Study material for Paper ZOO-HC-2026 (BHATTADEV UNIVERSITY)

UNIT 8: CELL SIGNALLING

- GPCR and Role of second messenger (cAMP)

BY:

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The process by which cells communicate with each other through extracellular messenger molecules is called cell signaling. Cell signaling can be of three types :-

- Autocrine signaling
- Paracrine signaling
- Endocrine signaling

Autocrinesignaling

The cell producing the messenger, expresses receptors on its surface as well which can respond to that messenger. Therefore, the cell that releases the message either stimulates or inhibitsthem.

Paracrine signaling

The secreted messenger molecules travel only short distances through the extracellular space to the nearby cells. In Paracrine signaling the messenger molecules secreted travels only for a short distance.

Endocrine signaling

The secreted messenger molecules reach the target cells through the bloodstream. Endocrine messengers are also known as hormones, and they exclusively act on the target cells situated at distant place in the body.

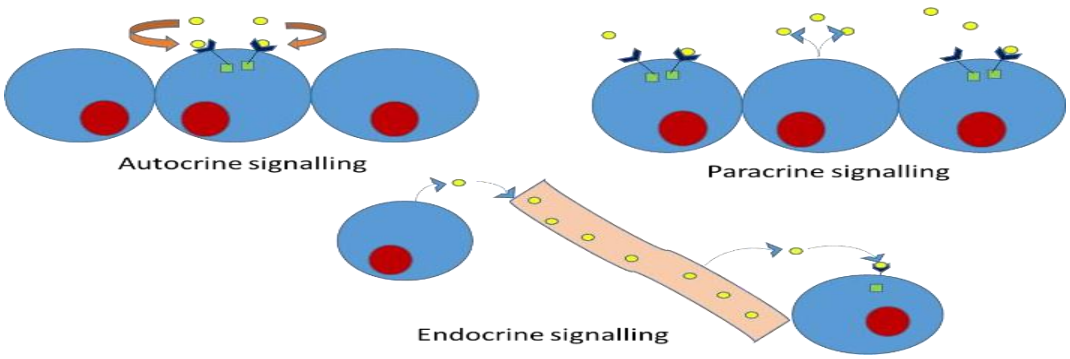

Fig 1: Different type of signal process

Ligand, Target cell and Receptors

Cell signaling is started by the release of a **messenger** molecule also known as **ligand** by a cell that is involved in sending messages to the **target cell** by binding to the specific **receptors**. **Ligand is a** messenger molecules that bind to the receptor include steroids and neurotransmitters, small, soluble protein hormones and huge glycoproteins. Cells tend to respond to a specific extracellular message only if they express receptors that exclusively recognize and bind to that messenger molecule. The cells that harbour those specific receptors are called as target cells. The most studied receptors are

- G-protein coupled receptor (GPCR)
- Receptor tyrosine kinase (RTK)

GPCR

The **G protein-linked receptor family** is named so because ligand binding causes a change in receptor conformation that activates a particular **G protein . It is** an abbreviation for guanine-nucleotide binding protein. G protein-linked receptors are remarkable in that they all have a similar structure yet differ significantly in their amino acid sequences. In each case, the receptor protein forms seven transmembrane helices connected by alternating cytosolic or extracellular loops. The N-terminus of the protein is exposed to the extracellular fluid, while the C-terminus resides in the cytosol. The extracellular portion of each G protein-linked receptor has a unique messenger-binding site, and the cytosolic loops allow the receptor to interact with only certain types of G proteins. GPCR superfamily members are also known as seven transmembrane (7TM) receptors as they are composed of seven transmembrane helices.

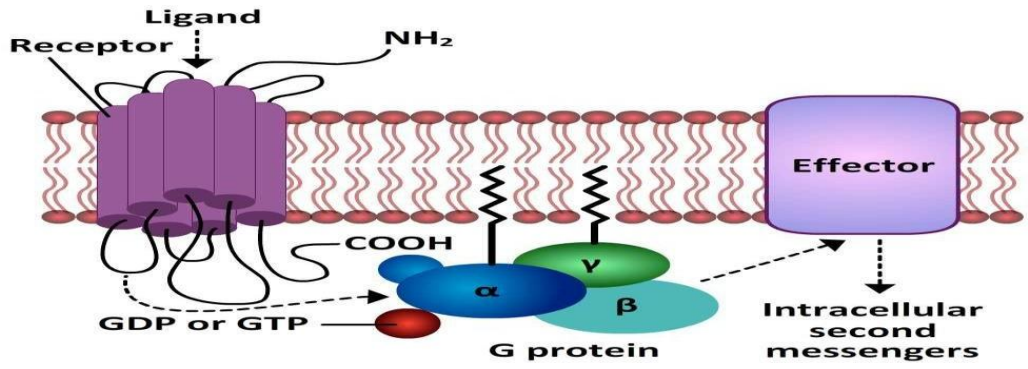

Fig 2: Structure of GPCR with effectore (Source: ePATHSALA: Paper-15;Module-20)

G proteins act very much like molecular switches, whose "on" or "off" state depends on whether the G protein is bound to GTP (guanosine triphosphate) or GDP (guanosine diphosphate). There are two distinct classes of G proteins: the large heterotrimeric G proteins and the small monomeric G proteins. The large heterotrimeric G proteins contain three different subunits, called G alpha (α), G beta (β), and G gamma (γ). Heterotrimeric G proteins mediate signal transduction through G protein-linked receptors. The small monomeric G proteins include Ras, .

G proteins have the same basic structure and mode of activation. Of the three subunits in the $G_{\alpha\beta\gamma}$ heterotrimer, G_α, the largest, binds to a guanine nucleotide (GDP or GTP). When G_α binds to GTP, it detaches from the $G_{\beta\gamma}$ complex. The G_β and G_γ subunits, on the other hand, are permanently bound together. Some G proteins, such as G_s , act as stimulators of signal transduction (hence s, for "stimulatory"); others, such as Gi , act to inhibit signal transduction (hence i, for "inhibitory").

When a messenger binds to a G protein-linked receptor on the surface of the cell, the change in conformation of the receptor causes a G protein to associate with the receptor, which in turn causes the G_α subunit to release its bound GDP. The G_α then acquires a new, different molecule of GTP and detaches from the complex . Depending on the G protein and the cell type, either the free GTP- G_α subunit or the $G_{\beta\gamma}$ complex can then initiate signal transduction events in the cell. Each portion of the G protein exerts its effect by binding to a particular enzyme or other protein in the cell. In some cases, both the GTP- G_α and $G_{\beta\gamma}$ subunits simultaneously regulate different processes in the cytosol.

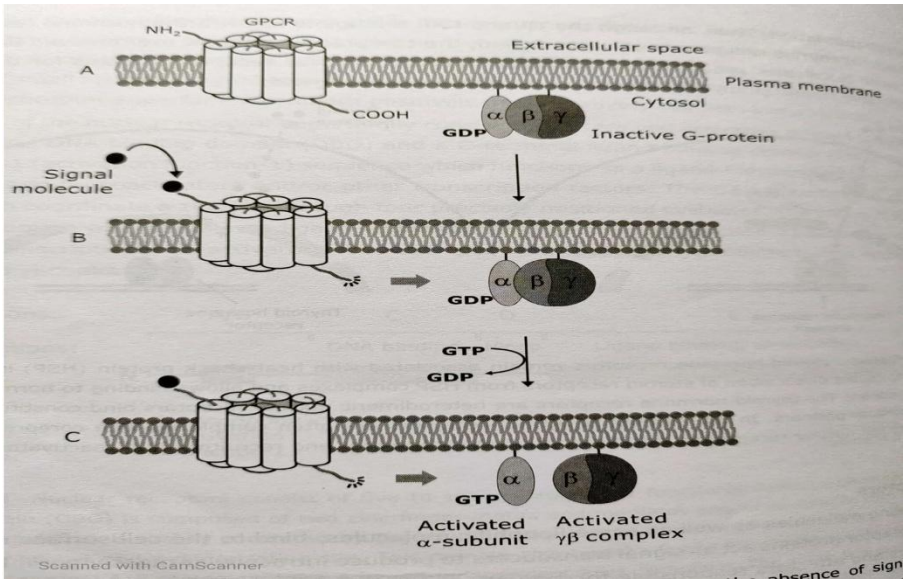

Fig 3: Activation of GPCR

The activity of a G protein persists only as long as the G_α subunit is bound to GTP, and the G_α and $G_{\beta\gamma}$ subunits remain separated. Because the G_α subunit catalyzes GTP hydrolysis, it remains active only until it hydrolyzes its associated GTP to GDP, at which time it reassociates with $G_{\beta\gamma}$. This feature allows the signal transduction pathway to shut down when the messenger is utilized. Some G_α proteins are very inefficient at catalyzing GTP hydrolysis; however, their efficiency is dramatically improved by **regulators of G protein signaling (RGS) proteins.** When R_{GS} proteins bind G_α , they stimulate GTP hydrolysis. Such GTPase activating proteins (GAPs) are important regulators of G protein function, as we will see later in the case of the R_{as} protein.

The large number of different G proteins provides for a diversity of G protein-mediated signal transduction events.The most important and widespread G protein-mediated signal transduction events are the release or formation of second messengers.

Role of second messenger (cAMP)

Cyclic AMP is a Second Messenger Whose Production Is Regulated by Some G Proteins. Adenylyl cyclase is anchored in the plasma membrane, with its catalytic portion protruding into the cytosol.

In the inactive state, the α, β and γ subunits are present as a complex, with GDP bound to the α subunit. When a ligand (L) binds its receptor, it binds and activates a Gs protein.

1). When a receptor is activated by ligand binding, the receptor-ligand complex associates with the Gs protein, causing the displacement of GDP by GTP and the dissociation of the Gsα -GTP complex.

2). The GTP-Gsα complex then binds to and activates membrane-bound adenylyl cyclase, which synthesizes cAMP.

3). Activation ends when the ligand leaves the receptor, the GTP is hydrolyzed to GDP by the GTPase activity of the Gsα subunit, and the Gsα dissociates from adenylyl cyclase.

4). Adenylyl cyclase then reverts to the inactive form, the Gs_α re-associates with the $Gs_{\beta\gamma}$ complex, and

5). cAMP molecules in the cytosol are hydrolyzed to AMP by the phosphodiesterase.

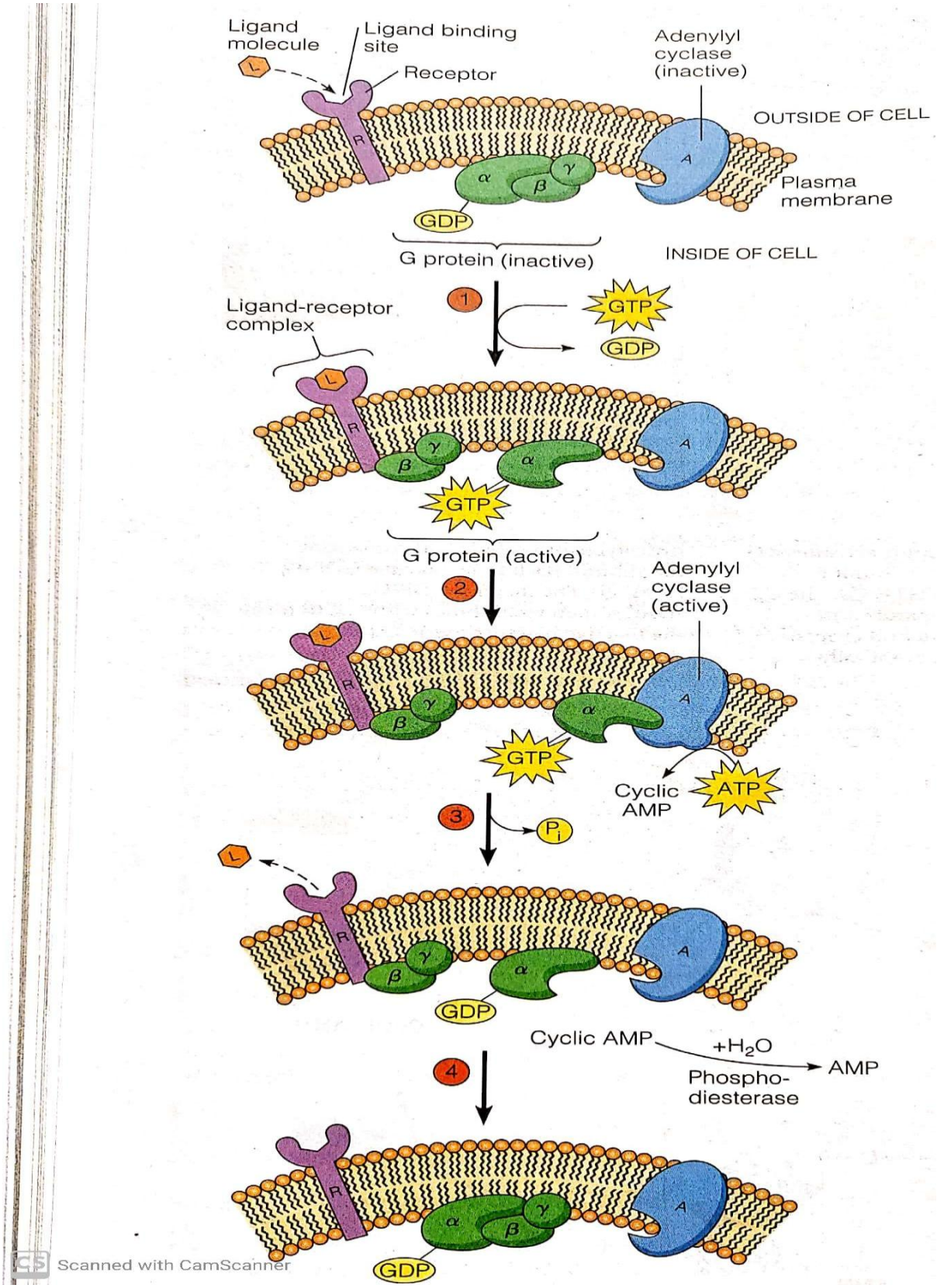

Fig 4: The Roles of G Proteins and Cyclic AMP in Signal Transduction. (source: Becker's World of The Cell: 8th Edn.)

G proteins respond quickly to changes in ligand concentration because they remain active for only a short time before the Gα subunit hydrolyzes its bound GTP and converts to the inactive state. Once the G protein becomes inactive, the adenylyl cyclase ceases to make cAMP. However, cAMP levels would still remain elevated in the cell if not for the enzyme **phosphodiesterase,** which degrades cAMP. This further ensures that the signal transduction pathway will shut down promptly when the concentration of the ligand outside the cell declines.

cAMP is important for many cellular events. An increase in cAMP concentration can produce different effects in different cells. When cAMP is elevated in skeletal muscle and liver cells, the breakdown of glycogen is stimulated. In cardiac muscle, the elevation of cAMP strengthens heart contraction, whereas in smooth muscle contraction is inhibited. In blood platelets, the elevation of cAMP inhibits their mobilization during blood clotting, and in intestinal epithelial cells, it causes the secretion of salts and water into the lumen of the gut.