

# TOXICODYNAMICS

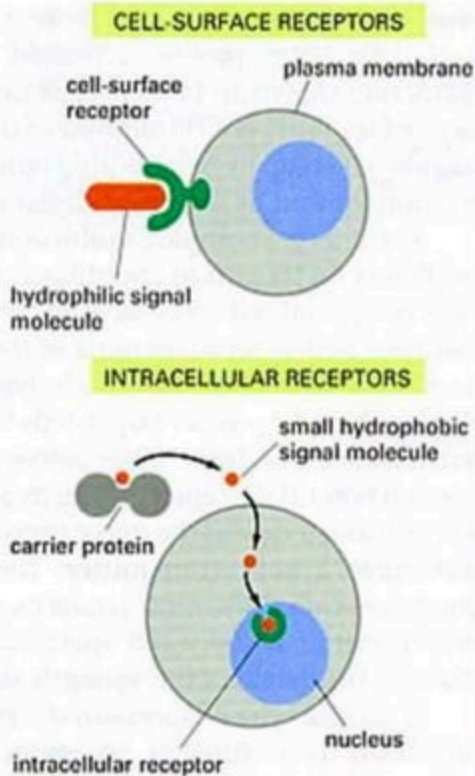
It is what the **toxicant does with body** or study of **biochemical and physiological effects of toxicants** on the body and their mechanism of action.

It is concerned mainly with the interactions of toxicants with the target site.

- ⊙ Two factors that determine the effect of toxicant **affinity** and **intrinsic activity**.
- ⊙ **AFFINITY** is a measure of the tightness that a toxicant binds to the receptor.
- ⊙ **INTRINSIC ACTIVITY** is a measure of the ability of a toxicant once bound to the receptor to generate an effect activating stimulus and producing a change in cellular activity.

# RECEPTORS

- Receptors are macromolecules usually made up of **proteins** or **glycoprotein** present on the membrane surface or within the cell to which specific hormones, neurotransmitters, drugs or toxicants combine to produce their action.
- Activation of receptors by toxicant may lead to toxic action while inhibition of receptors by blockers, stops the activity of toxicants.



# TYPES OF RECEPTORS

- Receptors have been classified into four super families according to their molecular structure and nature of signal transduction mechanism. These are
  - Ligand Gated ion-Channels/Iono Receptors
  - G-Protein Coupled Receptors
  - Enzymatic Receptors
  - Receptor Regulating DNA Transcription

# 1. LIGAND GATED ION-CHANNELS

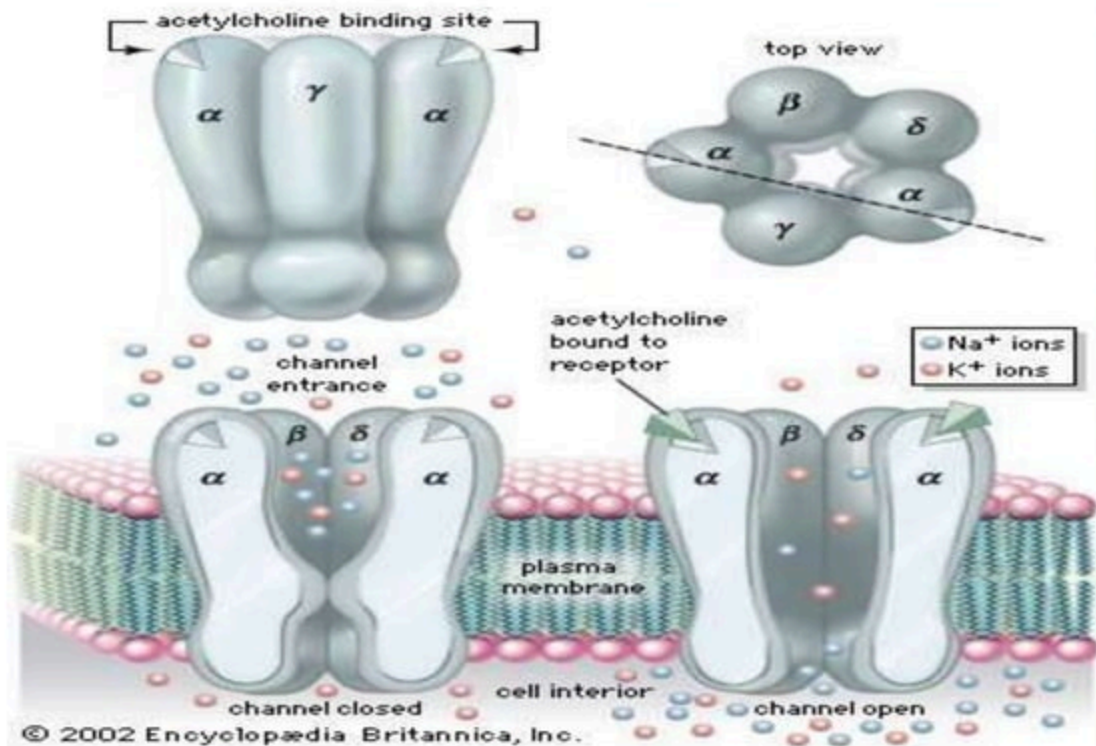
- ⦿ These are cell surface receptors that enclose selective ion-channels which allow the free movement of certain ions like sodium, potassium, calcium and chlorides.
- ⦿ Receptors of this type control the fastest **synaptic events in nervous system** where lag time between ligand binding and cellular response is only in milliseconds.
- ⦿ Examples includes nicotinic-cholinergic receptors, GABA receptors.

## STRUCTURE

All ligand gated ion channels are made up of subunit proteins. (Alpha, beta, gamma, delta kappa).

These subunit penetrate all the way through the membrane laying side by side in a circle to form a tubular channel (Like petals of lily).

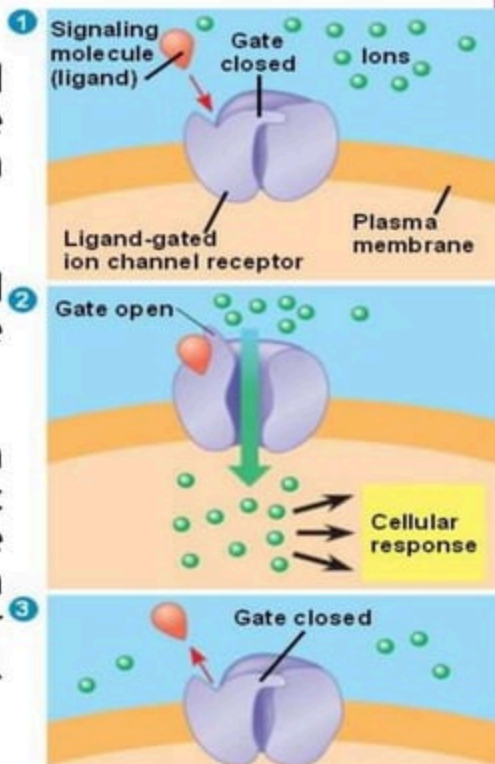
## STRUCTURE OF LIGAND GATED ION-CHANNELS





## SIGNALING MECHANISM

- ⊙ The toxicant molecule attached with the ligand binding site located on subunit protein directly.
- ⊙ The channel remain activated until the ligand attached to the extracellular binding site.
- ⊙ Due to the concentration gradient flow of ions the electric potential across the membrane changed causing depolarization ( $\text{Na}^+$  Channels) or hyperpolarization ( $\text{Cl}^-$  Channels) of cell



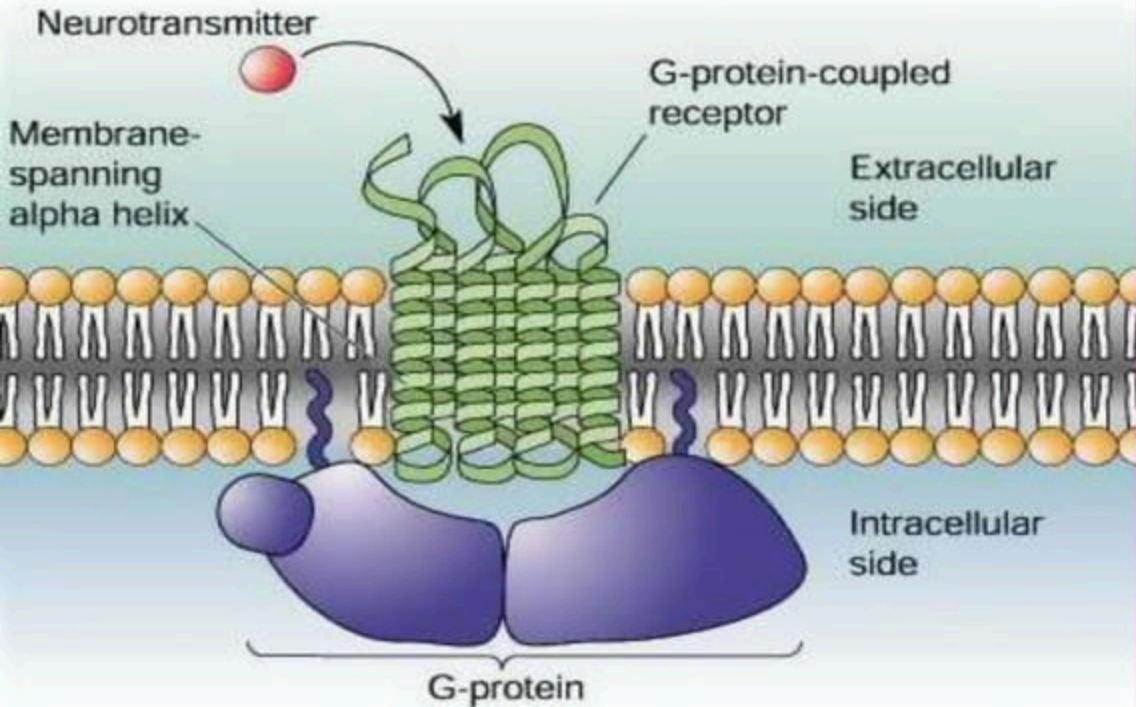
## 2. G-COUPLED RECEPTORS

- Large super family of membrane bound receptors which regulate distinct **effector proteins** (Enzymes, Channels, or Carriers) through mediation of **transducers**, a group of guanine nucleotides (GTP and GDP) binding proteins known as **G-Proteins**. These are heterotrimeric molecules consisting of three subunits ( $\alpha$ ,  $\beta$ , and  $\gamma$ ).
- Example of G-Protein Coupled receptors include muscarinic-cholinergic receptors, Histamine receptors, Adrenergic receptors and many peptide hormone receptors.

### STRUCTURE

- They consist of 400-500 chains of polypeptides, The amino terminus followed by amino acid sequence having 7 Alpha helical membrane spanning hydrophobic region and **3 extracellular** and **3 intracellular loops**.

- The agonist binding site locates between helices on extracellular face.





## SIGNALING MECHANISM

- ◉ In the resting stage the G-Proteins exists as an unattached  $\alpha$ ,  $\beta$ , and  $\gamma$  trimer with Guanosine diphosphate (GDP) occupying the site on  $\alpha$  subunit.
- ◉ When the agonist binds to G-Protein receptor, the agonist-receptor complex facilitates displacement of Guanosine diphosphate (GDP) by Guanosine triphosphate (GTP).
- ◉ Binding of GTP activates the  $\alpha$  subunit and the  $\alpha$ -GTP complex then dissociate from  $\beta$  and  $\gamma$  subunit and interact with membrane bound effector protein(Ion channel, enzyme, or transport protein).

- ⊙ The activation process terminated when **hydrolysis of GTP** to GDP occurs through GTPase activity of  $\alpha$ -subunit.
- ⊙ It has been estimated that initial agonist-receptor interaction lasts only for a few seconds but once a G-protein is activated it remain active for about 10 seconds. Which amplify the signals. Thus in G-Coupled system occupancy of only a fraction of receptor population is enough to produce maximal response.
- ⊙ Gs, Gi, Go, Gq and G13 are different type of G-Proteins
- ⊙ G-Coupled Effector system function by

1. ENZYME LINKED EFFECTOR SYSTEM

2. ION CHANNEL LINKED EFFECTOR SYSTEM

# 1. ENZYME-LINKED EFFECTOR SYSTEM

- ⊙ Three Effector systems through which these receptors function.
- ❑ Adenylate Cyclase or cAMP system
- ❑ Phospholipase C or IP3-DAG system
- ❑ Phospholipase A2 or AA System

## ADENYLATE CYCLASE OR cAMP SYSTEM

- ⊙ The effector protein is Adenylate cyclase which is activated by  $\alpha$ -GTP complex.
- ⊙ Activation of Adenylate Cyclase enzyme by stimulatory G-Protein (Gs) leads to increased synthesis of cAMP (3'-5' cyclic adenosine monophosphate).
- ⊙ Accumulation of cAMP within the cell activates cAMP-dependent Protein Kinase.
- ⊙ These Protein kinases phosphorylate and alter the function of cell.

- ◉ The intracellular effects of cAMP are terminated by degradation of cAMP to 5-cAMP by Phosphodiesterases (PDE) enzymes.

## PHOSPHOLIPASE C OR IP3-DAG SYSTEM

- ◉ The effector protein is phospholipase C.
- ◉ Activation of this protein cause hydrolysis of the membrane phospholipid phosphatidyl inositol 4,5-bisphosphate (PIP<sub>2</sub>) to generate Inositol 1,4,5, triphosphate (IP<sub>3</sub>) and diacyl glycerol (DAG).
- Inositol 1,4,5, triphosphate (IP<sub>3</sub>) mobilizes Ca<sup>++</sup> from the intracellular organelle to receptor on the membrane of endoplasmic reticulum.
- ◉ An increase in free intracellular calcium concentration from 10 to 100 fold produces a range of cellular responses including modulation of enzymes, contractile proteins.

- ◉ Important action includes smooth muscle contraction, secretion from exocrine glands, release of neurotransmitters.
- ◉ **Diacyl glycerol (DAG)** activate protein Kinase C (PKC) which control many functions of cell by phosphorylating a variety of intracellular proteins. Functions include, release of hormones from endocrine glands, contraction and relaxation of smooth muscles.

### **PHOSPHOLIPASE A<sup>2</sup> OR AA SYSTEM**

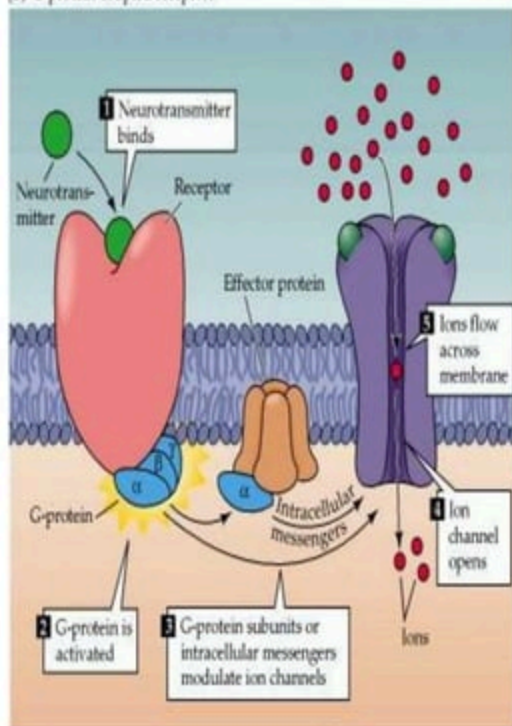
- ◉ Activation of phospholipase A<sub>2</sub> by G-proteins leads to production of **Arachidonic acid** from the membrane phospholipid.
- ◉ Arachidonic acid is further broken down to prostaglandins, leukotriens, and thromboxane.
- ◉ Arachidonic acid also control potassium channel functions in neurons.



## 2. ION CHANNEL-LINKED EFFECTOR SYSTEM

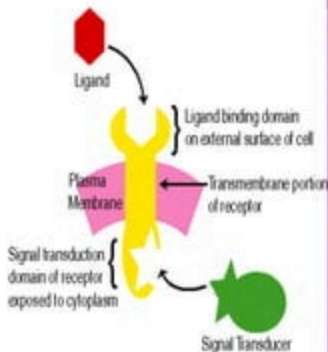
- G-coupled protein receptors can control some ion channels.
- Depending upon the type of protein ion channels remain opened or closed thereby causing hyperpolarization or depolarization.
- $G_s$  protein open  $Ca^{++}$  channels in myocardium and skeletal muscles. While  $G_i$  and  $G_o$  open  $K^+$  channels in heart and close  $Ca^{++}$  in neurons.

(B) G-protein-coupled receptors



### 3. ENZYMATIC RECEPTORS/TYROSINE KINASE LINKED RECEPTORS

- These receptors are membrane bound and have large extracellular and intracellular domains.
- Extracellular domain is connected with intracellular domain with the help of short single transmembrane stretch of peptide chain.
- Intracellular domain is made of protein kinase mostly tyrosine kinase.

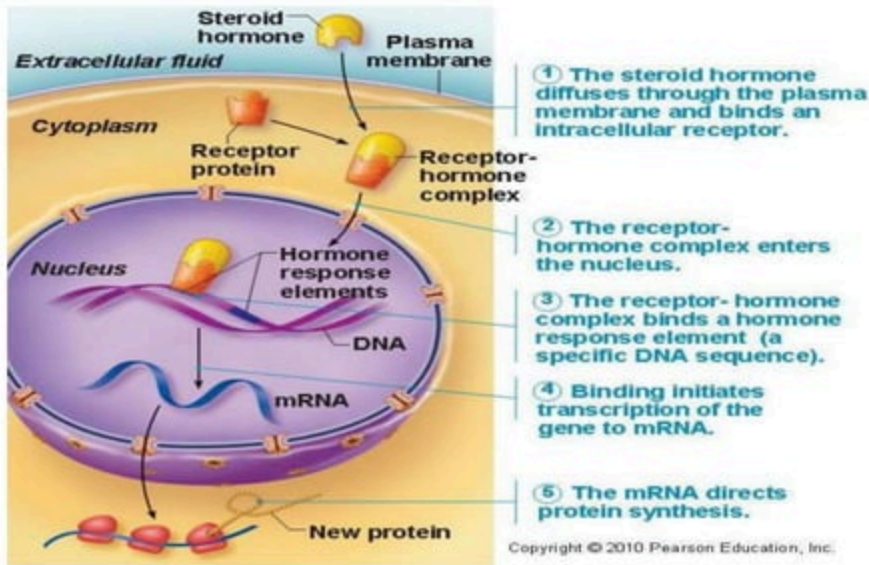


When specific ligand binds to extracellular the intracellular **protein kinase** get activated and phosphorylates the regulatory proteins. which either alter the activity of cell.

In some receptors ligand binding activates **Guanylate cyclase** cGMP (Cyclic Guanosine Phosphate) which activate cGMP-dependant protein kinase and modulate cellular activity.

## 4. RECEPTORS REGULATING DNA TRANSCRIPTION/STEROID RECEPTORS

- These are intracellular proteins that regulate transcription of specific gene. Steroid, thyroid hormone, Vit D and A mediate through these receptors.
- Cellular effect is produced as a result of protein synthesis.





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# G Protein Coupled Receptors

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