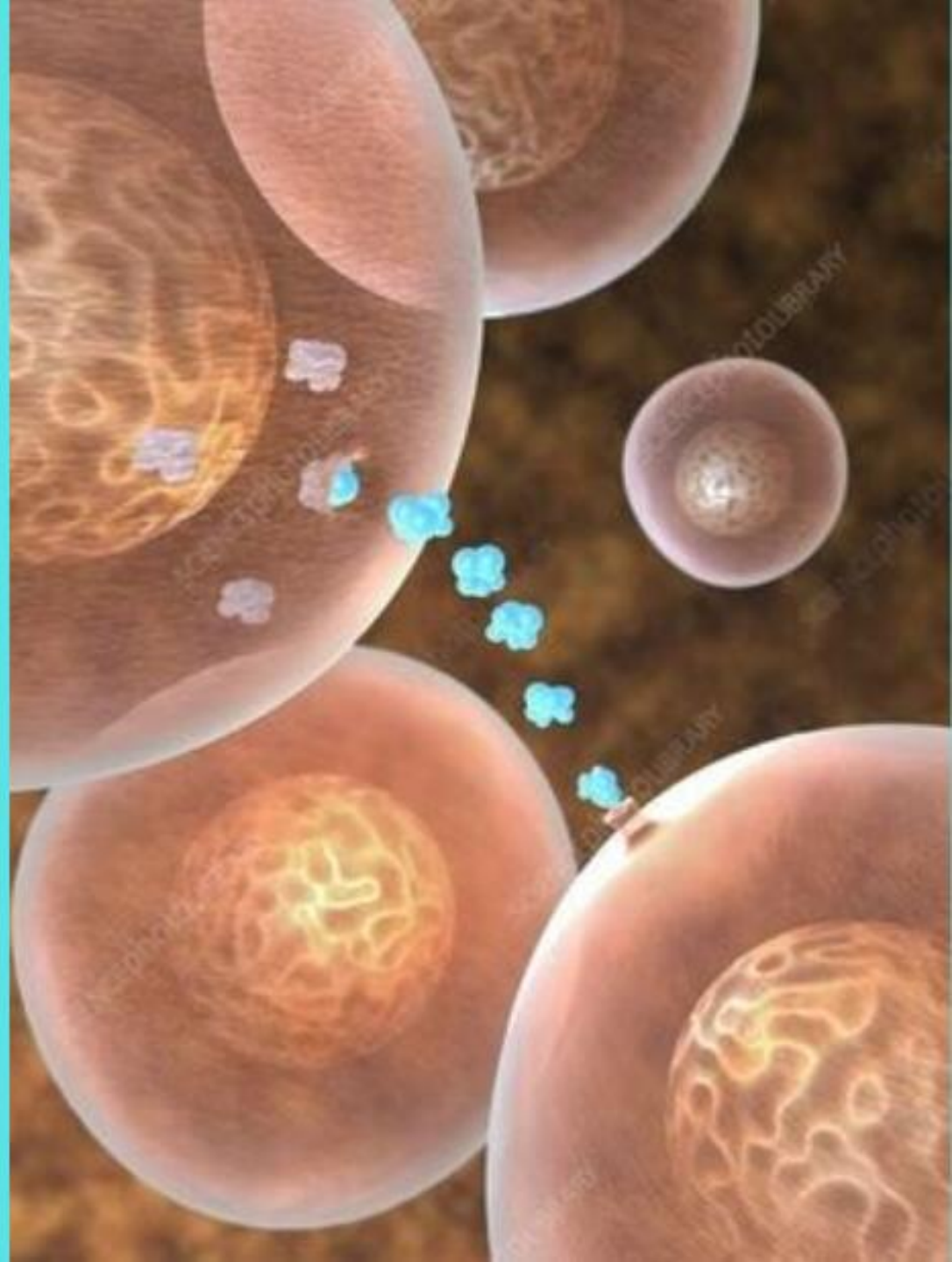
SEASON 2

Understanding Cancer

Lecture 4
Receptor activation

DR HAFSA WASEELA ABBAS
www.hafsaabbas.com



RECAP:

What you hopefully should understand so far from Lecture 3

- **Cell-to-cell communication** consists of **direct, paracrine, contact-dependent, autocrine and endocrine signalling pathways.**
- Cell signalling has three key steps: **receptor activation, signal transduction and cellular response**.
- **Dysregulation of cellular signal transduction pathways** underlies **most of hallmarks of cancer**.
- There are **different types of signalling pathways** and vary based on the **distance** travelled to reach the **target cells.**
- **Protein-based ligands are insoluble in the membrane and does not enter the cell.**
  Fat-based ligands are soluble and pass through the membrane.

What will we learn today?

- ***What is a receptor?***
- ***Where are receptors found?***
- ***What factors affect the binding between the receptor and ligand?***
- ***Types of receptors***
- ***Types of ligands.***
- ***Other types of ligands***

GENTLE REMINDER
An ideal way of learning:

Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday

Mini-lectures.

Approximate total time: 1 hour

Divide over 7 days at your **own pace**.

Challenge yourself with a quiz!

HN

www.hafsaabbas.com

RECAP: How to support your learning?

- **Key facts with diagrams by HN designs presented in a simplified way.**
- **Glossary to help understand what key words mean.**
- **Summary doodle revision posters by HN designs.**
- **Quizzes to test your knowledge and reflect.**
- **Reference list for further reading.**

Acknowledgements: Special thanks to my parents, family, friends and colleagues for their support and the respected teachers and health professions who taught me and installed the passion of cancer/oncology.

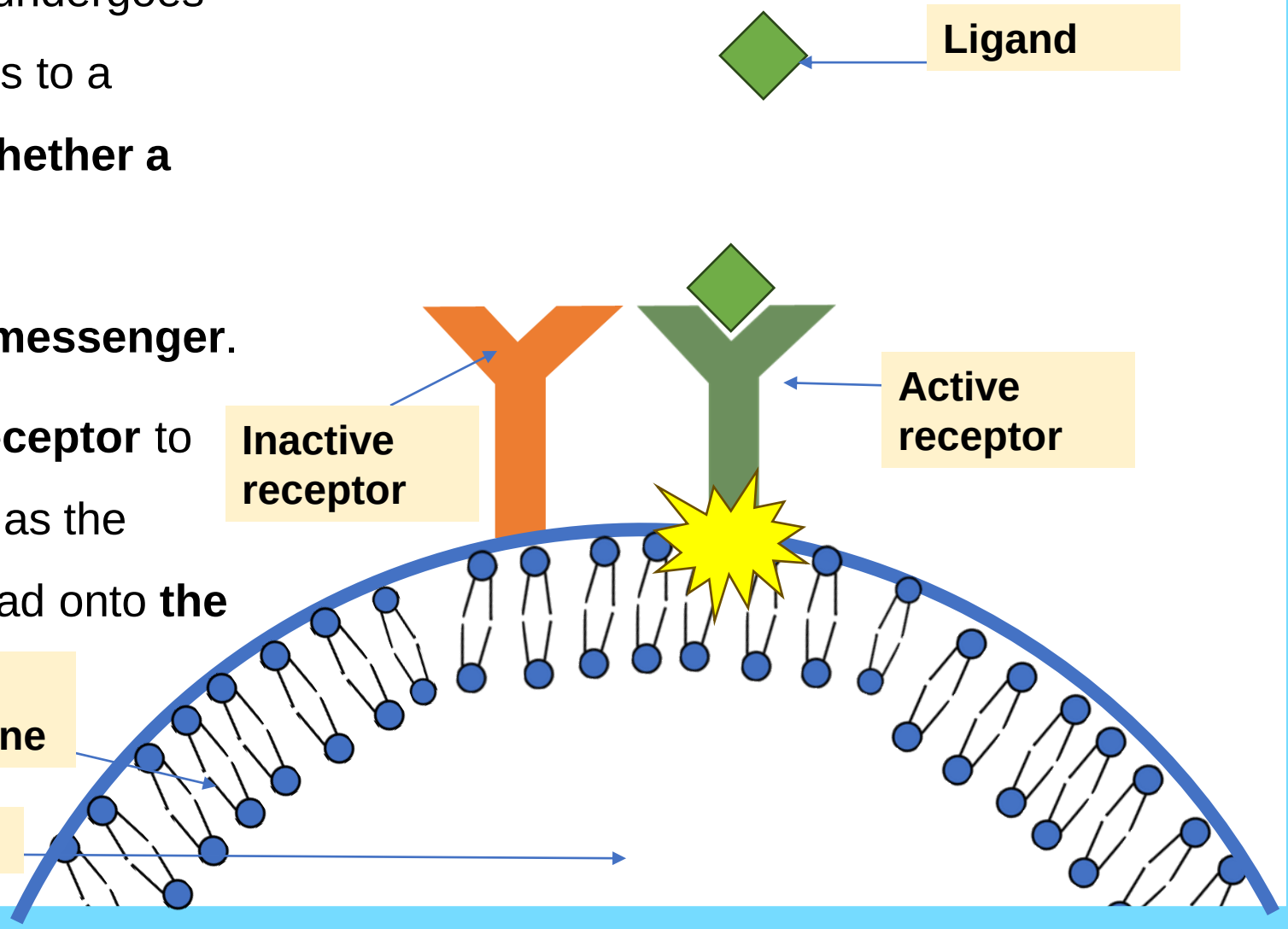
What is a receptor?

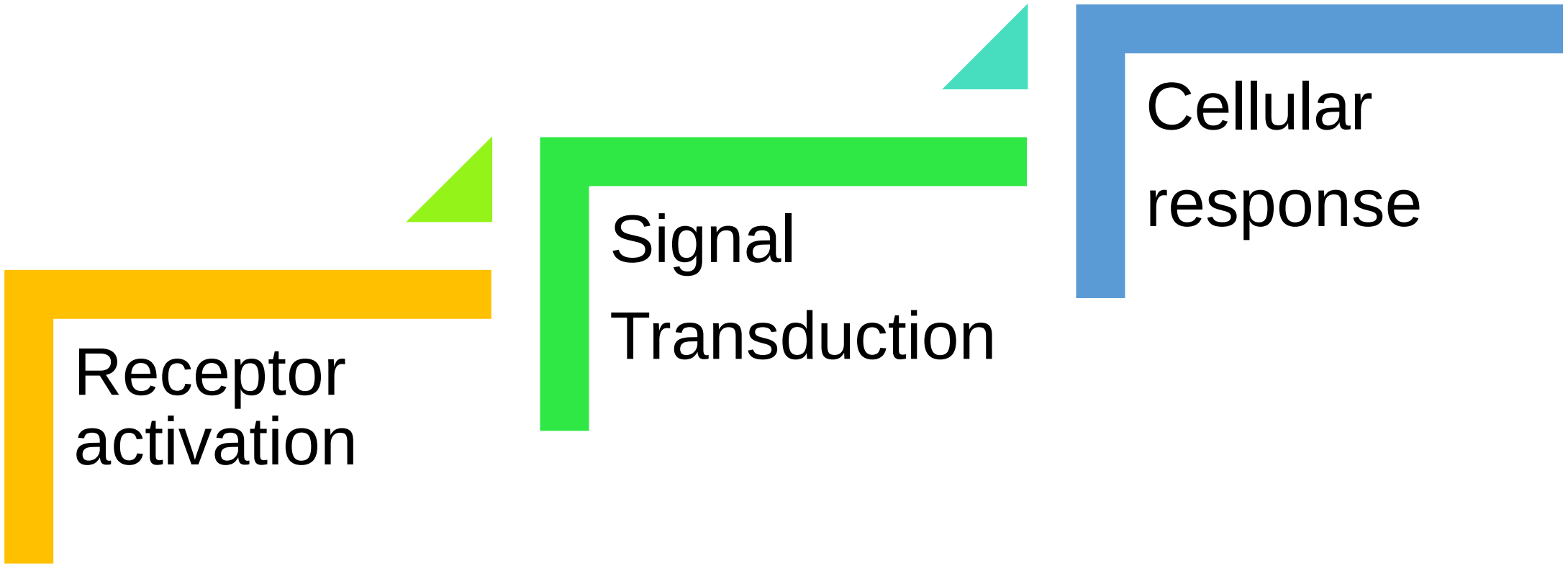
Key Facts: What is a receptor?

A **receptor** is a **cellular protein** that undergoes **conformational change** when it binds to a signalling molecule called a **ligand whether a steroid or protein**.

The ligand is considered as the **first messenger**.

This **activates the function of the receptor** to start a **sequence of changes** known as the **signal transduction pathway** that lead onto **the response**.





The three steps in cell communication

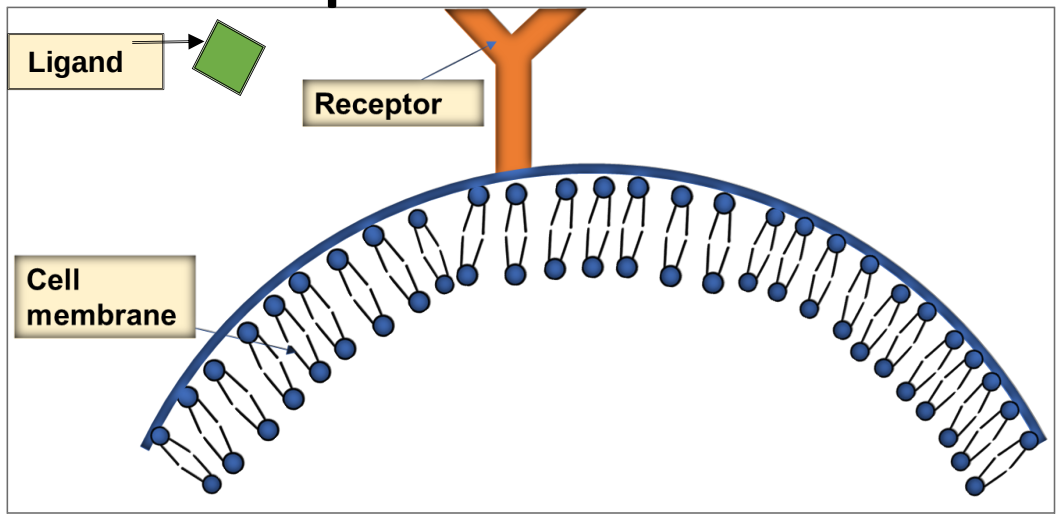
Where are receptors found?

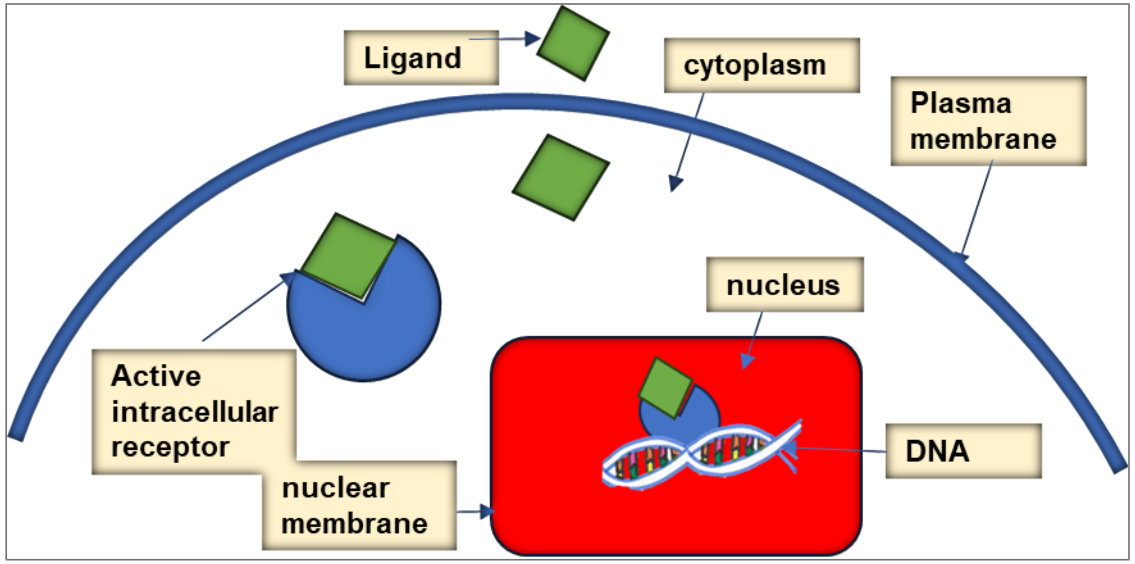
Key Facts: Where are receptors found?

Most receptors are found on the **surface of the cell.**

Location of receptors

Some receptors are found **inside the cells (intracellular)**



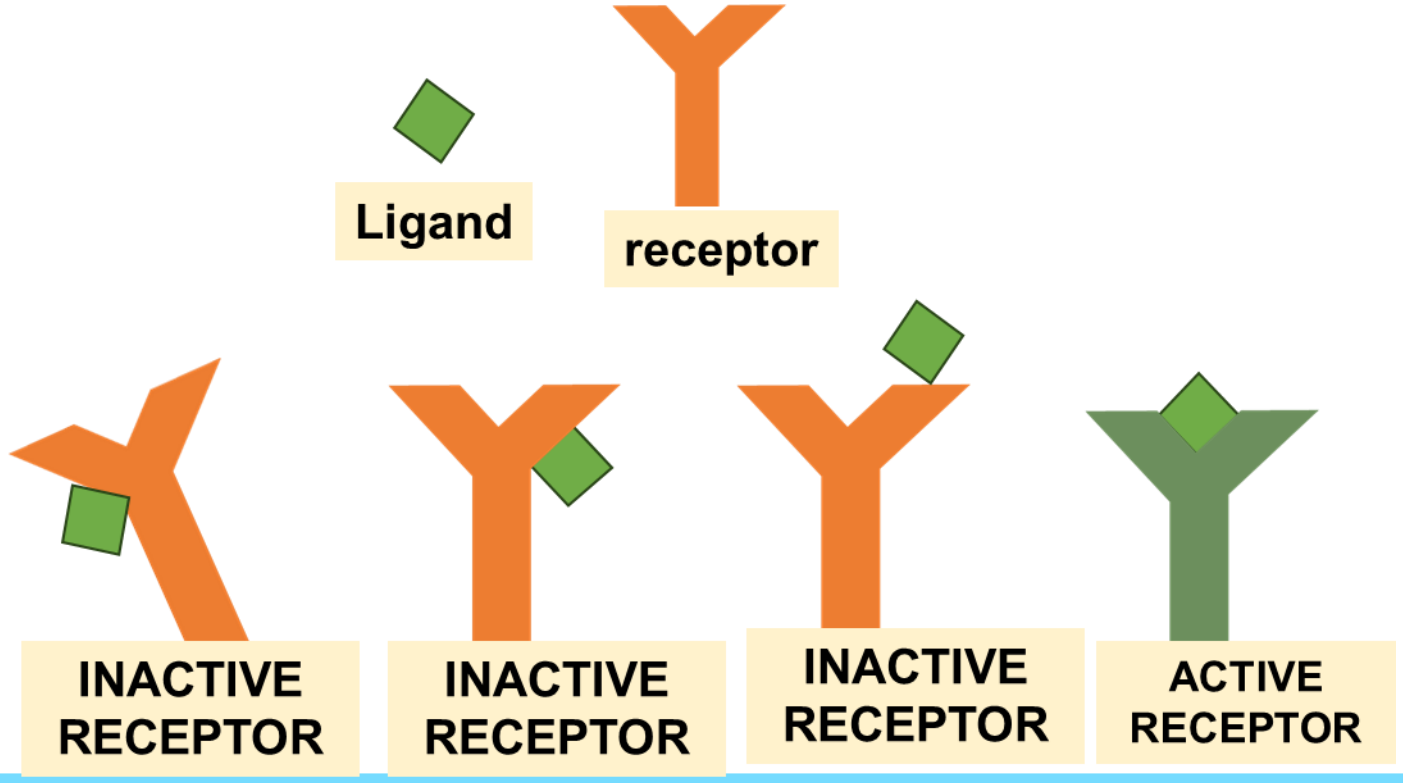


What factors affect the binding between the receptor and ligand?

Key Facts: What factors affect the binding between the receptor and ligand?

The **receptor and ligand bind specifically** and is **a rapid process** that require two key factors:

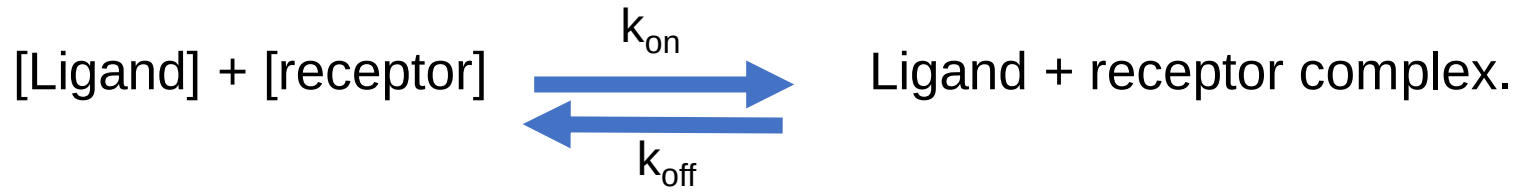
- ❑ **Right orientation (position)**
- ❑ **Sufficient energy**



Key Facts: The equilibrium

Cell to cell communication varies in the **method and distance the signal is travelling**.

The equation below presents **the association between the ligand and receptor**:



K_{on} → rate of binding occurs.

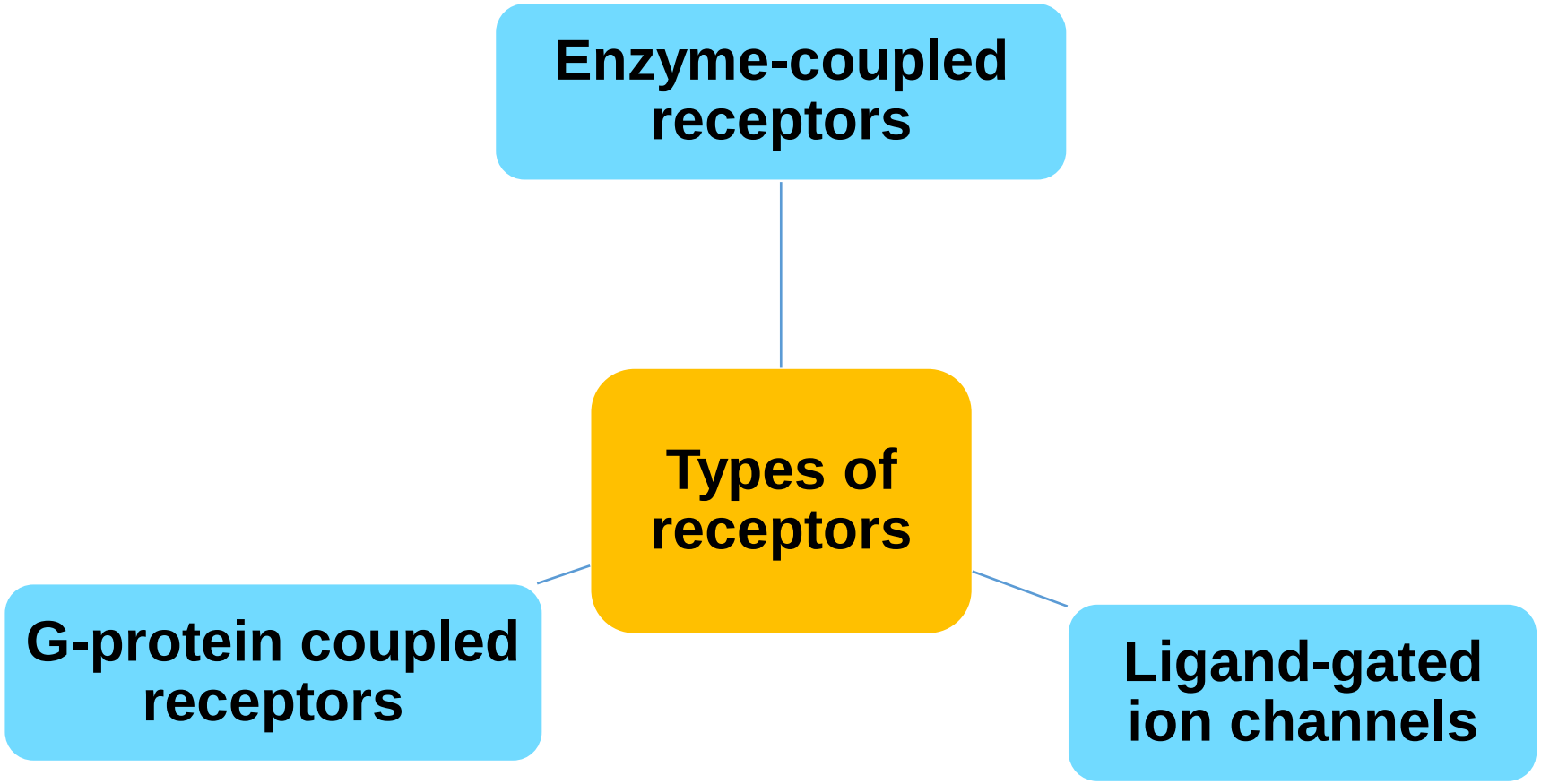
K_{off} → rate of dissociation/release occurs

K_d value → dissociation/equilibrium constant between the ligand + receptor

The **rate of the binding between a ligand and receptor <u>EQUALS</u>** the **rate of releasing the ligand from the receptor.**

Types of receptors

Key Facts: Types of receptors



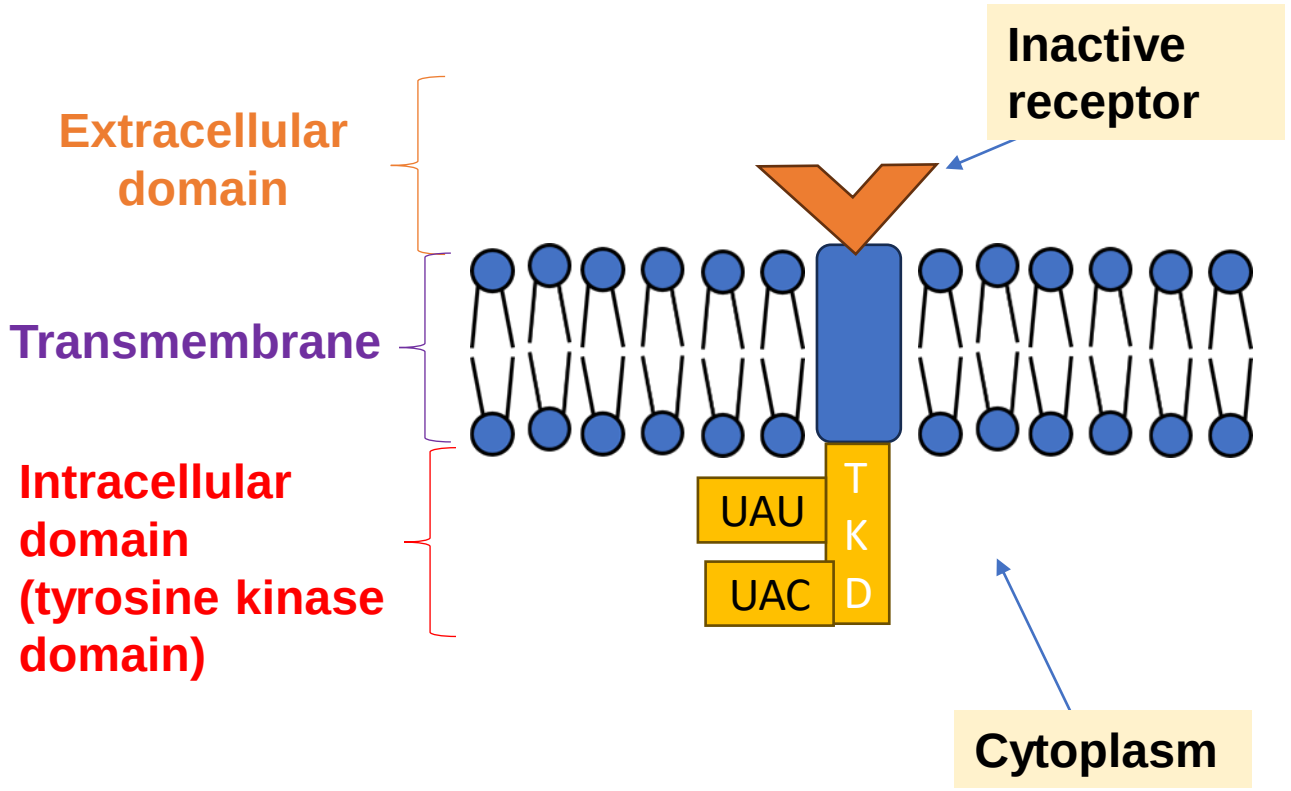
Key Facts: Enzyme-coupled receptors

They are found in **all living cells** particularly plants and animals.

There are **two domains** in the receptor:

- **Extracellular** → To **bind to a signalling molecule/ligand**
- **Intracellular → catalytic function/enzyme activity**

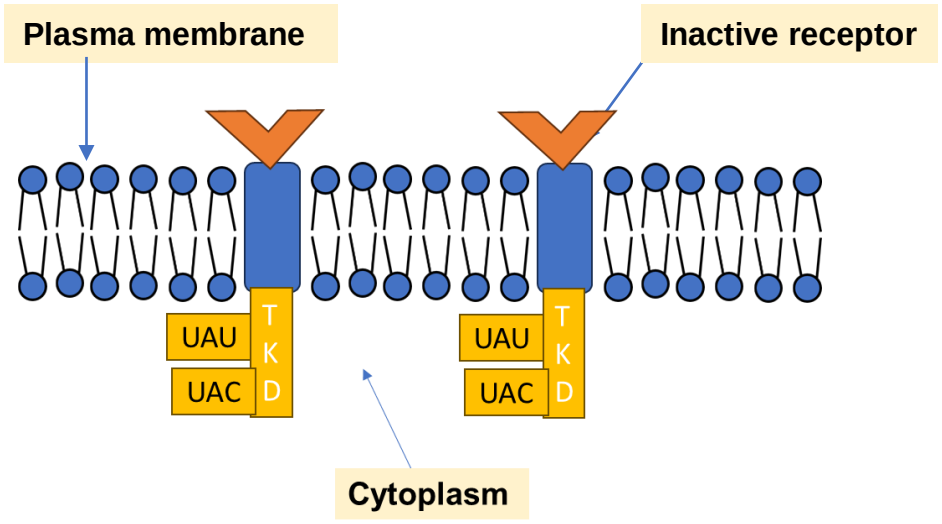
A structure called a **transmembrane alpha helix connects these two domains together.**



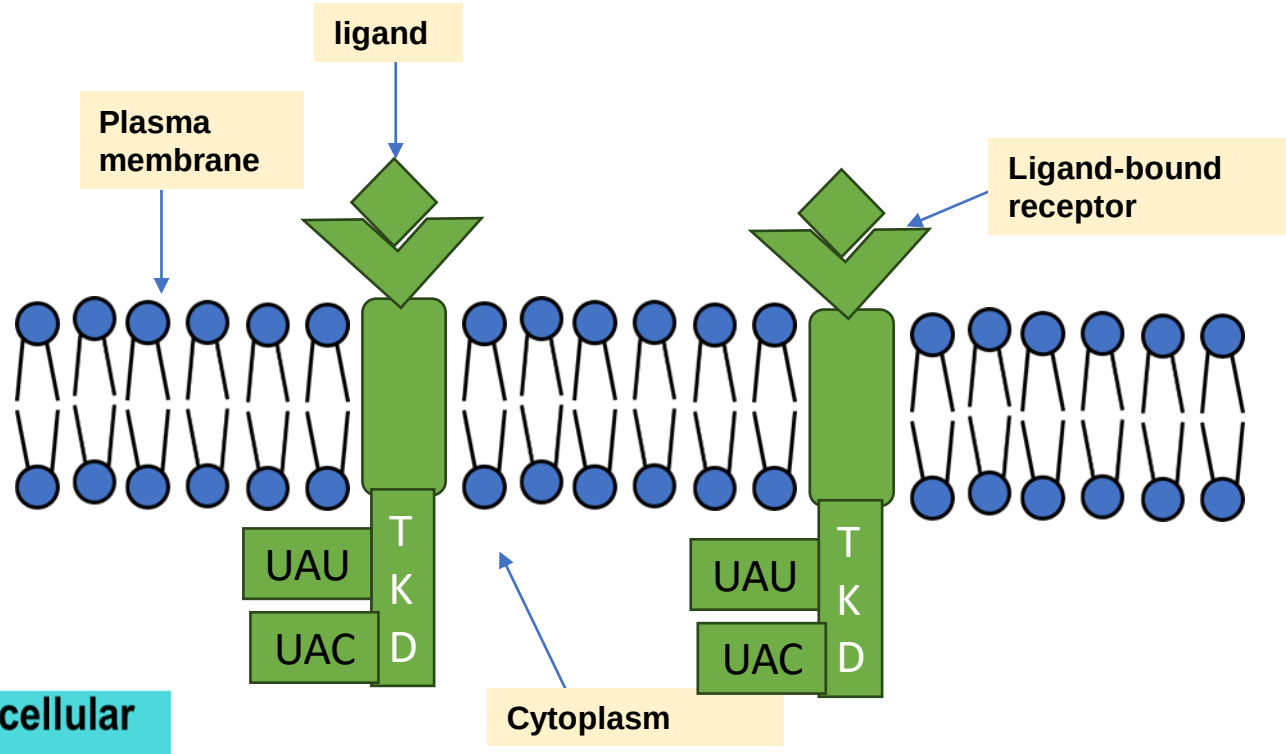
Example: Tyrosine-kinase receptors

Key Facts: Enzyme-coupled receptor activation process.

1. Receptor and ligand bind.
2. A conformation change occurs at the extracellular domain of the receptor
3. The two receptor molecules then associate together. This is called dimerization.
4. This effects the conformation of the intracellular domain where the tyrosine kinase activity is on.
5. Enzymes are proteins made of amino acids. One particular amino acid tyrosine is where phosphorylation takes place.
6. Tyrosine kinases are enzymes that transfer of phosphate groups (PO_4^{3-}) from ATP (adenosine triphosphate) to a protein.
7. They can phosphorylate each other. This is known as autophosphorylation



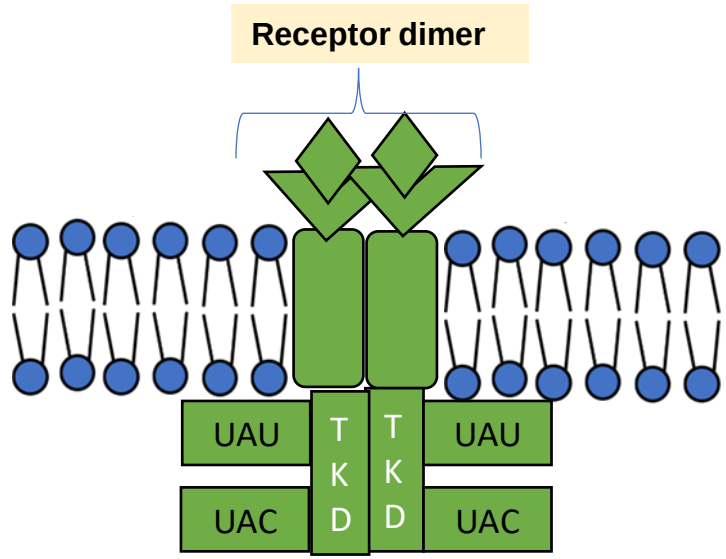
1. Receptor and ligand bind.

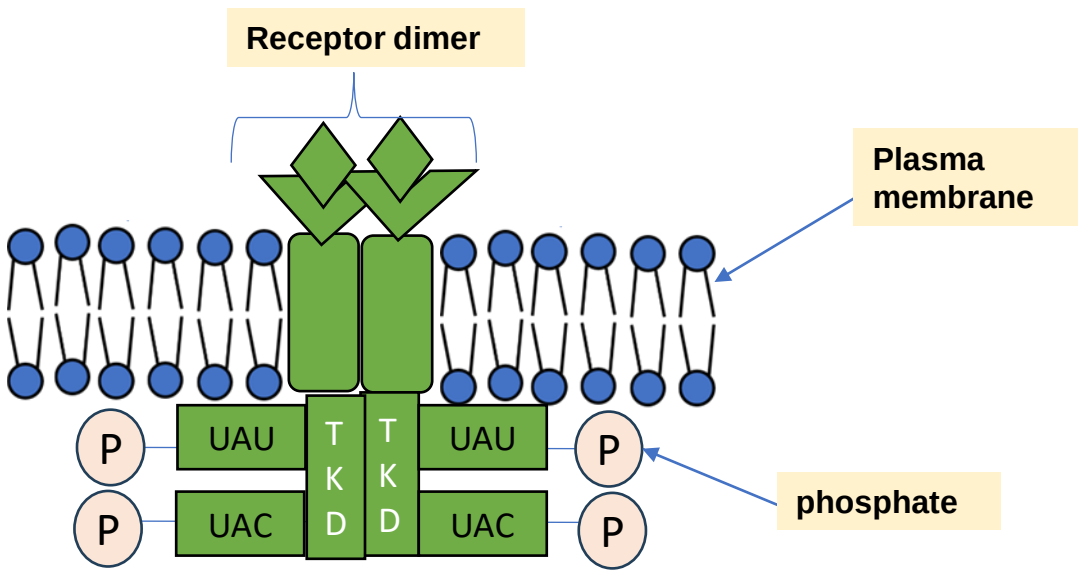


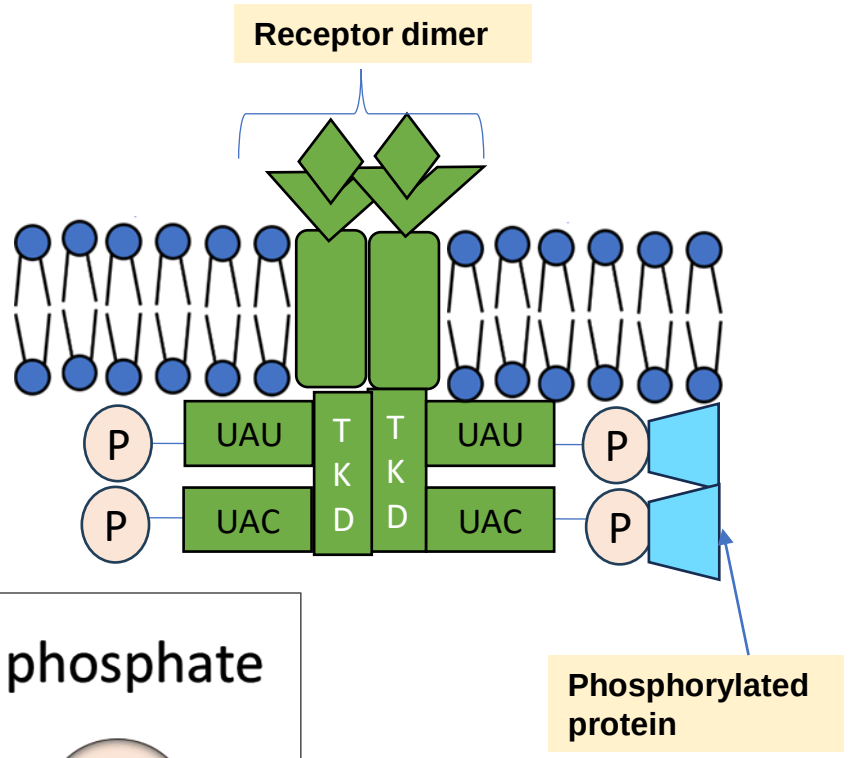
2. A conformation change occurs at the extracellular domain of the receptor

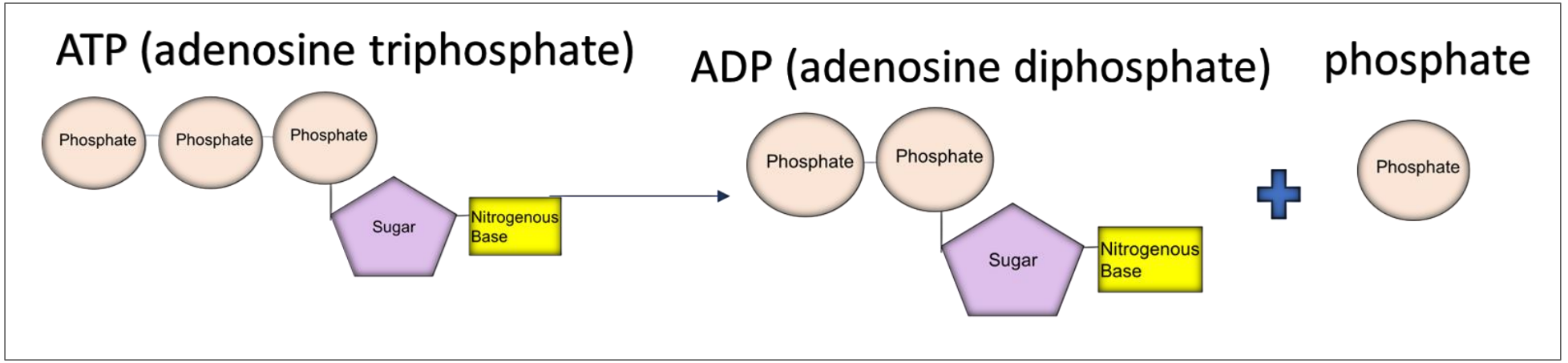
3. The two receptor molecules then associate together. This is called dimerization.

4. This effects the conformation of the intracellular domain where the tyrosine kinase activity is on.









5. Enzymes are proteins made of amino acids. One particular amino acid tyrosine is where phosphorylation takes place.

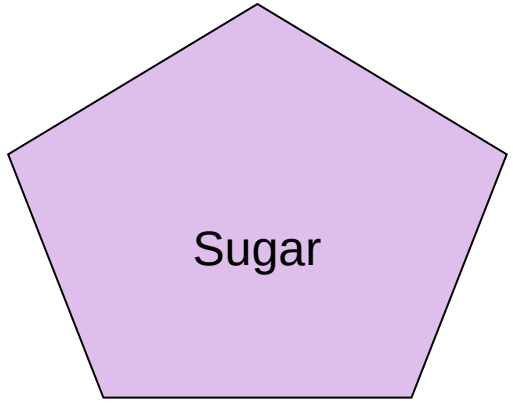
6. Tyrosine kinases are enzymes that transfer of phosphate groups (PO4-3) from ATP (adenosine triphosphate) to a protein.

7. They can phosphorylate each other. This is known as autophosphorylation

Nitrogenous base

- **Thymine**
- **Adenine**
- **Guanine**
- **Cytosine**

1.



Ribose sugar

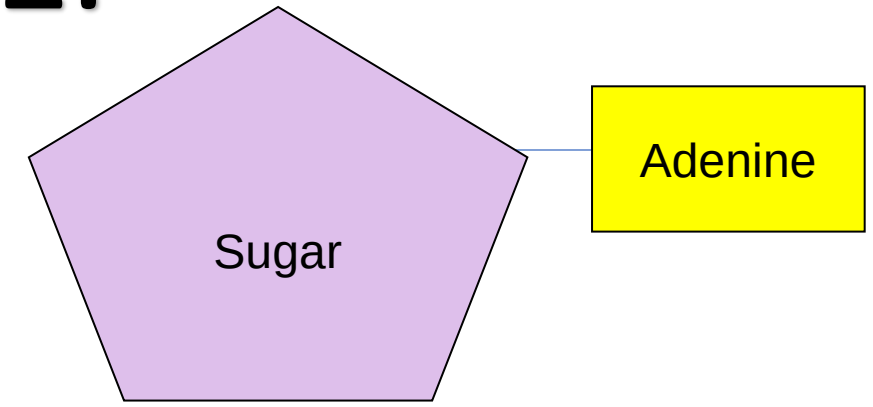
Formation of energy sources

Adenosine triphosphate

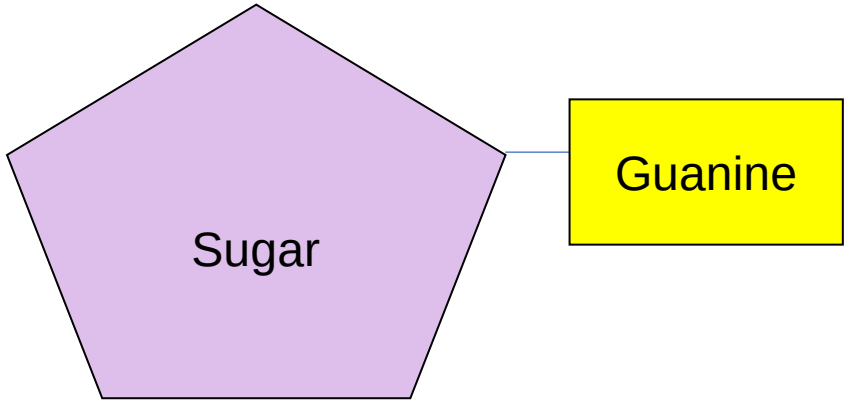
Guanosine triphosphate

Purines: Adenine and Guanine

2.



Adenosine

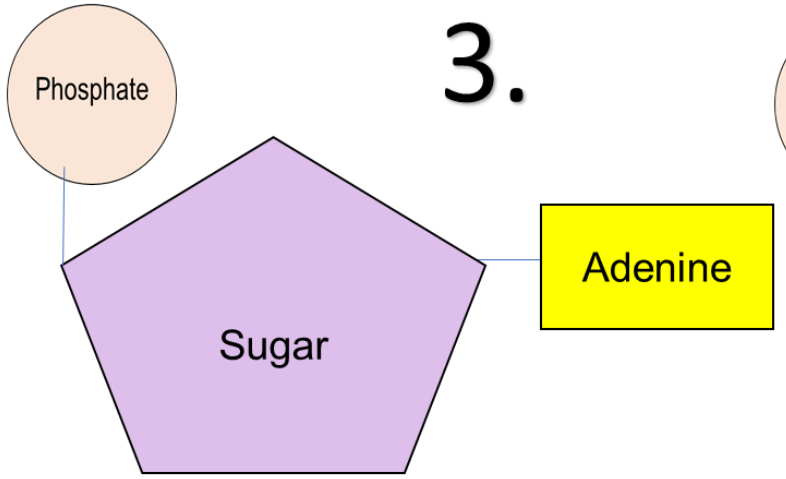


Guanosine

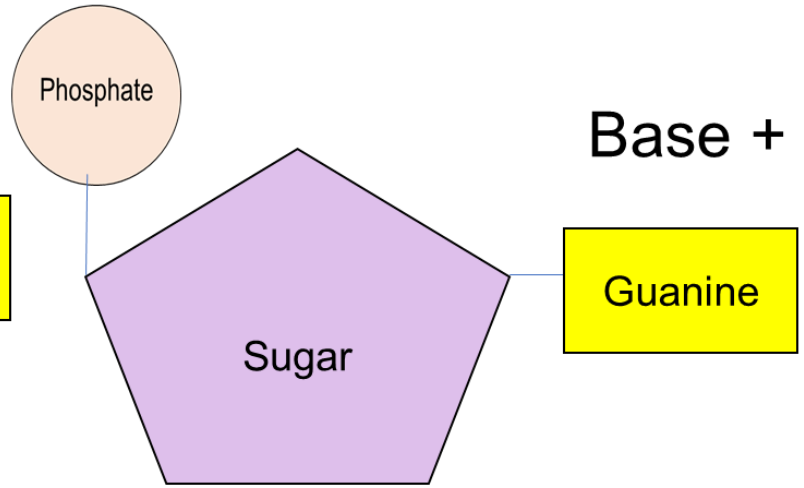
Nucleoside

Base + sugar + no phosphate.

3.



Adenosine monophosphate (AMP)



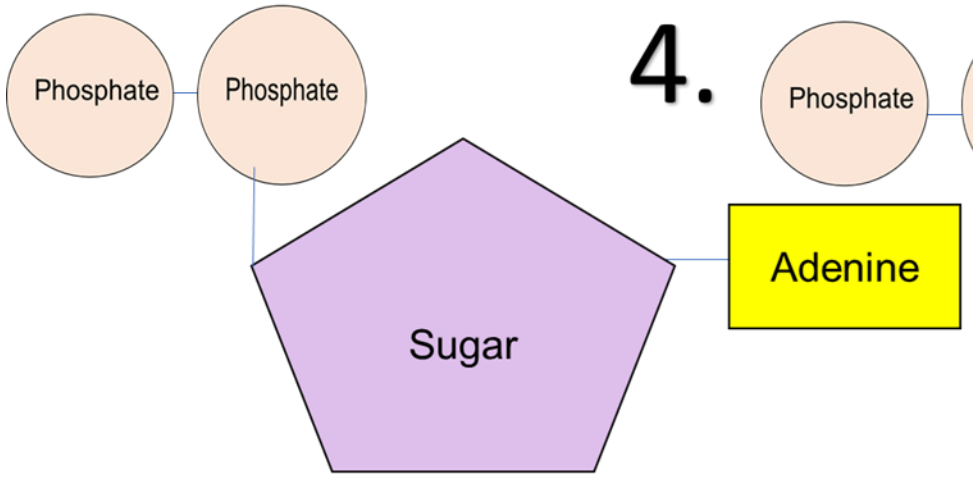
Guanosine monophosphate (AMP)

Nucleotide

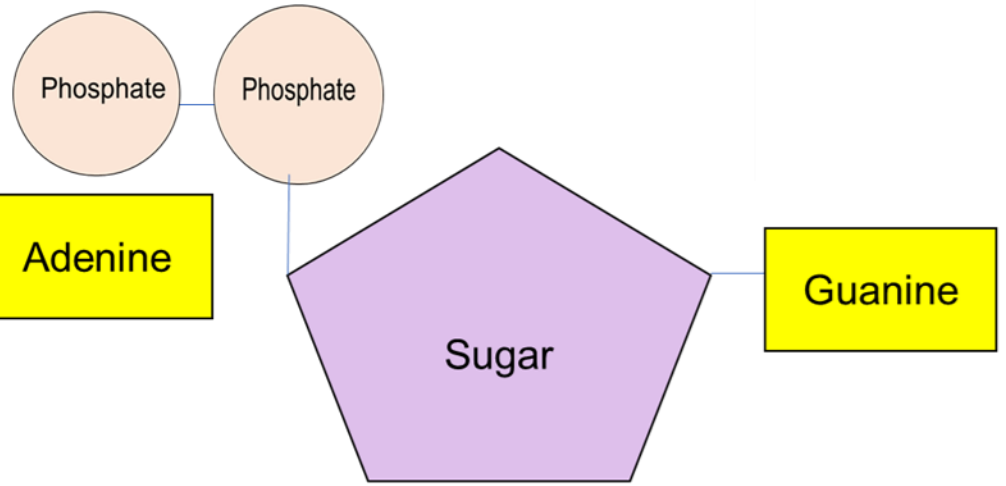
Base + sugar + phosphate.

Mono → ONE

4.



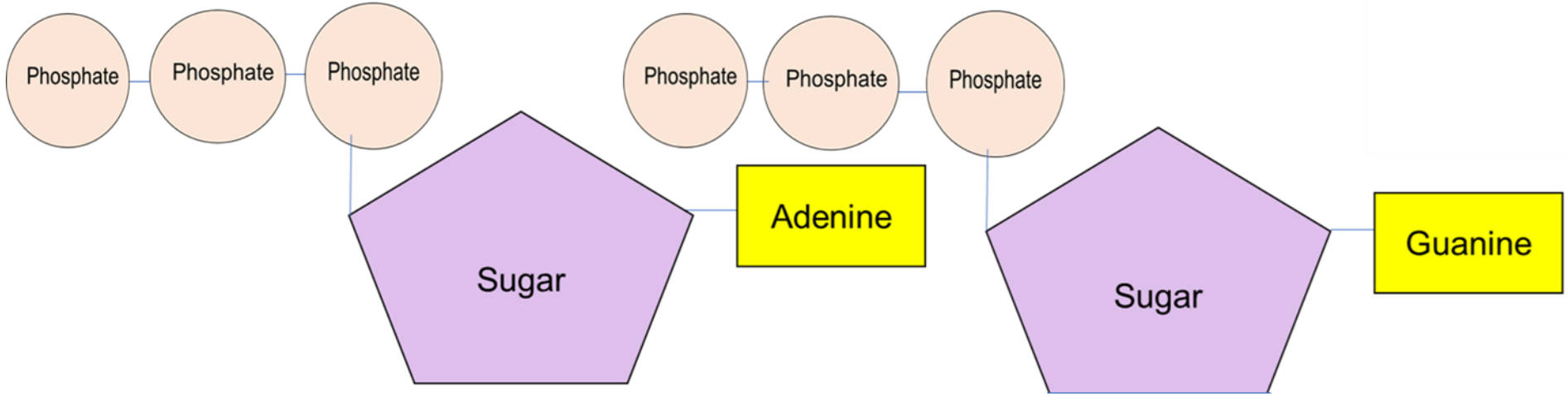
Adenosine diphosphate (ADP)



Guanosine diphosphate (GDP)

Di → TWO

5.



Tri → THREE

Adenosine triphosphate
ATP

Guanosine triphosphate
GTP

Energy is released when ATP is hydrolyzed/split/divided to form **ADP and a phosphate molecule**.

This process is catalysed by the enzyme **ATP hydrolase/ATPase.**

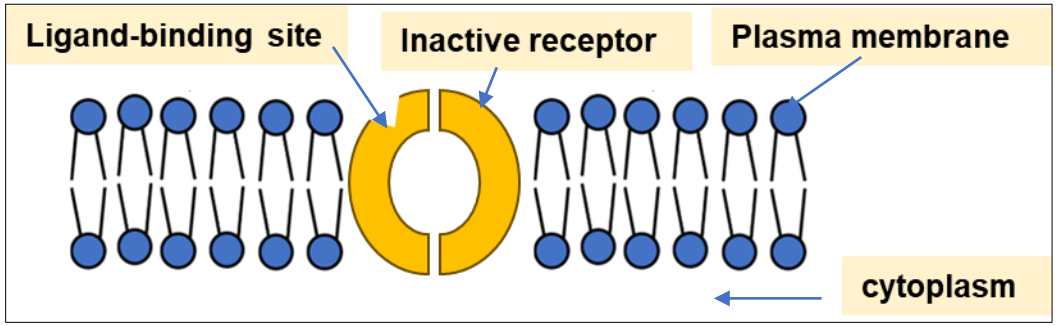
Key Facts: Ligand-gated ion channels

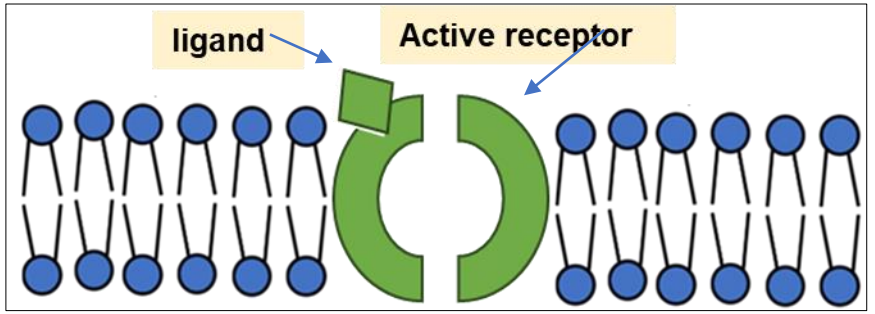
Ion channels are proteins that allow **diffusion of ions across cellular membranes.**

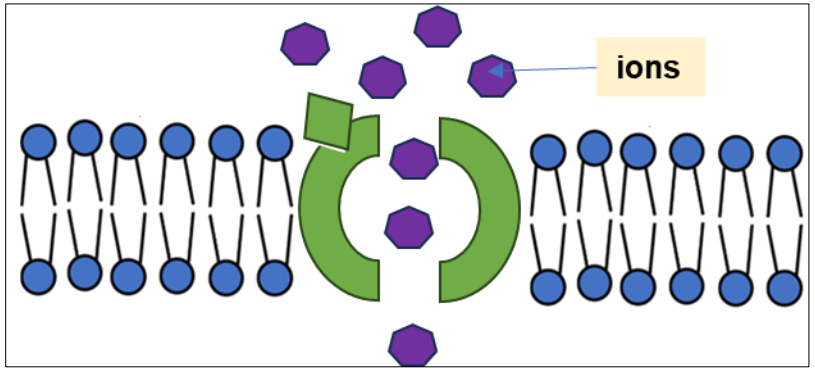
Ions are **atoms** that have either **loss or gained electrons.**

The channels open after when the ligand binds to the receptor.

Some ligands pass through plasma membrane and bind to intracellular receptors.



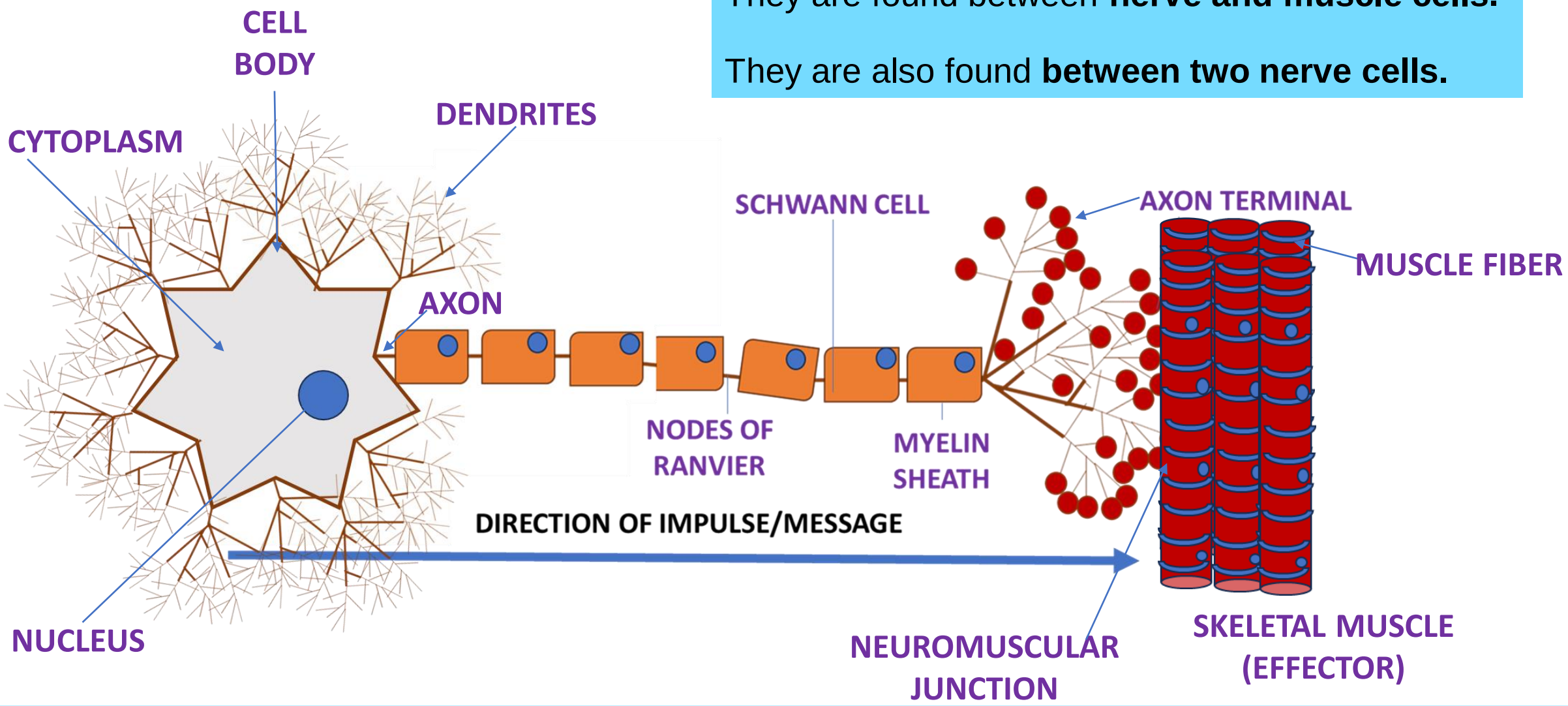




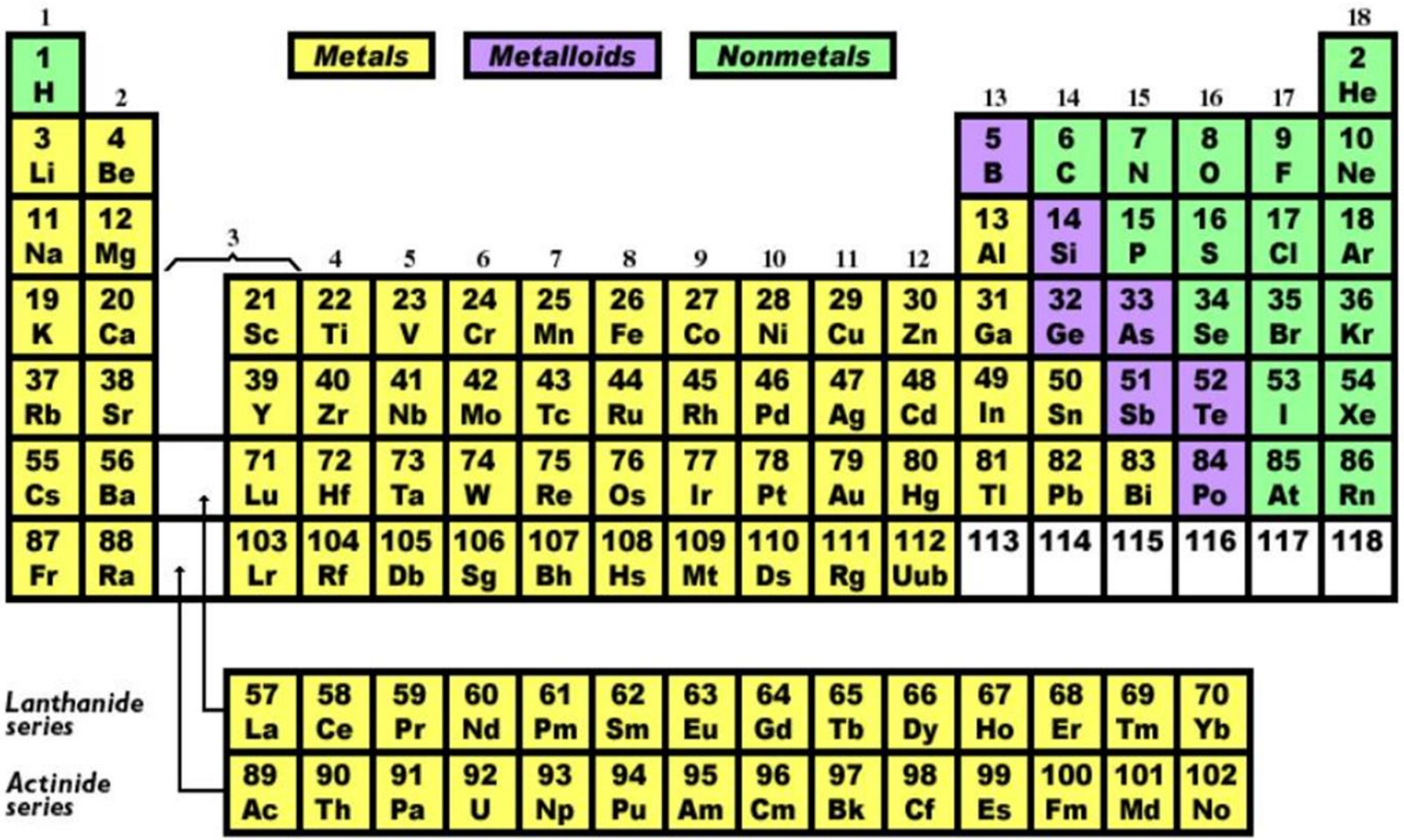
Key Facts: Where are Ligand-gated ion channels found?

They are found between **nerve and muscle cells.**

They are also found **between two nerve cells.**



Key Facts: Periodic table



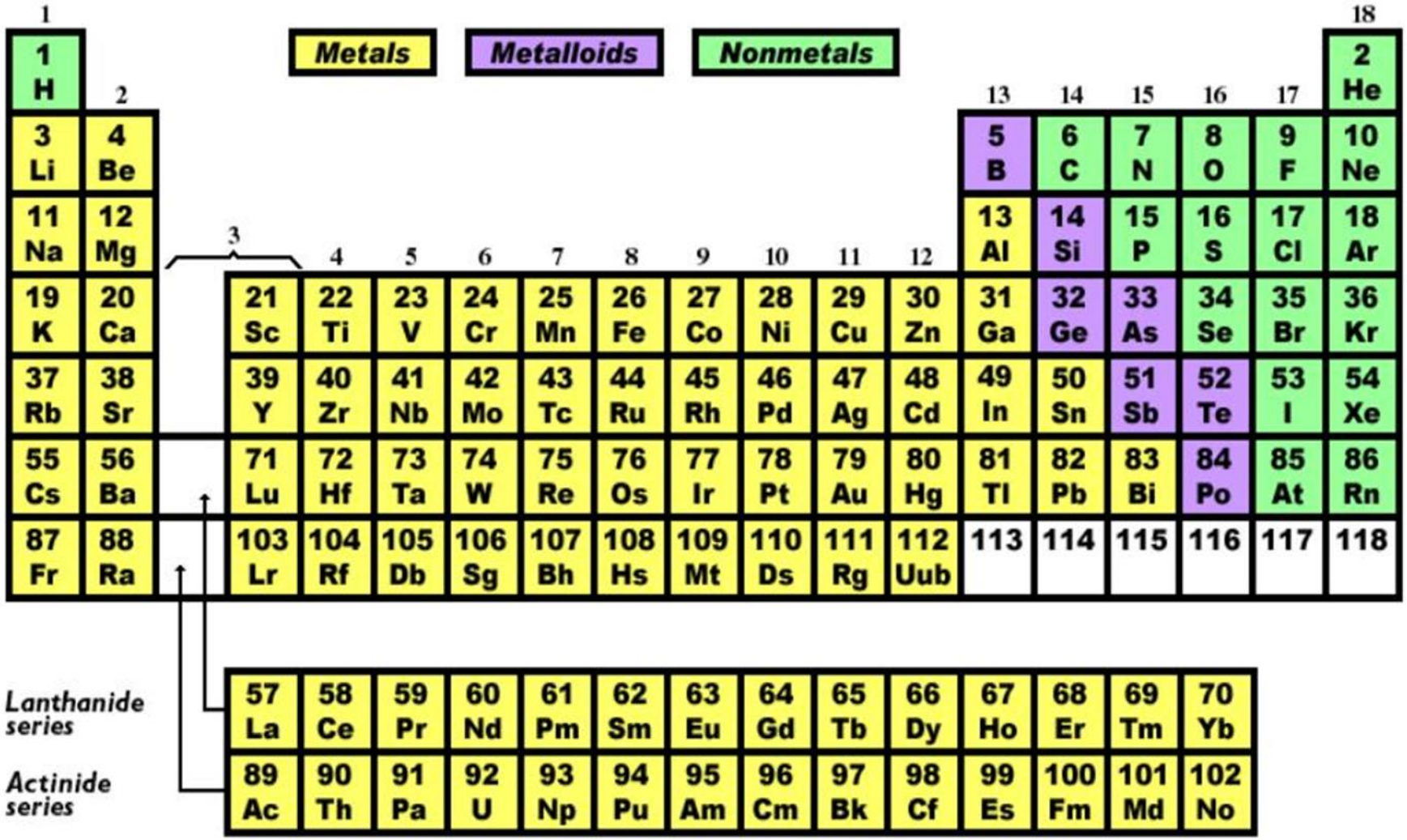
There are many **elements** around us.

Some are found naturally. Some need to be extracted.

The **Periodic table** was developed by **Dmitri Mendeleev.**

Source: (Zaire, I 2014)

Key Facts: Periodic table



They can readily **lose or gain electrons** (negatively charged particles)

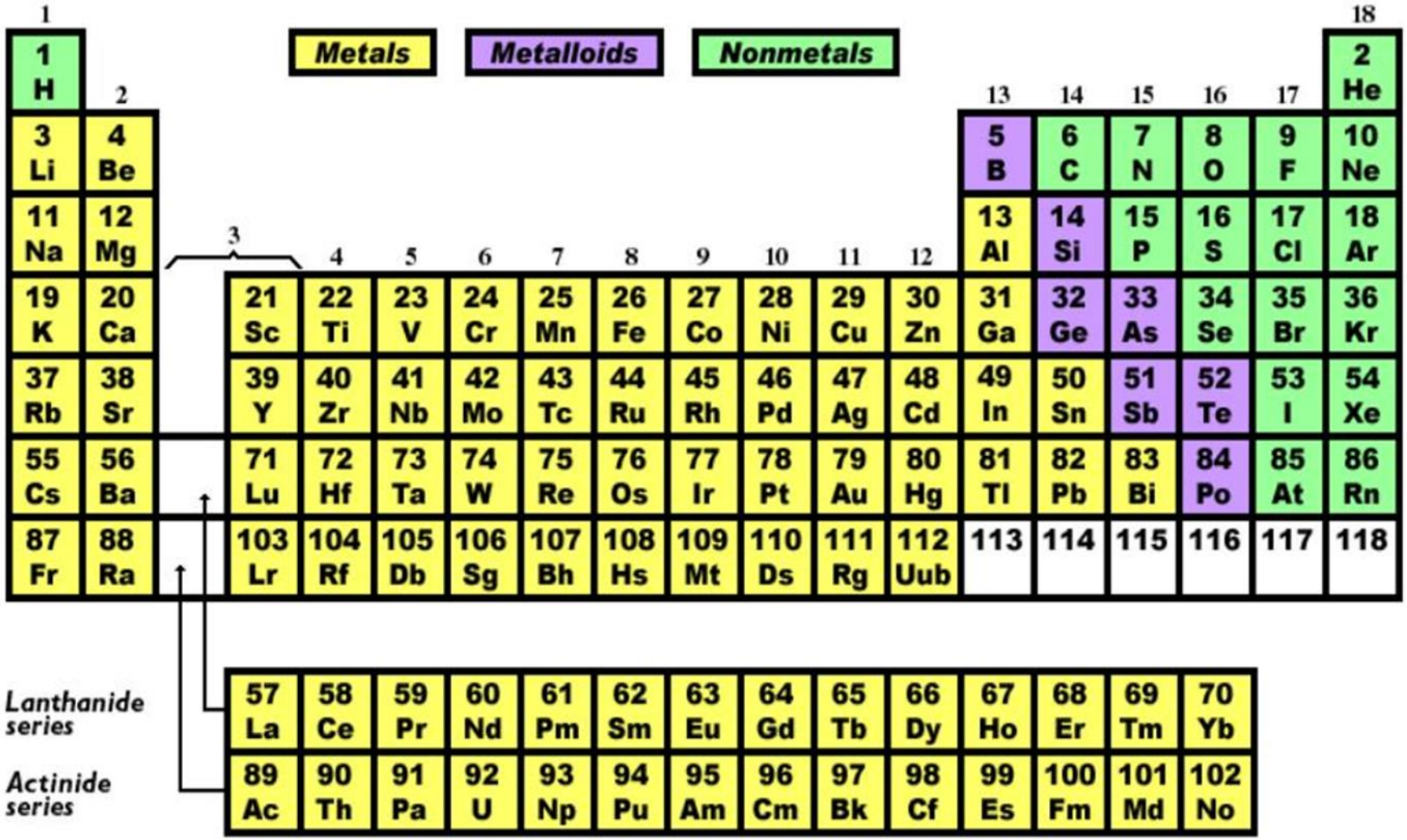
METALS lose electrons and become **POSITIVE ions.** They have a **(+) sign.**

Potassium
K^+

Sodium
Na^+

The Periodic table
Source: (Zaire, I 2014)

Key Facts: Periodic table



They can readily **lose or gain electrons** (negatively charged particles)

NON-METALS gain electrons and become **NEGATIVE ions.**

They have a **(-) sign.**

Chlorine
Cl^-

The Periodic table
Source: (Zaire, I 2014)

Sodium has **one electron** in its outer shell that makes it **unstable and can readily lose it.**

Very reactive.

The more electrons on the shell, the more stable it is.

When it **loses its electron,**
It becomes **positive ion. CATION**

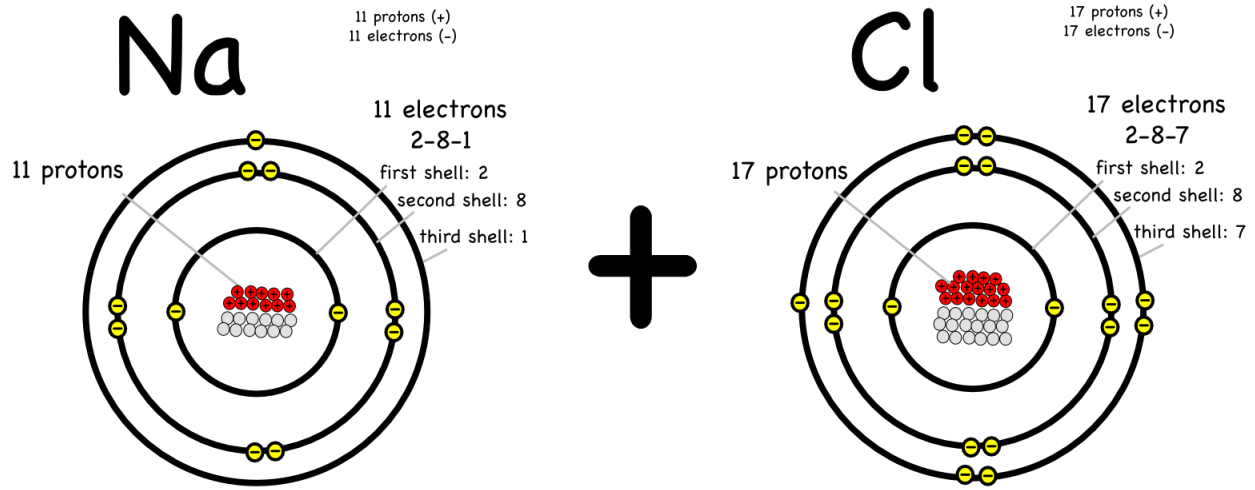
Chlorine has **more electrons in its outer shell (7).**

It is **more stable and cannot lose any electrons.**

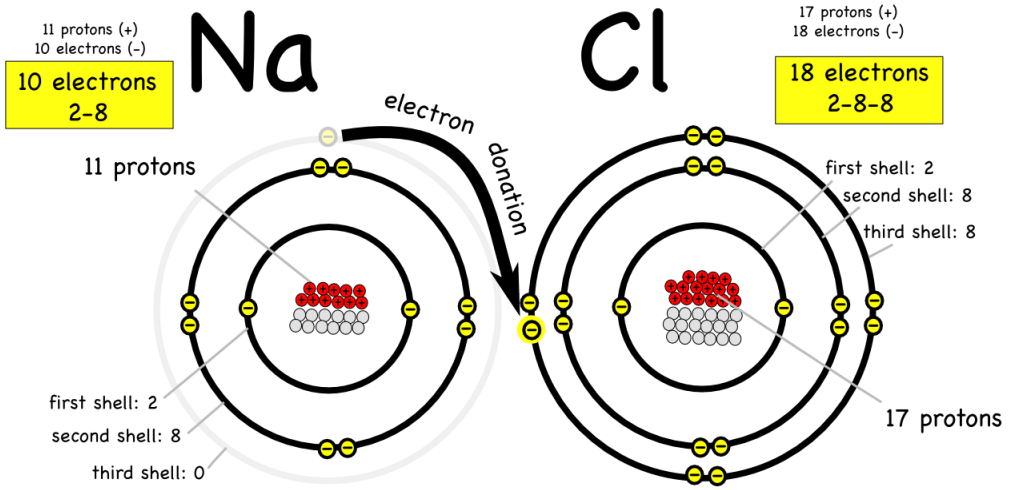
Non-metals **gain electrons.**
It becomes **negative ion. ANION**

It lacks one electron to be a complete shell.

Maximum number of electrons in a shell is 8.

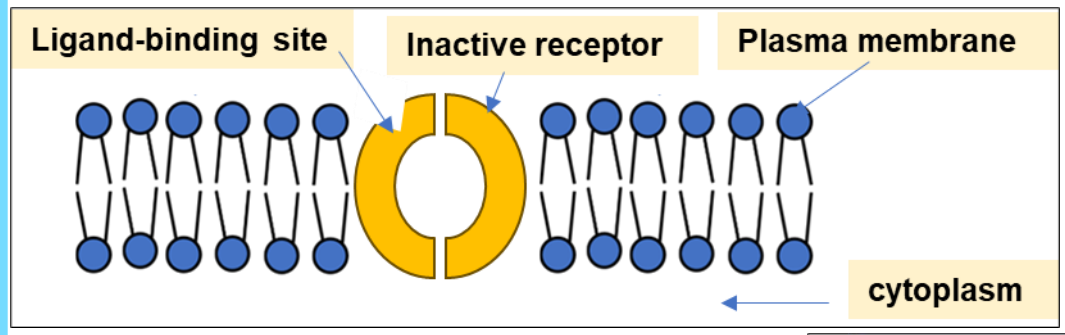


Sodium (Na) donates its outer-shell electron to chlorine (Cl)

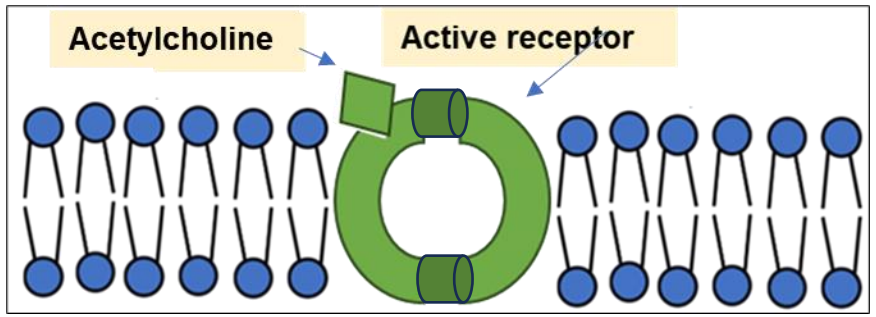


Chemical Formula: **NaCl**

Example: Acetylcholine (neurotransmitter)

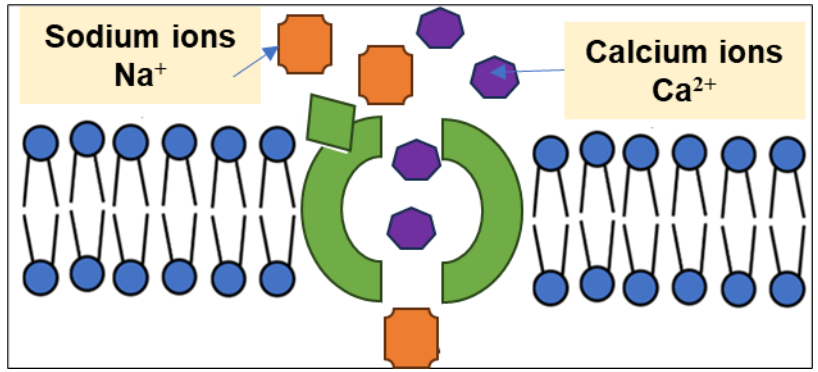


INACTIVE/RESTING
(GATE CLOSED)

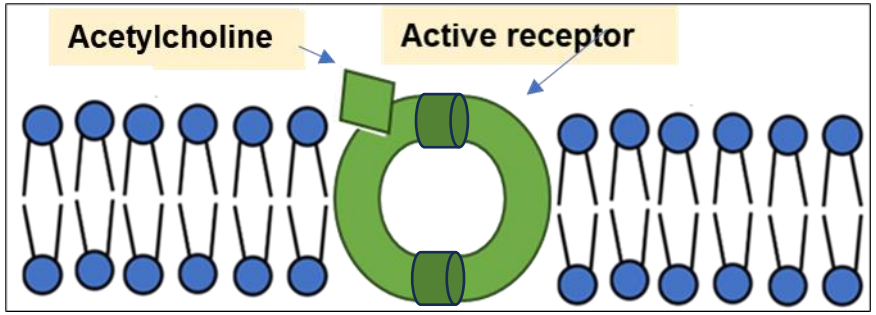


ACTIVE
(LIGAND BINDING OCCURS)

ACTIVE
(EXCITED GATE OPENS)



INACTIVE
(DESENSITIZATION IF HIGH LEVELS OF IONS ENTERS CHANNEL)
Enzyme=acetylcholinesterase lowers acetylchloline levels.

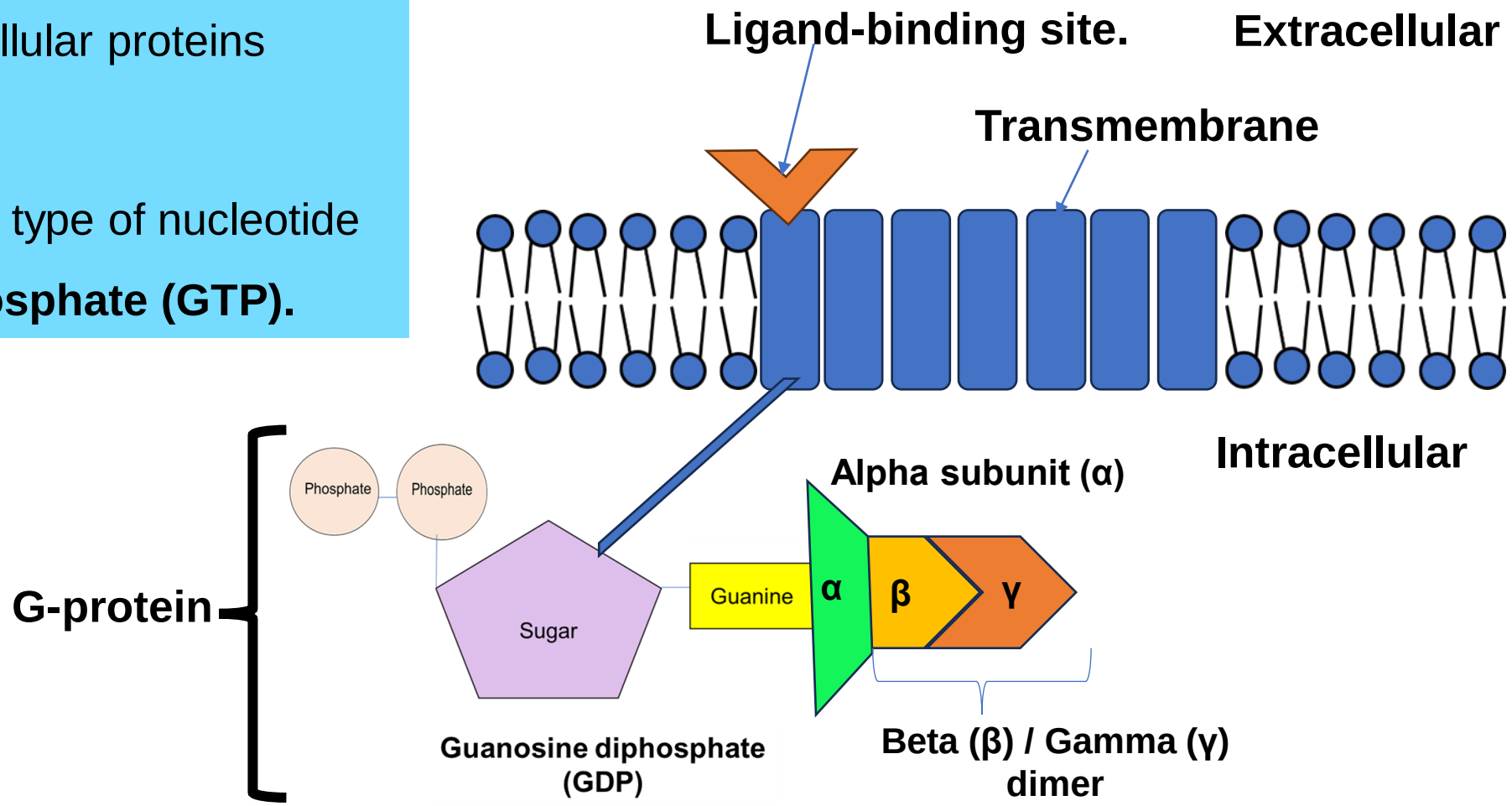


Key Facts: G-protein coupled receptors

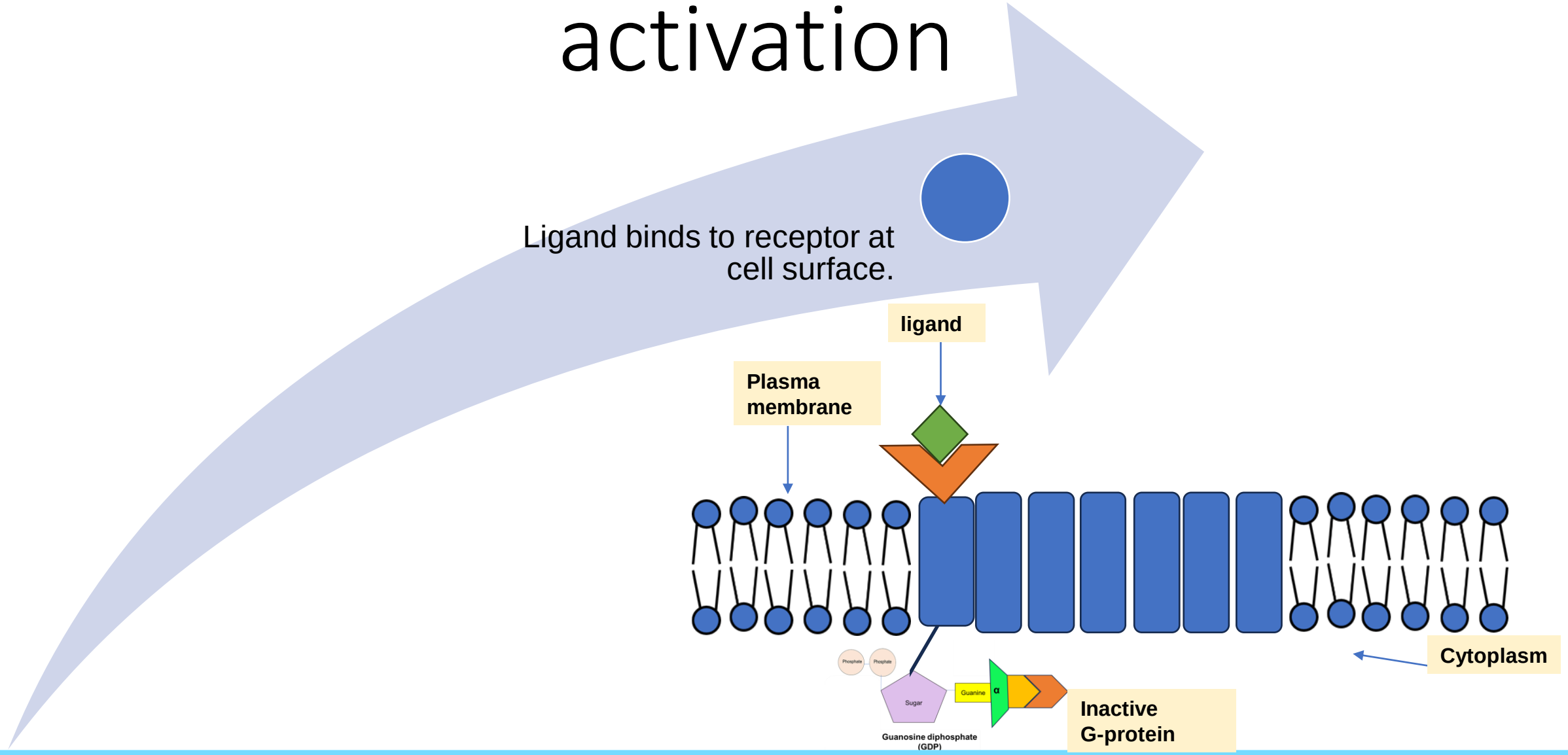
They have **7 transmembrane proteins**.

They interact with intracellular proteins called **G-proteins.**

G-proteins interact with a type of nucleotide **called guanosine triphosphate (GTP).**



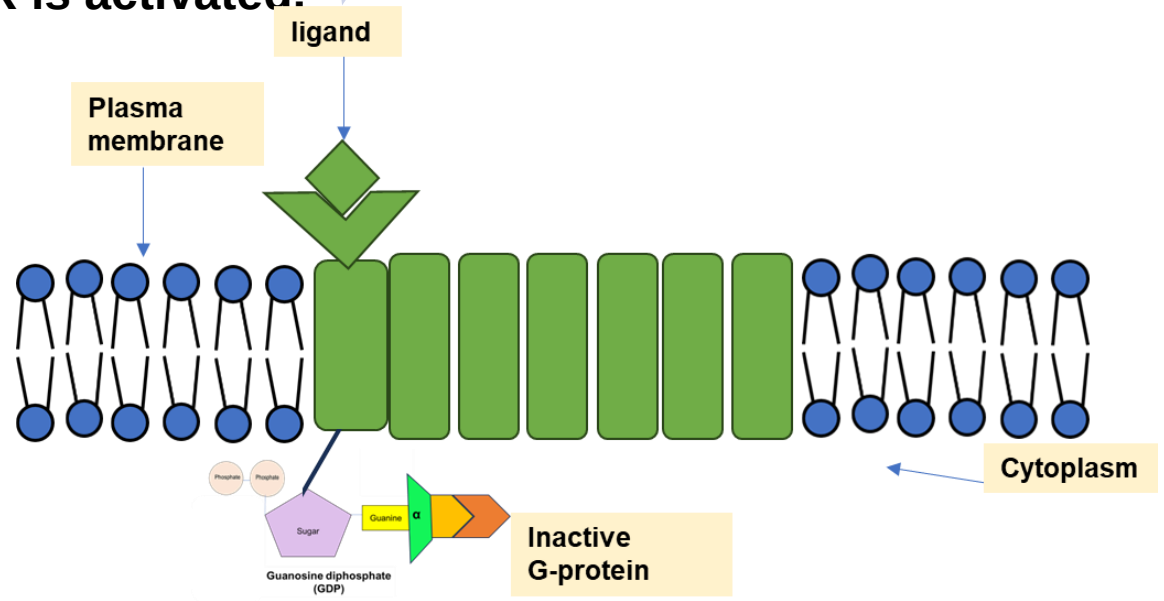
Key Facts: G-protein coupled receptor activation



Key Facts: G-protein coupled receptor activation

Ligand binds to receptor at cell surface.

This causes a conformational process where the GPCR is activated.



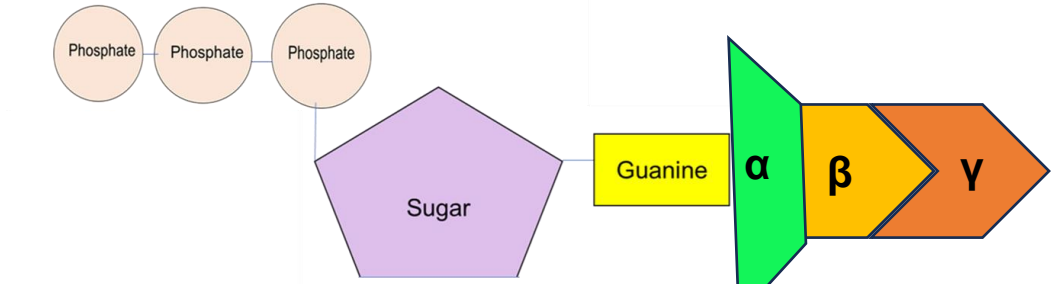
Key Facts: G-protein coupled receptor activation

Ligand binds to receptor at cell surface.

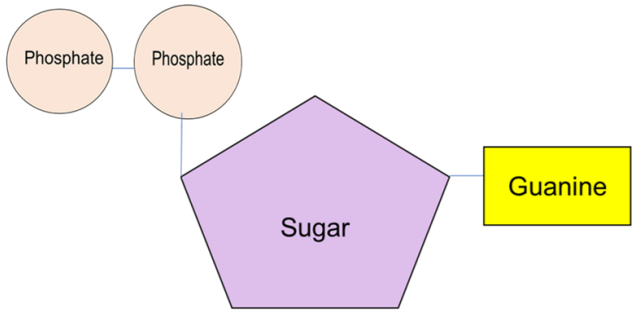
This causes a conformational process where the GPCR is activated.

The activated GPCR binds with G protein to release GDP and bind to GTP.

ACTIVE G-PROTEIN



Guanosine triphosphate (GTP)



Guanosine diphosphate (GDP)

Ligand binds to receptor at cell surface.

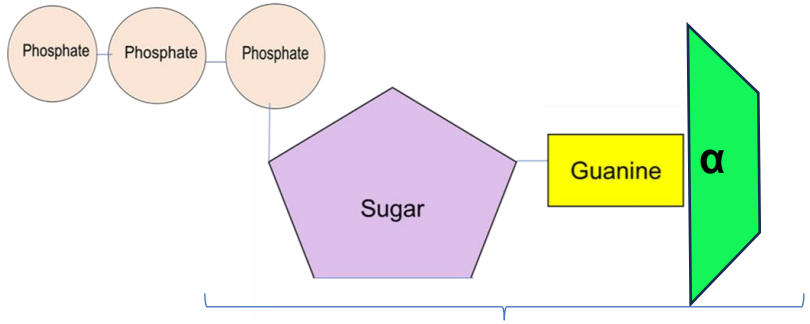
This causes a conformational process where the GPCR is activated.

The activated GPCR binds with G protein to release GDP and bind to GTP.

GTP causes a conformational change in G protein where the G-protein splits.

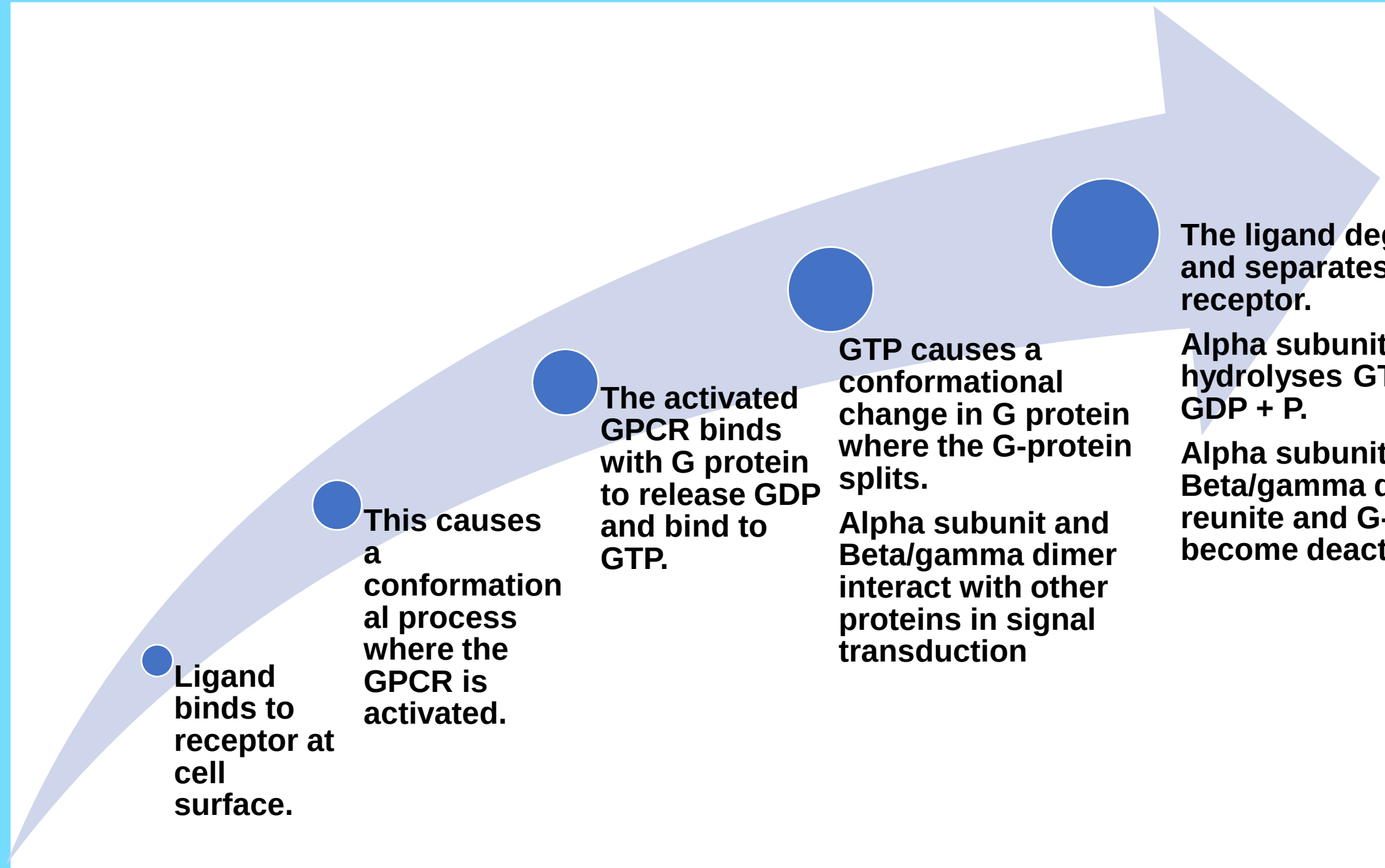
Alpha subunit and Beta/gamma dimer interact with other proteins in signal transduction

ACTIVE G-PROTEIN



Activated G protein alpha subunit

Activated Beta/gamma dimer


Ligand binds to receptor at cell surface.
This causes a conformational process where the GPCR is activated.
The activated GPCR binds with G protein to release GDP and bind to GTP.
GTP causes a conformational change in G protein where the G-protein splits.
Alpha subunit and Beta/gamma dimer interact with other proteins in signal transduction
The ligand degrades and separates from the receptor.
Alpha subunit hydrolyses GTP to GDP + P.
Alpha subunit and Beta/gamma dimer reunite and G-protein become deactivated.

Types of ligands.

Key Facts: Small Hydrophillic molecules

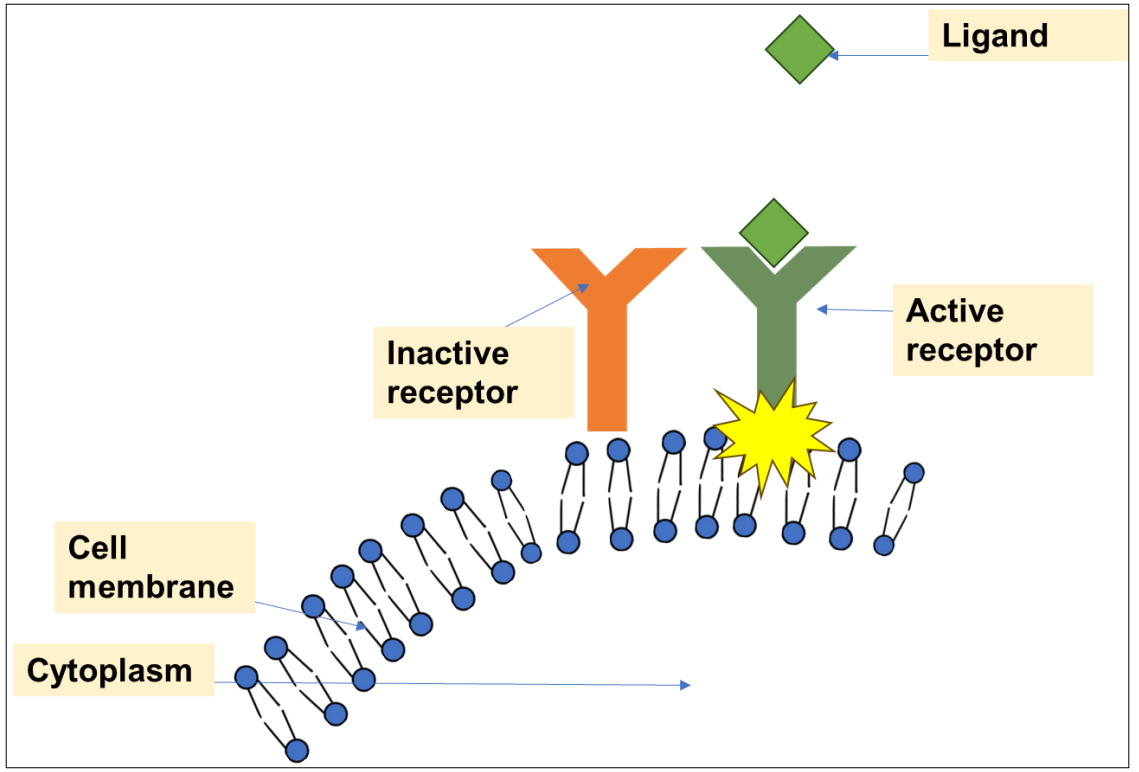
Most ligands are **small hydrophilic (water-soluble) molecules** that **do not readily pass through the plasma membrane** of cells due to their **molecular size.**

They need **cell surface receptors.**

Most associate to the **extracellular domain of cell-surface receptors.**

Key Examples:

- ❑ **Small molecules**
- ❑ **Peptides**
- ❑ **Proteins.**

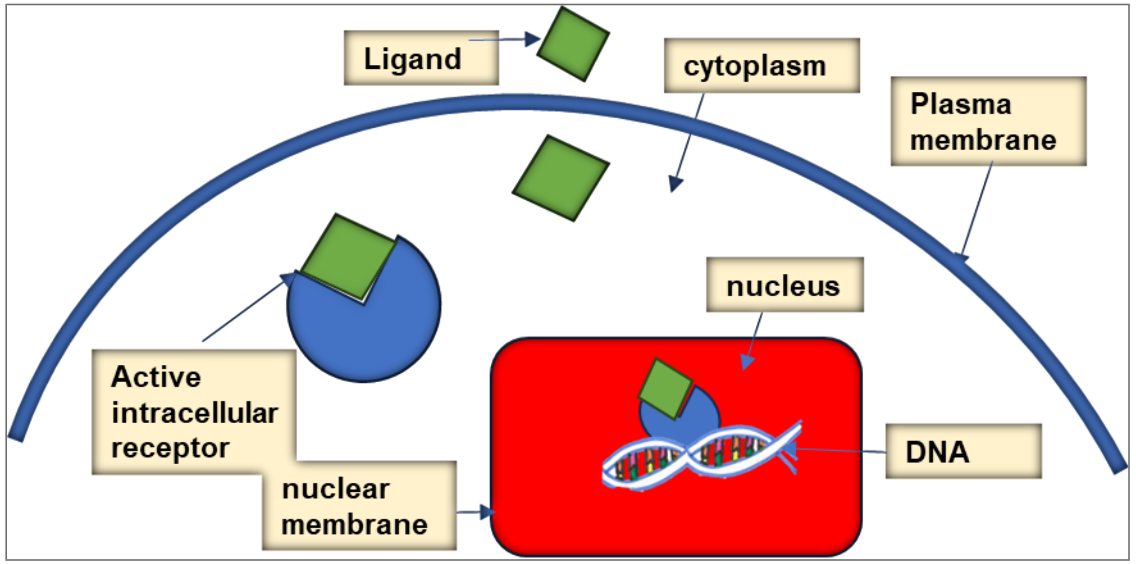


Key Facts: Small Hydrophobic molecules

They **bind to carrier proteins to be able to travel in the blood to target cells**

They **directly diffuse through the plasma membrane of target cells** and **interact with intracellular receptors**.

- ❑ These **receptors can be in the cytoplasm and travel to the nucleus**.
- ❑ Other steroid hormones **bind to receptors in the nucleus**.



Example: Steroid hormones

Steroid hormones are lipids that have a **hydrocarbon bound with four rings.**

Different steroids have different functional groups.

Oestrogen produced in the female reproductive system.

Testosterone produced in the male reproductive system.

Cholesterol is a structural part of membranes and help produce steroid hormones

Thyroid hormone regulate body activities and metabolic rate (total energy used by the body).

Vitamin D

Bone and teeth development by regulating calcium ion levels.

Other types of ligands.

Key Facts: Nitric oxide (NO)

It is a gas that cannalso acts as a ligand.

It is able to **diffuse directly across the plasma membrane**.

It **interact with receptors in smooth muscle** and **induce relaxation of the tissue by dilating (expanding) blood vessels restoring blood flow to the heart.**

It has a **short half-life** and functions over **short distances.**

By the end of this lecture, you should understand

- **Receptor activation** is the **first step of cell-to-cell communication (cell signalling).**
- **The ligand** is the **first messenger** that could be a **protein or a steroid** and can **complementary bind with the receptor like a lock and key.**
- Some receptors are found on the **cell surface** and other receptors are found **inside the cells i.e. in the nucleus and cytoplasm.**
- Some ligands are **hydrophilic i.e. proteins and cannot diffuse through the plasma membrane due to their size** and require cell surface receptors. Other ligands are **hydrophobic i.e. steroid hormones can diffuse through plasma membrane** and interact with **intracellular receptors.**
- **The rate of the binding between a ligand and receptor equals the rate of releasing the ligand from the receptor.**

Reference list for further reading

Ahern, D. and Rajagopal (2023*) '8.5: Receptor Tyrosine Kinases (RTKs)'* Available [online] https://bio.libretexts.org/Bookshelves/Biochemistry/Book%3A_Biochemistry_Free_and_Easy_(Ahern_and_Rajagopal)/08%3A_Signaling/8.05%3A_Receptor_Tyrosine_Kinases_(RTKs)

Basic medical Key (2016) *'Endocrine Regulation'* Available [online] *https://basicmedicalkey.com/endocrine-regulation/*

Brooker, R., Widmaier, E., Graham, L., Stiling, P. (2008) '*Biology: Chemistry, Cell Biology and Genetics'*. United States of America: McGraw Hill.

Pecorino, L. (2012) '*Molecular Biology of Cancer Mechanisms, Targets, and Therapeutics'* UK: Oxford University Press.

Urbano, L. (2013) '*Introducing Covalent Bonding'* Available [online] http://montessorimuddle.org/2013/02/21/introducing-covalent-bonding/

Zaire, I. (2014) '*Metals, Metalloids, and Non-metals'* Available [online] https://www.slideserve.com/ifama/metals-metalloids-and-nonmetals

HN

SEASON 2

Farah Saeed FS Farah Saeed

Understanding Cancer

Lecture 5
Signal transduction and cellular response

DR HAFSA WASEELA ABBAS

www.hafsaabbas.com