# Medicinal Chemistry

## Chapter 5

# DRUG TARGETS: RECEPTORS

# Contents

**Part 1.** Structure and function of receptors
**Part 2.** Neurotransmitters and hormones
**Part 3.** Receptor activation
**Part 4.** Receptor types and subtypes
**Part 5.** Ion Channel Receptors
**Part 6.** G-Protein Coupled Receptors
**Part 7.** The rhodopsin-like family of G-protein-coupled receptors
**Part 8.** Tyrosine Kinase Linked Receptors
**Part 9.** Intracellular Receptors

# 1. Structure and function of receptors

NOTES

• Globular proteins acting as a cell's 'letter boxes'

• Located mostly in the cell membrane

• Receive messages from chemical messengers coming from other cells

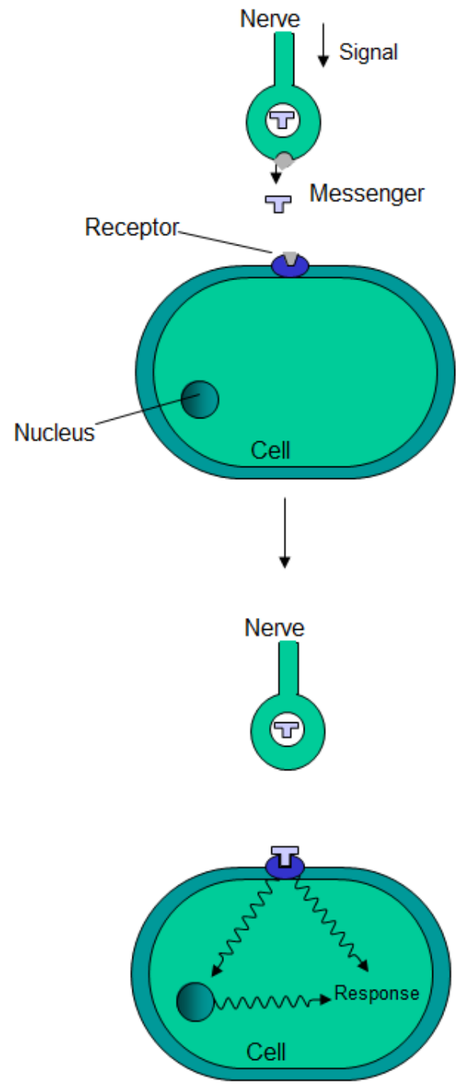
• Transmit a message into the cell leading to a cellular effect

• Different receptors specific for different chemical messengers

• Each cell has a range of receptors in the cell membrane making it responsive to different chemical messengers

# 1. Structure and function of receptors

- CNS receives and sends messages via a vast network of nerves,
- an electrical pulse which travels down the nerve cell "**neuron**" towards the target,
- 100 A° "gap" separates neurons from the cell surface,
- chemical messenger "**neurotransmitter**" carrying the message across the gap,
- neurotransmitter binds and interacts with a specific protein "**receptor**" embedded in the cell membrane,
- a flow of ions occurs across the cell membrane or in the switching on (or off) of enzymes inside the target cell, a biological response then results.

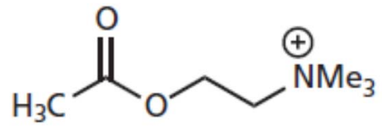


# 2. Neurotransmitters and hormones

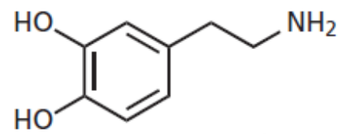
Neurotransmitter: A chemical released from the end of a neuron which travels across a synapse to bind with a receptor on a target cell. Usually short lived and responsible for messages between individual cells.

large variety of messengers that interact with receptors and they vary significantly in structure and complexity:

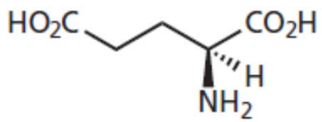
1. Monoamines, as **acetylcholine** and **dopamine**
2. amino acids, as **γ-aminobutyric acid** [GABA] and **glutamic acid**
3. more complex in structure and include lipids such as prostaglandins;
4. purines, such as adenosine or ATP



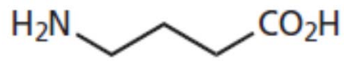

**acetylcholine**



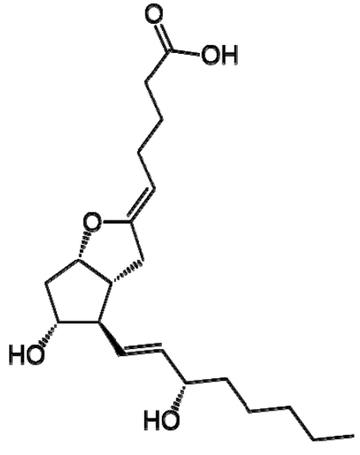

**dopamine**



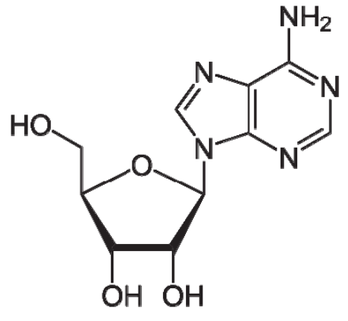

**glutamic acid**




**γ-aminobutyric acid**




**prostaglandin**



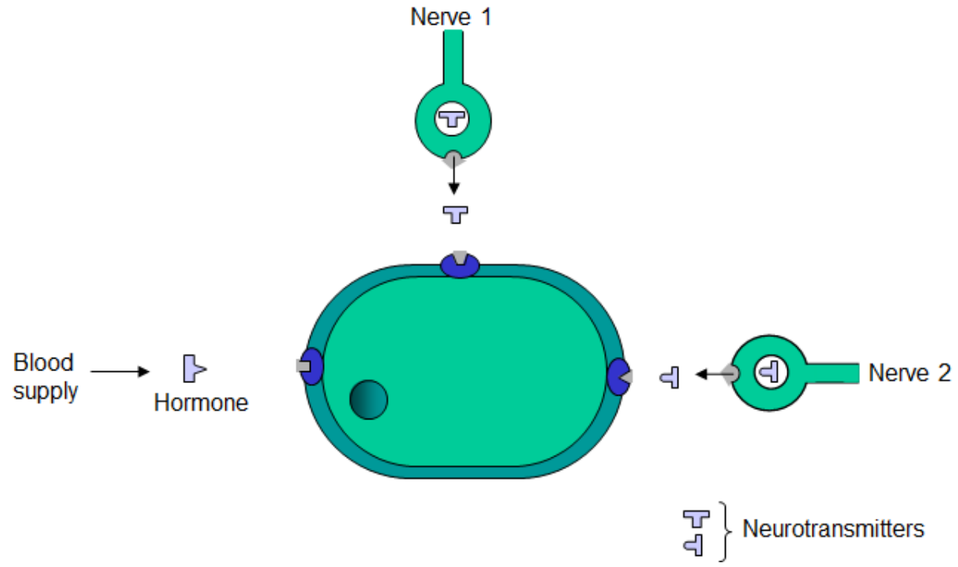

**adenosine**

A neuron releases mainly one type of neurotransmitter, and a special receptor which awaits it on the target cell.

Target cell has a large number of neurons communicating with it for different neurotransmitter. Therefore, the target cell will have other types of receptors specific for those other neurotransmitters.

It may also have receptors waiting to receive messages from chemical messengers that have longer distances to travel. These are the hormones released into the circulatory system by various glands in the body

Hormone: A chemical released from a cell or a gland and which travels some distance to bind with receptors on target cells throughout the body



## 3. Receptor types and subtypes

Receptors are identified by the specific neurotransmitter or hormone which activates them

Thus, the receptor activated by:
dopamine is called the dopaminergic receptor,
acetylcholine is called the cholinergic receptor,
adrenaline or noradrenaline is called the adrenergic receptor.

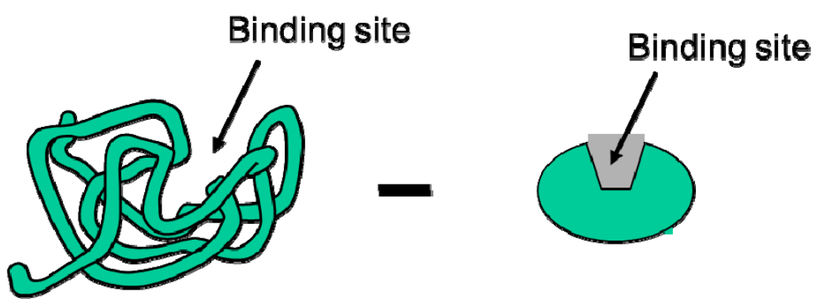
Not all receptors activated by the same chemical messenger are exactly the same throughout the body, according to the amino acid composition variations in the binding site as example, adrenergic drugs can be designed to be ‘lung’ or ‘heart’ selective.

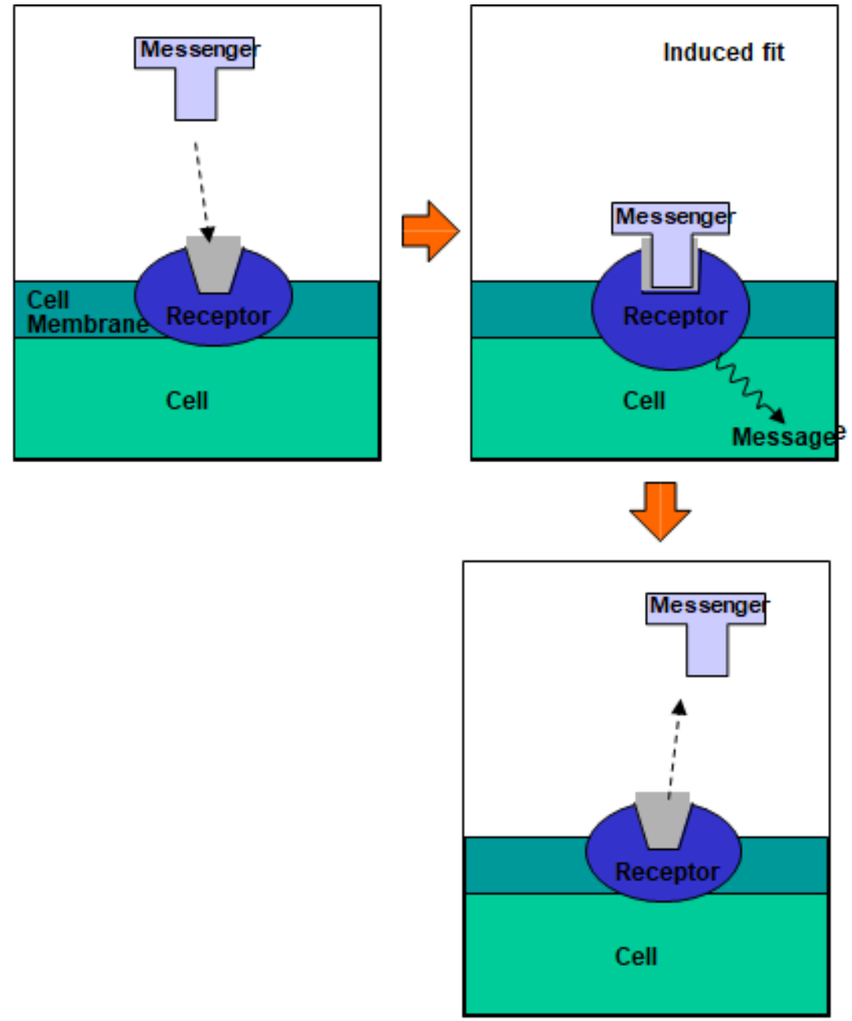
# 4. Receptor activation

Receptors contain a binding site (hollow or cleft on the receptor surface) that is recognised by the chemical messenger

Binding of the messenger involves intermolecular bonds, binding results in an induced fit of the receptor protein

When the chemical messenger fits into this site it **'switches on'** the receptor molecule and a message is received.

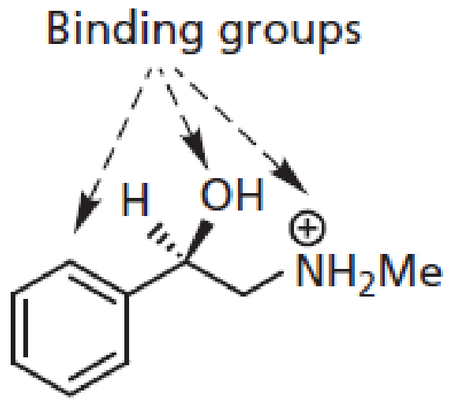


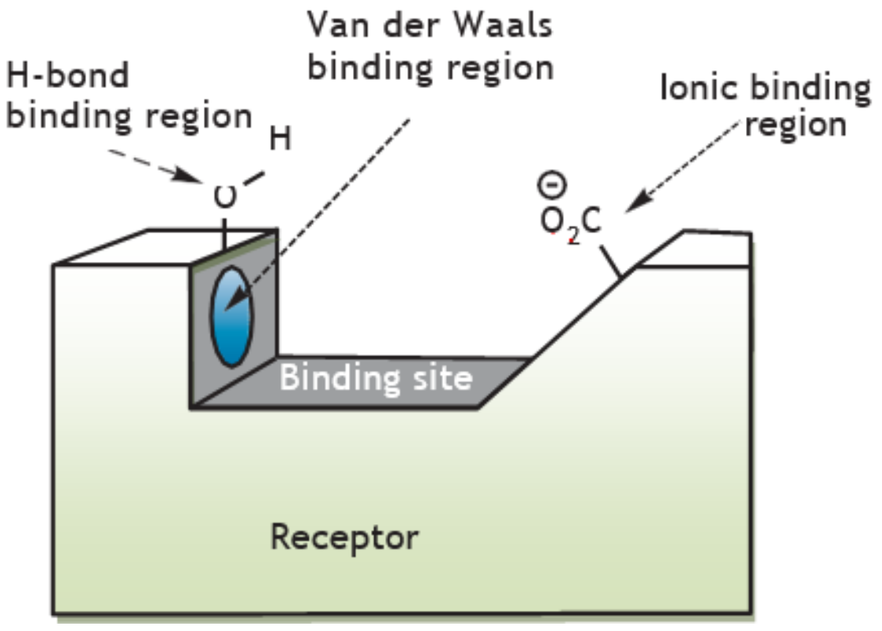
# Binding site change shape

When the messenger fits the binding site of the protein receptor it causes the binding site to change shape.

**Binding groups** of neurotransmitter has an aromatic ring, an alcohol OH group, and a charged nitrogen centre that can take part in ionic or electrostatic interactions.



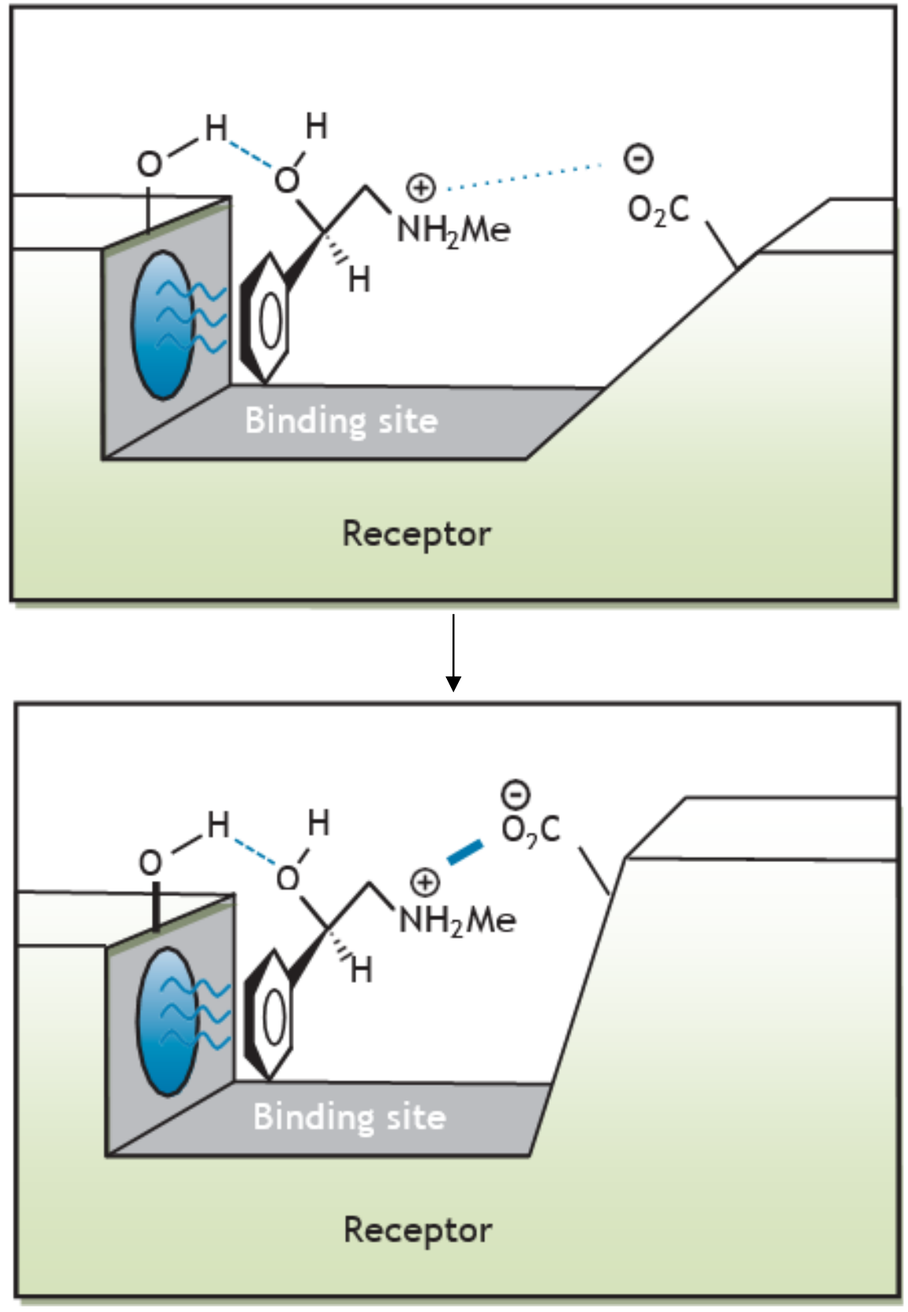

Neurotransmitter



The fit is not perfect, there are good van der Waals and H-bond interactions, but the ionic interaction is not as strong as it could be.

The receptor protein therefore alters shape to bring the carboxylate group closer to the positively charged nitrogen and to obtain a stronger interaction.

This induced fit has a knock-on effect “domino effect” which alters the overall shape of the protein, this process called signal transduction

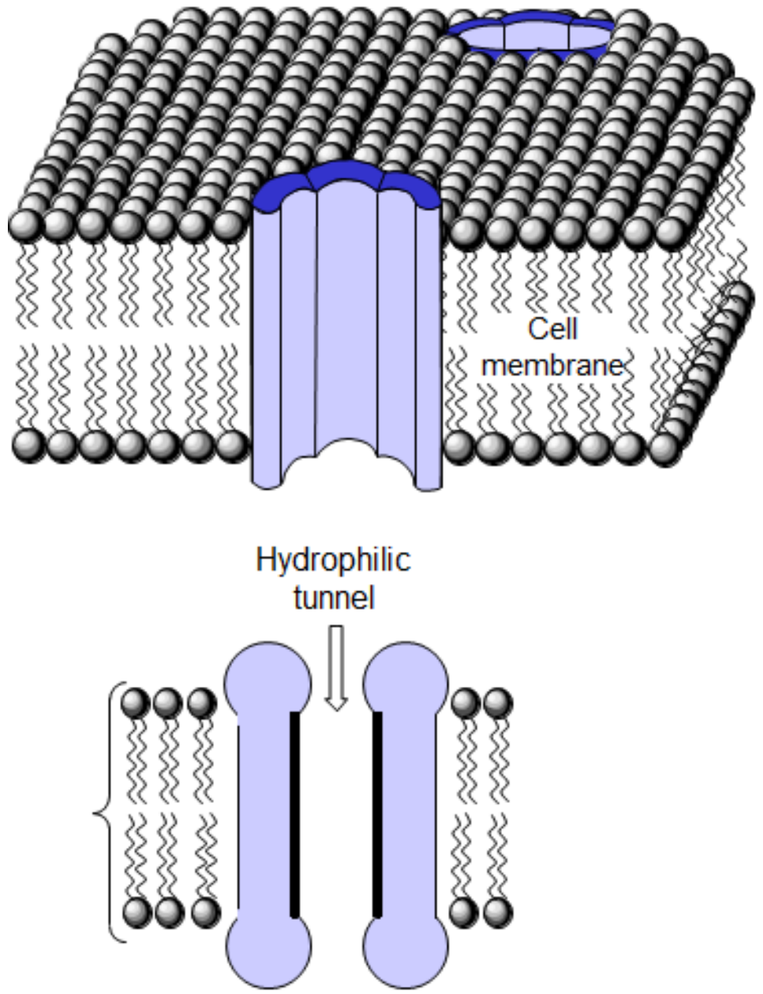


## 5. Ion Channel Receptors

Membrane is made up of a bilayer of phospholipid molecules so the middle of the cell membrane is ‘fatty’ and hydrophobic. Such a barrier makes it difficult for polar molecules or ions to move in or out of the cell.

Ion channels are complexes made up of five protein subunits which traverse the cell membrane. The centre of the complex is hollow and lined with polar amino acids to give a hydrophilic tunnel, or pore.

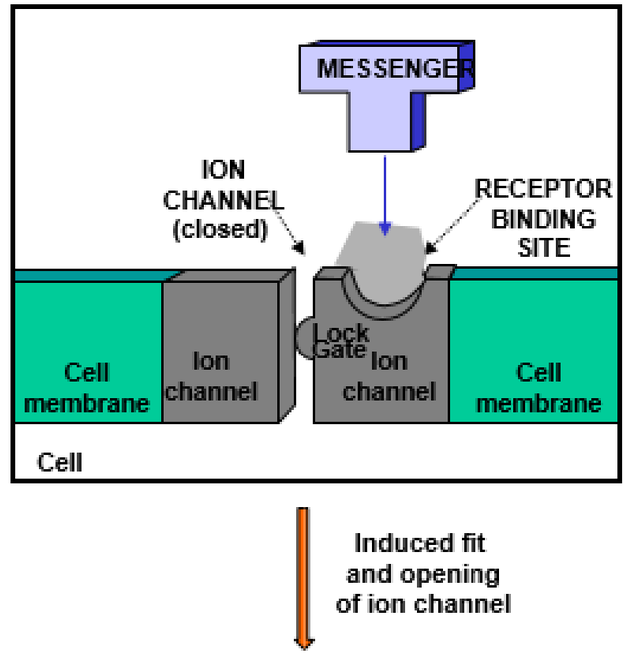
Ions can cross the fatty barrier of the cell membrane by moving through these hydrophilic channels or tunnels.

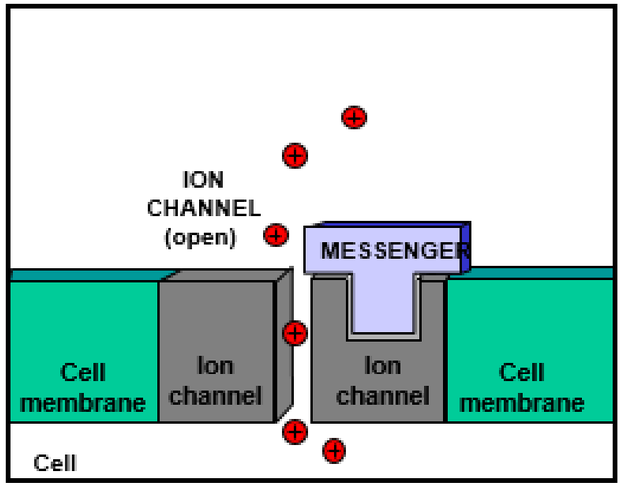


# Ion flow controlling

This lock gate should be controlled by a receptor protein sensitive to an external chemical messenger,

In the resting state, the ion channel is closed (i.e. the lock gate is shut). However, when a chemical messenger binds to the external binding site of the receptor protein, it causes an induced fit which causes the protein to change shape. This, in turn, causes the overall protein complex to change shape, opening up the lock gate and allowing ions to pass through the ion channel.



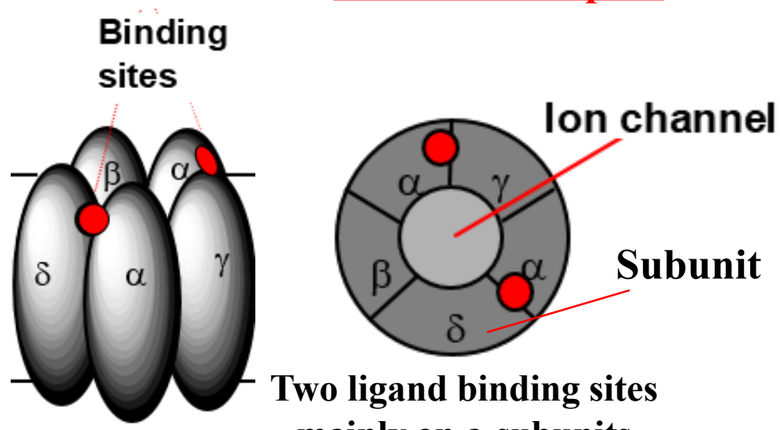
# Structure of Ion Channel Receptors

The protein subunits in an ion channel are not identical

The ion channel controlled by the nicotinic cholinergic receptor is made up of five subunits of four different types [α (×2) β, γ, δ]; were the most of the binding site is on the α-subunit of acetylcholine, but there is some involvement from others subunits.

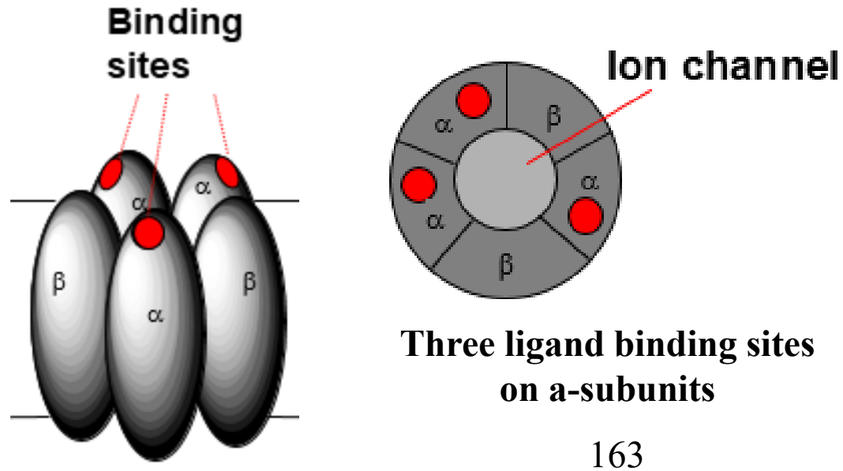
The ion channel controlled by the glycine receptor is made up of five subunits of two different types [α (×3), β (×2)], were α-subunits is the receptor protein by glycine.

**Nicotinic receptor**



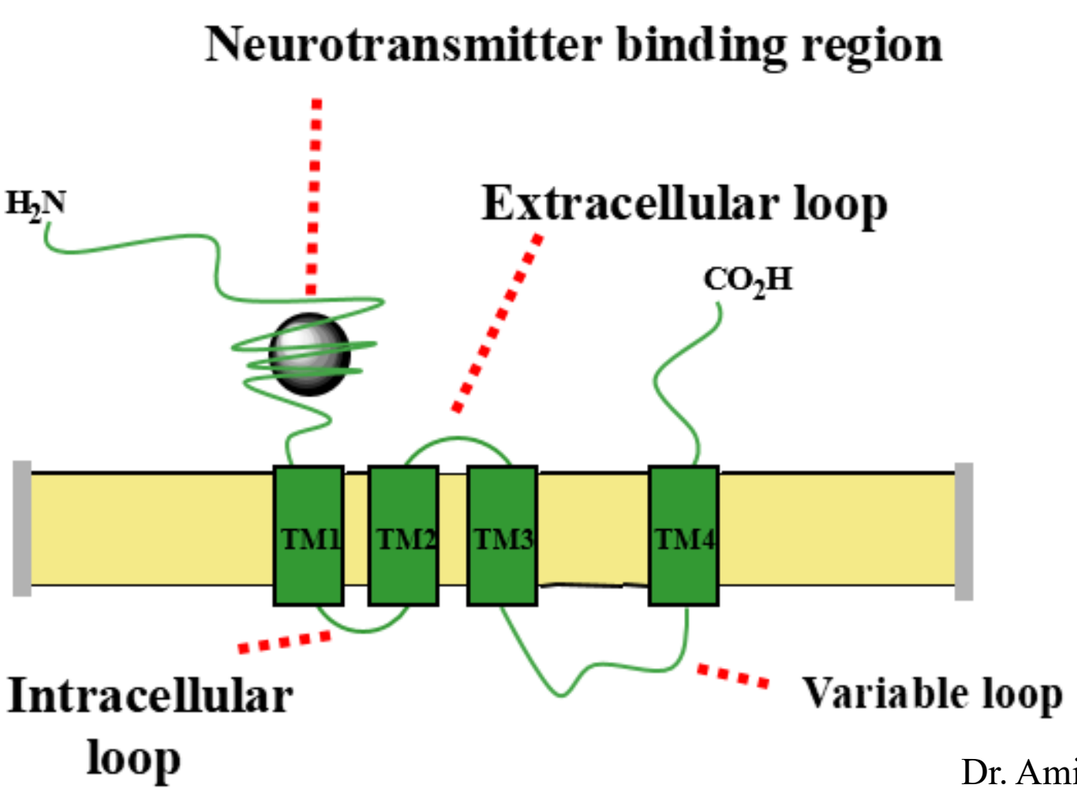

**Two ligand binding sites mainly on a-subunits**

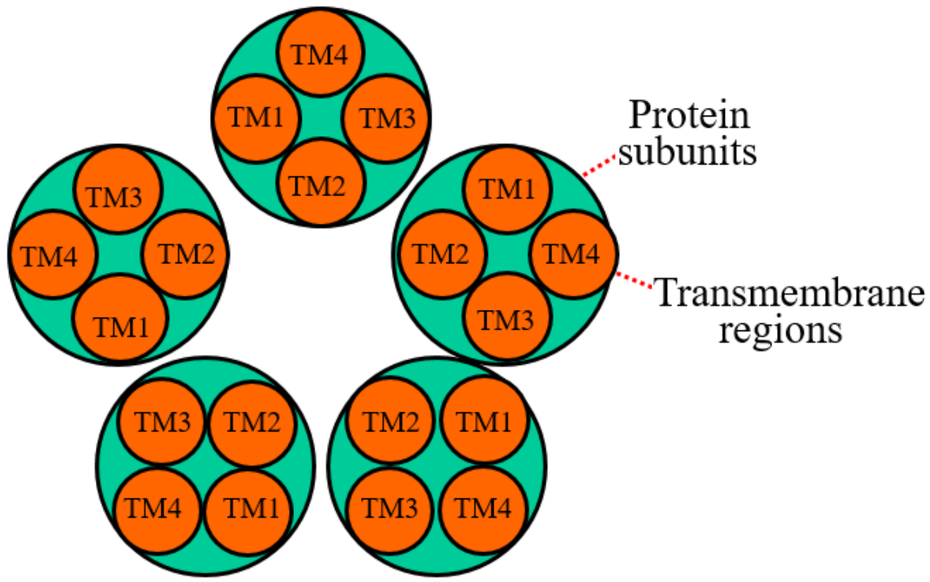
**Glycine receptor**




**Three ligand binding sites on a-subunits**

- Protein subunits fold up in a similar manner such that the protein chain traverses the cell membrane four times.
- Each subunit has four transmembrane (TM) regions which are hydrophobic in nature. These are labelled TM1–TM4.



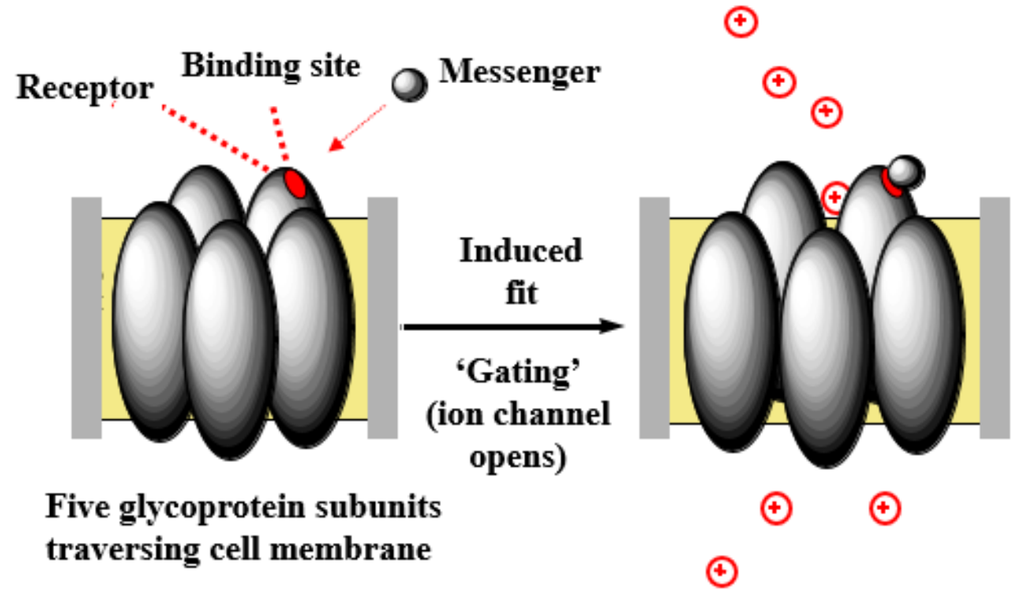



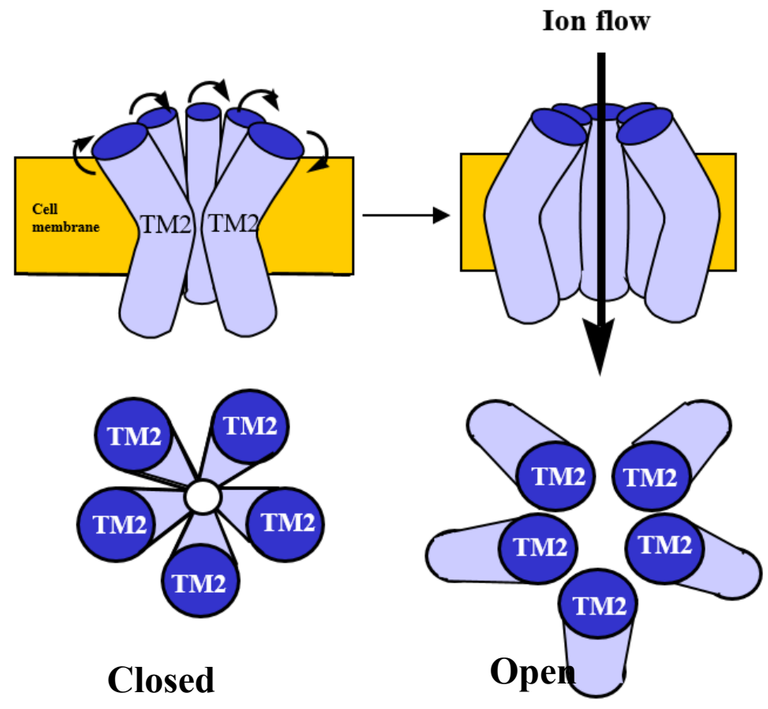

**Note: TM2 of each protein subunit 'lines' the central pore**

# Gating

The lock gate is made up of five kinked α-helices where one helix (the 2-TM region) is contributed by each of the five protein subunits.

In the closed state the kinks point towards each other. The conformational change induced by ligand binding causes each of these helices to rotate such that the kink points the other way, thus opening up the pore.



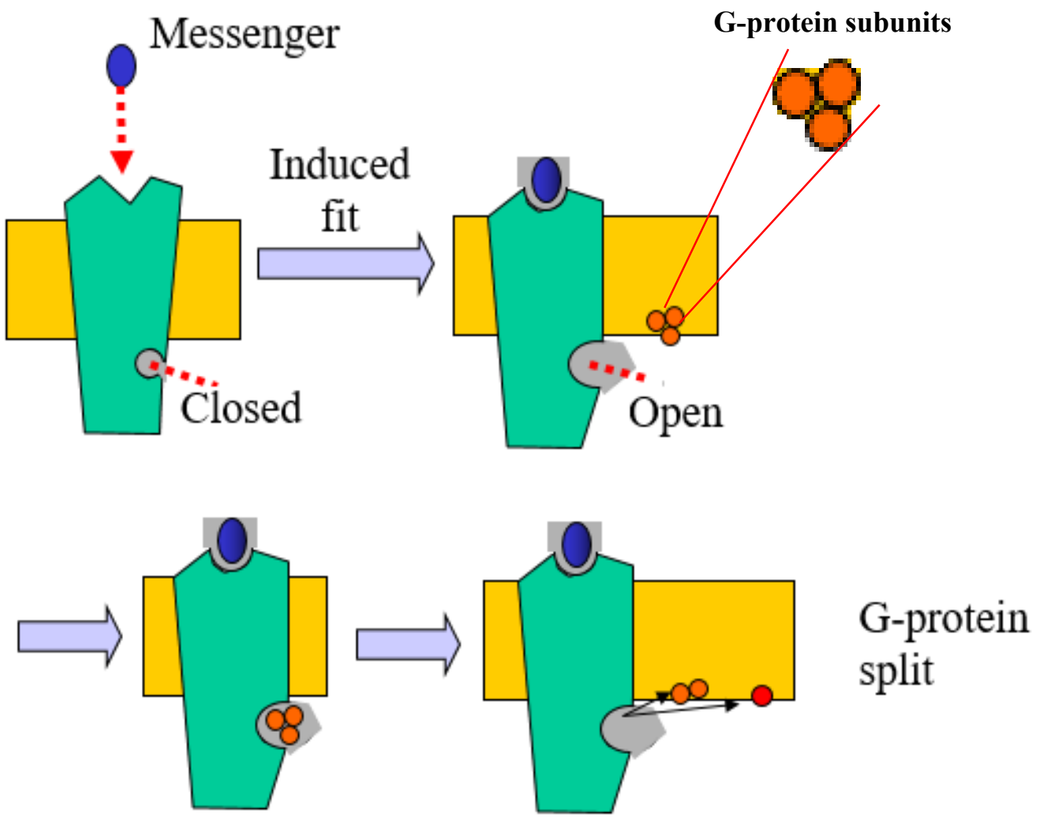
## 6. G-Protein Coupled Receptors

- G-Protein are activated by hormones and slow-acting neurotransmitters.
- They include the muscarinic receptor, adrenergic receptors, and opioid receptors.
- Slower than the response of ion channels, but faster than the response of kinase-linked receptors
- There are a large number of different G-protein-coupled receptors interacting with important neurotransmitters, such as acetylcholine, dopamine, histamine, serotonin, glutamate, and noradrenaline.
- Other G-protein-coupled receptors are activated by peptide and protein hormones, such as the enkephalins and endorphins.
- Located on the inner surface, made up of three protein subunits, but once it binds to the receptor

- When the chemical messenger binds to its binding site, the receptor protein changes shape, opening up the binding site on the inner surface,

- This new binding site is recognized by the G-protein, which then binds the G-protein is attached to the inner surface of the cell membrane,

- The complex is destabilized and fragments to a monomer and a dimer, these then interact with membrane-bound enzymes to continue the signal transduction process.

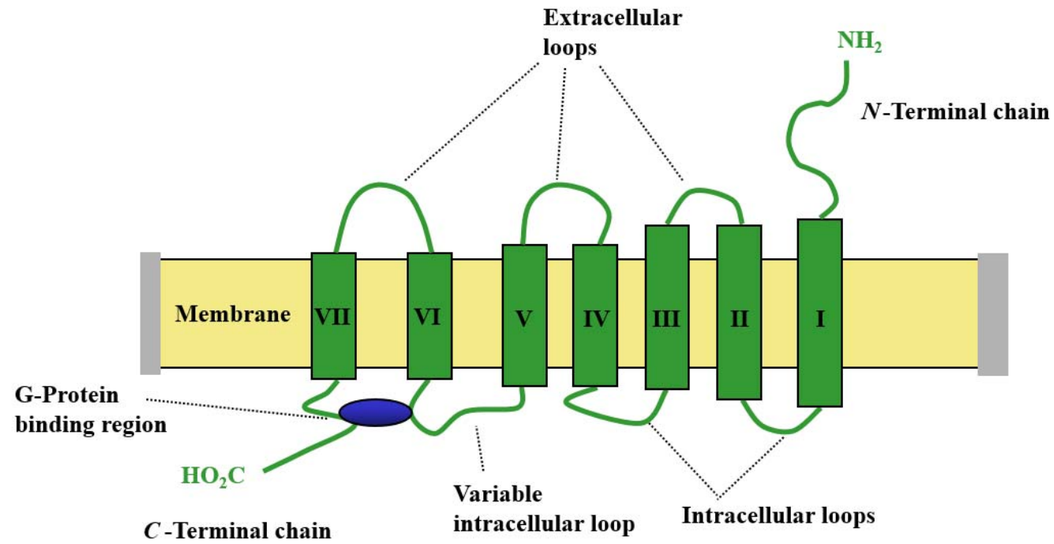


# Structure

## Single protein with 7 transmembrane regions

The G-protein-coupled receptors fold up within the cell membrane such that the protein chain winds back and forth through the cell membrane seven times

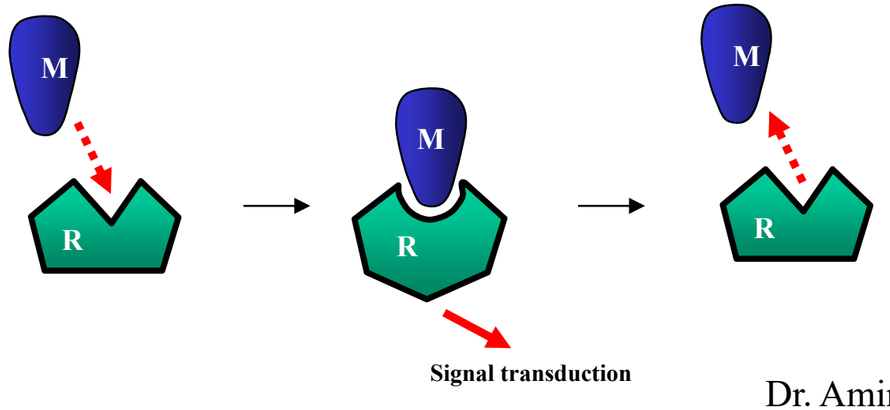
Each of the seven transmembrane sections is hydrophobic and helical in shape, and it is usual to assign these helices with roman numerals (I, II, etc.) starting from the N-terminus of the protein.

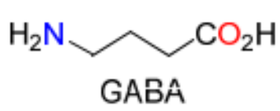


## 7. The rhodopsin-like family of G-protein-coupled receptors

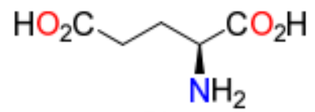
The G-protein-coupled receptors include the receptors for some of the best-known chemical messengers, glutamic acid, GABA, noradrenaline, dopamine, acetylcholine, serotonin, and adenosine.

Considering the structural variety of the chemical messengers involved, it is remarkable that the overall structures of the G-protein-coupled receptors are so similar.

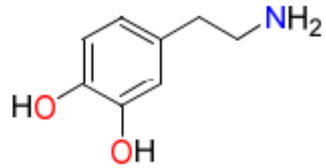


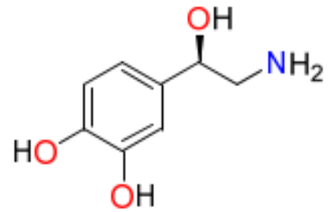
GABA



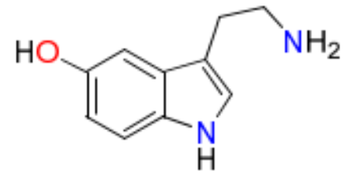
Glu



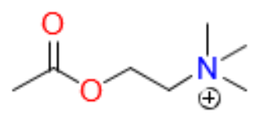
Dopamine



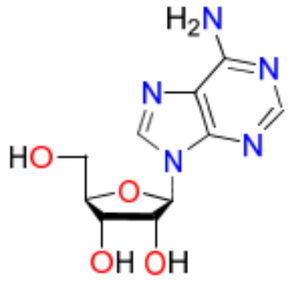
Norepinephrine



Serotonin



Acetylcholine



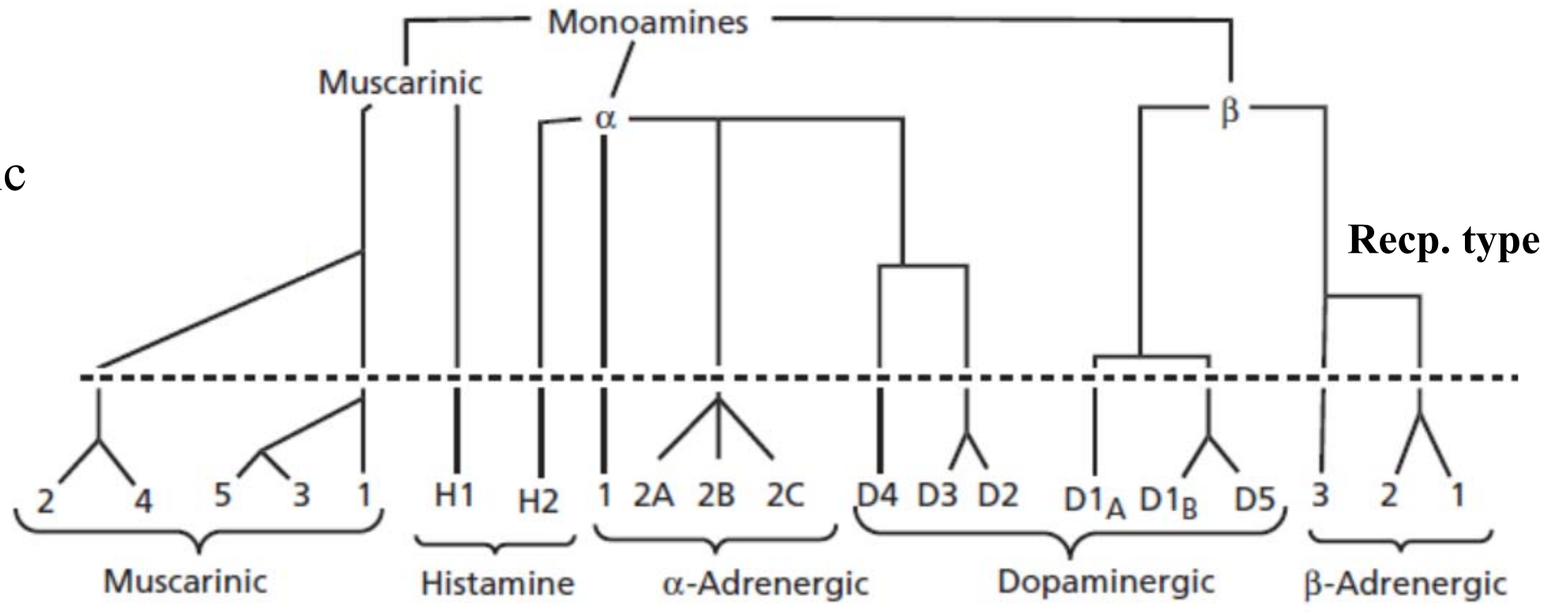
Adenosine

The existence of receptor subtypes allows the possibility of designing drugs that are selective for one receptor subtype over another.

Receptors have further evolved to give receptor types and subtypes which recognize the same chemical messenger, but are structurally different. For example,

Adrenergic receptor (α and β), with various subtypes (α1, α2A, α2B, α2C, β1, β2, β3).

Five subtypes of the muscarinic cholinergic receptor have been identified.



# 8. Kinase Linked Receptors

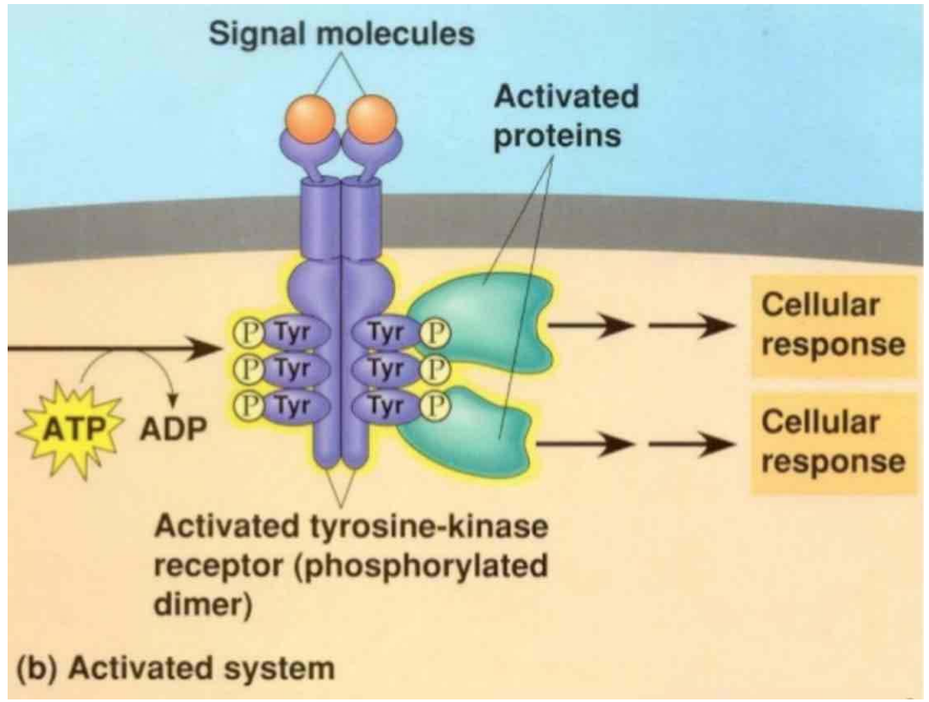
Kinase-linked receptors (KLR) are a superfamily of receptors which activate enzymes directly and do not require a G-protein and depend on phosphorylation reactions.

Tyrosine kinase receptors are important examples of kinase-linked receptors

NAMED: An enzyme that catalyses phosphorylation reactions is known as a kinase enzyme and so the protein is referred to as a tyrosine kinase receptor.

Protein concerned plays the dual role of receptor and enzyme.

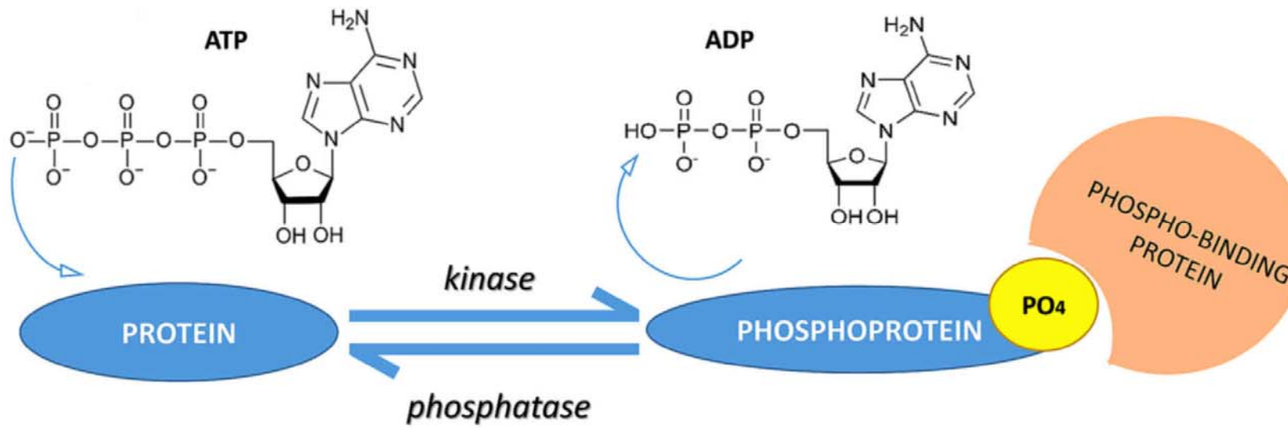
The receptor protein located outer surface of the cell and part exposed on the inner surface.

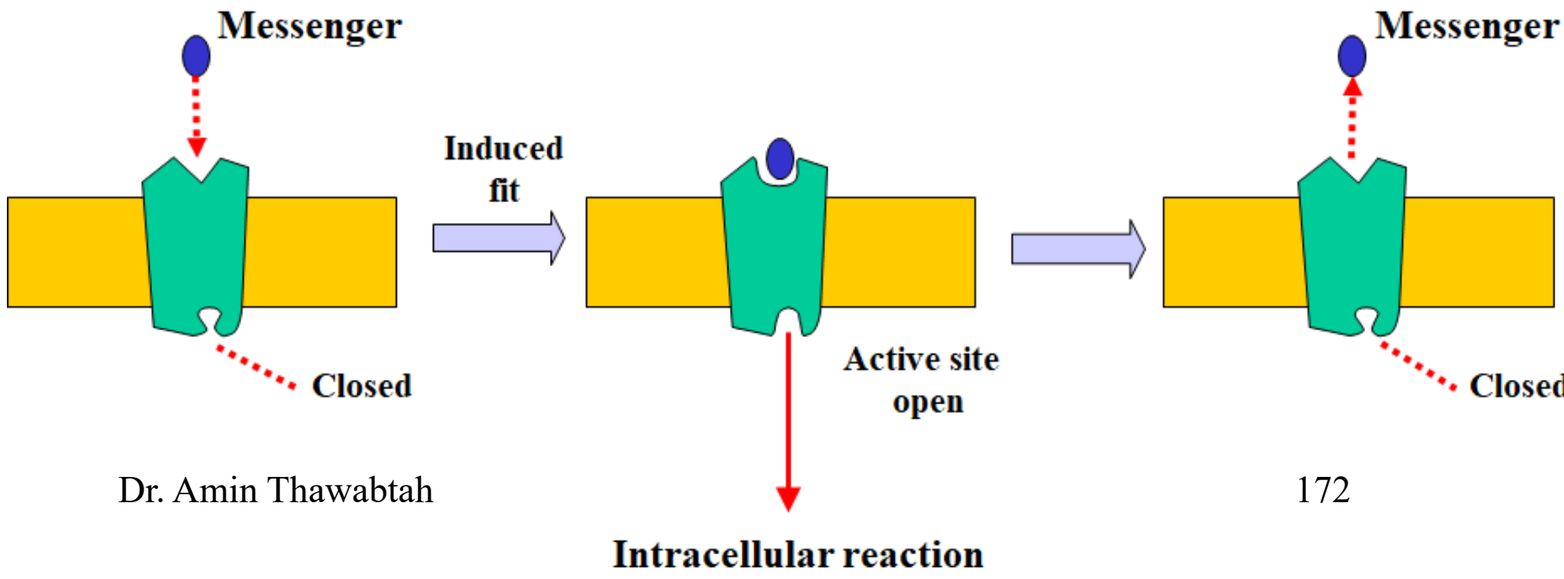


## Mode of Action

- The outer surface contains the binding site for the chemical messenger and the inner surface has an active site that is closed in the resting state.
- When a chemical messenger binds to the receptor it causes the protein to change shape.
- This results in the active site being opened up, allowing the protein to act as an enzyme within the cell.

The reaction that is catalysed is a phosphorylation reaction where tyrosine residues on a protein substrate are phosphorylated. **ATP is required as a cofactor to provide the necessary phosphate group.**



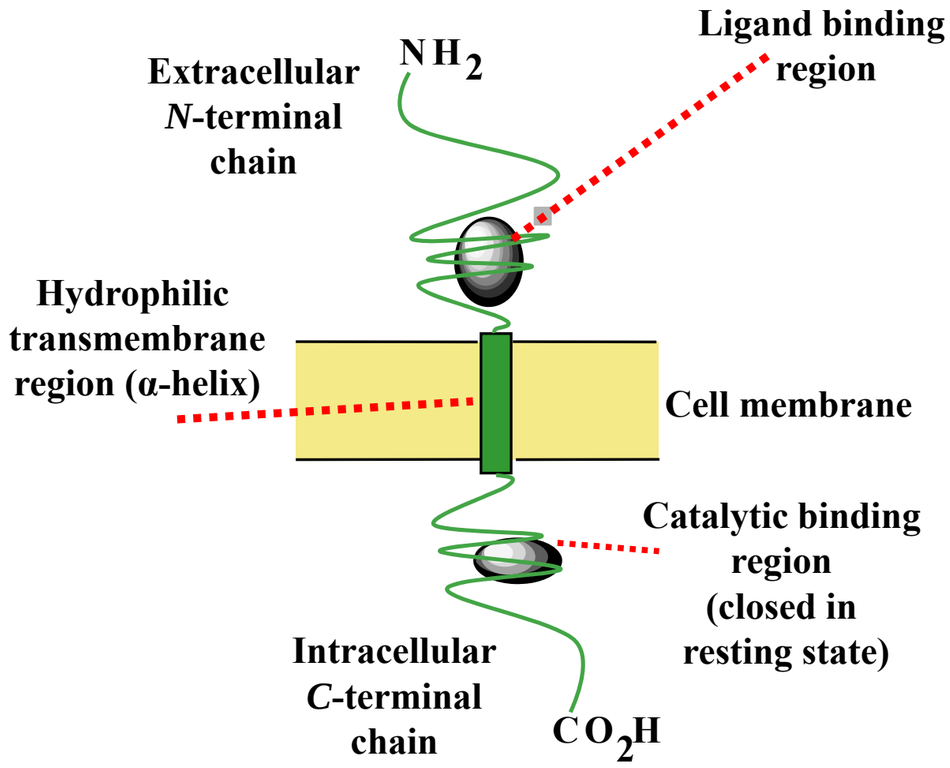



# Structure

The basic structure of a tyrosine kinase receptor consists of a single extracellular region (the N-terminal chain) that includes the binding site for the chemical messenger,

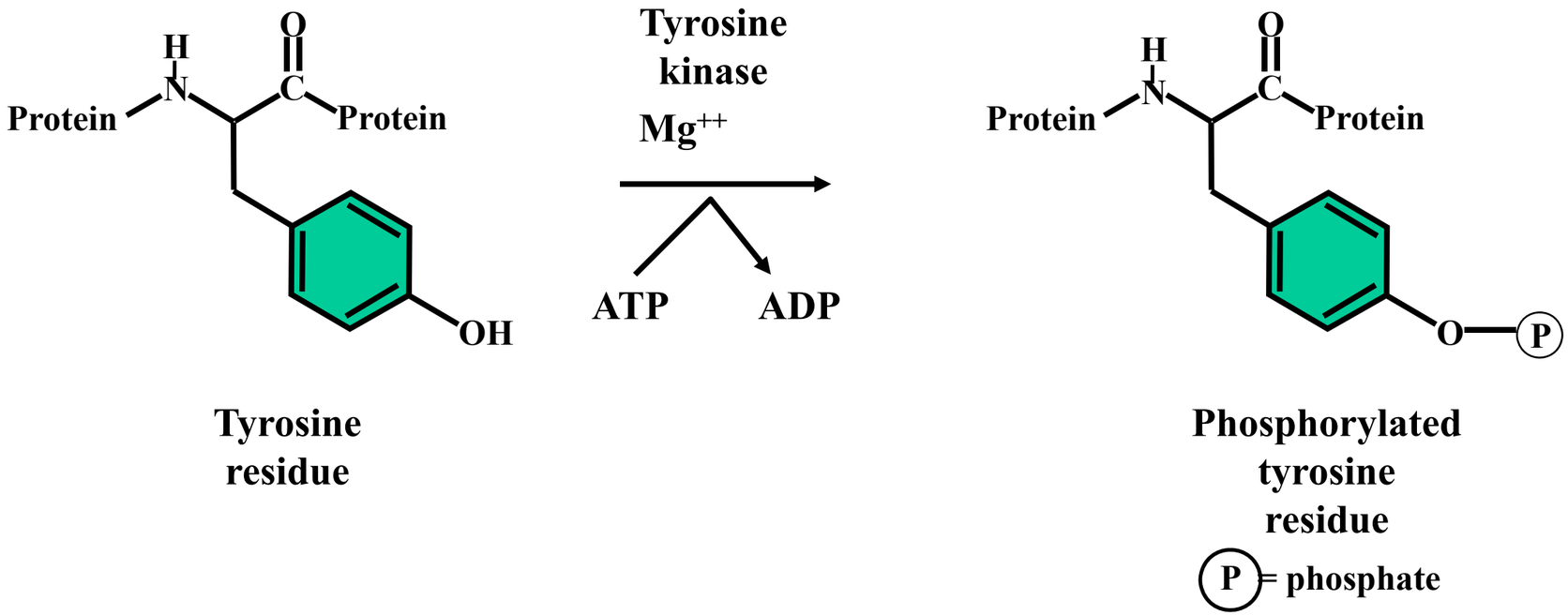
A single hydrophobic region that traverses the membrane as an α-helix of seven turns, and a C-terminal chain on the inside of the cell membrane

The C-terminal region contains the catalytic binding site.



## Reaction catalysed by Tyrosine Kinase

The reaction that is catalysed is a phosphorylation reaction where tyrosine residues on a protein substrate are phosphorylated



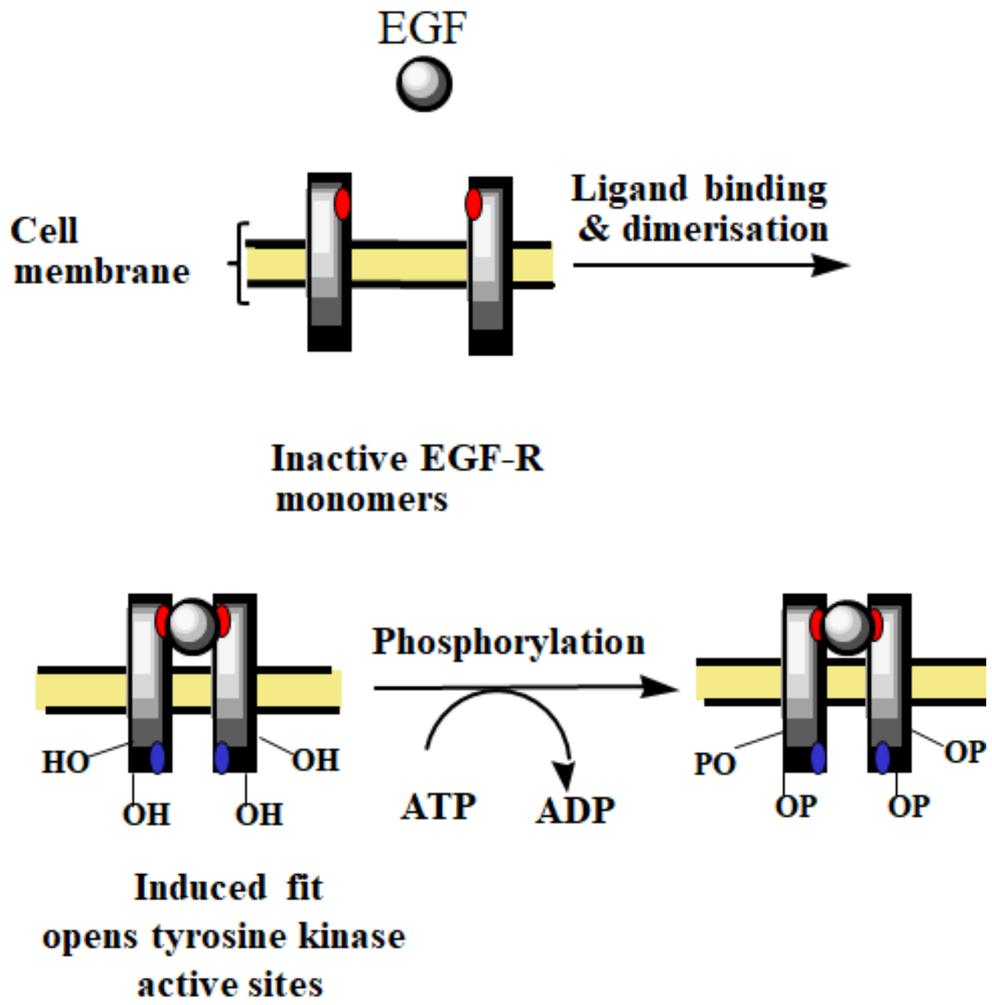
# Epidermal growth factor receptor hormone (EGF- R) -Dimers Complex-

Example TKR

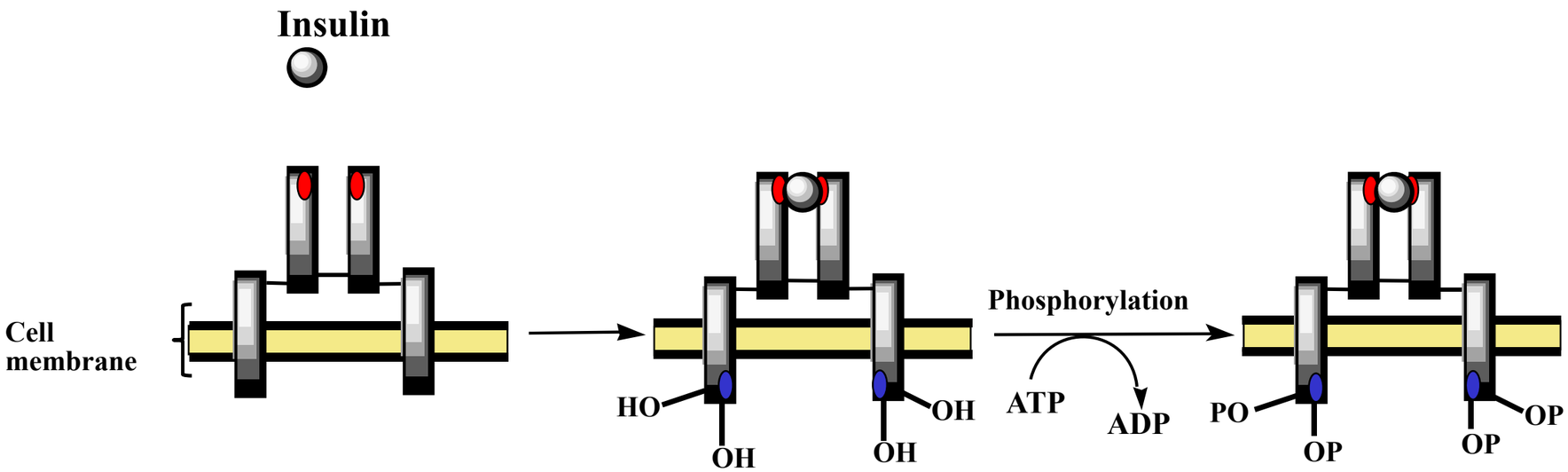
EGF can bind to two receptors at the same time. This results in receptor dimerization, as well as activation of enzymatic activity.

The dimerization process is important because the active site on each half of the receptor dimer catalyses the phosphorylation of accessible tyrosine residues on the other half.

Phosphorylated regions act as binding sites for further proteins and enzymes. Results in activation of signalling proteins and enzymes. Then message carried into cell



# Insulin receptor (tetrameric complex)

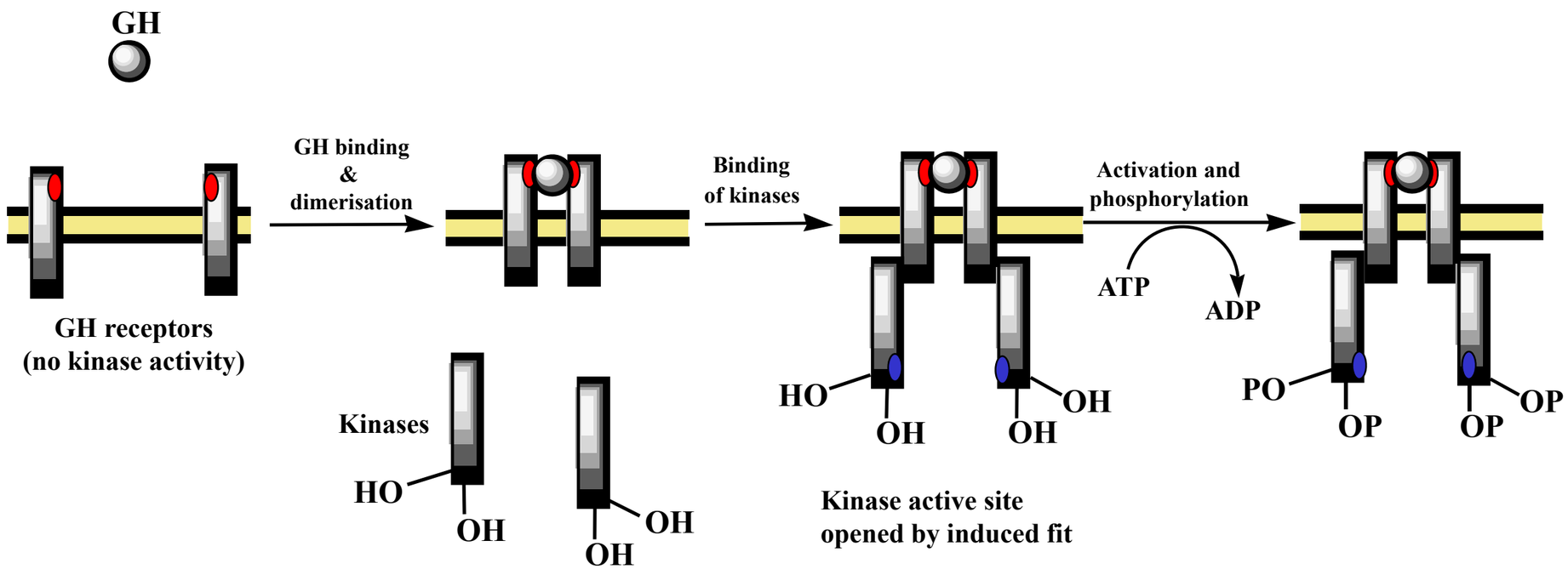



Activation of
tyrosine kinase activity

# Growth hormone receptor

**Tetrameric complex constructed in presence of growth hormone**

Occurred when their C-terminal chain haven't catalytic activity. However, once they have dimerized, they can bind and activate a **tyrosine kinase enzyme from the cytoplasm.**



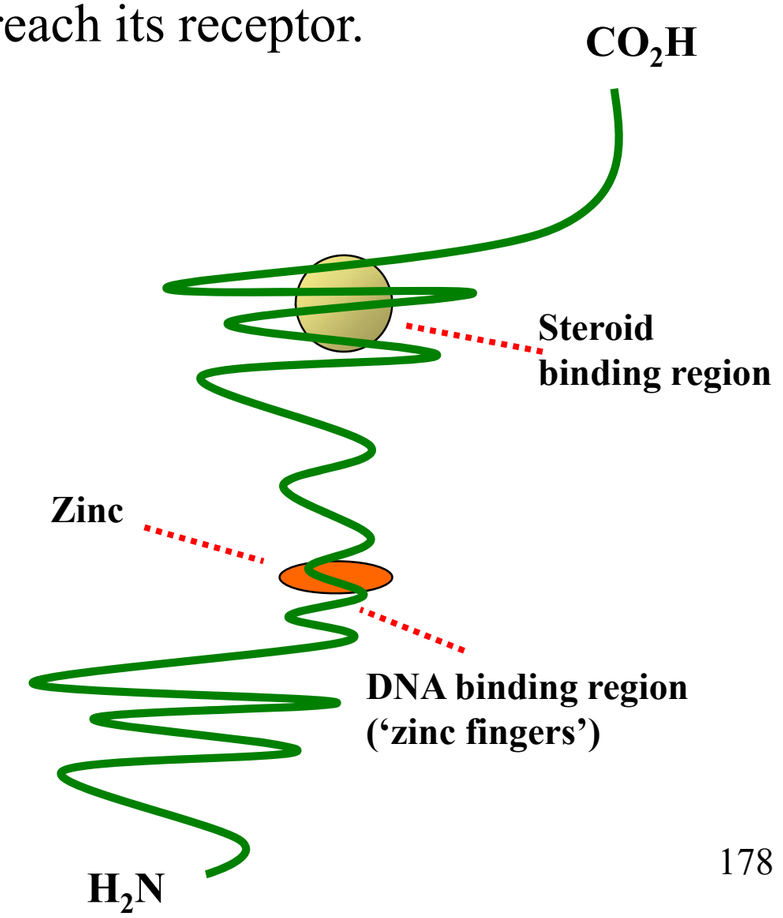
# 9. Intracellular Receptors

Some receptors are within the cell and are defined as intracellular receptors, they are often called nuclear hormone receptors or nuclear transcription factors.

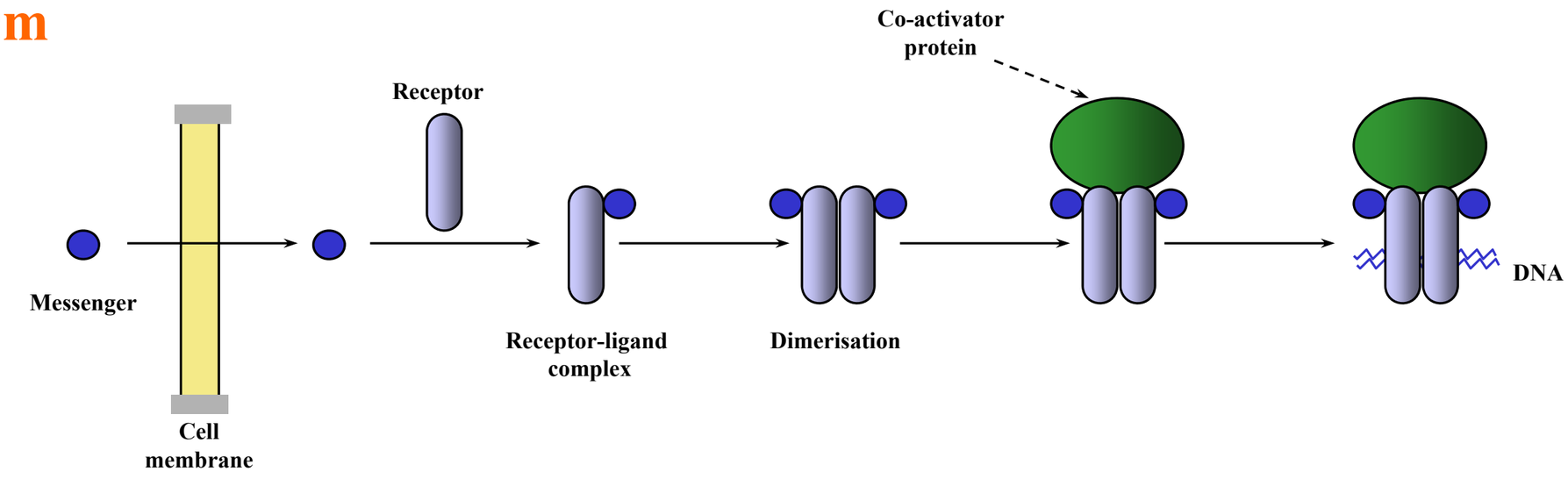
The chemical messengers for these receptors include steroid hormones, thyroid hormones, and retinoid, so it's hydrophobic. And it pass through the cell membrane in order to reach its receptor.

STRUCTURE: They consist of a single protein containing a ligand binding site at the C-terminus and a binding region for DNA near the centre, the DNA binding region contains nine cysteine residues, eight of which are involved in binding two zinc ions.

The zinc ions play a crucial role in stabilizing and determining the conformation of the DNA binding region. As a result, the stretches of protein concerned are called the zinc finger domains.



# Mechanism




1. Messenger crosses membrane
2. Binds to receptor
3. Receptor dimerisation
4. Binds co-activator protein
5. Complex binds to DNA

As there are two receptors in the complex and two DNA binding regions, the complex recognizes two identical sequences of nucleotides in the DNA separated by a short distance.

**Homework:**

**Q2 in page 57**