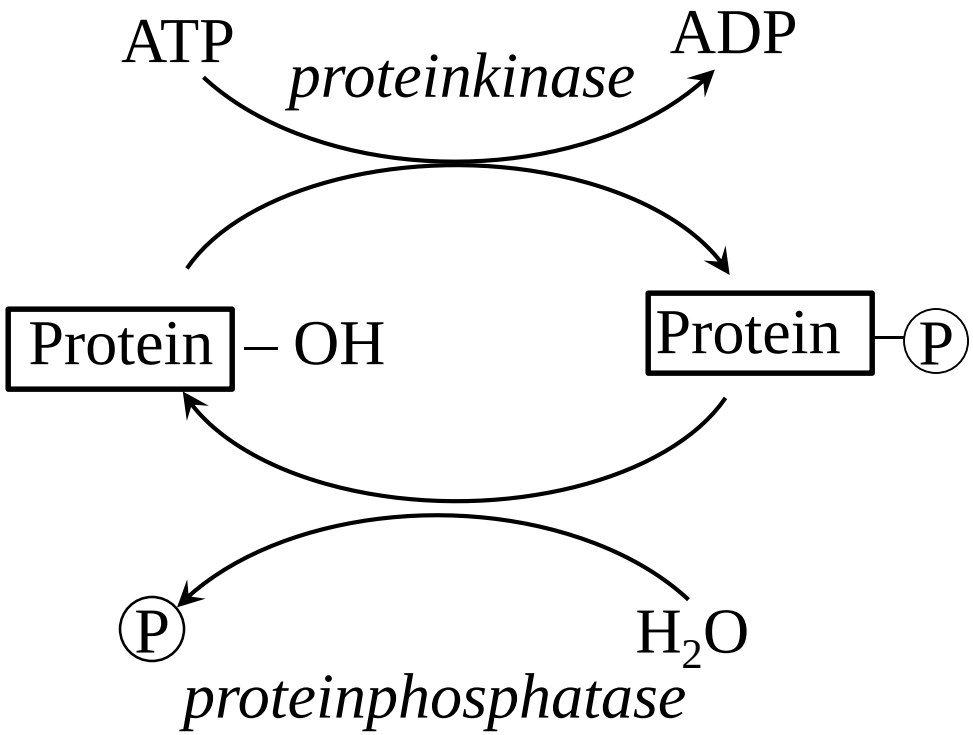
ADP-ribosylation:



Regulation at the cell level

Covalent modfication of enzymes

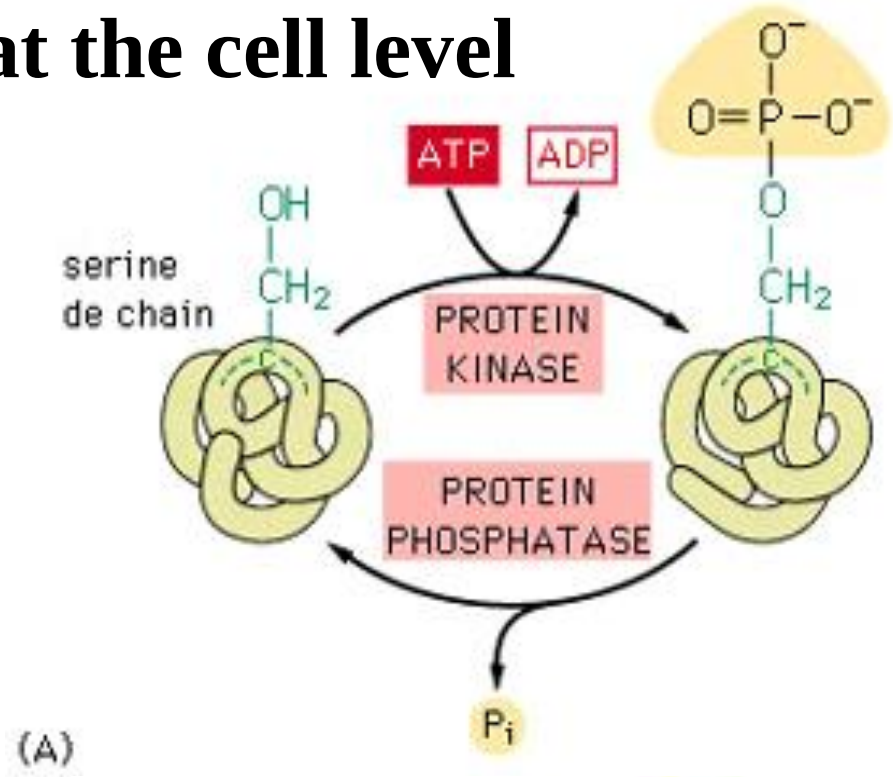
Phosphorylation/ dephosphorylation of enzymes:



- phosphate binds to -OH groups of amino acid residues – serine, threonine, tyrosine

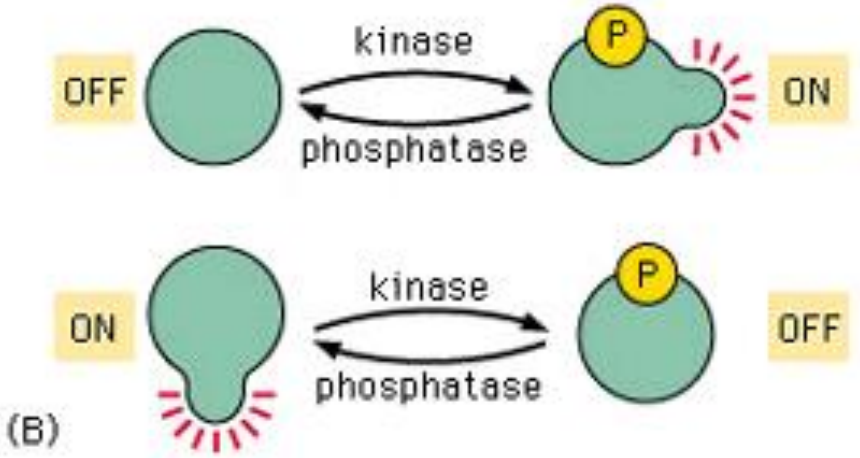
Regulation at the cell level

Reversible ATP-dependent covalent modification:



- phosphorylated enzyme can be:
  - **active (*glycogen phosphorylase*)**
  - **inactive (*glycogen synthase*)**

- each enzyme activity is affected differently



Regulation at the cell level

Change in amount of enzyme

- change in the absolute concentration of the regulatory enzyme by activation or inhibition of the gene expression of the given enzyme

- induction
- repression

Constitutive enzymes - stable amounts during the life of the cell

Inductive enzymes - variable quantities according to need of the cell

Regulation at the organism level

Receptors for signal molecules

1. **Intracelular** – for lipophilic molecules:
   - **cytosolic** (steroids, vitamin D)
   - **nuclear** (vitamin A, thyroid hormone)

2. **Membrane** – for hydrophilic molecules (proteins):
   - **ion channel-linked receptors**
   - **catalytic receptors**
   - **G-protein linked receptors**

Specificity of the response:

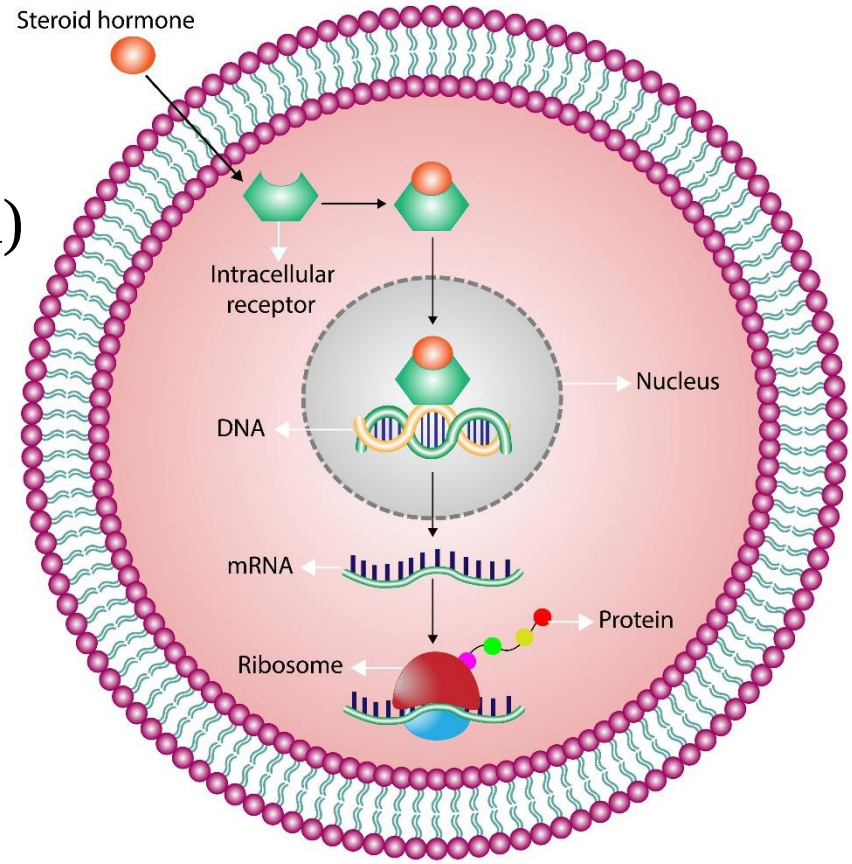
- type of the receptor
- metabolic characteristics of the cell

Regulation at the organism level

- **hydrophobic (lipophilic) molecules**

Intracelullar receptors

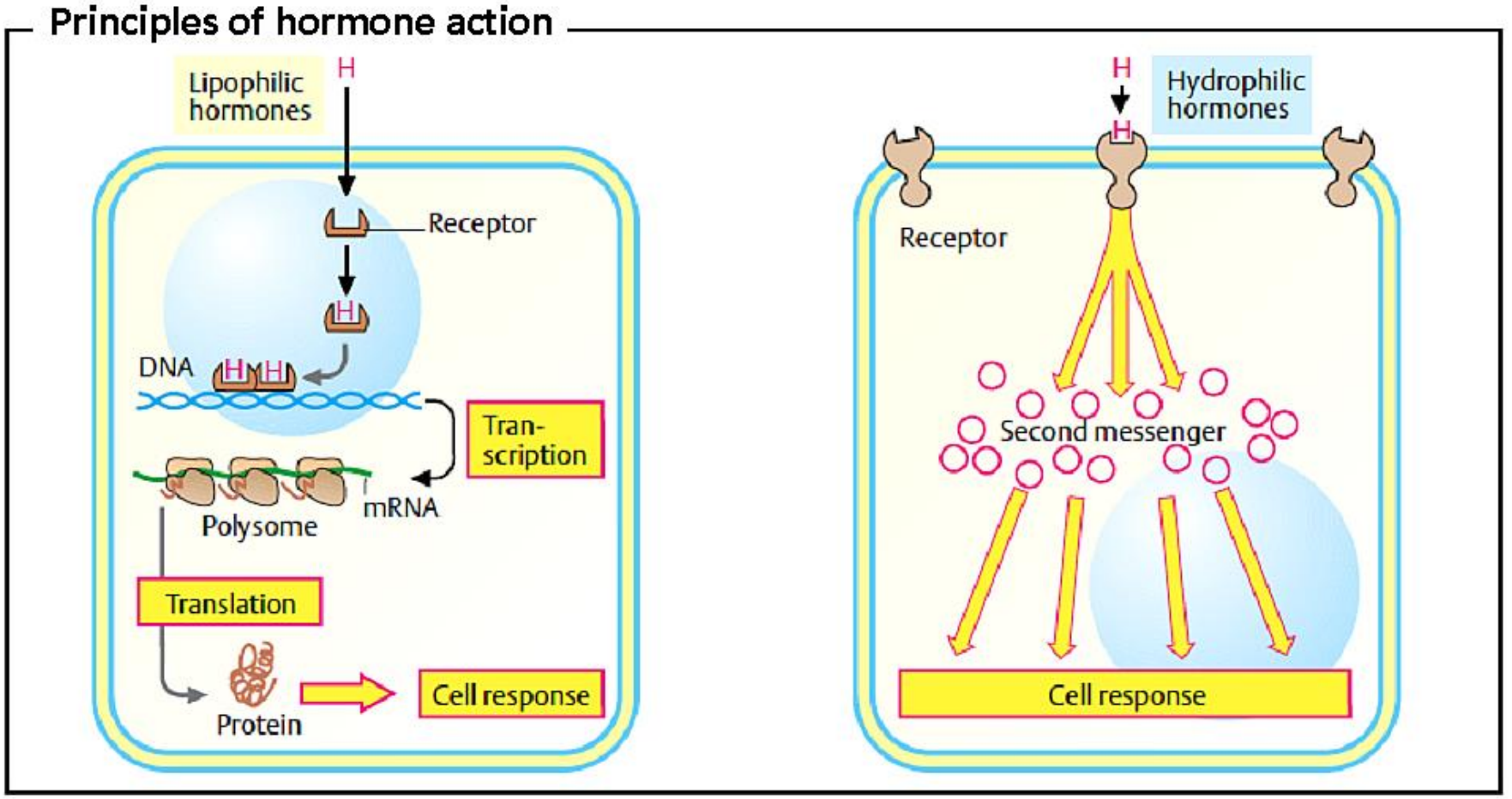
- **cytosolic** (steroids, vitamin D)
- **nuclear** (thyroxine, vitamin A)



Regulation at the organism level

- **hydrophobic (lipophilic) molecules**

Intracelullar receptors



Regulation at the organism level

- **hydrophilic molecules**

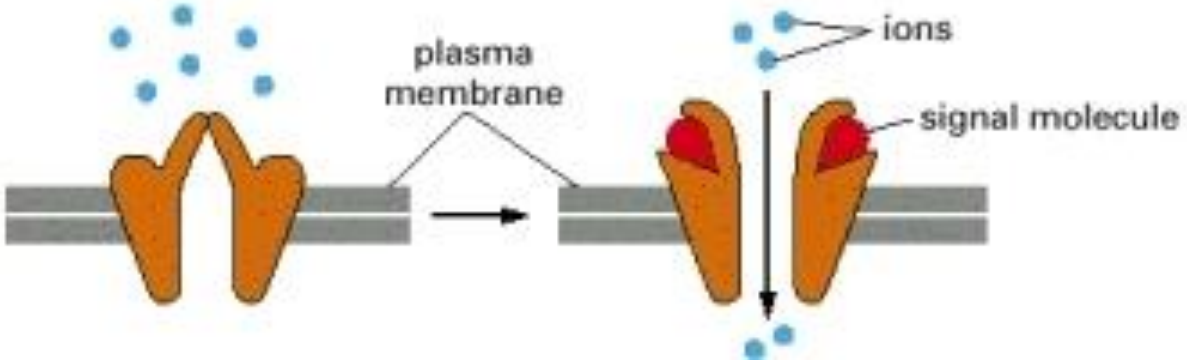
1. Ion channel-linked receptors

- binding a ligand opens a channel through the membrane which allows specific ions to pass through

- often found in neurotransmission; the activation of this type of receptor occurs mainly by changing the voltage on the membrane

Regulation at the organism level

1. Ion channel-linked receptors



change in ion concentration

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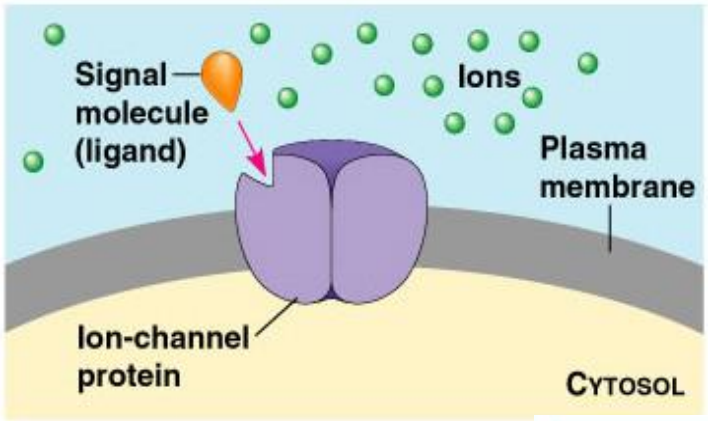
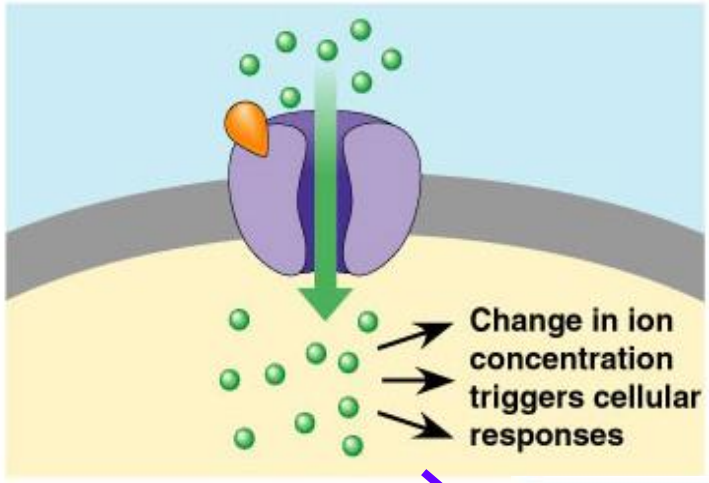
effects in metabolism

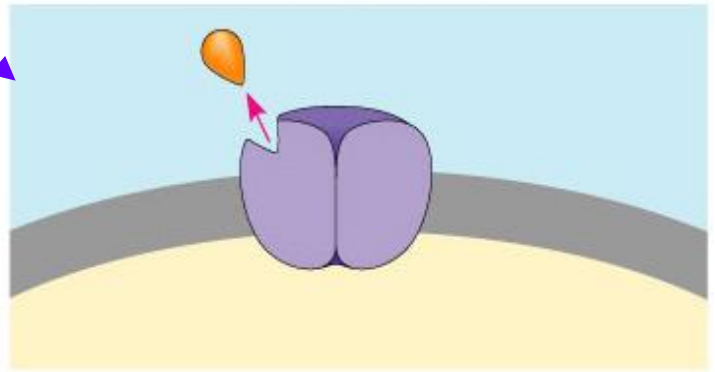
1. Ion channel-linked receptors



Ligand binds;
channel opens;
ions flow through



Ligand dissociates;
channel closes



Regulation at the organism level

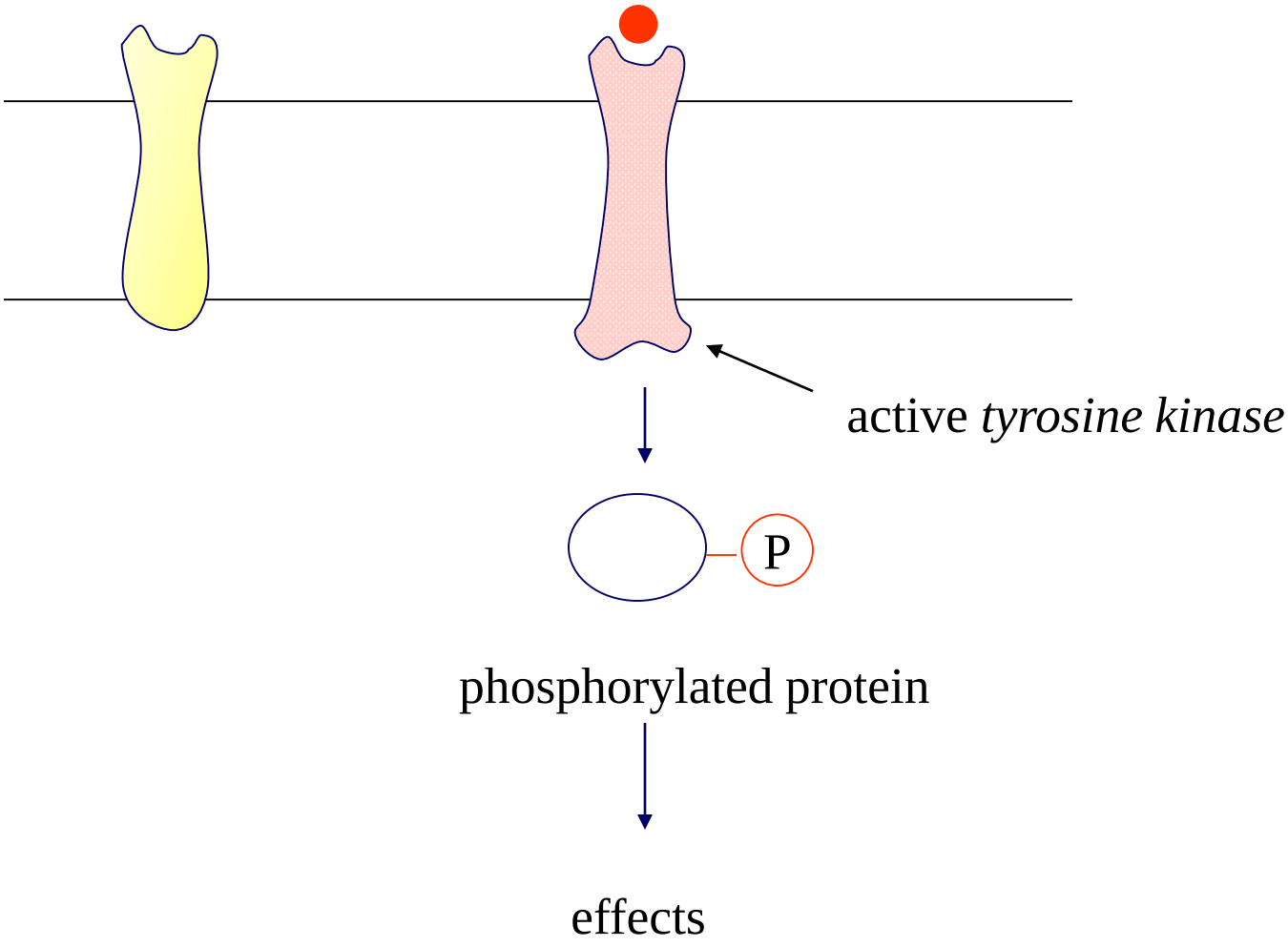
2. Catalytic receptors

- with its own enzymatic activity or coupled with an enzyme:
  - ***tyrosine kinase***
  - ***guanylate cyclase***

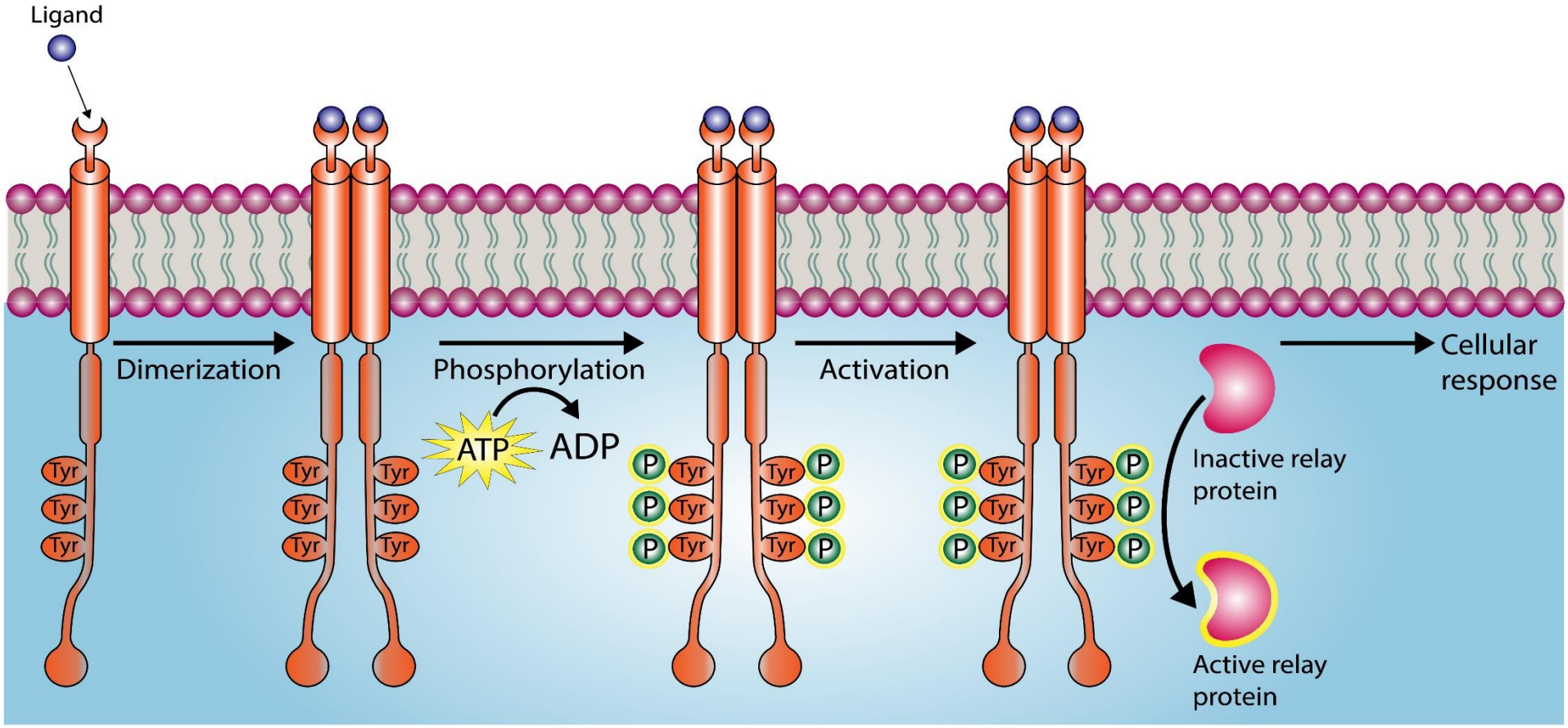
- activated receptors homodimerize and mutually phosphorylate some amino acids (tyrosine/serine)

Regulation at the organism level

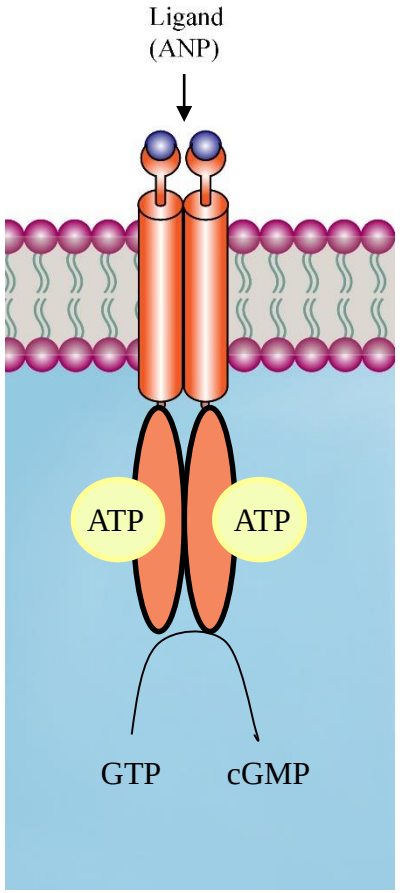
2. Catalytic receptors



Tyrosine kinase receptor



Guanylate cyclase receptor



eg. ANP receptor

Regulation at the organism level

3. G-protein linked receptors

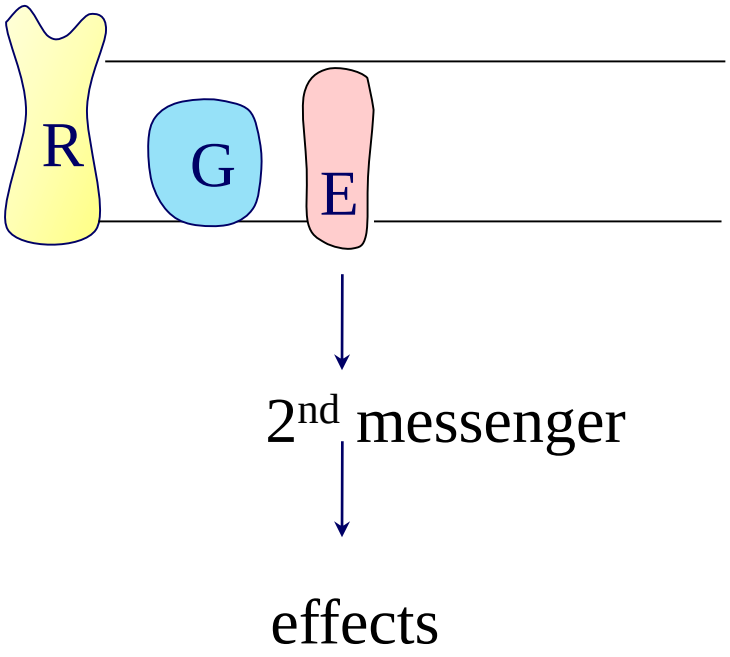
G – proteins:

- **3 subunits** – α, β and γ
  - α subunit binds guanine nucleotides GDP and GTP (GDP – inactive state, GTP – active state)
  - α subunit cleaves GTP (**GTP-ase activity**) specificity of α subunit

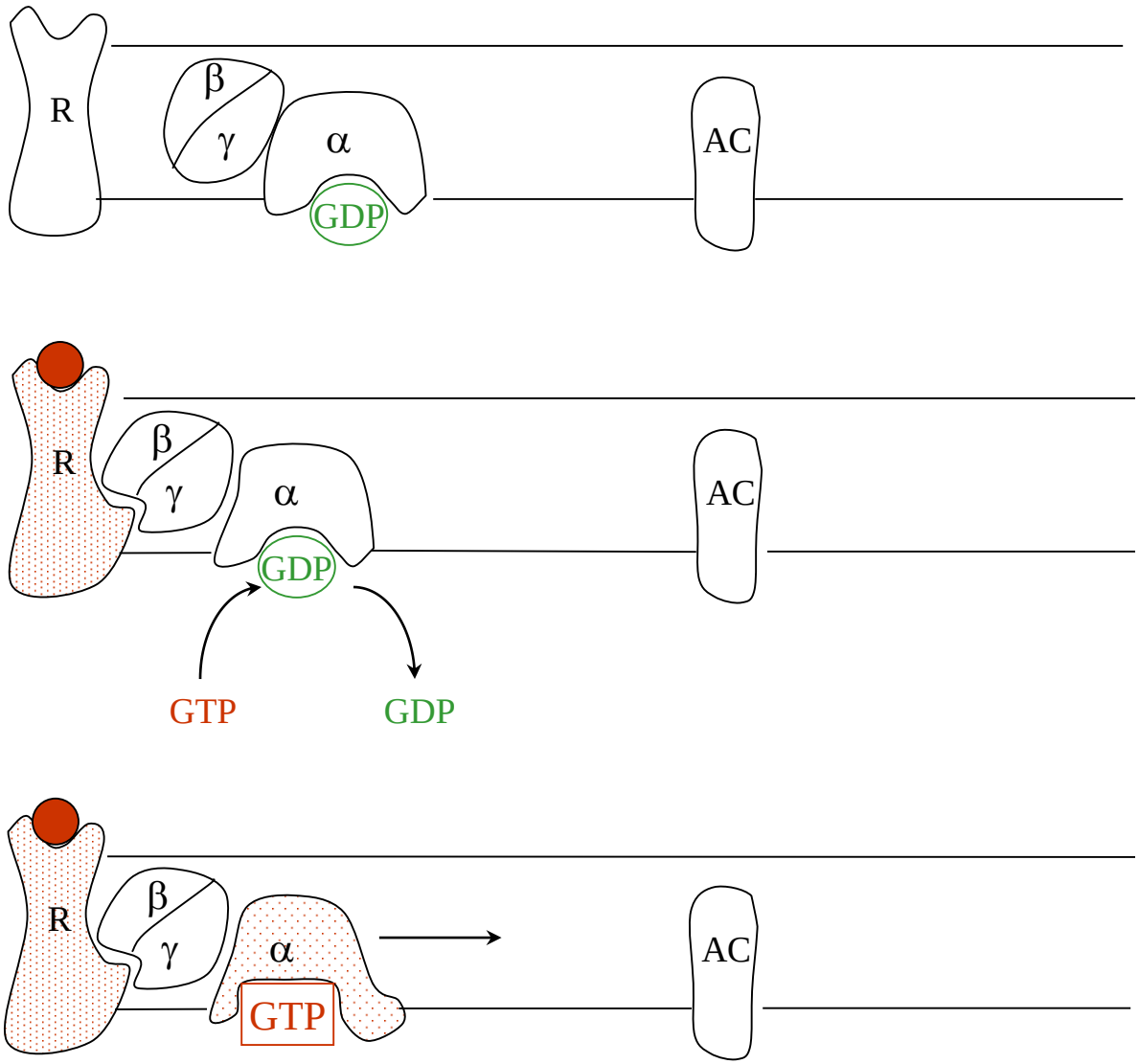
G_s contains **α_s** subunit – activation of adenylate cyclase (AC)
G_i contains **α_i** subunit – inhibition of adenylate cyclase (AC)
$G_{p(q)}$ contains **$\alpha_{p(q)}$** subunit – activation of phospholipase C (PLC)

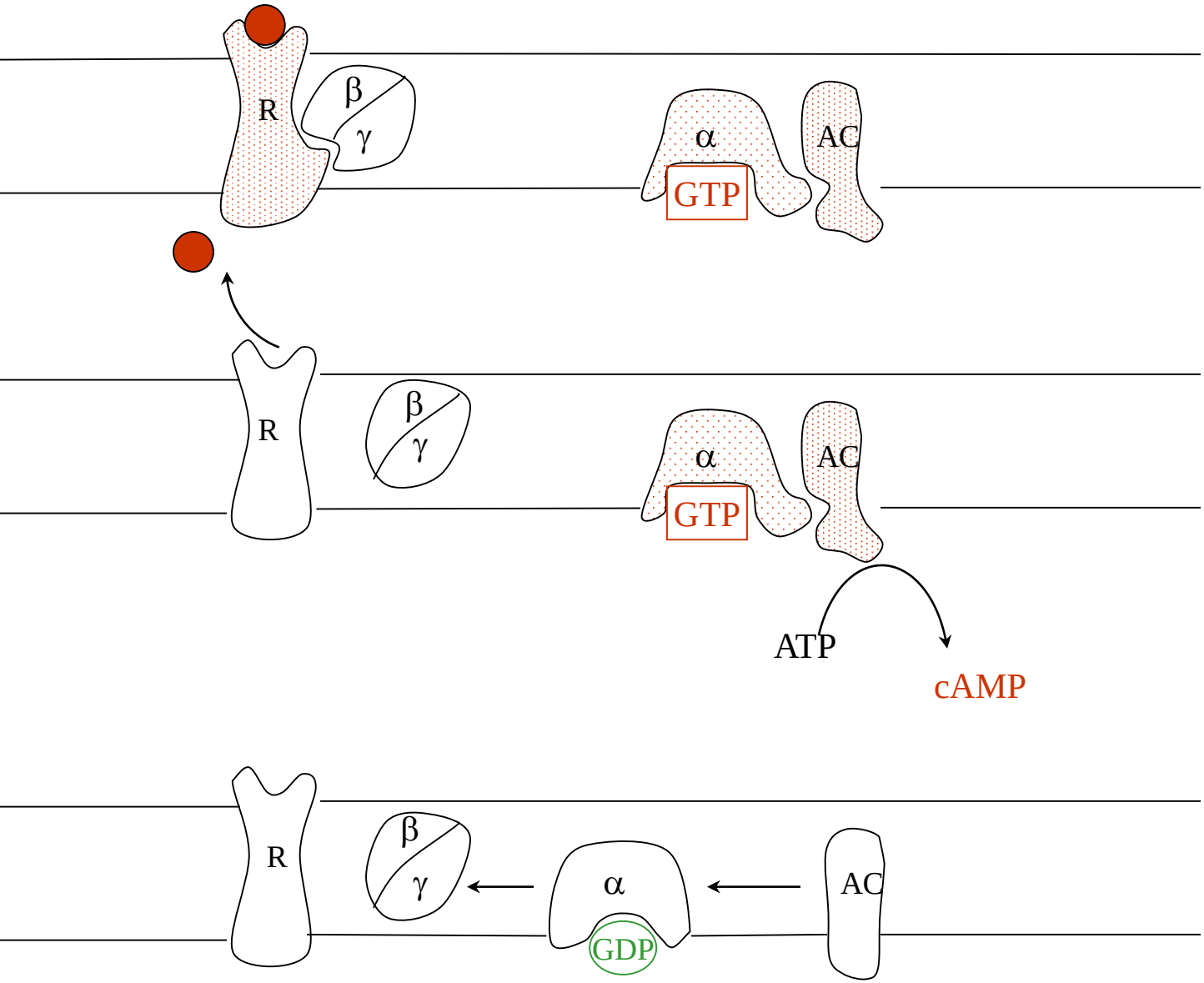
Regulation at the organism level

3. G-protein linked receptors



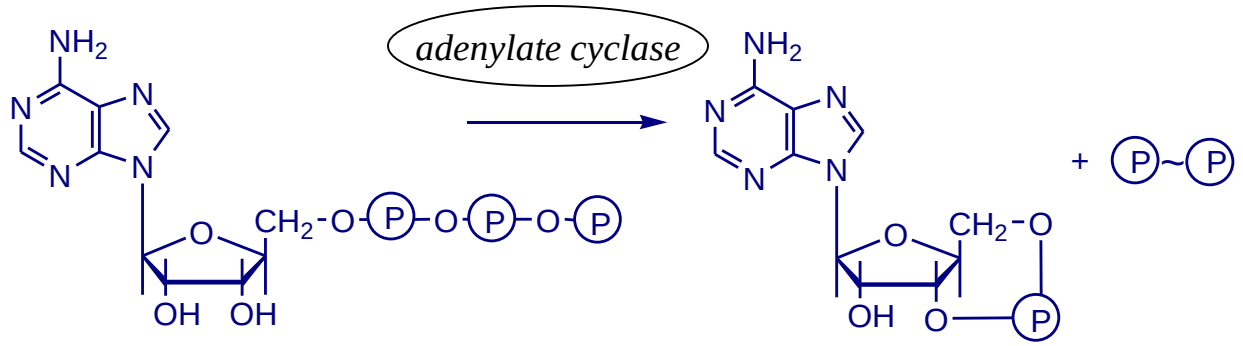
Role of G_s-protein in activation of adenylate cyclase




R
β
γ
α
AC
GTP
R
β
γ
α
AC
GTP
ATP
cAMP
R
β
γ
α
AC
GDP

3. G-protein linked receptors - Gs

Sythesis of cAMP



cAMP

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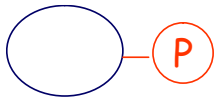
proteinkinase A



phosphorylated protein

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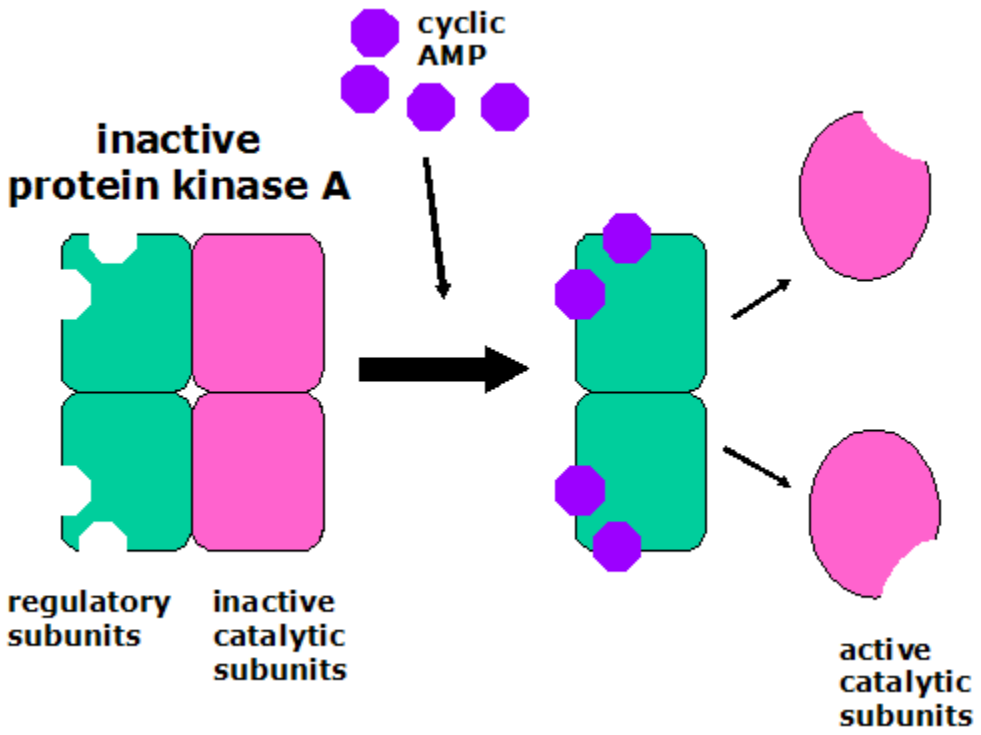
effects

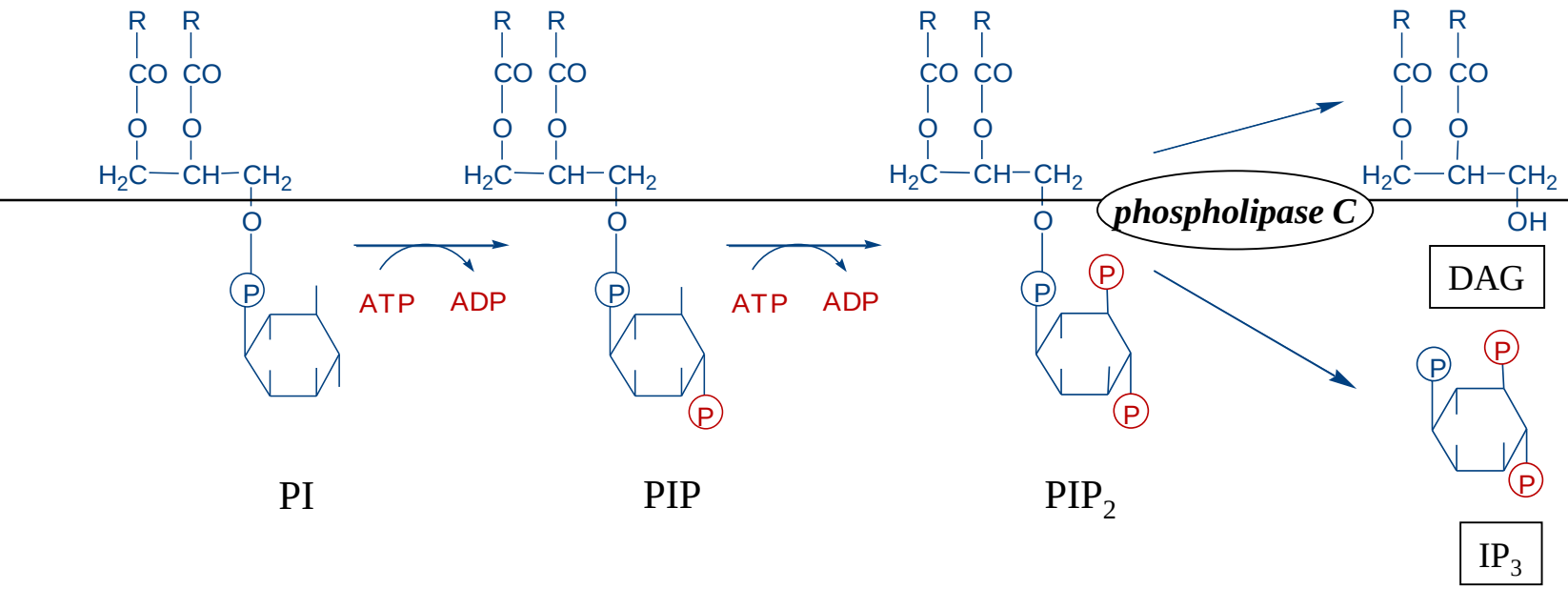
3. G-protein linked receptors - Gs

- activation of ***protein kinase A***
- binding of cAMP to ***protein kinase A*** regulatory subunits



3. G-protein linked receptors - Gp

Phosphatidylinositols and synthesis of 2nd messengers DAG a IP_3



3. G-protein linked receptors - Gp

Phosphatidylinositols and synthesis of 2nd messengers DAG a IP_3