**Dr. Seenaa / clinical Biochemistry 2nd stage**

**Signal transduction**

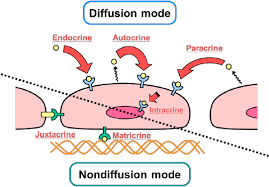
Signal transduction is process of transferring the signal into the cell. There are two types of cells in signal transduction—the **sender cell** where the signal originates and the **target cell** that receives the signal. The signal alters or modulates the activity or function of the cell.

**Autocrine** signaling occurs when same cell acts as sender and recipient, e.g. immune and inflammatory response.

**Paracrine** signaling occurs when cell produces a signal to induce changes in nearby cells.

**Juxtacrine** signaling occurs when the two type of cells are adjacent to each other so that contact is established through gap junctions or through protein molecules on the surface of the two cells.

**Endocrine** signaling is between cells which are located at a distance from each other and the signal may be hormones or chemical messengers secreted into circulation.



**Types of signaling**

Hormone is substances released from ductless or endocrine glands directly to the blood. There are three types of hormone depend on chemical basis:

1. Amino acid derivatives hormones ,like epinephrine
2. Peptide hormones, like prolactin
3. Lipid derivatives or steroid hormones, like estrogen

Plasma carrier proteins exist for all classes of endocrine hormones. Carrier proteins for peptide hormones prevent hormone destruction by plasma proteases. Carriers for steroid hormones allow these hydrophobic hormones to be present in the plasma. Carriers for small, hydrophilic amino acid-derived hormones prevent their filtration through the renal glomerulus.

Based on mechanism of action, the hormones may be classified into two groups:   
**I. Hormones with cell surface receptors**

**I.A.** Hormones bind with cell surface receptors with **cAMP** as the second messenger such as ACTH, ADH, FSH HCG, LH, TSH , Calcitonin and Glucagon.

**I. B.** Hormones having cell surface receptors;with **cGMP** as second messenger such as ANF (atrial natriuretic factor), NO (nitric oxide).

**I. C.** Hormones having cell surface receptors; second messenger is   
**calcium** or phosphatidyl inositol **(PIP2)** such asTRH, GnRH catecholamines, Acetylcholine and Oxytocin.

**I .D** Hormones having cell surface receptors and mediated through **tyrosine kinase** such as Insulin and Somatomedin.

**I. E** Hormones having cell surface receptors, but intracellular messenger is a **kinase** and **phosphatase** cascade such as Erythropoietin, GH,PRL, TNF, Adiponectin, Leptin and Resistin.

**II. Hormones with intracellular receptors**

Such as Mineralocorticoids, Estrogens, Androgens, Calcitriol and Thyroxin

**Signal Transduction of Hormones with cell surface receptors through G-Protein**

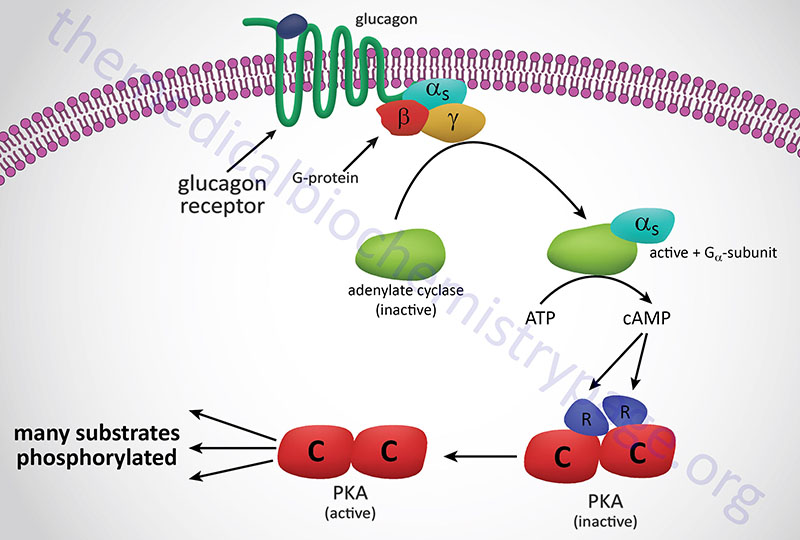
Binding of different types of signal molecules to G-protein coupled receptors (GPCRs) is a general mechanism of signal transduction.

When any ligand (like hormone-first messengers) binds, the GPCRs activate heterotrimeric **GTP** binding regulatory proteins so named (G-proteins). The G-protein in turn will interact with effector proteins which may be enzymes or ion channel proteins (second messengers), which result in the desired effect. Different types of G-proteins are present in the cells that are coupled with different receptors and activating different effector proteins.

The inactive G-protein is a trimer with alpha, beta and gamma subunits. When activated, GTP binds and the beta-gamma subunits dissociate from the alpha subunit.

***Cyclic AMP***

Adenyl cyclase or adenylate cyclase converts ATP to CAMP (3’,5’-cyclic AMP), and phosphodiesterase hydrolyzes cAMP to 5’ AMP. Cyclic AMP is a second messenger produced in the cell in response to activation of adenylate cyclase by active G-protein. During hormonal stimulation, cyclic AMP level in the cell increases several times. The cAMP, in turn, activates the enzyme, PKA (Cyclic AMP dependent protein kinase). Cyclic AMP binds to the regulatory subunits of PKA so that the catalytic subunits having kinase activity can phosphorylate proteins. This PKA is a tetrameric molecule having two regulatory (R) and two catalytic (C) subunits (R2 C2). This complex has no activity but when cAMP binds to the regulatory subunit and dissociates the tetramer into regulatory and catalytic subunits, the catalytic subunit is now free to act. The catalytic subunit then transfers a phosphate group from ATP to different enzyme proteins. Phosphorylation usually takes place on the OH groups of **serine, threonine or tyrosine** residues of the substrates. Hence, these kinases are called Ser/Thr kinases. The enzymes may be activated or inactivated by this phosphorylation. This is an example of covalent modification.

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**Hormone binding activates G-protein**

