PHARMACODYNAMICS III
RECEPTOR FAMILIES

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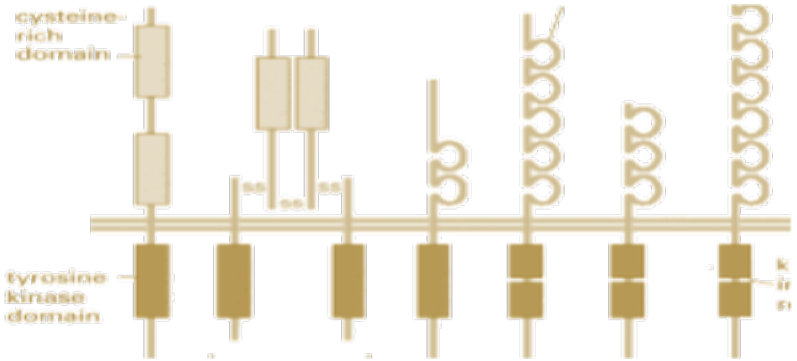
(Slides are adopted and modified from Prof. Hanan Hajar)

Receptor Families

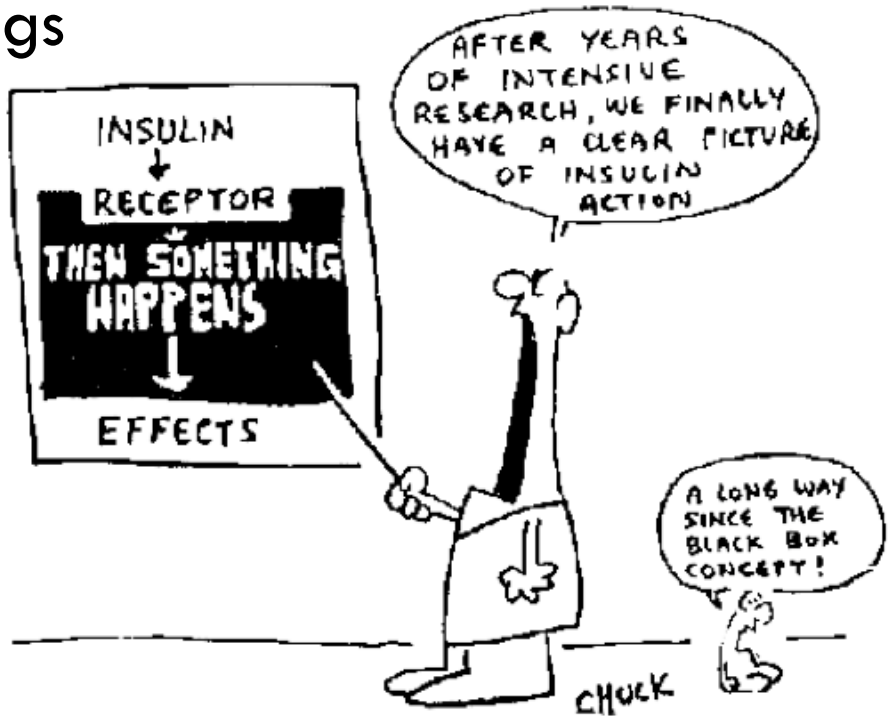
By the end of this lecture, you should:

- Classify receptors into their main superfamilies
- Recognize their different transduction mechanism
- Identify the nature & time frame of their response classify.

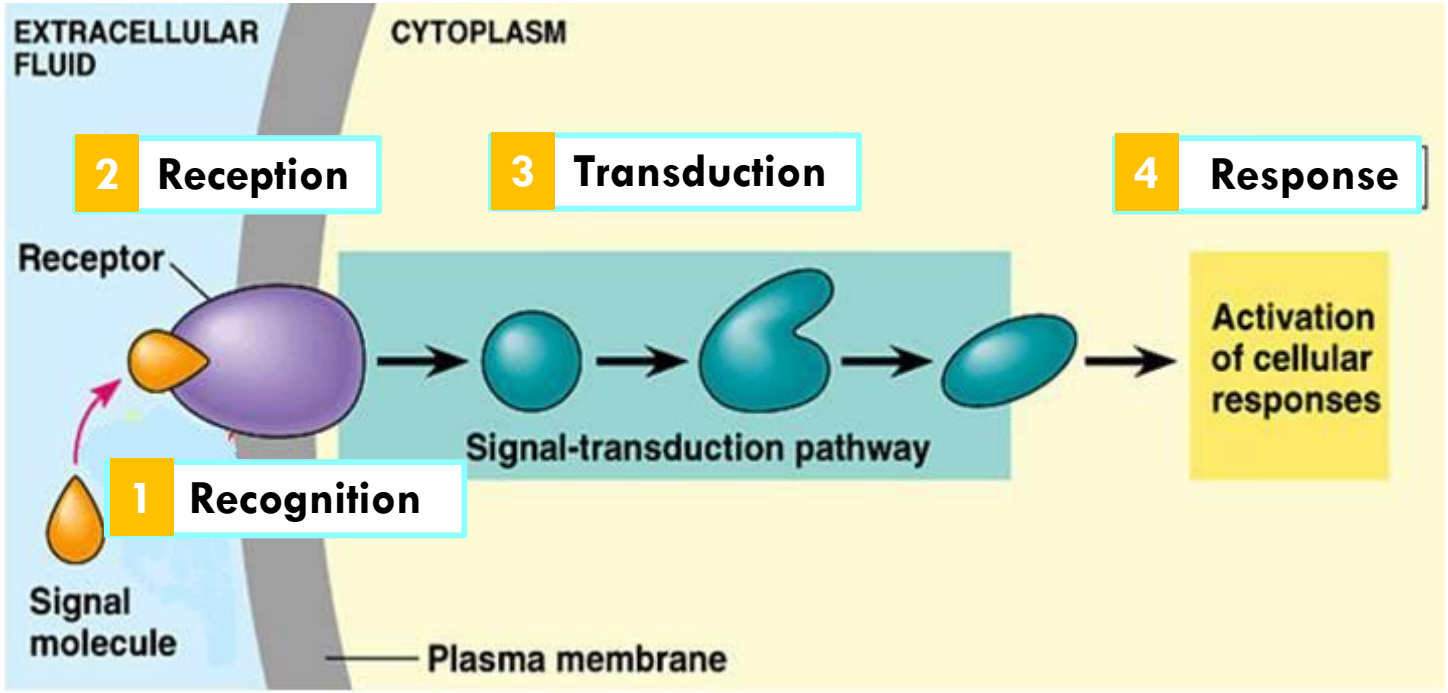


Main Receptor Classes (Receptor Families)

- Effect Persistency of drugs
- Cellular mechanism of the drugs
- Selectivity of drugs
- Development of new drugs

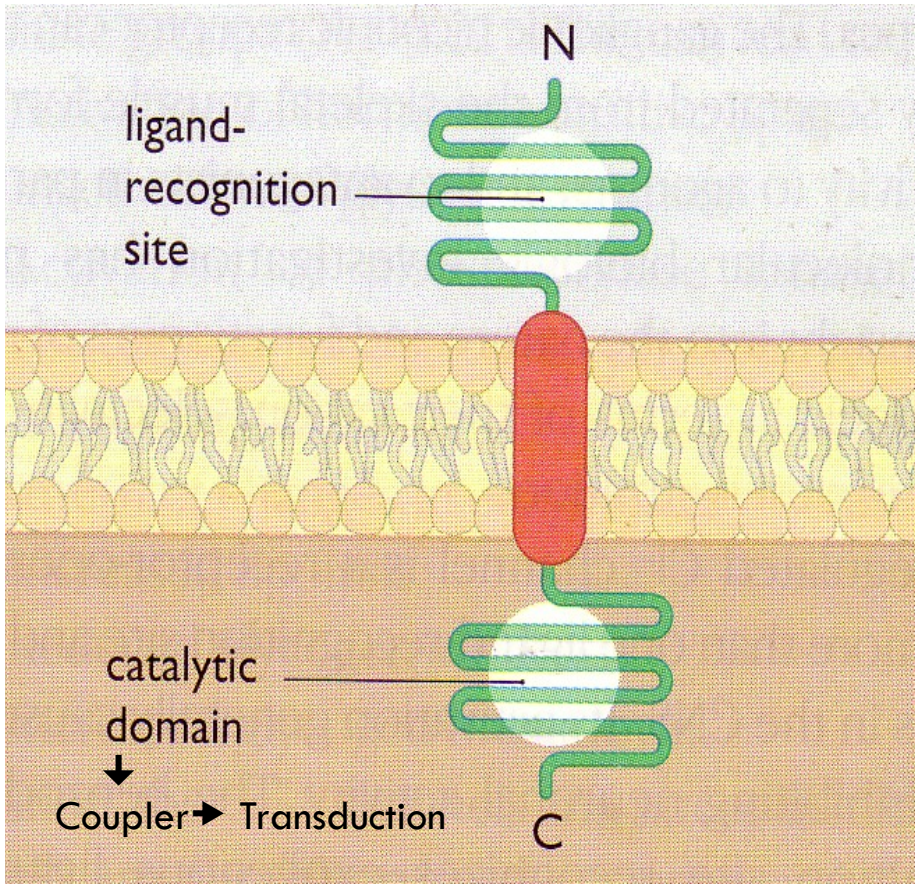


RECEPTORS


EXTRACELLULAR FLUID
CYTOPLASM
2 Reception
3 Transduction
4 Response
Receptor
Activation of cellular responses
Signal-transduction pathway
1 Recognition
Signal molecule
Plasma membrane

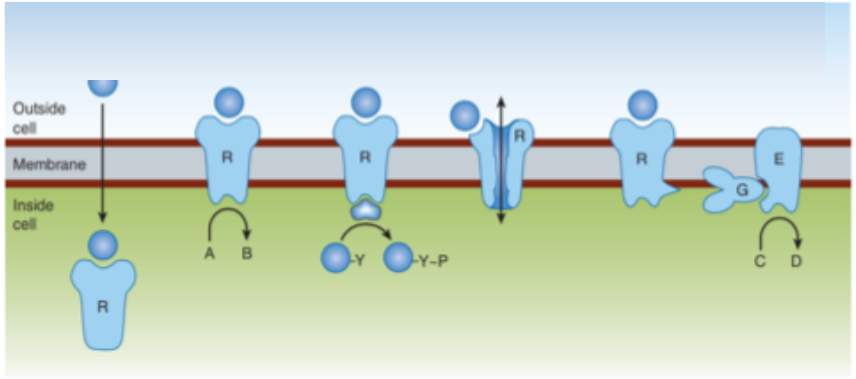
RECEPTORS STRUCTURE

- Ligand recognition site
- Inner catalytic domain

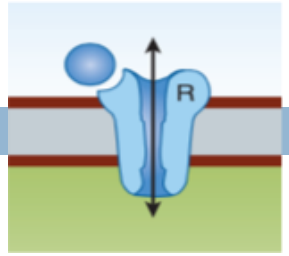


Receptor Families

- **Type I** (Ion Channel-Linked receptors)
- **Type II** (G-Protein coupled receptors)
- **Type III** (Enzyme-Linked receptors)
- **Type IV** (Receptors linked to gene transcription)



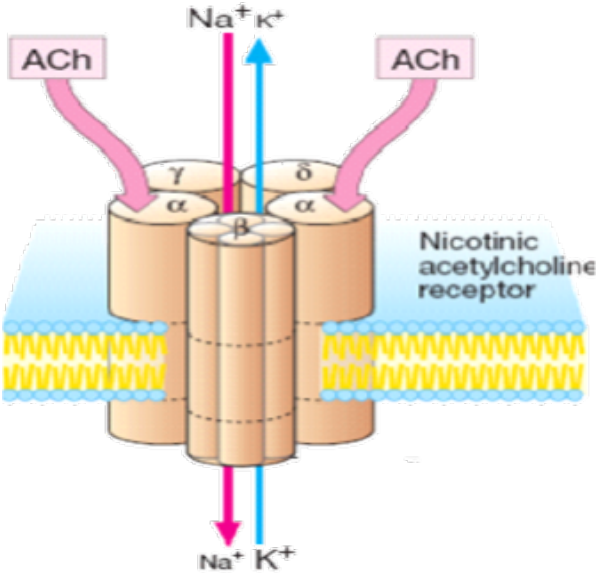
Receptor Families



Type I (Ion Channel-Linked receptors)

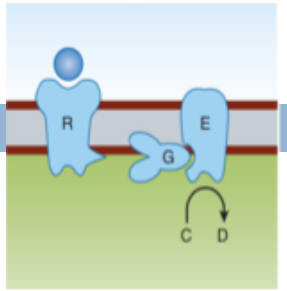
Ligand gated ion channels

Ionotropic receptors



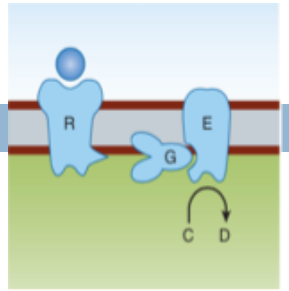
- Located at cell membrane
- Directly activated by ligand binding
- Involved in fast synaptic transmission.
- Directly related to channels.
- Response occurs in milliseconds.
- E.g. Nicotinic receptors activated by acetylcholine

Receptor Families



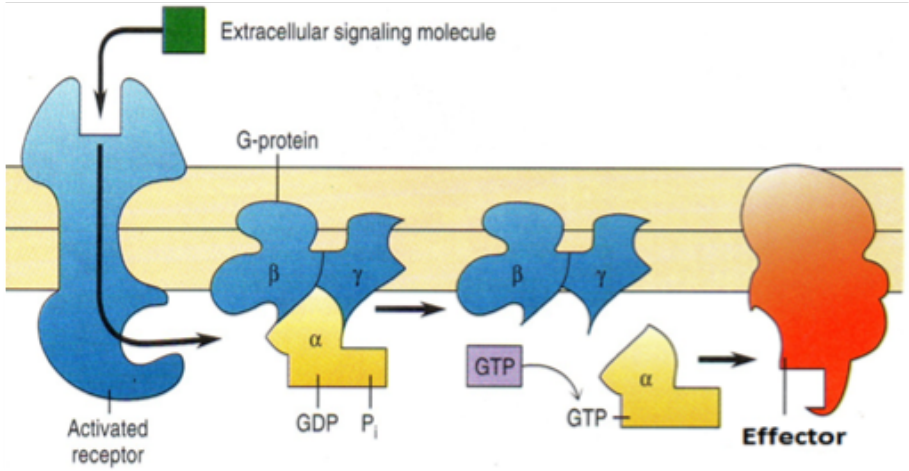
- **Type II** (G-Protein coupled receptors)
  - The largest family that accounts for many known drug targets
  - Located at cell membrane
  - Coupled to **G-protein**
  - Response through ion channels or enzymes.
  - Involved in rapid transduction
  - Response occurs in seconds.
  - Examples
    - Muscarinic receptors of Ach (M)
    - Adrenergic receptors of Noradrenaline (α and β)

Receptor Families

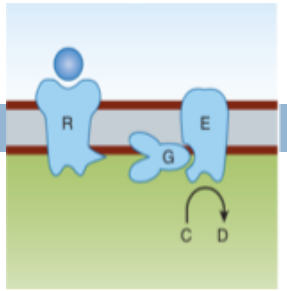


- **Type II** (G-Protein coupled receptors)

- Is composed of 3 subunits [α β γ]
- Difference G-Protein classes according to their α-subunits into
  - Gs and Gi produce, respective, stimulation and inhibition of the effector (Adenyl Cyclase)
  - Gq is linked to activation of the effector (PLC-IP3 -Ca^{++} CaM & PKC)



Receptor Families



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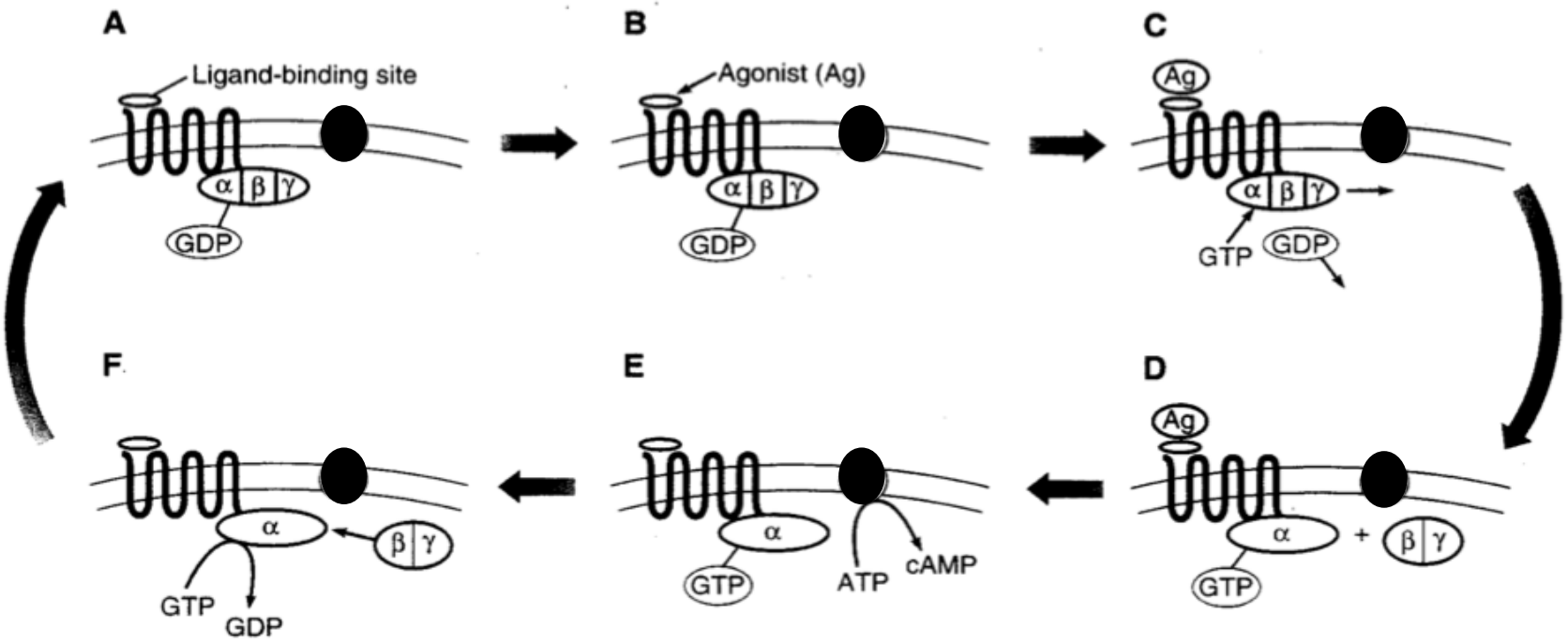
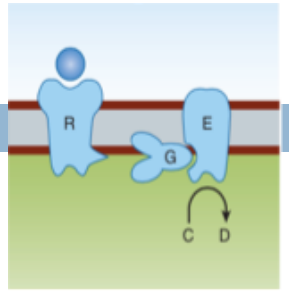


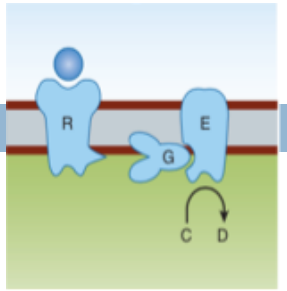
http://youtu.be/0nA2xhNiAow

Receptor Families



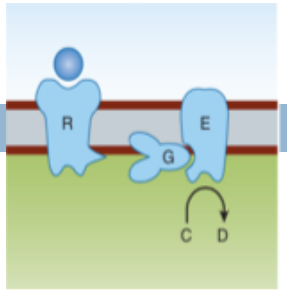
- **Type II** (G-Protein coupled receptors)
  - GTP-binding regulatory proteins
  - Regulate guanine nucleotides GDP, GTP.
  - Comprise of three subunits ($\alpha\beta\gamma$), α subunits possess GTPase activity
  - **Receptors in this family respond to agonists**
    - By promoting the binding of GTP to the G protein alpha (α) subunit.
    - GTP activates the G protein and allows it, in turn, to activate the effector protein.
    - The G protein remains active until it hydrolyzes the bound GTP to GDP and returns to its ground (inactive) state.

Receptor Families



- **Type II** (G-Protein coupled receptors)
  - Targets for G-proteins
    - Ion channels
      - Muscarinic receptors in heart (K-channel), decrease heart rate
    - Second messengers
      - Cyclic AMP system (cAMP)
      - Inositol phosphate system (IP3+DAG)

Receptor Families



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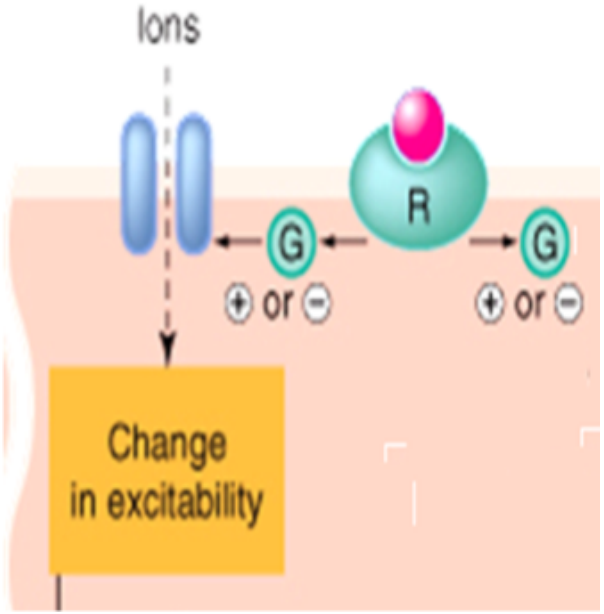
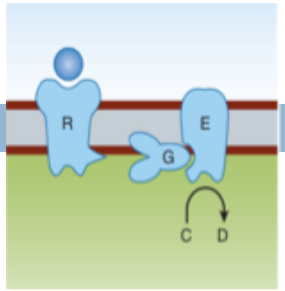


Receptor Families



- **Type II** (G-Protein coupled receptors)
  - Targets for G-proteins
    - Second messengers
      - Cyclic AMP system (cAMP)

G Protein

Adenyl cyclase enzyme (AC)

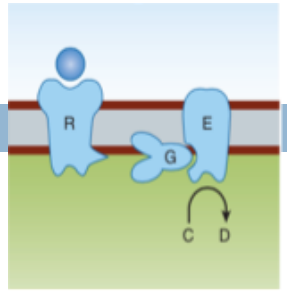
ATP

cAMP

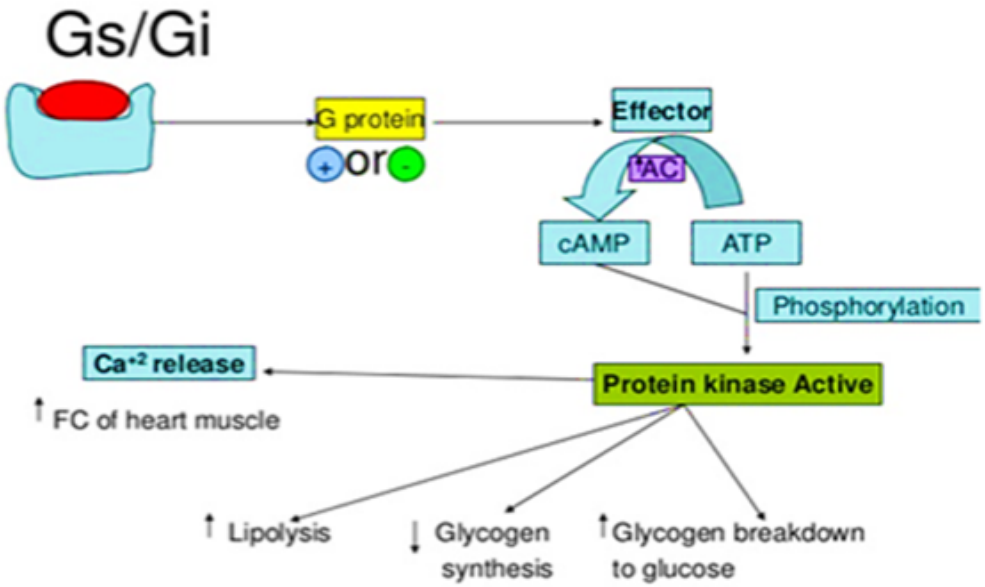
Phosphorylation of Protein kinase A (PKA)

Activation or inhibitions of ion channels or enzymes

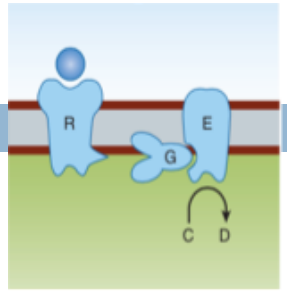
Receptor Families



- **Type II** (G-Protein coupled receptors)
  - Targets for G-proteins
    - Second messengers
      - Cyclic AMP system (cAMP)
      - M_2 & M_4 Ach receptors couple to Gi to inhibit AC
      - α_2 Adrenoceptors couple to Gi to inhibit AC.
      - $\beta_{1\&2}$ Adrenoceptors couple to Gs to stimulate AC



Receptor Families



- **Type II** (G-Protein coupled receptors)
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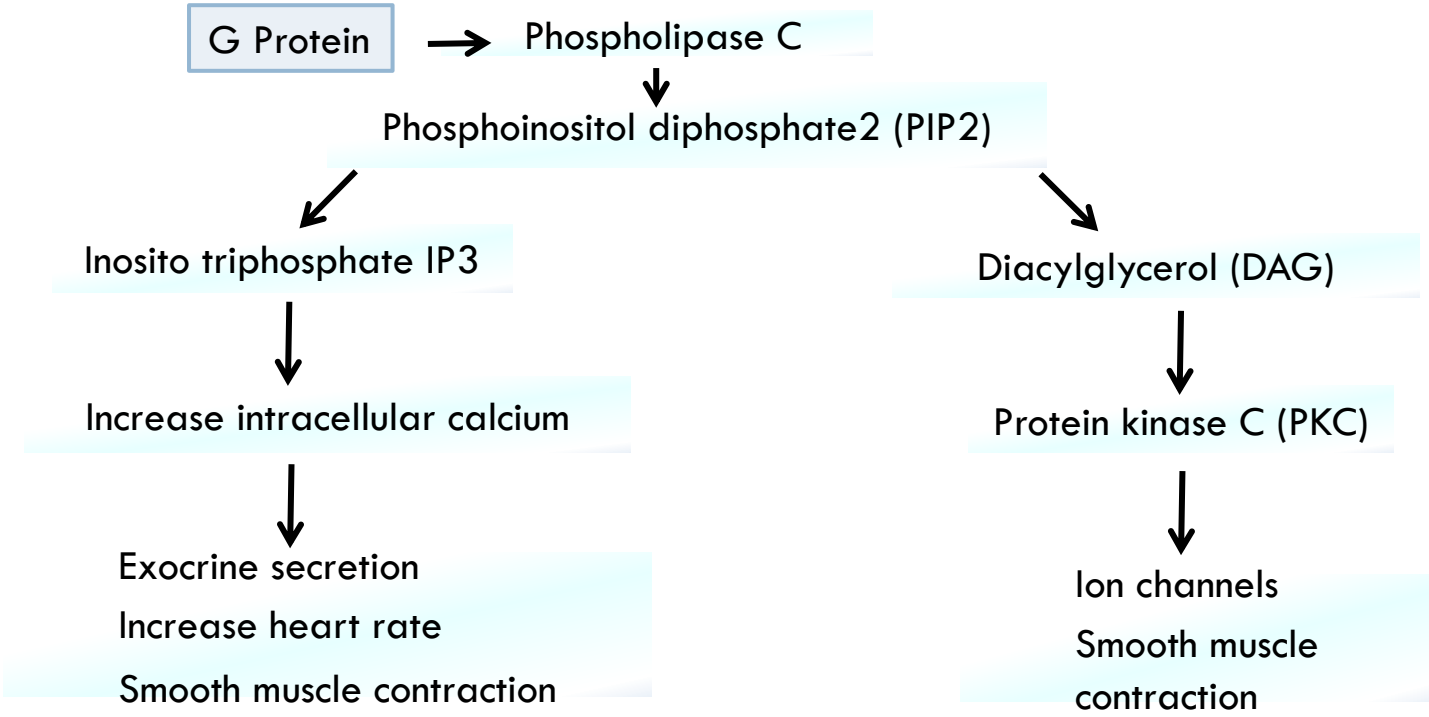
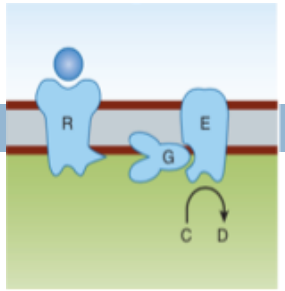
      - Inositol phosphate system (IP3+DAG)



Receptor Families



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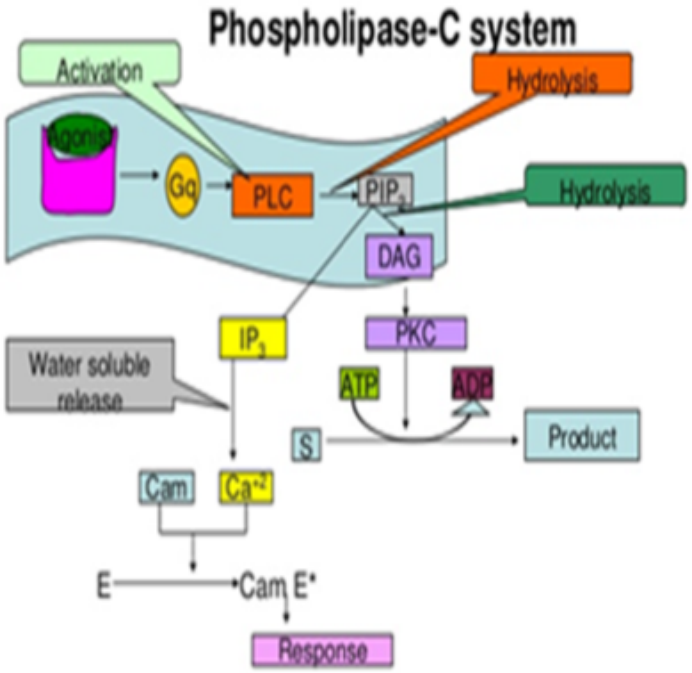
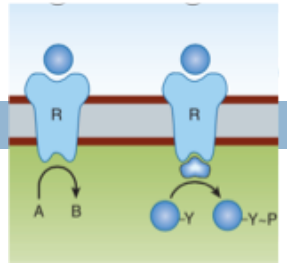
  - Targets for G-proteins
    - Second messengers
      - Inositol phosphate system (IP3+DAG)
      - M_1 & M_3 Ach receptors couple to Gq to stimulate PLC
      - α_1 Adrenoceptors couple to Gq to stimulate PLC.

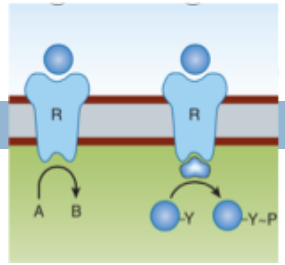


Receptor Families



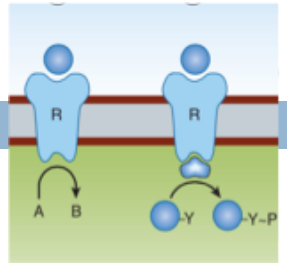
- Type III (Enzyme-Linked receptors)
  - (Kinase-linked receptor)
- Located at cell membrane with intrinsic enzymatic activity
- **Activation of receptors results in**
  - Activation of protein kinases as **tyrosine kinase** with phosphorylation of **tyrosine residue** on their substrates and activation of many intracellular signaling pathways in the cell.
  - **E.g. Insulin receptors**

Receptor Families



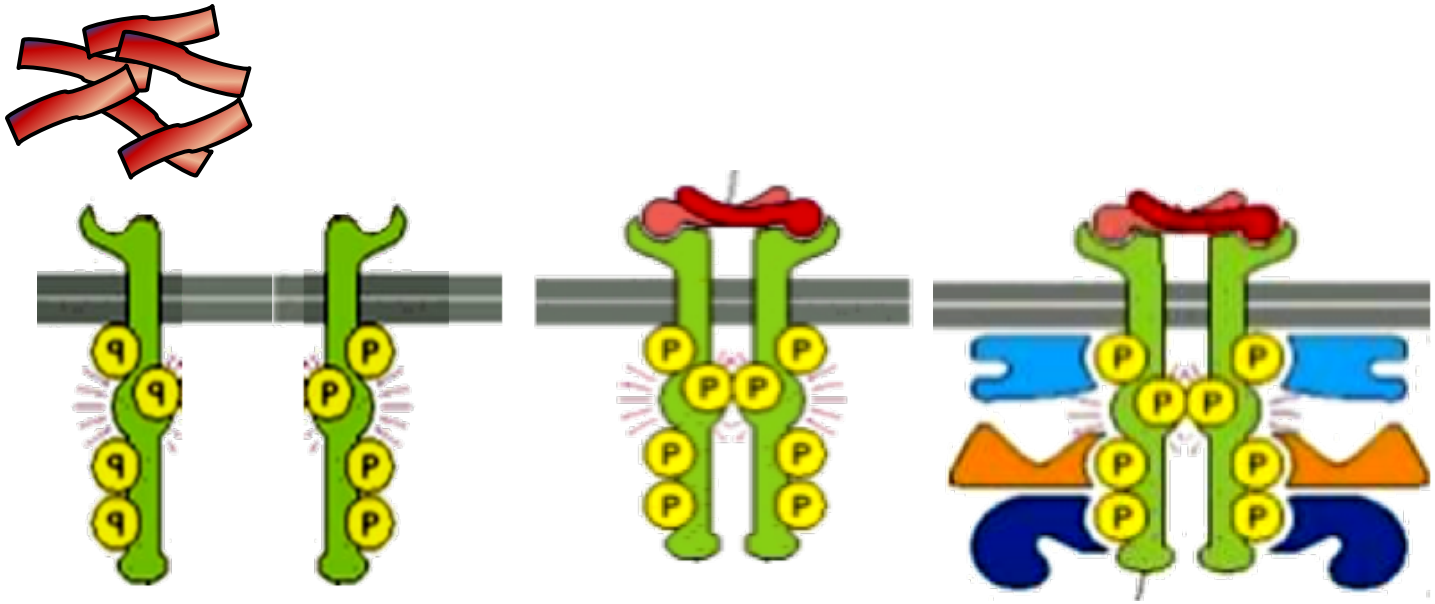
- Type III (Enzyme-Linked receptors)
  - (Kinase-linked receptor)
- Involved in response to hormones, growth factors.
- Response occurs in minutes to hours.
- They control many cellular functions as metabolism and growth.

Receptor Families



- Type III (Enzyme-Linked receptors)

  Example : Insulin Receptor

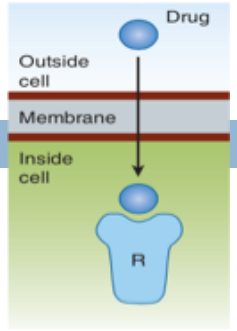


Ligands dimerize receptors

Activated Receptor autophosphorylates

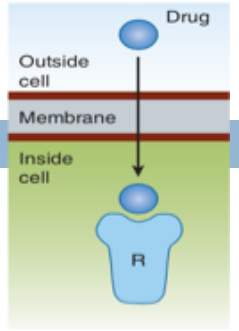
Phosphorylate other proteins that it docks

Receptor Families



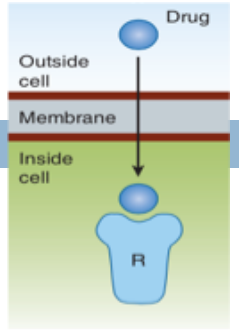
- Type IV (Receptors linked to gene transcription)
  - Nuclear receptors
- Located intracellularly
- Directly related to DNA (Gene transcription).
- Activation of receptors either increase or decrease protein synthesis
- Response occurs in hours or days and persists longer.
- Their natural ligands are lipophylic hormones; steroids, thyroids, estrogen.

Receptor Families



- Type IV (Receptors linked to gene transcription)
  - Nuclear receptors
- They possess an area that recognizes specific DNA sequence in the nucleus which can bind it. This sequence is called a Responsive Element [RE]
- This means that the activated receptors are acting as TRANSCRIPTION FACTORS [TF] → expressing or repressing target genes.

Receptor Families



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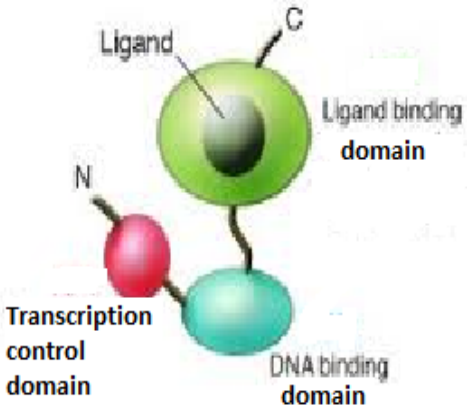
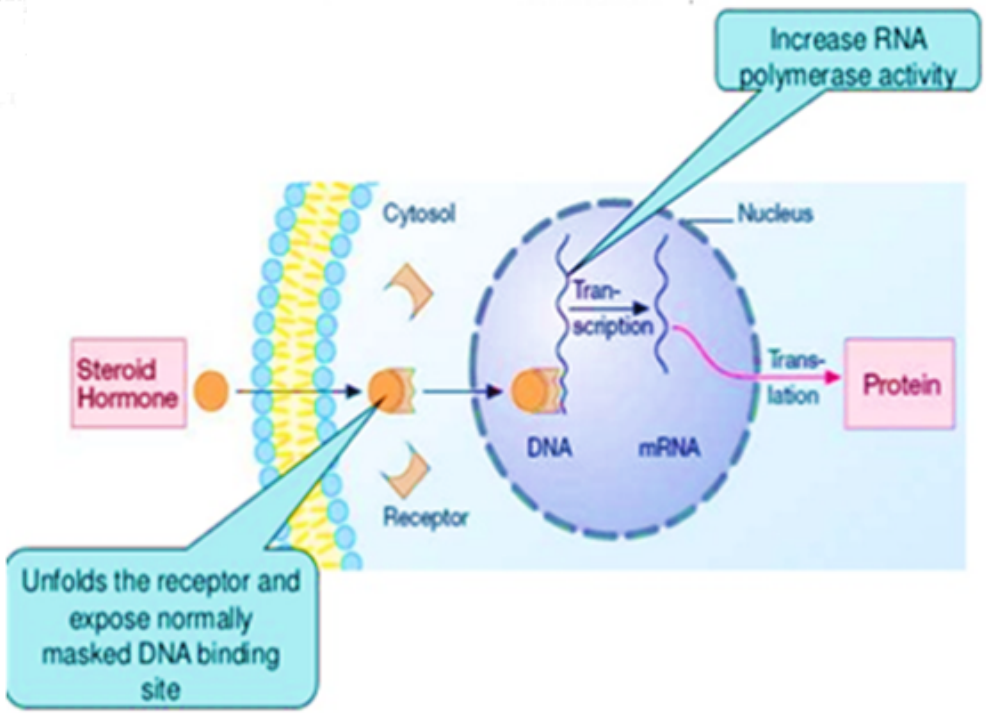


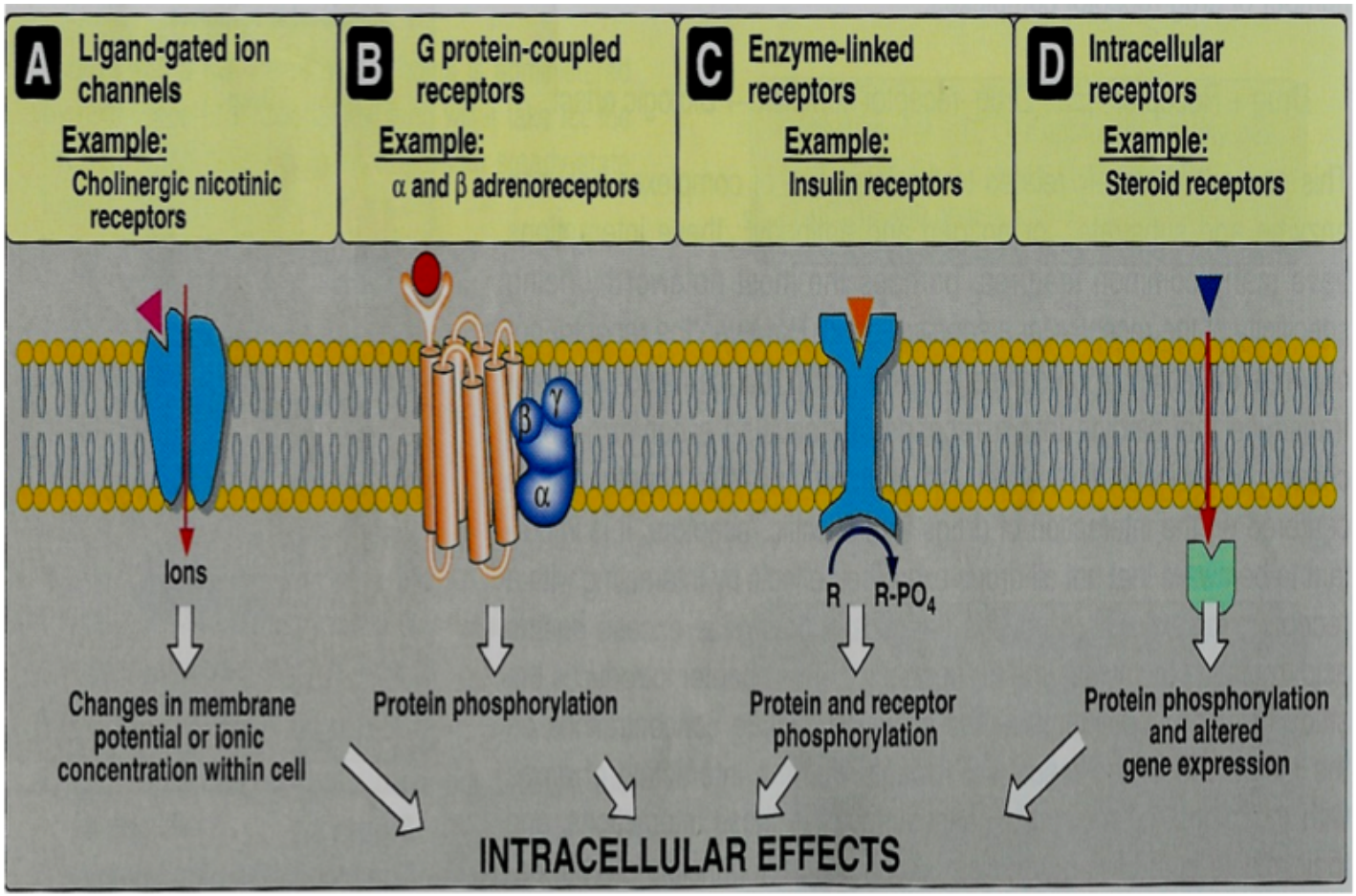


Receptor Families

	Type I (Ion Channel-Linked)	Type II (G-PCR)	Type III (Enzyme-Linked R)	Type IV (Intracellular R)
Location	Membrane	Membrane	Membrane	Nucleus
Coupling	Direct	G-Protein	Direct	Via DNA
Synaptic transmission	Very Fast	fast	slow	Very slow
Response	milliseconds	Seconds	minutes	Hours or days
Examples	Nicotinic receptors	Muscarinic receptors	Insulin receptors	Estrogen Steroid receptors
Effectors	channels	Channels/ enzymes	Enzymes	DNA

Receptor Families

- Signaling Mechanisms



Receptor Families

- Signaling Mechanisms