BIO-1

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Introduction

- Intracellular communication is necessary for adaptation to a constantly changing environment
- Human body synthesizes many hormones that can act specifically on different cells of the body
- These hormones respond to changes to bring the body back to its normal state

Introduction

- More than one hormone can affect one cell
- More than one cell type can be affected by the same hormone
- A target is any cell in which the hormone (ligand) binds to its receptor
- The same hormone can have very different effects. Why is that ?
  - It depends on the receptor type
  - So different actions can be achieved through receptor change even though you are using the same substance

For your understanding

- When a ligand binds to a receptor. this binding will activate the receptor
- Now lets say we have type A receptors and Type B receptors and each one of them has a different action .
- So when the ligand binds to receptor A it will give an action different of the action that will appear if it binds to receptor B.
- That's how one hormone can have different effects

Factors determining the response of a target cell to a hormone

- The rate of synthesis & secretion of the hormones
- The conversion of inactive forms of the hormone into the fully active form
  - The target tissue will exert physiological action of hormones are in fully active form and inversely it will exert no action if the hormones are inactive form
- The rate of hormone clearance from plasma (half-life & excretion)
  - The more the hormone is bound to a plasma protein (i.e. albumin) the more its action will last in the body
- The number, relative activity, and state of occupancy of the specific receptors
- Post-receptor factors

Hormone types

- This is with respect to the nature of the hormone
- Remember that the plasma membrane is a lipid bi layer membrane. So lipid structures can cross easily
- 2 main types
  - Hormones that do not cross the plasma membrane
    - They are lipophobic or hydrophilic in nature
  - Hormones that cross the plasma membrane
    - They are lipophilic in nature

So?

- So hormones that can cross the plasma membrane will do the job they want by themselves , and since they can cross the membrane their location of binding will be intracellular
  - These are called hormone-receptor complex
- And hormones that cannot cross will need someone to do the job for them , they need a SECOND MESSENGER! so where do they bind ? Outside the cell on the plasma membrane
  - There are many second messenger mechanisms
- Understand?

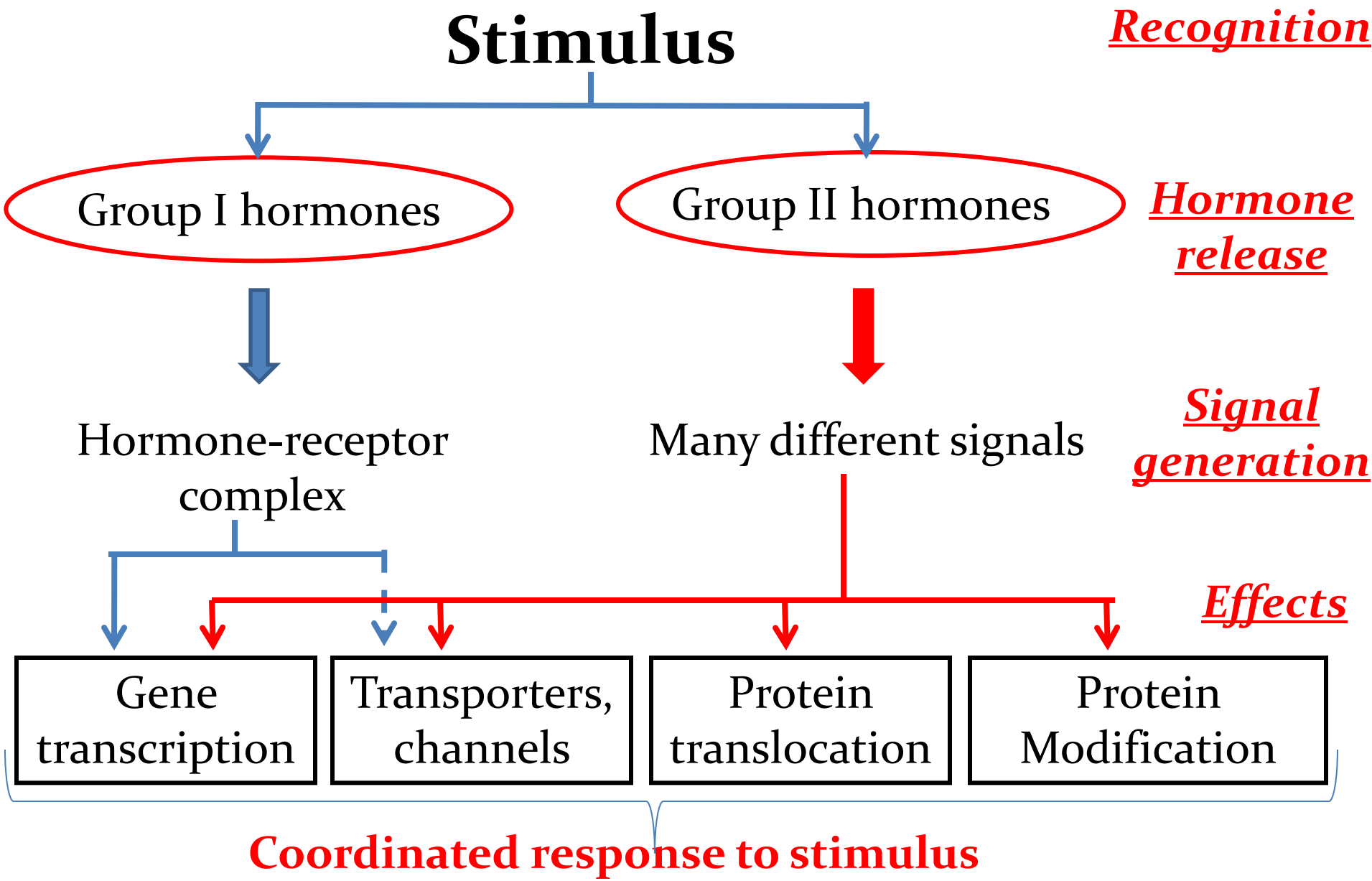
Remember

- all hormones working through second messenger systems are lipophobic and because they are lipophobic they cannot cross the cell membrane , meaning they need a messenger to form their action inside the cell
- It cannot enter the cell > binds to receptor > the receptor activates a second messenger > gives physiological action

General Features of Hormone Classes

	Group I	Group II
Types	Steroids, iodothyronines, calcitriol, retinoids	Polypeptides, glycoproteins, catecholamines
Solubility	Lipophilic	Hydrophilic
Transport proteins	Yes	No
Plasma half-life	Long (hours – days)	Short (minutes)
Receptor	Intracellular	Plasma membrane
Mediator	Receptor-hormone complex	cAMP, cGMP, Ca^{2+}, metabolites of complex phosphoinositols, tyrosine kinase cascades

- What happens after the hormones bind?
  - physiological action
- And how is this action achieved ? By intracellular responses :
  - Modifying and making proteins
  - Opening channels for transport of substances
  - Gene modification to make new protiens


Stimulus
Recognition
Group I hormones
Group II hormones
Hormone release
Hormone-receptor complex
Many different signals
Signal generation
Effects
Gene transcription
Transporters, channels
Protein translocation
Protein Modification
Coordinated response to stimulus

- Effects inside the cell can be :
  - protein modification : i.e. by phosphorylation
  - protein translocation : i.e. moving parts of the protein from a compartment to another
  - opening/closing transporter channels : i.e. GLUT channels with insulin
  - Gene transcription , which causes induction and repression

Classification of Hormones by Mechanism of Action

I. Hormones that bind to intracellular receptors (Steroid-Thyroid super family):

Steroid hormones
Thyroid Hormones (T_3 & T_4)
Calcitriol ($1,25[OH]_2$-D_3)
Retinoic acid

These hormones are :

- Lipophilic
- Bind intracellular
- Work on gene modification mainly

II.Hormones that bind to cell surface receptors

The second messenger is cAMP	The second messenger is cGMP	second messenger is Calcium or phosphatidylinositol (or both)	second messenger is a tyrosine kinase cascade
1. Catecholamines (α_2- Adrenergic) 2. Catecholamines (β- Adrenergic) 3. Ant. Pituitary: ACTH, FSH, LH & TSH 4. ADH (Renal V2-receptor) 5. Calcitonin & PTH 6. Glucagon	1. Atrial natriuretic peptide(ANP) 2. Nitric oxide	1. Acetylcholine (muscarinic) 2. Catecholamines (α_1- Adrenergic) 3. Angiotensin II 4. ADH (vasopressin): Extra-renal V1-receptor	1. GH & Prolactin 2. Insulin 3. Erythropoietin

MOA of each and every one :D

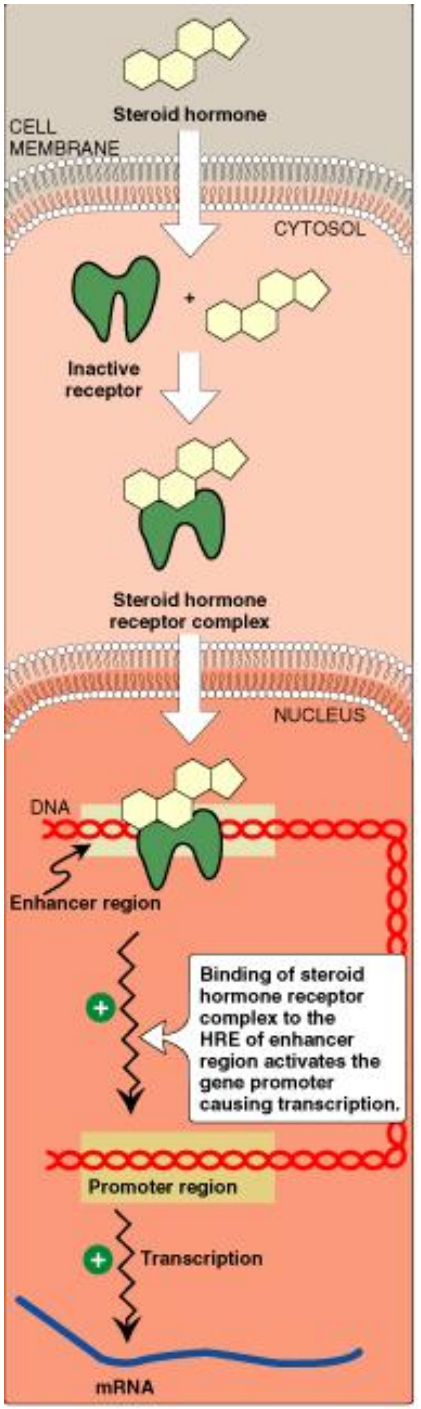
1 Mechanism of Action of Steroid-Thyroid Hormones

Steroid Hormones:

- Glucocorticoids
- Mineralocorticoids
- Sex hormones:
- Male sex hormones: Androgens
- Female sex hormones:Estrogens & Progestins

Thyroid Hormones (T_3 & T_4)

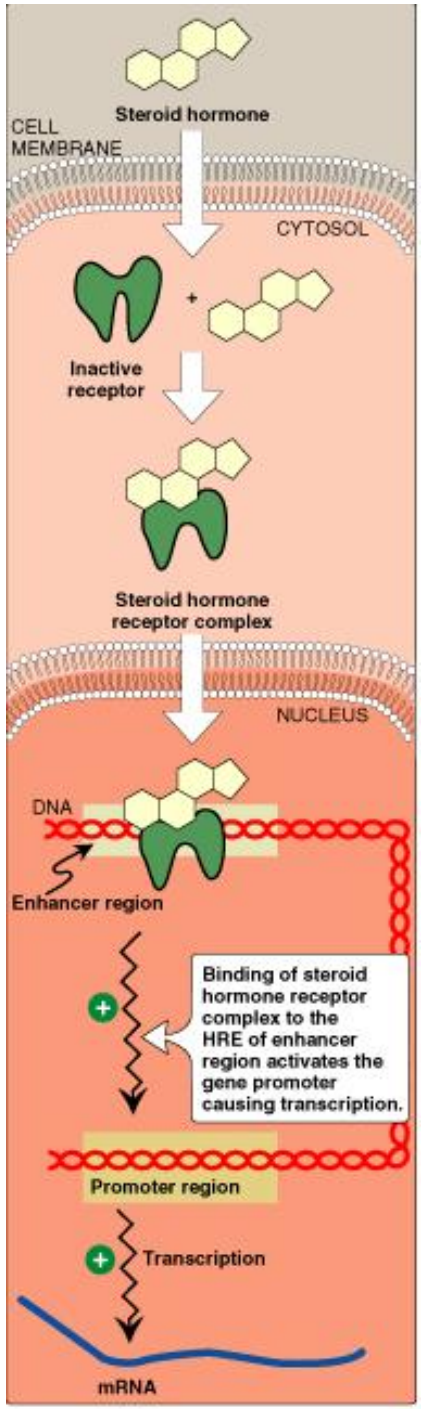
Calcitriol ($1,25[OH]_2$-D_3)
Retinoic acid



1. Because they are lipophilic , that means they can cross the plasma membrane
2. After diffusing inside the cell with the receptor it forms steroid-receptor complex
3. These accumulate in the nucleus and then dimerise
4. After that they bind to specific DNA sequences called HRE (hormone receptor elements)
5. The binding causes the gene to transcript new mRNA which will go to the cytoplasm and make new proteins

Specifics

- The hormone-receptor complex binds to the HRE found on the enhancer region
- This activates the gene promotor region which synthesises mRNA and so on

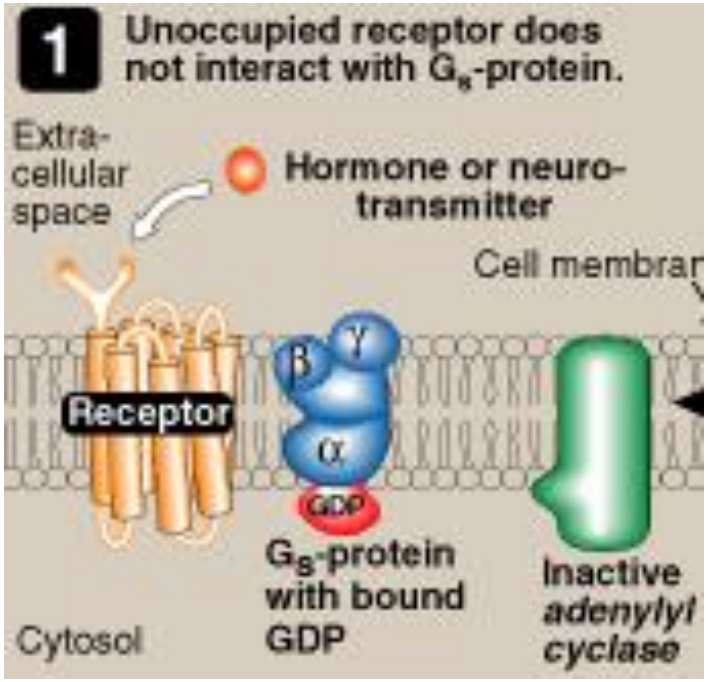


Revision

- Where does steroid hormones exert action ?
- Thyroid hormones achieve physiological action via ?
  - Protein modification
  - Gene modification
  - Increased intracellular calcium channels
  - Increases permeability of plasma membrane to sodium

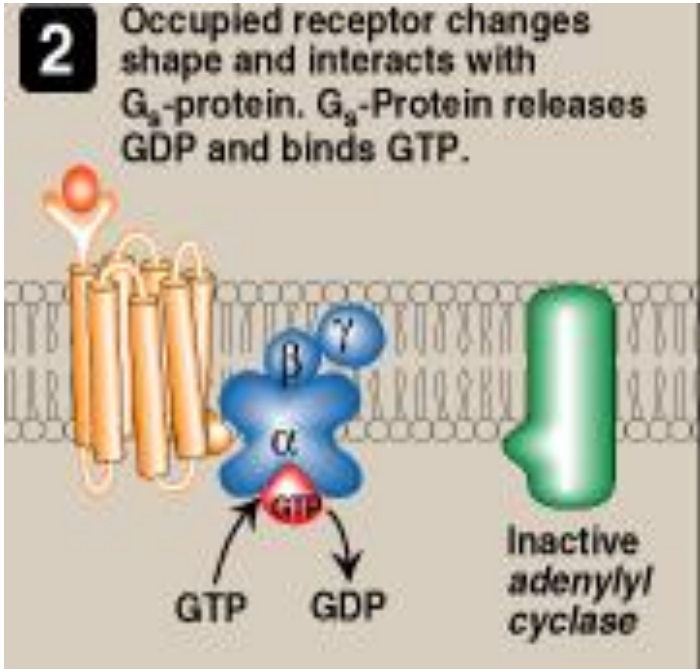
2 cAMP

1. These hormones are lipophobic so they cannot cross the plasma membrane
2. Hormones bind to the receptor and causes conformational change
3. This changed(activated) receptor then interacts with G protein

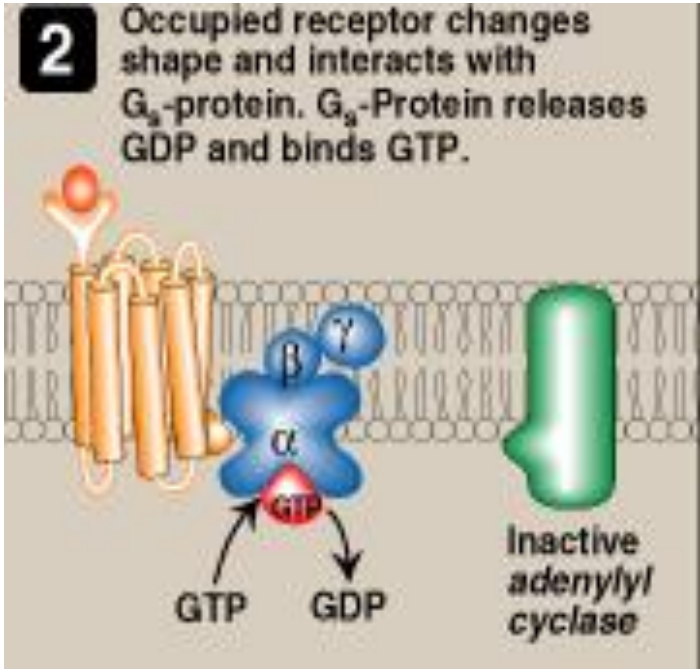


G proteins

- Are messenger proteins
- They have 3 subunits and a binding site for GDP/GTP & surface receptors
- 2 forms
  - Active G protein
    - GTP + the alpha subunit
  - Inactive G protein
    - GDP + all three subunits

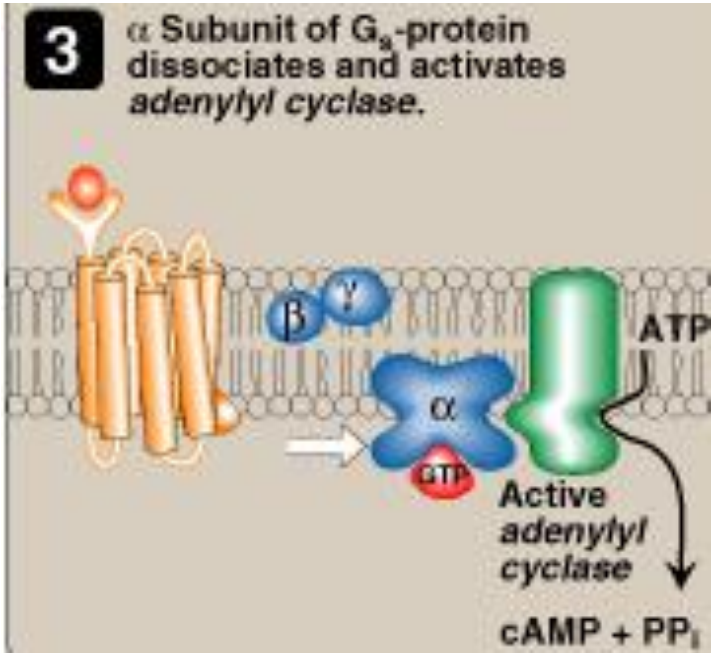


4. When G proteins are inactivated they are interact with GDP and once they are activated by the activated receptor the GDP is changed to GTP
5. After the G protein is coupled with GTP it loses the beta and gamma subunits and keeps the alpha this complex of GTP and alpha subunit then activates adenylylcylase



6. As a result adenylylcylase changes ATP to cAMP

- And now we have cAMP

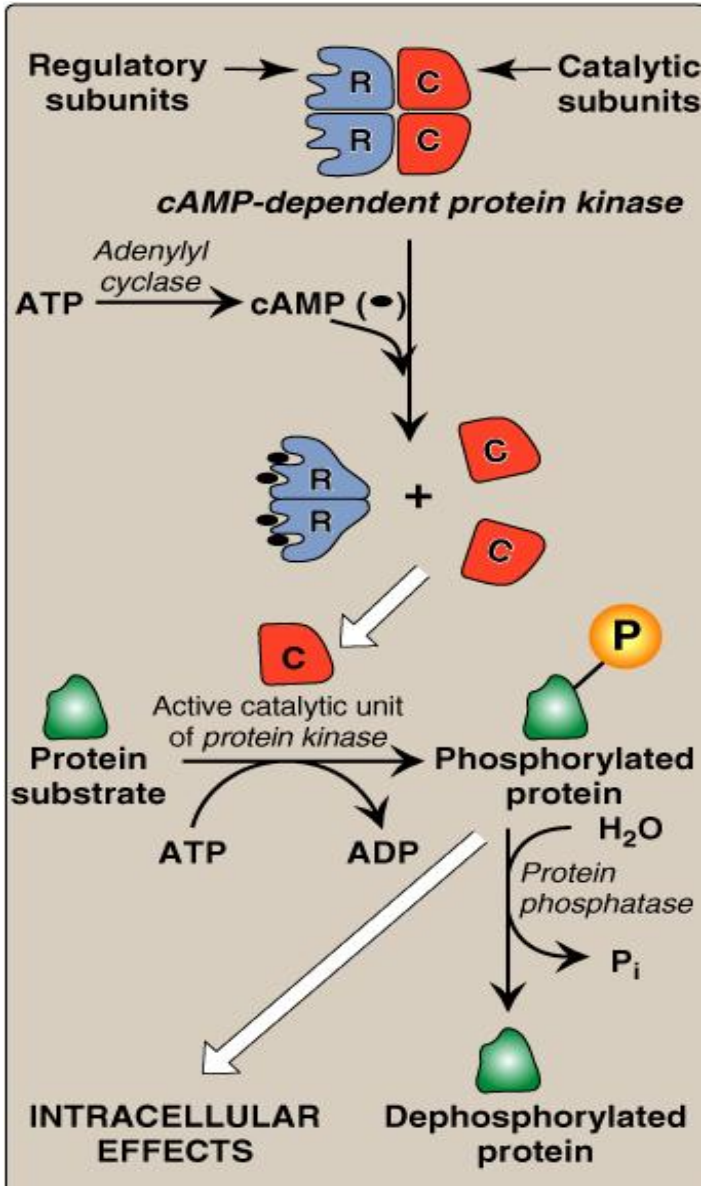


7. After cAMP is formed it interacts with protein kinase A

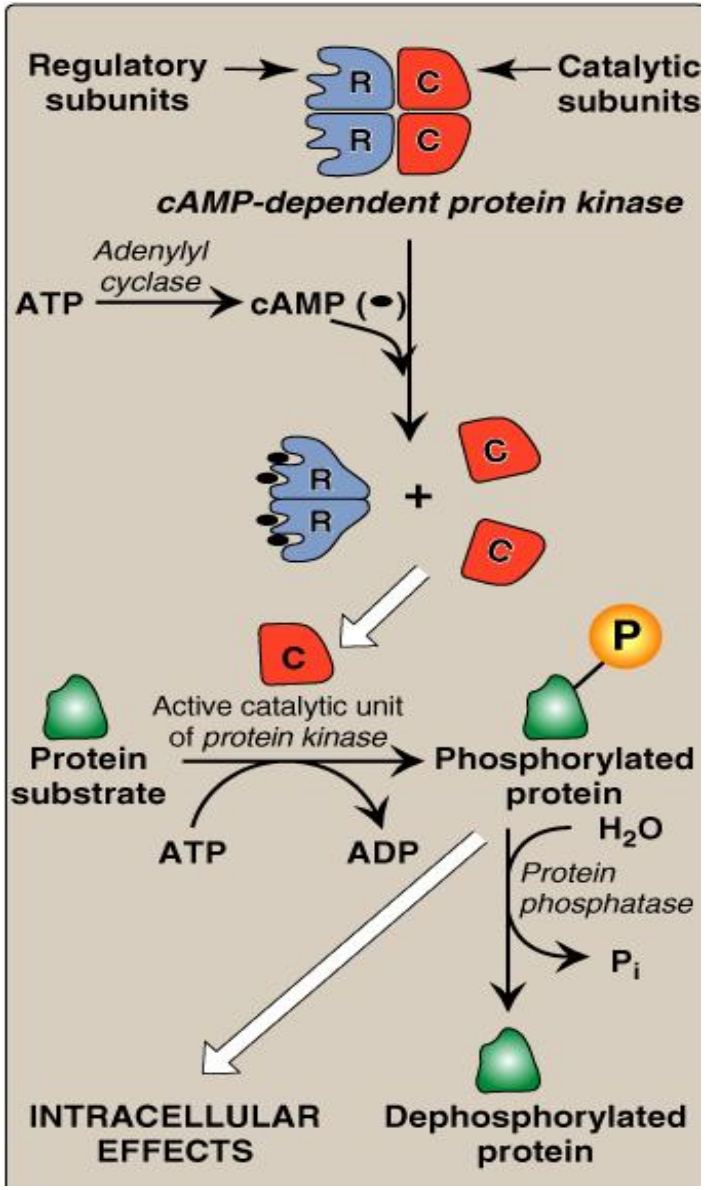
Protien kinase A

- It has 4 subunits: 2 regulatory and 2 catalytic

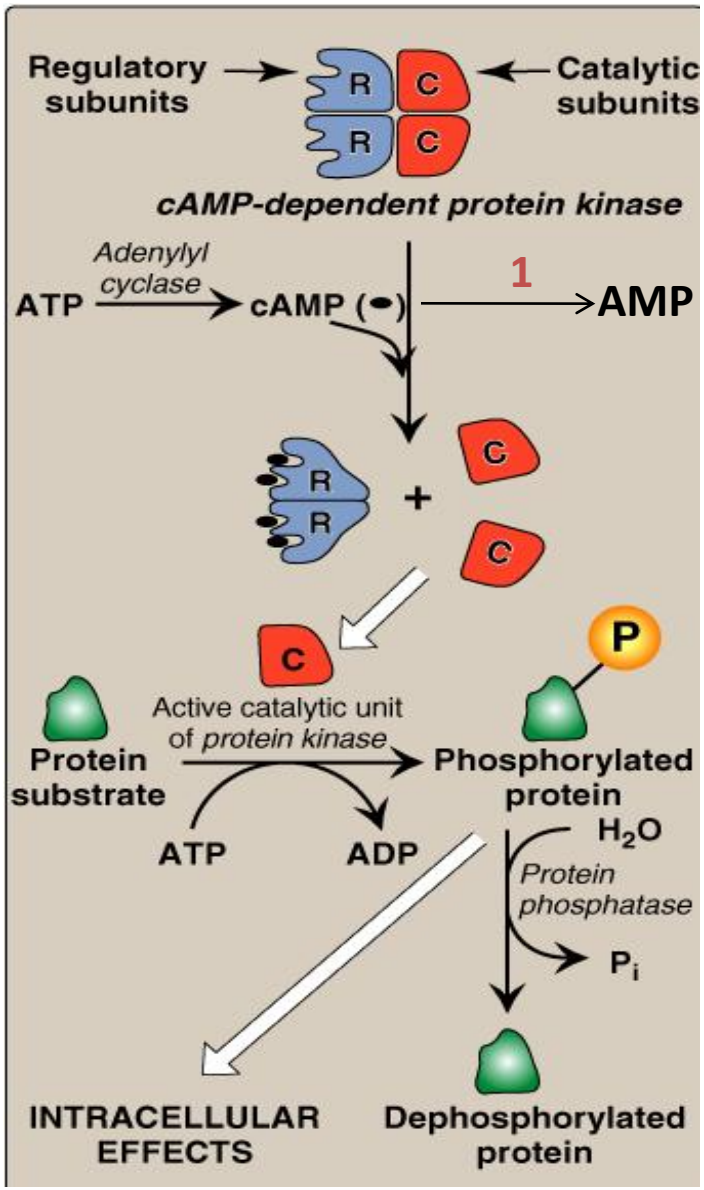
8. cAMP binds to the regulatory subunits and causes detachment , then the catalytic subunits can perform their action



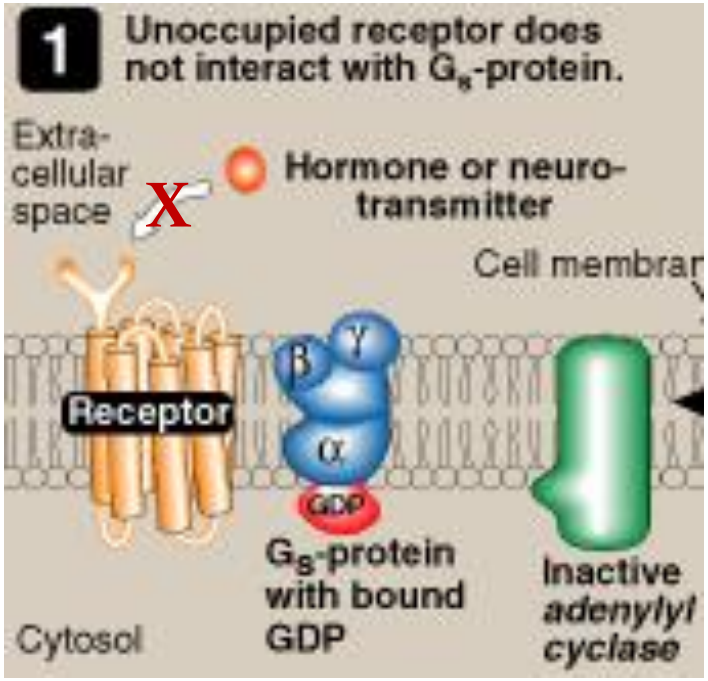
- 9. Then these 2 catalytic subunits of protein kinase A causes phosphorylation of proteins leading to activation or inactivation thus regulating cellular function

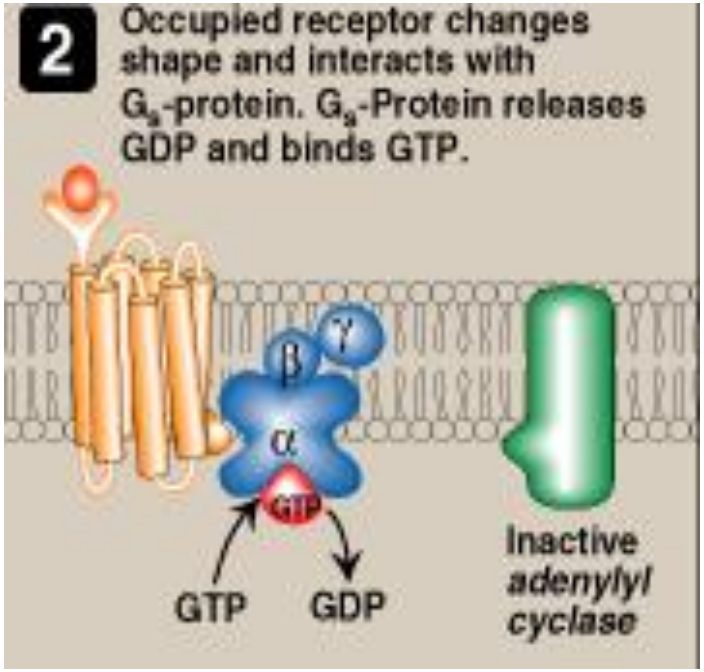


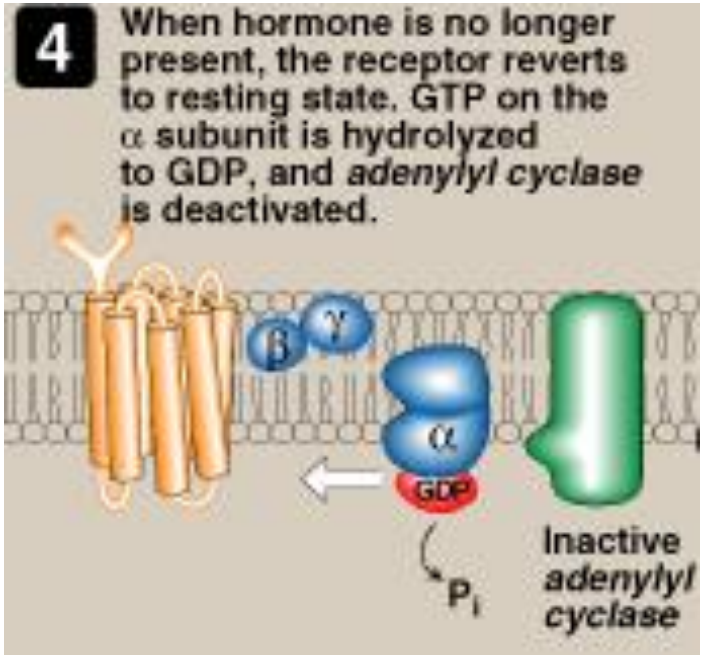
You should know that phosphodieterase is an enzyme that changes cAMP to AMP



[1]Phosphodiesterase







This is a slide to show you how can you reverse the actions

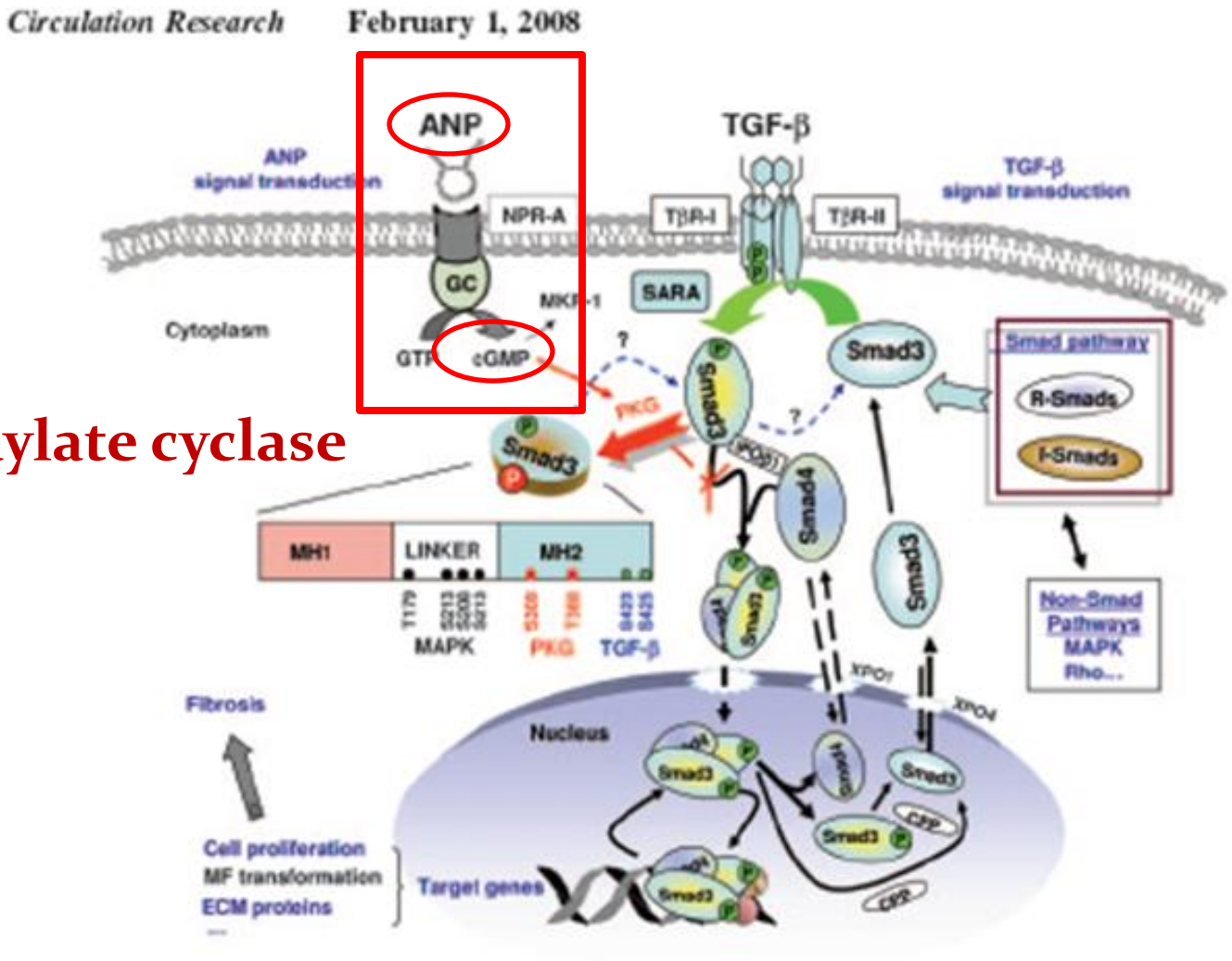
Revision

- **α2- Adrenergic receptor action depends on :**
  - **Phospholipase C**
  - **Protein kinase A**
  - **Protien kinase C**
  - **Genomic modification**

3 cGMP

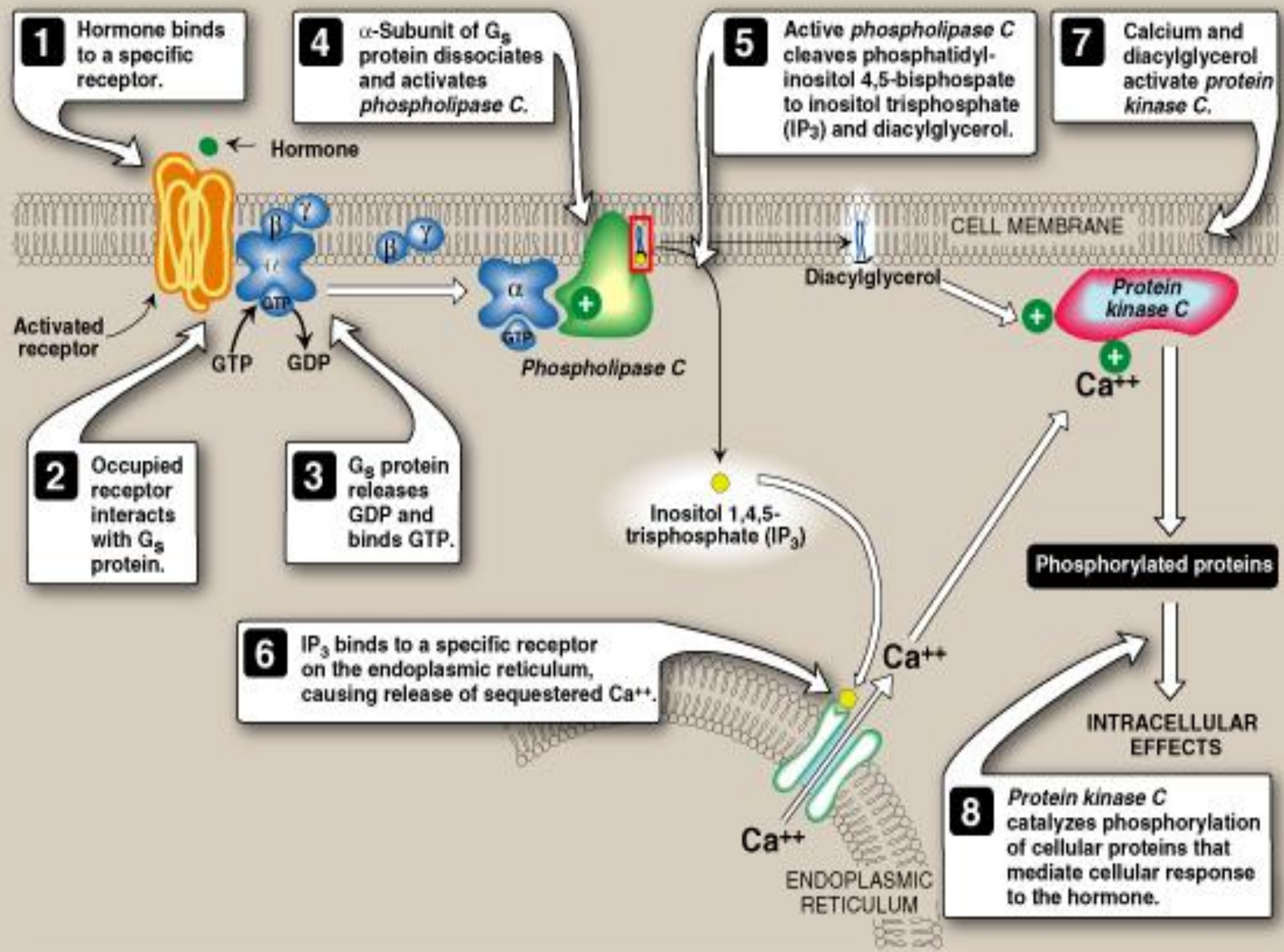
- Same mechanism but instead of cAMP the messenger is cGMP
- And instead of adenylylcyclase the enzyme is Gunaylate cyclase

Atrial Natriuretic Peptide (ANP)



GC: Gunaylate cyclase

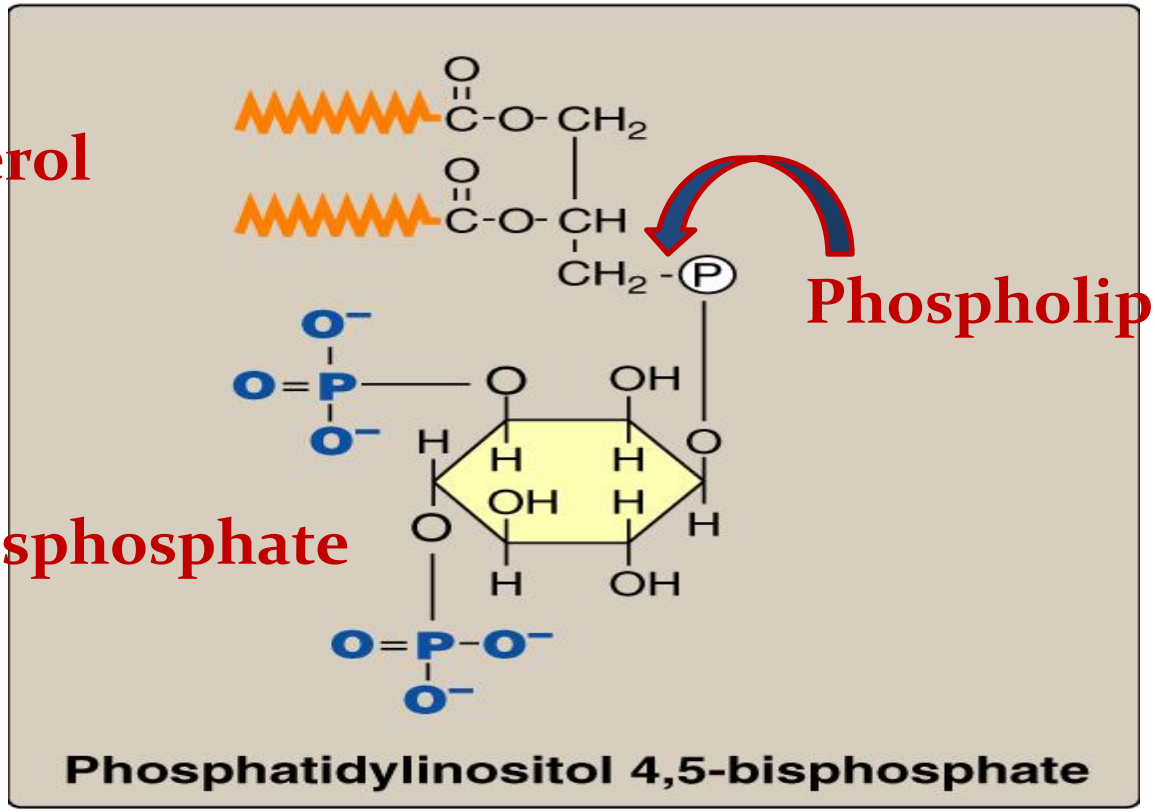
4 calcium or phosphatidylinositol


1 Hormone binds to a specific receptor.
Hormone
4 α-Subunit of G_s protein dissociates and activates *phospholipase C*.
5 Active *phospholipase C* cleaves phosphatidyl-inositol 4,5-bisphospate to inositol trisphosphate (IP_3) and diacylglycerol.
7 Calcium and diacylglycerol activate *protein kinase C*.
CELL MEMBRANE
Diacylglycerol
Protein kinase C
Activated receptor
GTP
GDP
Phospholipase C
Ca++
2 Occupied receptor interacts with G_s protein.
3 G_s protein releases GDP and binds GTP.
Inositol 1,4,5-trisphosphate (IP_3)
Phosphorylated proteins
6 IP_3 binds to a specific receptor on the endoplasmic reticulum, causing release of sequestered Ca++.
Ca++
INTRACELLULAR EFFECTS
Ca++
ENDOPLASMIC RETICULUM
8 *Protein kinase C* catalyzes phosphorylation of cellular proteins that mediate cellular response to the hormone.

- Phosphatidylinisitol 4,5 bisphosphate = DAG + IP3
- Phoshpholipase C separates DAG from IP3 so that everyone can perform a different action

Diacylglycerol (DAG)

Inositol Trisphosphate (IP_3)



Phospholipase C

Explinatory

- The hormone binds to receptor > activate Gs protein > G protein activates phospholipase C
- Phospholipase C then cleaves part phosphatidyl-inositol 4,5 bisphosphate to
  - Inositol triphosphate (IP3) which binds to the endoplasmic reticulum and cause increase of intracellular Ca++ (that is the only function of IP3)
  - Diacyelglycerol (DAG)
- Then both DAG and Ca++ activate protein kinase C which gives cellular responses

Revision

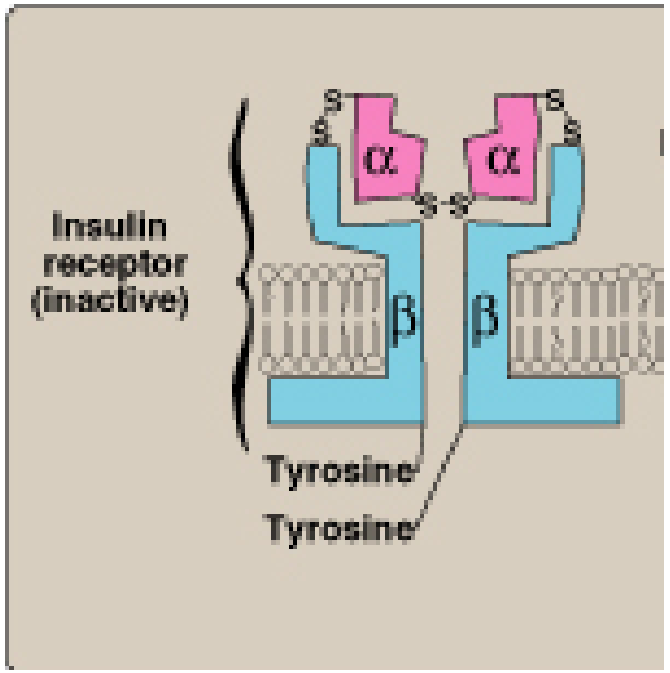
- What is the action of phospholipase C ?
- What is the action of IP3 ?
- How is protein kinase C activated ?

Remember!!!!

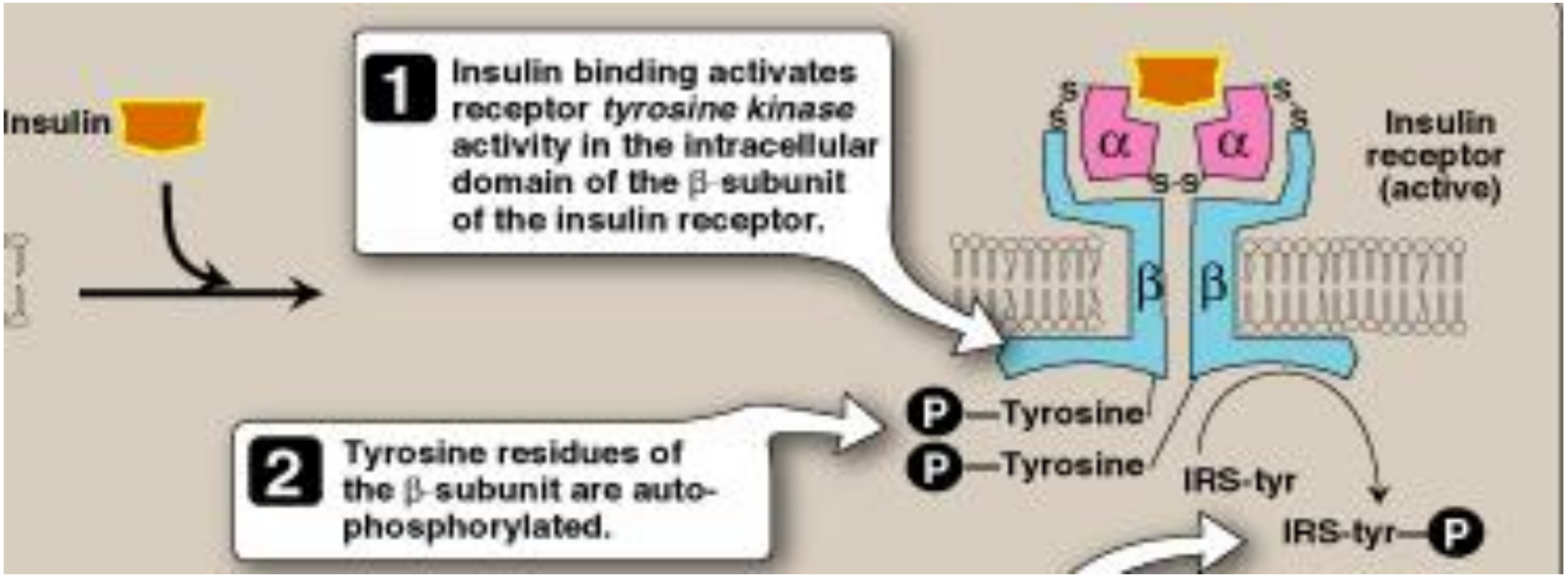
- in the cAMP mechanism the protein kinase was protein kinase A
- In the calcium or phosphatidylinositol mechanism the protein kinase is protein kinase C

5 tyrosine kinase cascade

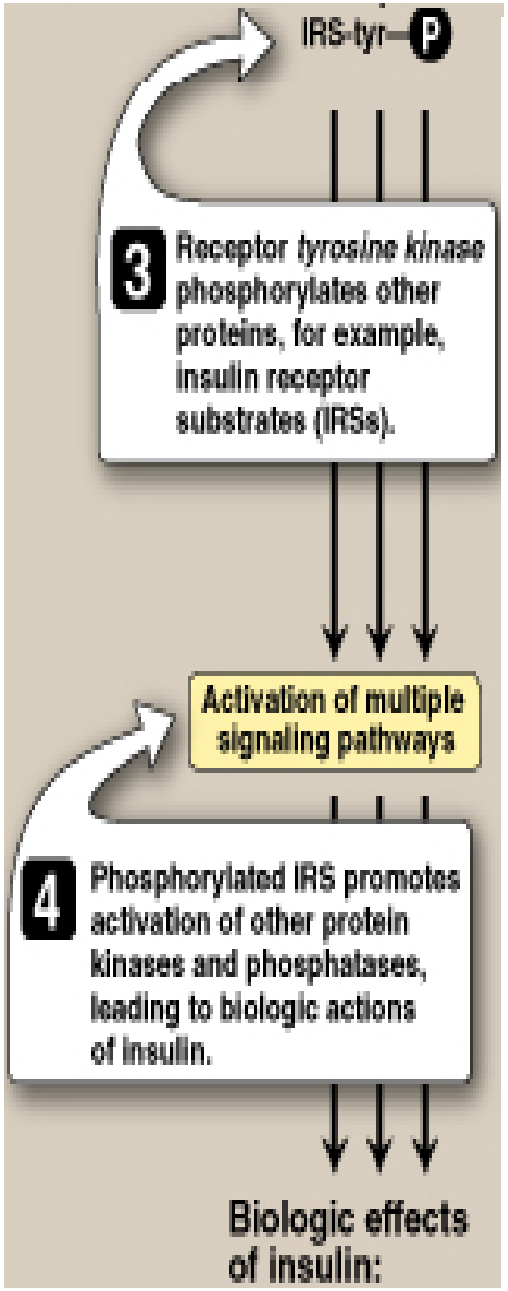
- Insulin receptor has two subunits
  - Subunit alpha which lies outside the cell membrane and this is where insulin binds
  - Subunit beta which lies within the cell and this is a tyrosine kinase protein that is activated when insulin binds to alpha subunit



- After the binding of insulin to the receptor the tyrosine residues (on beta subunit) are AUTOPHOSPORYLATED



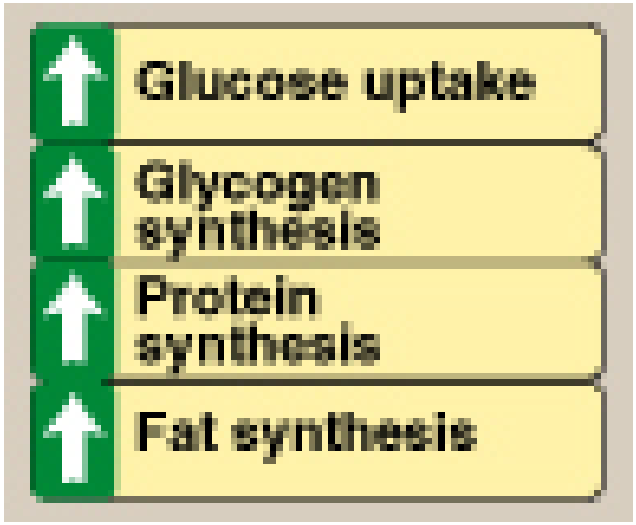
- This phosphorelated receptor then phosphorolates other proteins like IRS (insulin receptor substrates)
- IRS causes physiological effects of insulin.
- *Note from dr amr:*
  - *Although GH uses a tyrosine kinase method , it does not have a receptor that autophosphorylates itself*

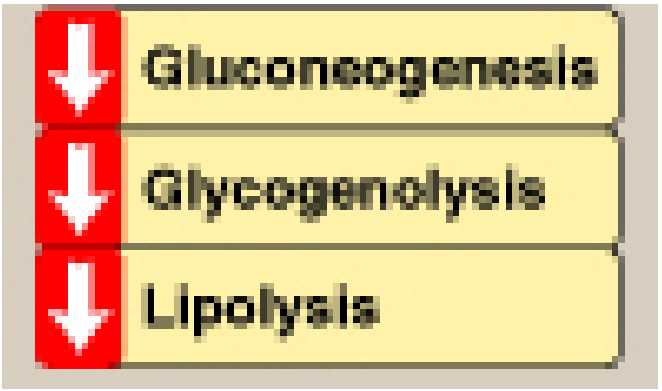


At least remember this

- The tyrosine kinase mechanism ends by phosphorylation of tyrosine residue on the same receptor and this action starts the signalling inside the cell.

Biologic Effects of Insulin





Altered gene expression

Biomedical Importance

- **Excessive, deficient, or inappropriate production /release of hormones are major causes of diseases**
- **Many drugs act through influencing the pathways of hormones**