



Solution-Pharmacy

RECEPTOR

A General Introduction with Diagrams

Important Definitions

Pharmacology- Pharmacology is made-up of two main words- 'Pharma' + 'Logy' in some books there is Pharmakon in the place of Pharma, but to make you better understand we have made little changes. Pharma is related with drug or medicine and logy means- to study. So if we merge these two words together, this will become- **PHARMACOLOGY**.

“To study the complete life cycle of drugs as per pharmacodynamic and pharmacokinetic profile is known as Pharmacology” now again we have got two new words- Pharmacodynamic and pharmacokinetic. Let's understand them also.

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Pharmacodynamic- Pharmacodynamic is a study of drug's effect on body, so we can say it's a study of- what does **DRUG** do to the **BODY**. Let's illustrate it in a very easy language.

Pharmacokinetic- “What does **BODY** do to the **DRUG** ” we have simple interchanged the **BODY** and **DRUG** to make a definition. And as per the definition our body responds to any drug by giving **ADME** effects.

A stands for - Absorption

D stands for - Distribution

M stands for - Metabolism

E Stands for- Excretion or elimination

Principle of Drug Action

Principle of drug action means how any drug produce the effect for which it has been administered. These are working methodology of drugs.

| Principle | Explanation | Example |
|--------------------|--|---|
| Irritation | Senna and some other drug used in constipation irritate the intestine and increase defecation. Other balm in case of headache will irritate the forehead tissue and gives relief from pain for short duration. <small>Solution Pharmacy- https://www.facebook.com/pharmavideo/</small> | Counter Irritant like- drugs for constipation |
| Stimulation | Stimulation means to increase the function of any specialized organ, which will result in extra work, like in case of fear or fight adrenaline is get secreted and heart rate increase which give FFF response. <small>Solution Pharmacy- https://www.facebook.com/pharmavideo/</small> | Adrenaline. Stimulates heart, pilocarpine stimulates salivary glands |
| Depression | The simple meaning of depression is the reduction of specialized activity. For example- Barbiturate and benzodiazepine depress the CNS and give depression action. As same Omeprazole reduce gastric acid secretion. <small>Solution Pharmacy- https://www.facebook.com/pharmavideo/</small> | Barbiturate depresses CNS, Quinidine depresses heart, and Omeprazole depress gastric acid secretion |
| Replacement | When any hormone or biochemical substance is in inadequate quantity and there recovery is not possible then there is one option of replacement. The replacement is done for insulin in case of insulin dependent diabetes; here insulin is given by injection to maintain the requirement <small>Solution Pharmacy- https://www.facebook.com/pharmavideo/</small> | Levodopa in Parkinson's, Insulin in diabetes and Iron in Anemia. |
| Cytotoxic | When there is entry of any parasite, or there is no other option to control the growth of own body cell then Cytotoxic drugs are used. They kill the microorganism of kill the uncontrolled and excessive growing cells. <small>Solution Pharmacy- https://www.facebook.com/pharmavideo/</small> | Penicillin, Zidovudine, Chloroquine, cyclophosphamide |

Mechanism of Drug Action

Majority of drug produce their effect by interacting with specific target molecule which are basically are proteins.

Functional protein that are target of drug action can be grouped into four major categories- (1) Enzymes (2) Ion Channels (3) Transporters (4) Receptors

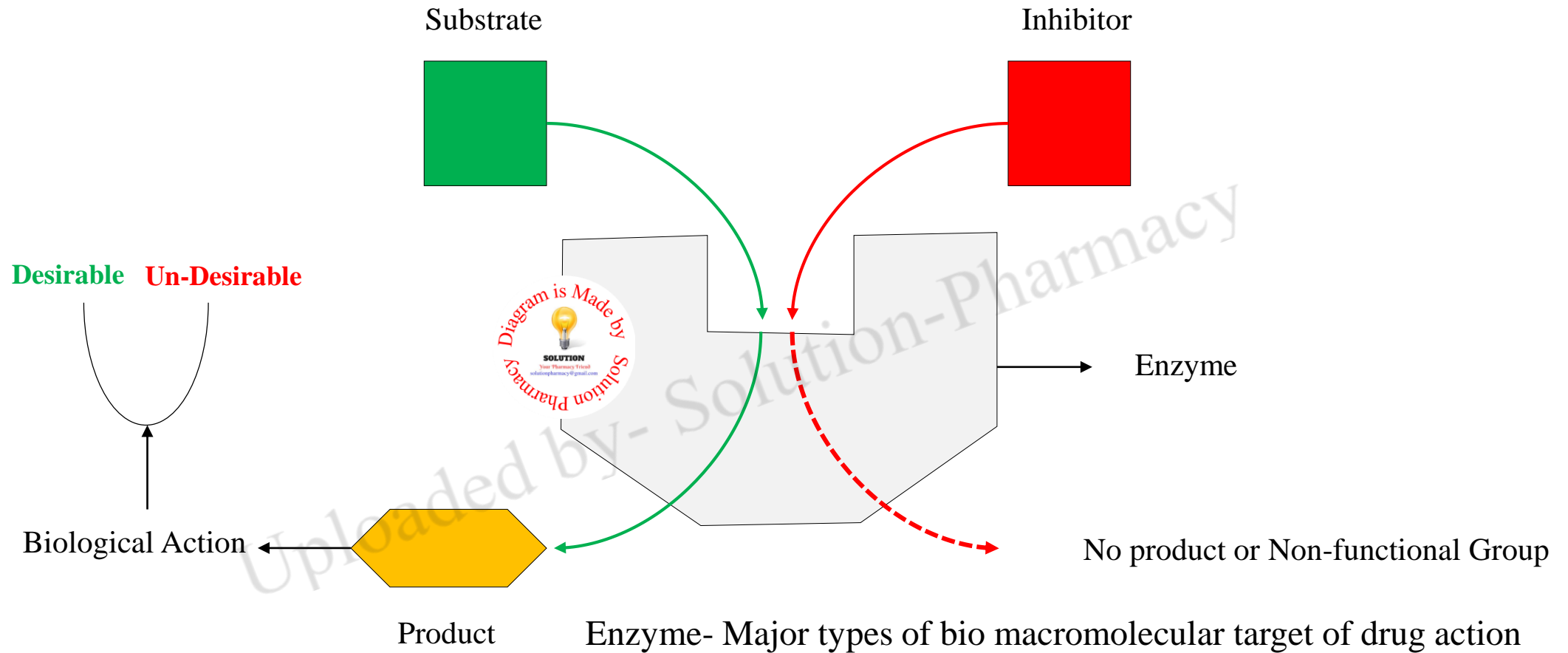
Enzymes- Almost all biological reaction are carried out under the influence of enzymes and this is the reason why enzymes are very useful target for drug action. Drugs can either increase or decrease the rate of enzymatically mediated reactions. However in physiological system enzyme activities are in optimum condition and amount.

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Enzyme Inhibition- some chemicals like heavy metals, strong acids and base, formaldehyde and phenols denature the protein and inhibit all enzyme non selectively. Selective inhibition of a particular enzyme is a common mode of drug action. Enzyme inhibition may be either competitive or non competitive.

Competitive Inhibitors- these drugs are structurally similar and competes with the normal substrate for the catalytic binding sites of the enzymes so that the product is not formed or the non functional product is formed. But if the substrate concentration is sufficiently increased then it can displace the inhibitor and same action is achieved again. This is equilibrium type of competitive inhibition. But if the inhibitor forms strong bond with site of enzyme bonding and substrate can not displace inhibitor again.

Example- The comitative inhibitors of Cholinesterase and xanthine oxidase are- Physostigmine and Allopurinol.



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Ion Channels

Ion channels are the path or way through which any molecule move in or out in corresponding to cell membrane.

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Protein which act as ion selective channels participate in transmembrane signalling and regulate intracellular ionic composition. These makes them a common target of drug action. Drugs can affect ion channels, some of which actually are receptors, because they are operated by specific signal molecule either directly and are called ligand gated channels or through G protein and called G protein regulated ion channels.

Drugs can also act on voltage operated and stretch sensitive channels by direct binding to the channel and affecting ion movement through it. Example- Local anaesthetic which block the voltage sensitive ion channels.

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Some drugs modulate opening and closing of the channels.

Example- (1) Quinidine blocks myocardial Na^+ channels

(2) Nicorandil opens ATP sensitive K^+ channels.

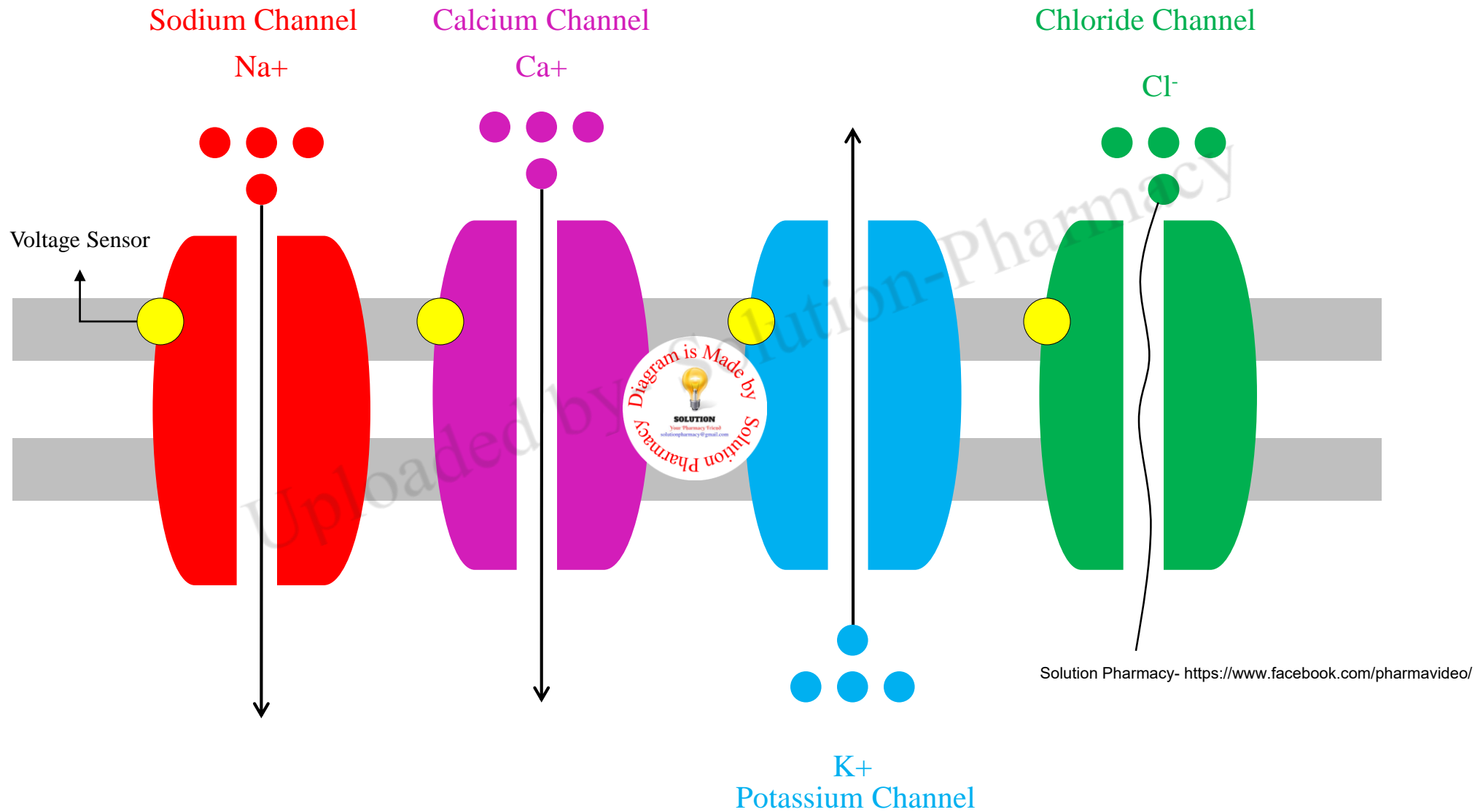
(3) Nifedipine block L-Type of voltage sensitive Ca^{2+} channel.

(4) Phenytoin modulate voltage sensitive neuronal Na^+ channel.

(5) Ethosuximide inhibit T type of Ca^{2+} channels in thalamic neuron.

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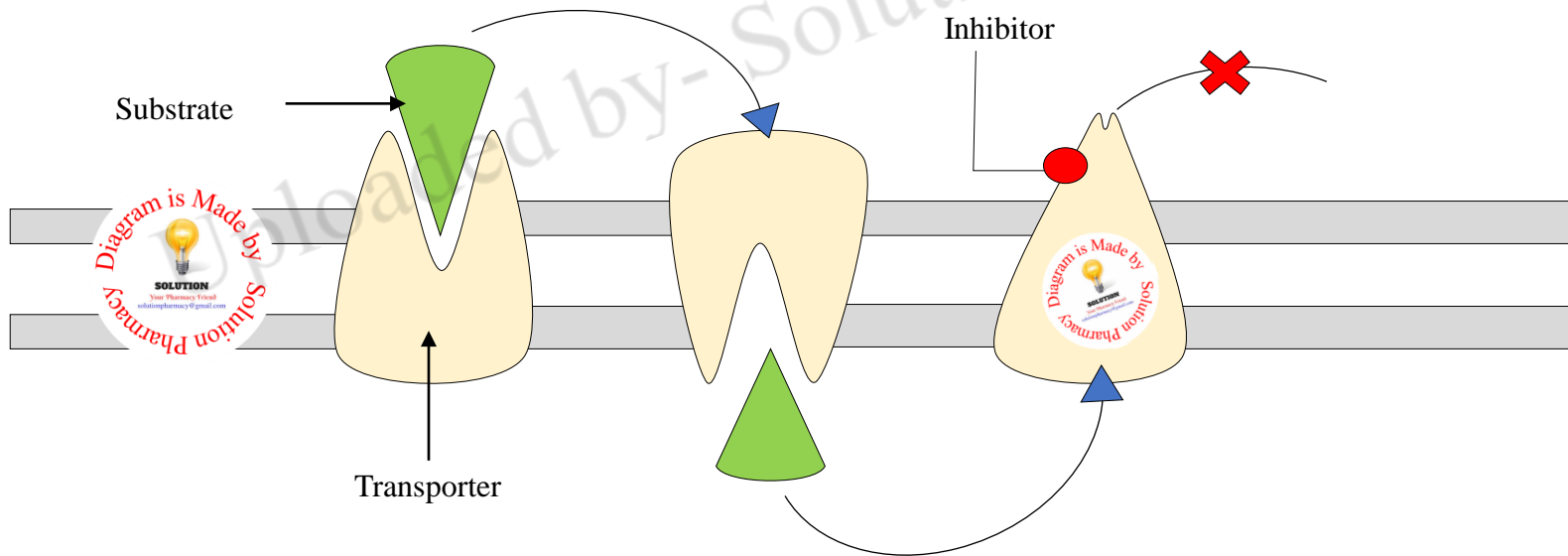


Transporters

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These are the specific carriers which transport drug molecule from one region to another according to concentration gradient. Several substrate are translocated across membrane by binding to specific transporter (Carriers) which either facilitate diffusion in the direction of the concentration gradient or pump the metabolite against the concentration gradient using metabolic energy.

Example-Amphetamine selectively block dopamine reuptake of 5HT by interacting with serotonin transporter.



RECEPTOR

Receptors are the macromolecule or binding site located on the surface or inside the effector cell that serve to recognize the signal molecule or drug and initiate the response to it, but they don't have other functions.

The largest number of drug that do not bind directly to the effectors like- Enzyme, Channels, Transporter structural protein, template biomolecule but act through specific regulatory macromolecule or the site on them which bind and interact with the drugs are called "Receptor"

Few Basic terms related to receptor and drug-receptor complex Solution Pharmacy- <https://www.facebook.com/pharmavideo/>

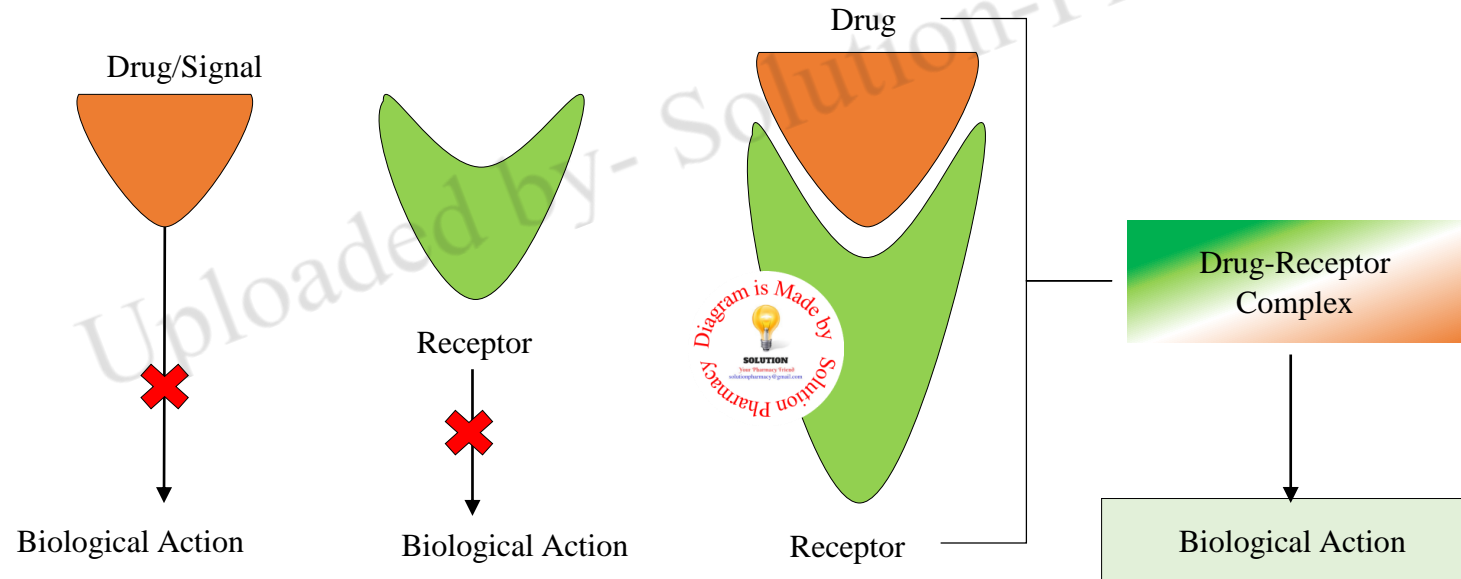
1. Agonist- Agonist are the agent which activates the receptor to produce an effect similar to the of the physiological signal molecule
2. Antagonist- Antagonists are agent which prevent the action of agonist on a receptor or the subsequent response, but does not have any effect of its own
3. Inverse Agonist- Inverse Agonist is the agents which activates a receptor to produce an effect in the opposite direction to that of the agonist
4. Partial Agonist- An agent who activates receptors to produce a sub maximal effect but antagonize the effect of full agonist.

Receptor Occupation Theory

When a drug bind to a receptor it makes DRUG+ RECEPTOR Complex. Single drug without receptor and single receptor without drug will not be able to produce any of effect.

Drug + **Receptor** = Drug-Receptor Complex \longrightarrow **Biological Action**

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Classification of Receptors

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1. **Pharmacological Criteria-** This is based on relative potency of selective agonist and antagonist. This was used in delineating M and N cholinergic, Alpha and Beta adrenergic, H1 and H2 histaminergic receptors etc.
2. **Tissue distribution-** the relative organ/tissue distribution is basis for designing the subtype. Example- The cardiac Beta adrenergic receptor as- Beta 1 while bronchial as Beta2
3. **Ligand binding-** Measurement of specific binding of high affinity radio-labelled ligand to cellular fragment in vivo and its displacement by various selective agonist and antagonist is used to find receptor subtypes. Multiple 5-HT receptors were distinguish by this approach.
4. **Transducer pathway-** receptor subtypes may be distinguish by the mechanism through which their activation is linked to response. Example- M cholinergic receptors acts through G-protein, while N cholinergic receptors get influx of Na⁺ ions, Alfa adrenergic receptors via IP3-DAG pathway and by decreasing cAMP pathway.
5. **Molecular cloning-** The receptor protein is cloned and its detailed amino acid sequence as well as three dimensional structure is worked out.

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Silent receptor- These are sites which bind specific drug but no pharmacological response is elicited.

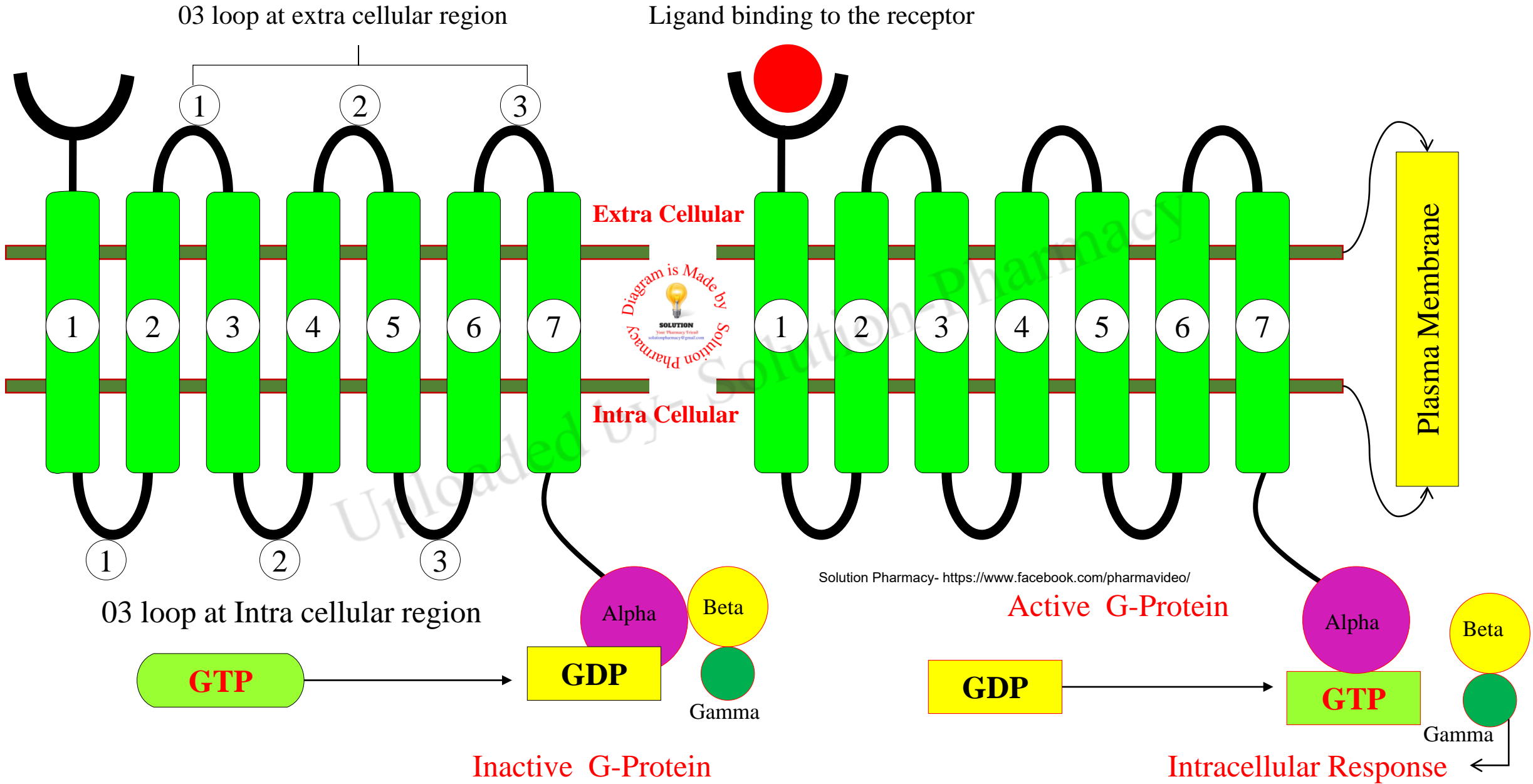
G-protein Coupled Receptors (Gpcrs)

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Important points and steps to be remember about GPCRs

1. This is a large family of cell membrane receptors
2. The molecule have 7 Alfa helical membrane spanning hydrophobic amino acid (AA)
3. There are 06 loops- 03 extracellular and 03 intracellular
4. It have 03 subunits- Alfa, Beta and Gamma
5. Agonist binding site is located somewhere in between helices on extracellular faces.
6. In the inactive state GDP is bound to Alfa subunits at the exposed domain.
7. Activation through the receptor leads to displacement of GDP by GTP.
8. The activated alfa subunits carrying dissociate from the other two subunits and either activate or inhibit effectors.
9. The remaining Beta- Gamma dimer has also been shown to activate receptor operated K^+ channels, to inhibit voltage gated Ca^{2+} channels and to promote desensitization at higher rates of activation.
10. The bound GTP is slowly hydrolysed to GDP then Alfa subunits dissociate from effectors and re-join its other subunits.

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Phospholipase C- IP₃-DAG Pathway

To make the concept clear we have converted paragraph into points, so this pathway contains following important points

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1. Activation of phospholipase C by the activated GTP carrying Alfa subunits of Gq hydrolyses the membrane phospholipids inositol 4,5 biphosphate to generate the second messenger inositol 1,4,5 triphosphate (IP₃) and diacylglycerol (DAG)
2. the IP₃ being water soluble diffuse to the cytosol and mobilize Ca²⁺ from endoplasmic reticulum depot.
3. The lipophilic DAG remain within the membrane but recruits protein kinase and activate it with the help of Ca²⁺
4. The activated protein kinase phosphorylates many intra cellular proteins and mediates various physiological response. That's why it serve in signalling function.
5. The cytosolic concentration of Ca²⁺ is kept very low (About 100nM) by specific pumps located at plasma membrane and at the endoplasmic reticulum.
6. Triggering by IP₃ the released Ca²⁺ (3rd Messenger) act as a highly versatile regulator acting through calmodulin.

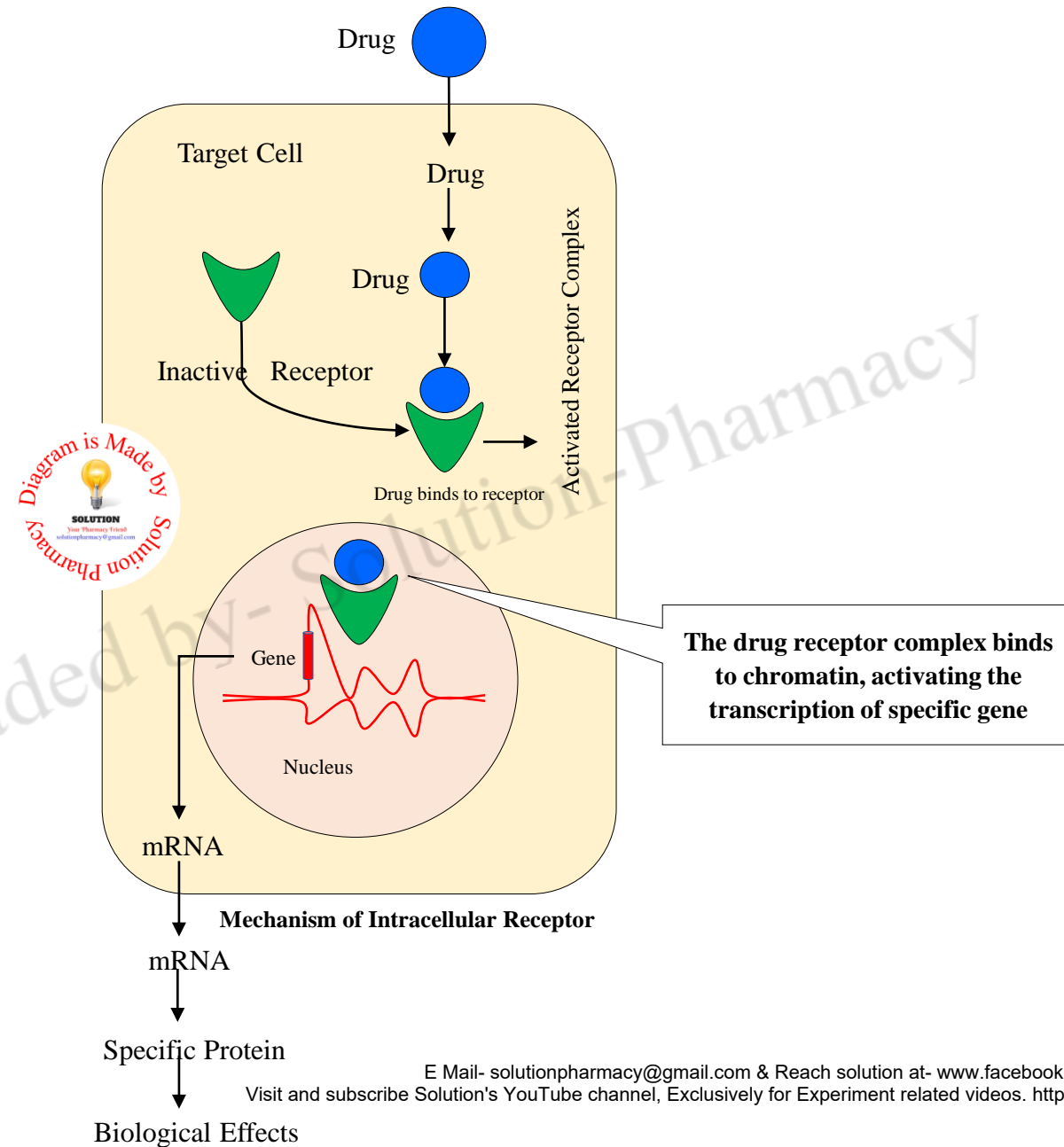
Ion Channel Receptors

1. The extracellular portion of ligand-gated ion channels usually contains the ligand binding site.
2. This site regulates the shape of pore through which ions can flow across the cell membrane
3. The channel is usually closed until the receptor is activated by an agonist, which opens the channel briefly for a few milliseconds. Solution Pharmacy- <https://www.facebook.com/pharmavideo/>
4. Depending on the ion conducted through these channels, these receptors mediate various functions like- neurotransmission, cardiac or muscle contraction. Example- stimulation of nicotinic receptor by acetylcholine results in sodium influx and potassium outflux, generating an action potential in a neuron.
5. Agonist stimulation of GABA receptor increases chloride influx and hyperpolarizes neurons.
6. Thus in these receptors the agonist directly operates ion channels, without the intervention of any coupling protein or second messenger.
7. The onset and offset of response through this class of receptors are fastest.

Example- GABA_A, Glycine, Excitatory AA glutamate and 5HT₃ receptors are the examples.

Intracellular Receptor

1. This is entirely different from other receptors because it is present in the intracellular region.
2. Ligand must diffuse into the cell to interact with the receptor.
3. In order to move across the target cell the target cell membrane the ligand must have sufficient lipid solubility
4. The primary target of these ligand-receptor of these ligand-receptor complex are transcription factor in the cell nucleus.
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5. Binding of ligand with its receptor generally activates the receptor via dislocation from a variety of binding proteins.
6. The activated ligand-receptor complex is then translocate to nucleus, where it often dimerizes before binding to transcription factor that regulate gene expression. Example- steroid hormones exert there action on target cell via intracellular receptor.
7. The activation and inactivation of these factors causes the transcription of DNA to RNA and translocation of RNA into an array of protein
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8. Other target of intracellular ligands are structural proteins, enzymes, RNA and ribosome.



Function of Receptors

Receptors have various functions. Few of Important functions are-

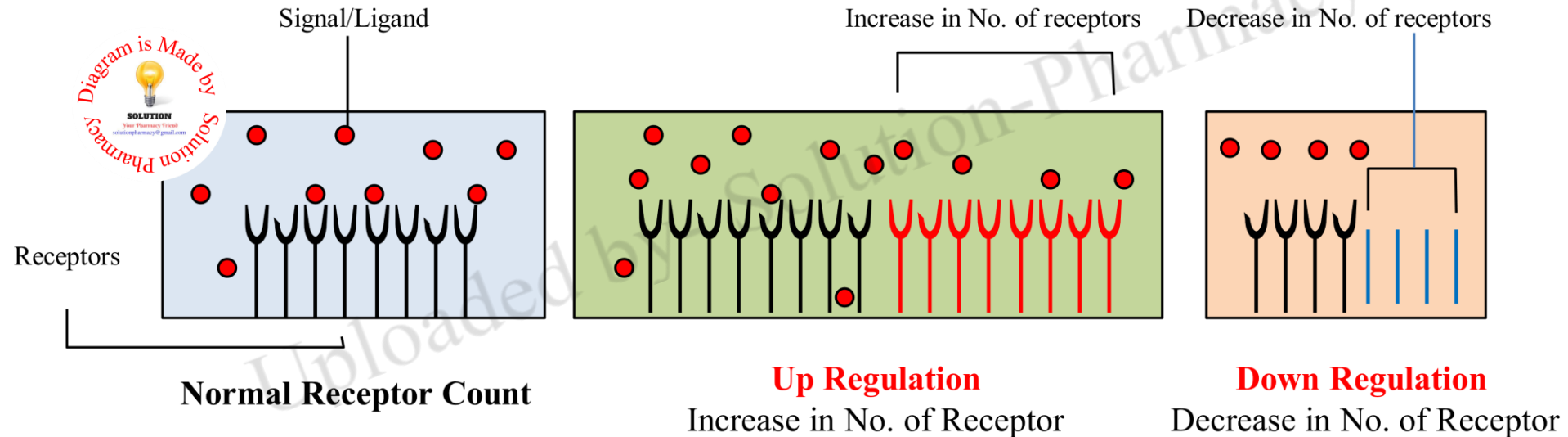
1. To propagate regulatory signals from outside to inside the effector cell when the molecular species carrying the signal can't itself penetrate the cell membrane .
2. To amplify the signals Solution Pharmacy- <https://www.facebook.com/pharmavideo/>
3. To integrate various extracellular and intracellular regulatory signals.
4. To adapt to short term and long term changes in the regulatory milieu and maintain homeostasis.

Receptors

Upregulation and Downregulation

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Downregulation- An example of downregulation is the cellular decrease in the number of receptors to a molecule, such as a hormone or neurotransmitter which reduces the cell's sensitivity to the molecule. This is an example of a locally acting (negative feedback) mechanism



Upregulation- An example of upregulation is the response of liver cells exposed to such xenobiotic molecules as dioxin. In this situation, the cells increase their production of cytochrome P450 enzymes which in turn increases their degradation of these molecules

* **Diagrams and Explanations by- Solution-Pharmacy**

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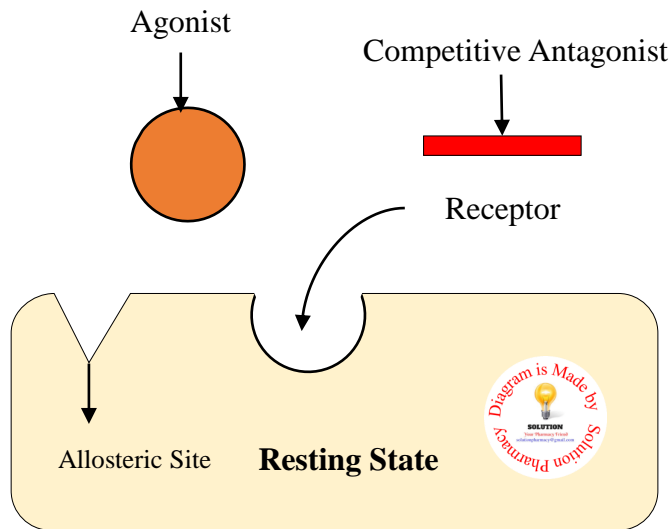


Image 1- Site of action for agonist & antagonist

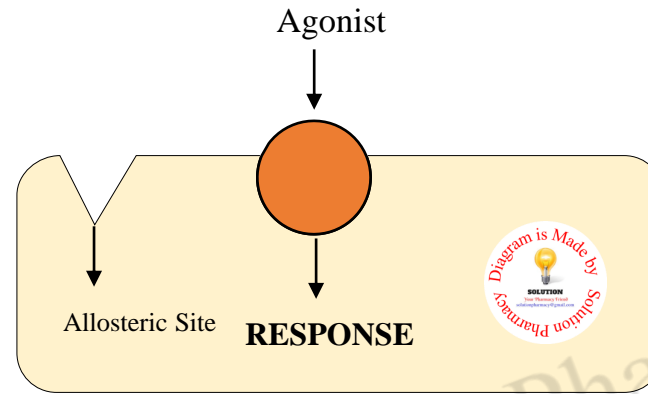


Image 2- Site of action for antagonist

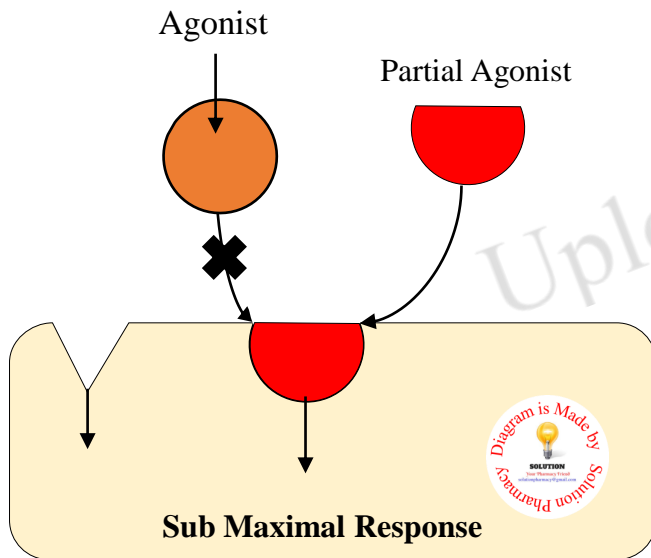


Image 3- Partial Agonist

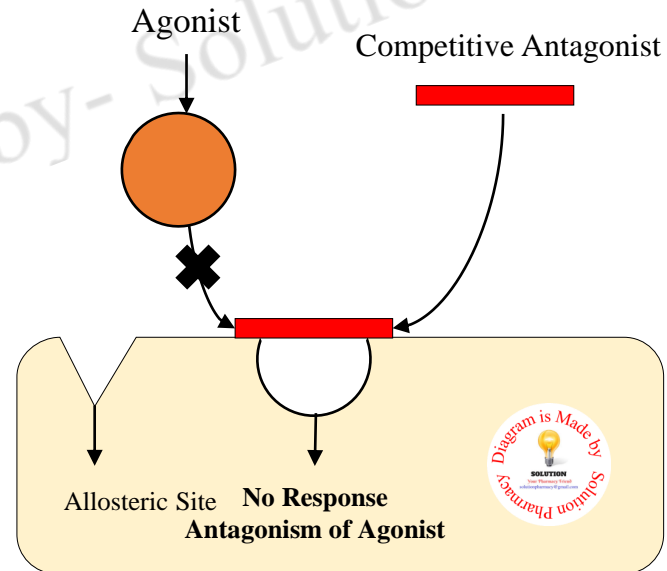


Image 4- Competitive Antagonist

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Definitions

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- 2. Antagonist-** Antagonists are agent which prevent the action of agonist on a receptor or the subsequent response, but does not have any effect of its own
- 3. Partial Agonist-** An agent who activates receptors to produce a sub maximal effect but antagonize the effect of full agonist.
- 4. Competitive Antagonist-** The antagonist is chemically similar to the agonist an compete with it for the binding site.

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