بسم الله الرحمن الرحيم

# Pharmacodynamics (1)

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# Definitions

- Drug: any chemical substance that affect a biological system.
- Pharmacodynamics studies the effects of drugs on the living beings and their mechanisms of action.
- Drug action, means how the drug works “the mechanism of action".
- Drug effect, means consequences of drug’s action on the body.

➢ For example: the mechanism of action of Aspirin is inhibition of Prostaglandin synthesis and its effects are analgesia and anti-pyresis.

# Mechanisms of drug actions

## A- Non-receptor mediated:

1. Interaction with **enzymes**: e.g. Neostigmine inhibits acetyl cholinesterase enzyme.

2. Some drugs act by direct **chemical interaction** such as sodium bicarbonate (antacid) which neutralize gastric acidity.

3. Inhibition of **cellular division**: e.g. some anticancer drugs like vincristine.

4. Other drugs act through their **physical properties.**

**Examples:**

✓lactulose acts as osmotic laxative.

✓Kaolin and pectin can adsorb fluids and treat diarrhea.

✓Radioactive iodine emits beta particles which can destroy adjacent thyroid cancer cells.

5. **Nutrients:** e.g. iron, calcium and vitamins.

6. The Vaccines act through **immune modulations.**

## B- Receptor-mediated:

- Most drugs act by binding to specific receptors located on the cell membrane (e.g. adrenoceptors) or inside the cells (e.g. steroid receptors).
- "**Receptor" means any cellular macromolecule to which a drug binds to initiate its effect.**
- Most drug receptors are **protein in nature, or nucleic acids (e.g. DNA and RNA).**

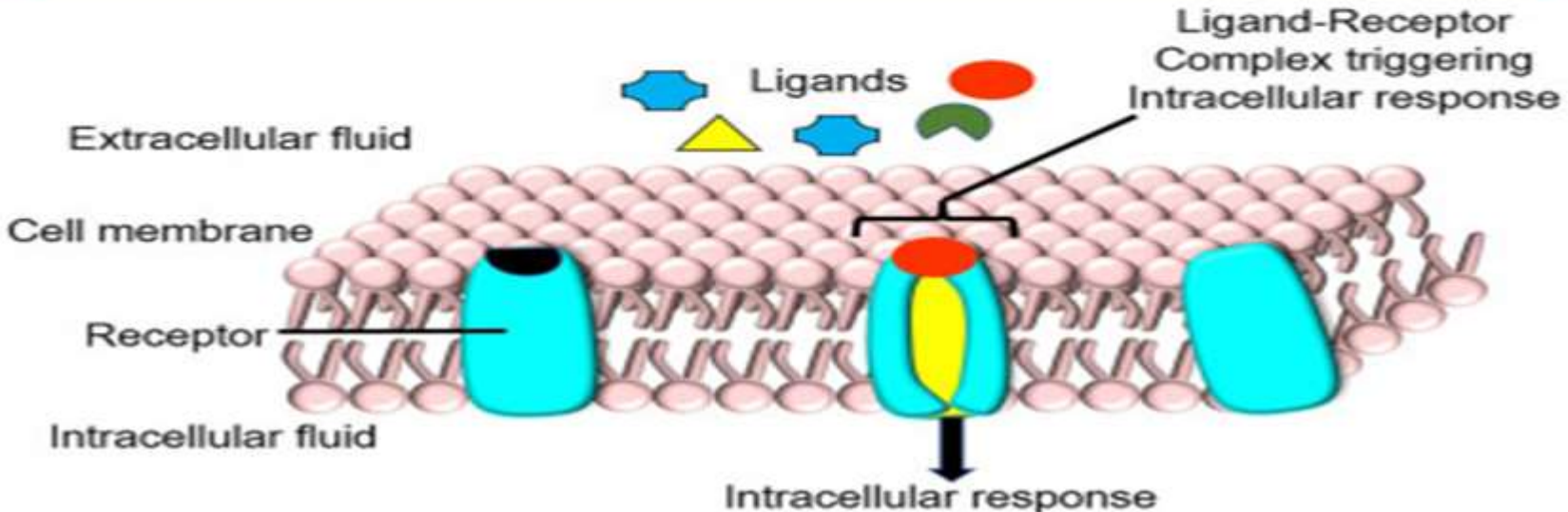
The receptor has two functions:

- Ligand (drug) binding.
- Message propagation (i.e. signaling) to produce the intended response of drugs.

Ligands are molecules (e.g. drugs or endogenous hormones or neurotransmitters) that attach selectively to a particular receptor.

The interaction of the drug with the receptor is analogous to "**lock and key" where the drug would fit properly into the receptor and activate it.**

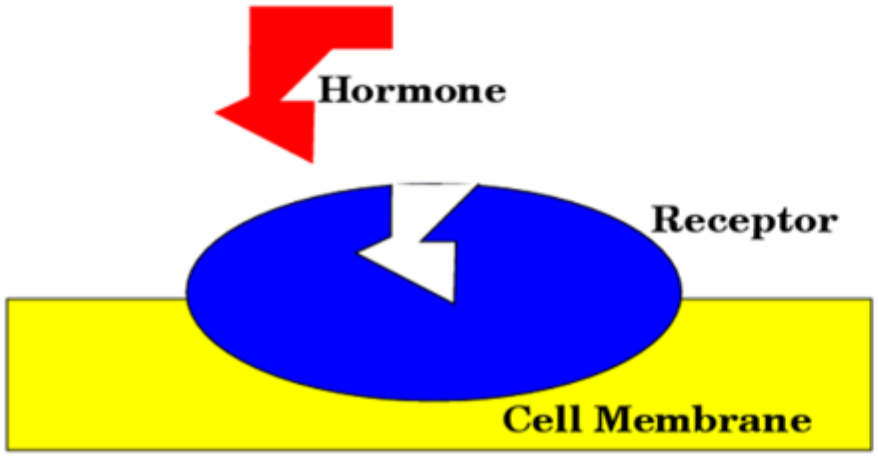
*- Following this binding, the receptor exerts its regulatory actions directly on its cellular targets, effector proteins or intermediate cellular signaling molecules.*

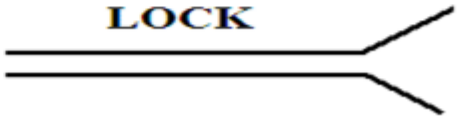


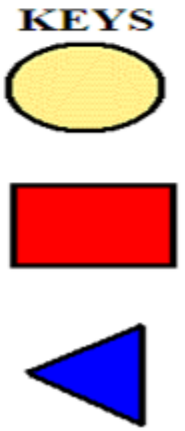
# Drug receptor interaction
# (Lock and key mechanism)

The chemical structure of a drug makes it suitable to bind to a specific receptor and not suitable to bind to other receptors (**specificity**) like the key and the lock.

- The ability of a drug to bind to a specific receptor is called "**affinity**".
- The cellular changes occurring due to drug receptor binding is called **"efficacy or intrinsic activity".**



# Drug receptor coupling and signaling mechanisms

When a receptor becomes bound to a ligand (hormone or a drug, etc.), it undergoes a conformational change which allows it to interact productively with other components of the cells, leading to an alteration in the physiologic state of the cell.

Binding of hormone to receptor initiates a series of events which leads to generation of so-called second messengers within the cell (the hormone is the first messenger).
The second messengers then trigger a series of molecular interactions that alter the physiologic state of the cell. Another term used to describe this entire process is *signal transduction* or *coupling*.

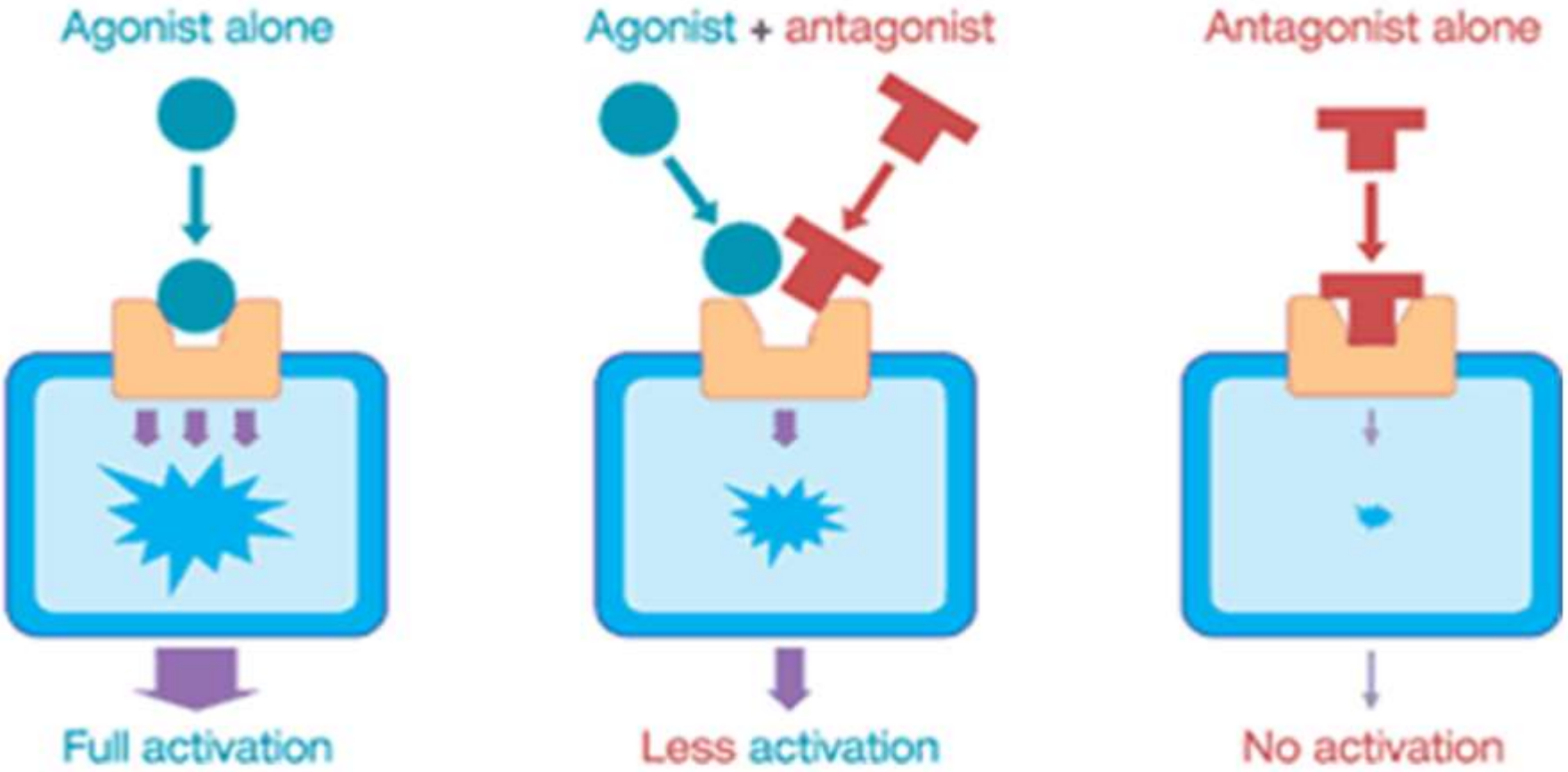
## Pharmacological basis of drug-receptor interaction

- When a drug binds to a receptor and produces an action like the action of an endogenous regulatory substance already present in the body such as hormones or neurotransmitters, the drug is called "***Agonist***"
- When a drug binds to a receptor and leads to inhibition of the action of a regulatory substance on that receptor, it is called "***Antagonist***".
- Some drugs bind to a receptor but activate it partially and not fully. They are called "***Partial Agonist***"
- If a full agonist has an intrinsic activity = 1, that of pure antagonist is = 0 and that of a partial agonist is between 0 and one.

# Agonists and Antagonists

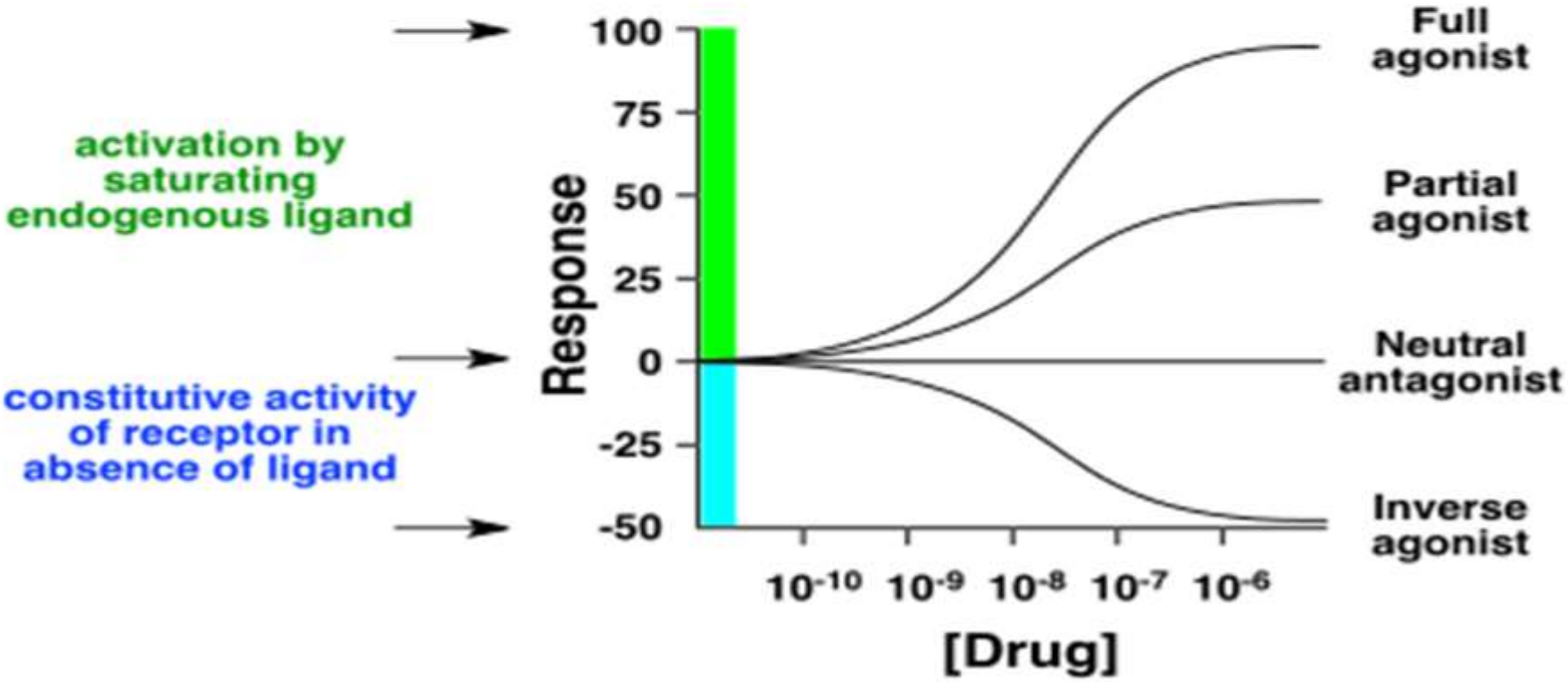
**Agonists** Drugs that occupy receptors and activate them.

**Antagonists** Drugs that occupy receptors but do not activate them. Antagonists block receptor activation by agonists.



**Inverse agonists**: drugs that bind to the receptors but has *negative efficacy*.

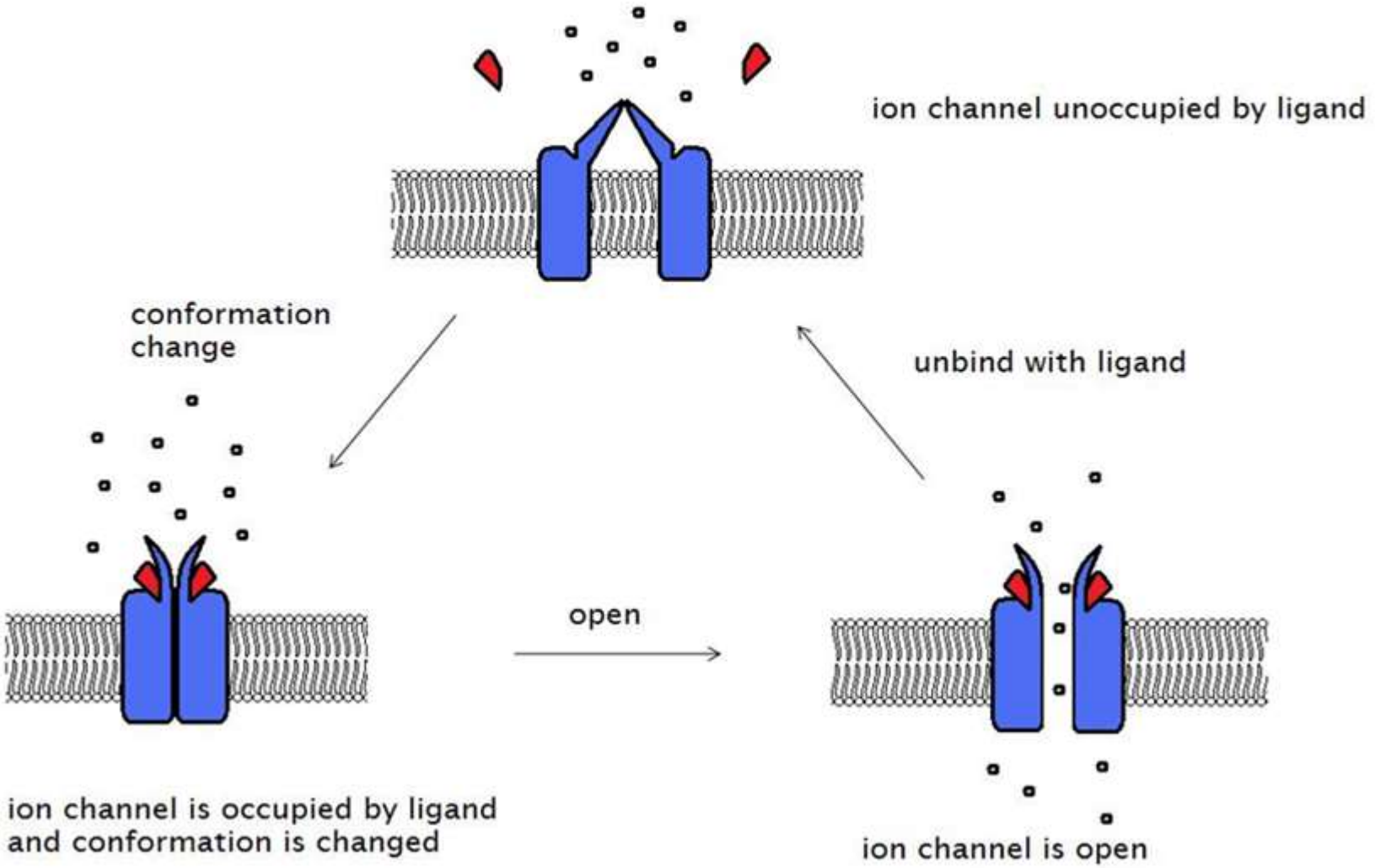
Example: Agonists for the $GABA_A$ receptor (such as benzodiazepines) open chloride channels while beta-carbolines actively close the chloride channels



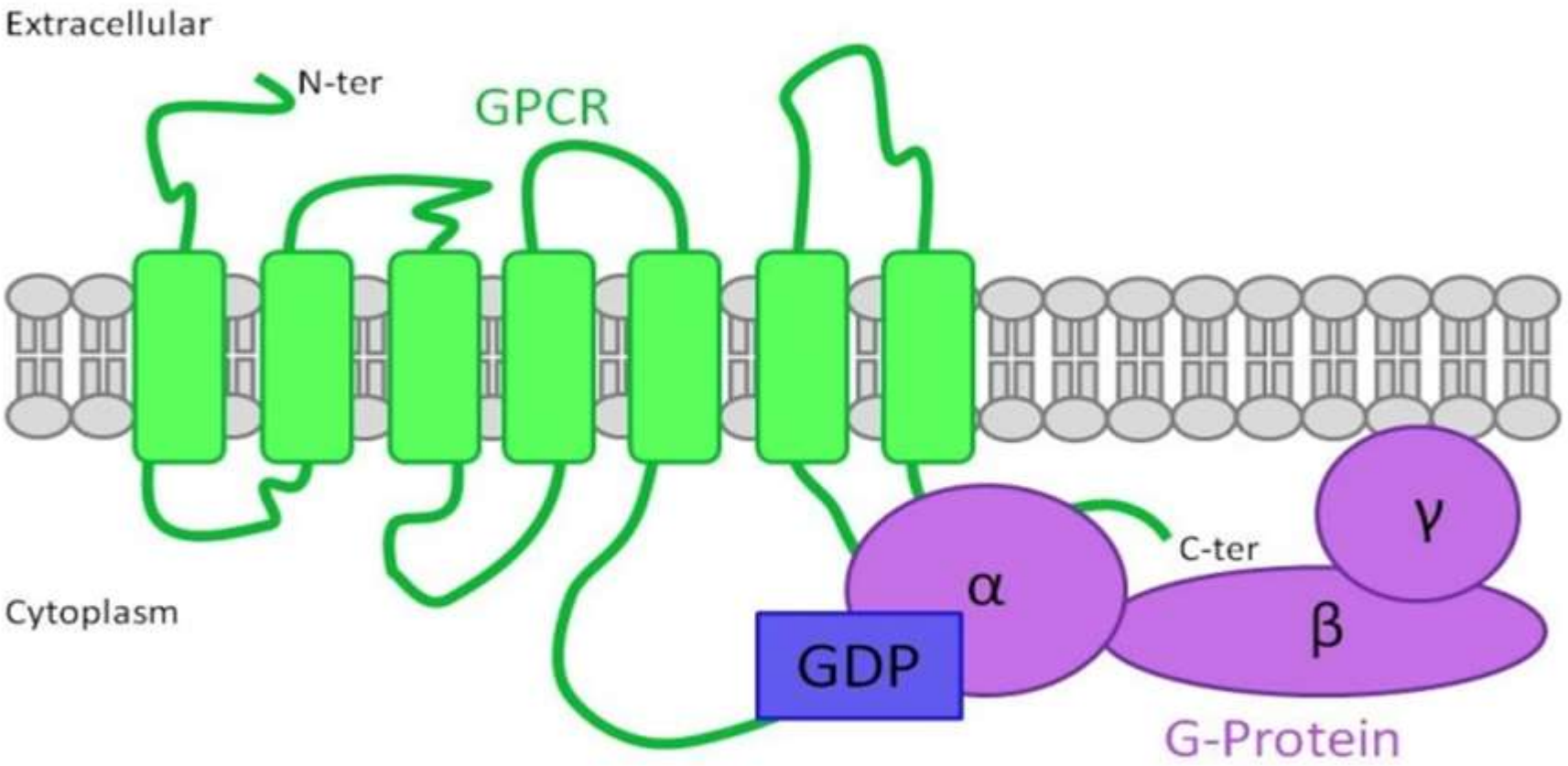
# Types of receptors and signaling mechanisms

| | Type 1<br>Ligand gated ion channels or Ionotropic receptors | Type 2<br>G-protein coupled receptors or metabotropic receptors | Type 3<br>Tyrosine -kinase linked receptors | Type 4<br>Nuclear receptors |
|---|---|---|---|---|
| **Location** | Trans membrane | Trans membrane | Trans membrane | Intracellular |
| **Effectors** | Ion channel | Channel or enzyme | Enzyme | Gene transcription |
| **Coupling** | Direct | G-protein | phosphorylation | Via DNA |
| **Example** | Nicotinic receptor and GABA type A receptors | Muscarinic receptor and adrenoceptors | Insulin, growth factor and cytokine receptors | Steroid & thyroid hormone receptors |
| **Response** | Very fast (fraction of millisecond) | Fast (few milliseconds) | Long lasting | Long lasting |

# Type 1
# Ligand gated ion channels or Ionotropic receptors



# Type 2
# G-protein coupled receptors or metabotropic receptors



❑Activation of G-protein coupled receptors leads to:

1- Activation or inhibition of adenylcyclase

2- Activation of phospholipase C

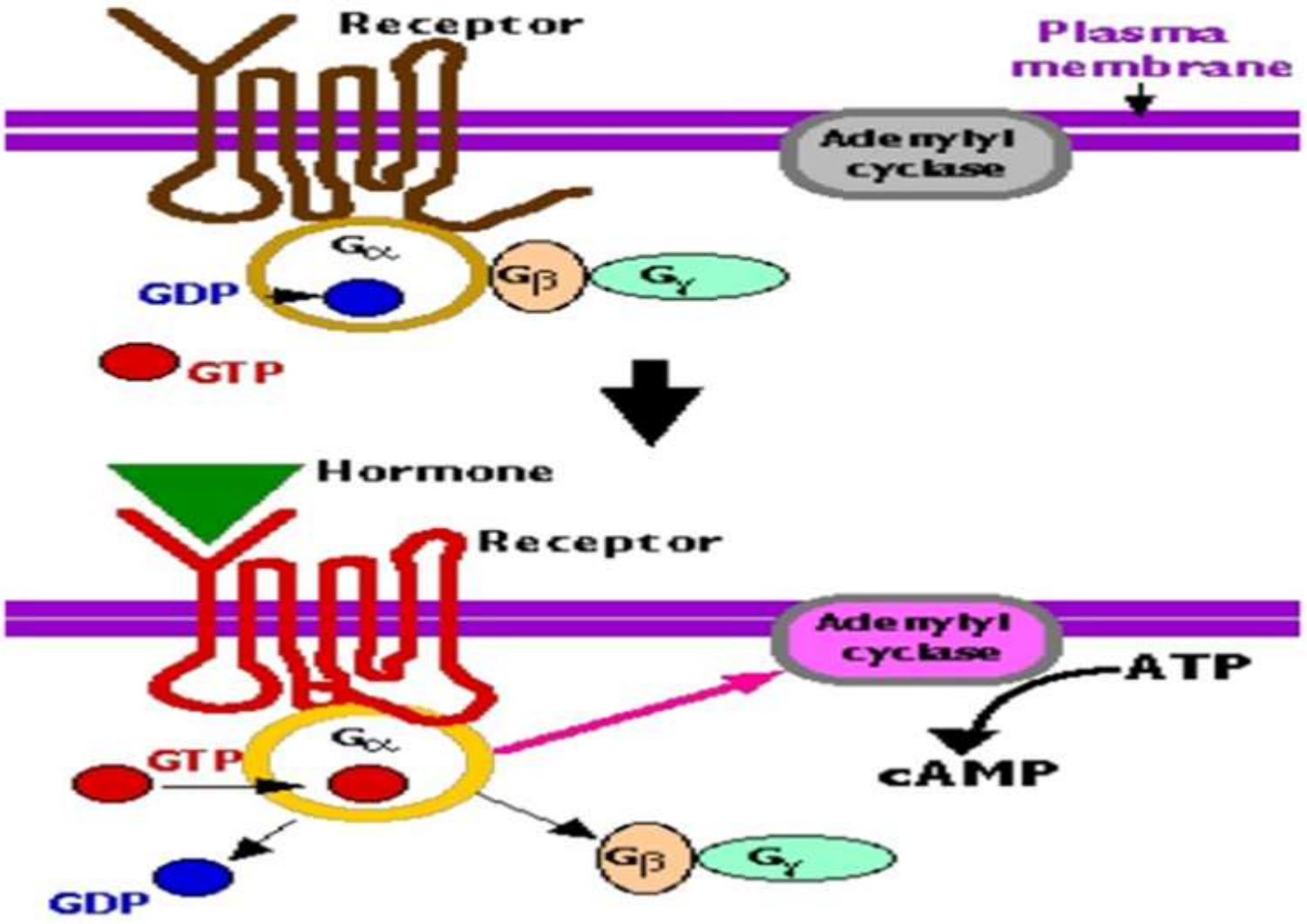
3- Activation of ion channels (e.g. calcium channels)

- Activation of adenylcyclase by (Gs) would increase cellular cAMP
- Inhibition of adenylcyclase by (Gi) would decrease cellular cAMP
- Activation of phospholipase C (Gq) would increase cellular inositol triphosphate (IP3) and diaceylglycerol (DAG)
- Activation of calcium channels would increase cellular calcium.

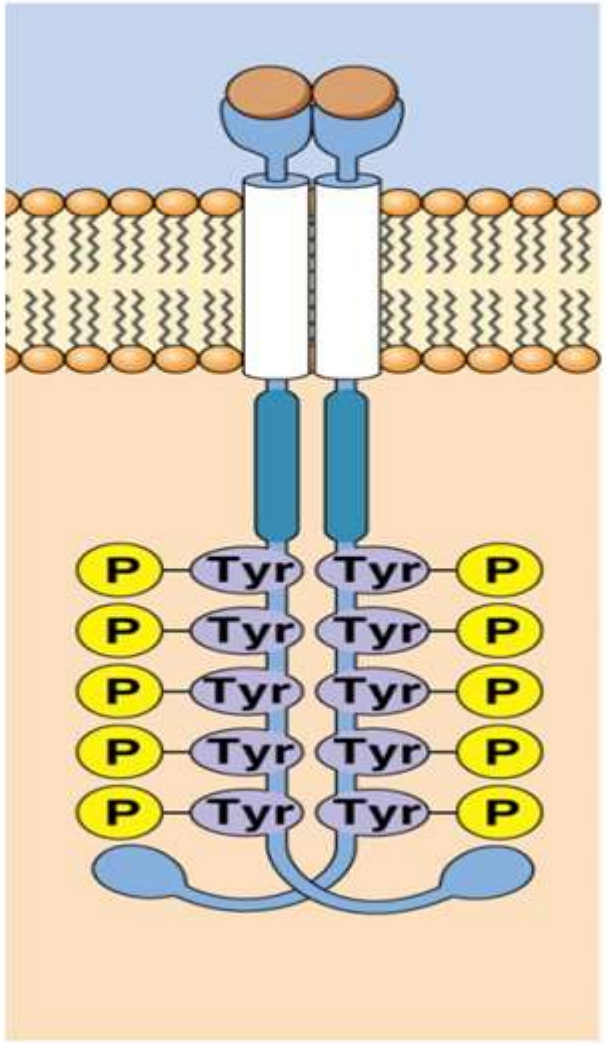
❑Secondary messengers produce the final cellular response (e.g. contraction, relaxation, secretion, etc).

1. cAMP
2. IP3
3. DAG
4. Calcium

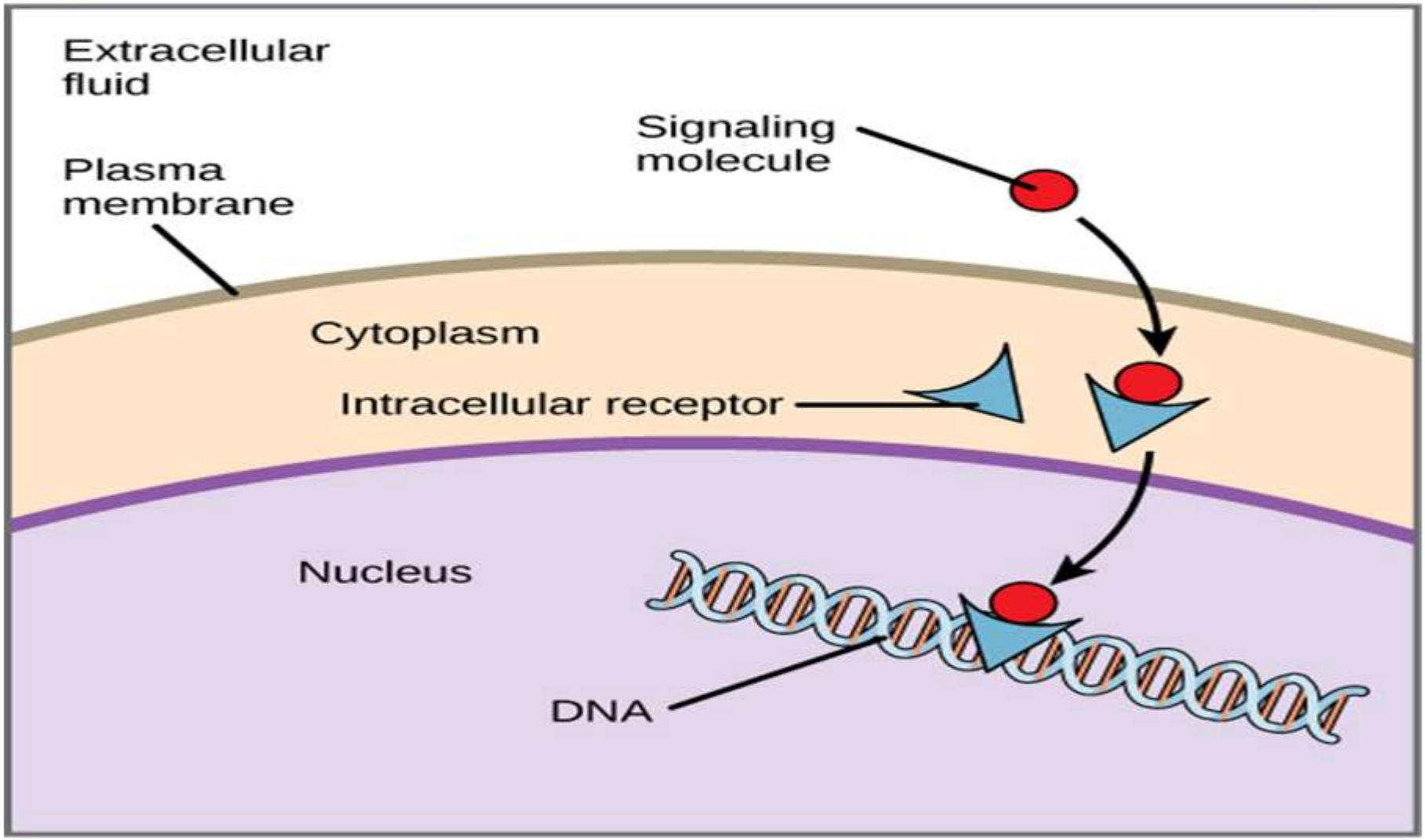
# Type 2
# G-protein coupled receptors (Gs) signaling



# Type 3
# Tyrosine -kinase linked receptors



# Type 4
# Nuclear receptors

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