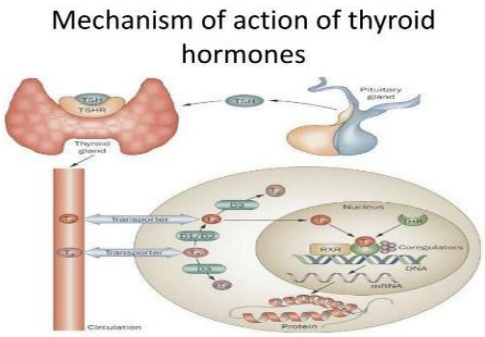
MECHANISM OF ACTION OF HORMONES

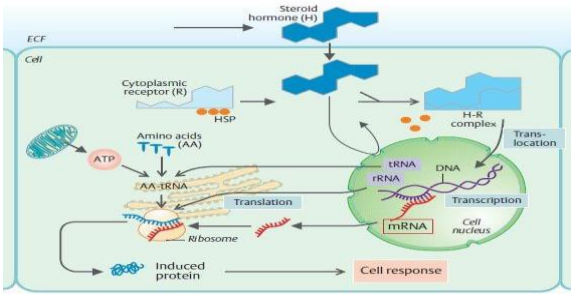
Although the physiological, apparently secondary effects of most of the hormones have been rather completely known for a number of years, their primary biochemical mechanisms of action at a cellular/molecular level are also known in much detail now. Many hormones serve as inducers or repressors in the genetically controlled synthesis of certain key cellular enzymes.

Protein (Enzymes or Channels) Synthesis	Protein (Enzymes or Channels) Synthesis
Genomic action. **Lipid soluble hormones** **i.e., steroid, T3, T4.**	Non-genomic action. Lipid insoluble hormones i.e., protein, peptide hormone, catecholamines, serotonin & melatonin.

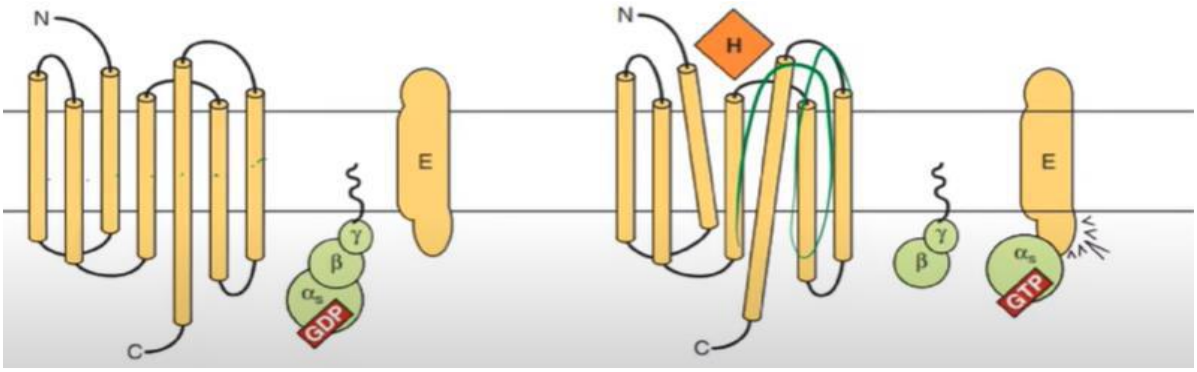
1. Interaction with nuclear chromatin (nuclear action or genomic action):

Steroid hormones act mostly by changing the transcription rate of specific genes in the nuclear DNA. The steroid hormone has a specific soluble, oligomeric receptor protein (mobile receptor) either in the cytosol and/or inside the nucleus. This brings about conformational changes and also changes in the surface charge of the receptor protein to favor its binding to the nuclear chromatin attached to the nuclear matrix. The ***receptor-steroid complex*** is translocated to the nuclear chromatin and binds to a steroid-recognizing acceptor site called the hormone-responsive element (HRE) of a DNA strand on the upstream side of the promoter site for a specific steroid-responsive gene. The consequent change in the intracellular concentration of m-RNA alters the rate of synthesis of a structural, enzymatic, carrier, or receptor protein coded by it. This results in ultimate cellular effects. The receptor-steroid complex subsequently leaves the acceptor site as the free receptor and the steroid. In addition to regulating the transcription, some steroid hormones may also act as regulatory agents for post-transcriptional processing, stability, and transport of specific mRNAs**.**





2. Membrane receptors (non-genomic action): certain molecules cannot enter target cells through the membrane lipid bilayer. This is achieved by the specific receptor molecules present on the surface of the plasma membrane. Many hormones are seen as specifically involved in the transport of a variety of substances across cell membranes. In general, these hormones specifically bind to the receptors on the cell membrane. They cause rapid secondary metabolic changes in the tissue but have little effect on the metabolic activity of membrane-free preparations. Most protein hormones and catecholamines activate the transport of membrane enzyme systems by directly binding to specific receptors on the membrane.

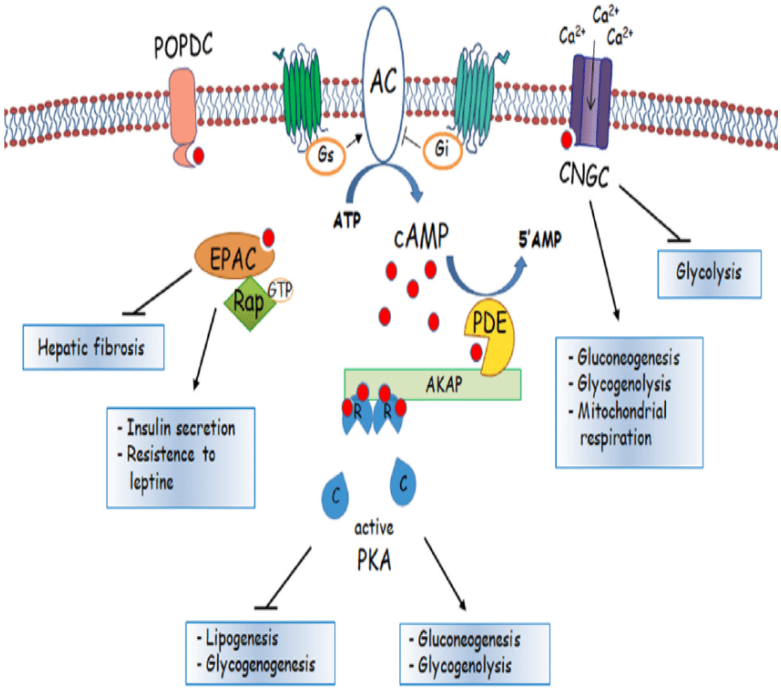


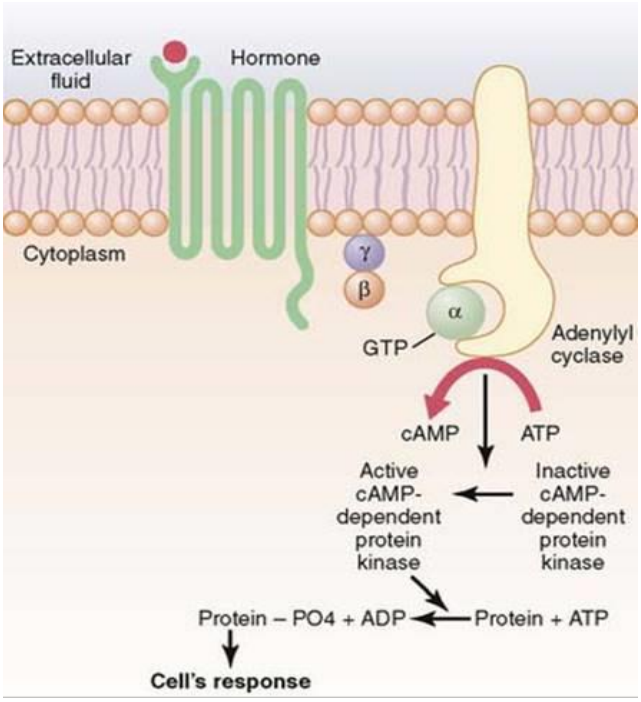
3. c-AMP and hormone action:

3'-5' c-AMP plays a unique role in the action of many protein hormones. Its level may be decreased or increased by hormonal action as the effect varies depending on the tissue. The Hormones such as glucagon, catecholamines, PTH, etc., act by influencing a change in intracellular c-AMP concentration through the adenylate cyclase c-AMP system. The hormone binds to a specific membrane receptor. Different types of these receptors remain associated with either Gs or Gi type of GTP-dependent trimeric nucleotide regulatory complexes of the membrane. Both Gs and Gi are made up of 3 subunits: Gs contains αs βγ while Gi contains αi βγ. Formation of the receptor-hormone complex promotes the binding of GTP to the α subunit of either Gs or Gi. When αs-GTP is released, it

binds to adenylate cyclase located on the cytoplasmic surface of the membrane and changes its conformation to activate it. ***Adenylate cyclase*** catalyzes the conversion of ATP to c-AMP, thus increasing the intracellular concentration of the latter**.** On the other hand, αi-GTP inhibits ***adenylate cyclase*** by binding with it. This lowers the intracellular concentration of c-AMP.

Note: Insulin can decrease hepatic c-AMP in opposition to the increase caused by glucagon.

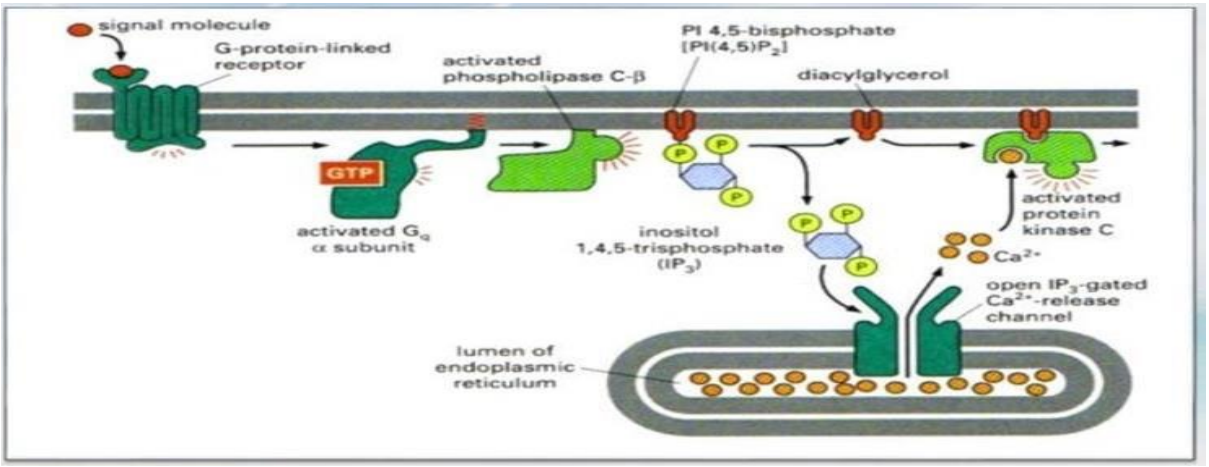




4. Role of polyphosphoinositol and diacylglycerol in hormone action:

Just like c-AMP, other compounds such as 1, 4, and 5 inositol triphosphate (ITP) and diacylglycerol (DAG) act as second messengers. This is especially found in vasopressin, TRH, GnRH, etc. These hormones activate the phospholipase C-polyphosphoinositol system to produce ITP and DAG. By binding with the specific receptor protein on cell membrane, the hormone activates a trimeric nucleotide regulatory complex. The complex, in turn, activates phospholipase C on the inner surface of the membrane. Inositol triphosphate enhances the mobilization of Ca++ into the cytosol from the intracellular Ca++ pool of mitochondria; calcium ions then act as a tertiary messenger. DAG activates the Ca++ phosphatidyl-serine-dependent protein kinase C located on the inner surface of the membrane by lowering its Km

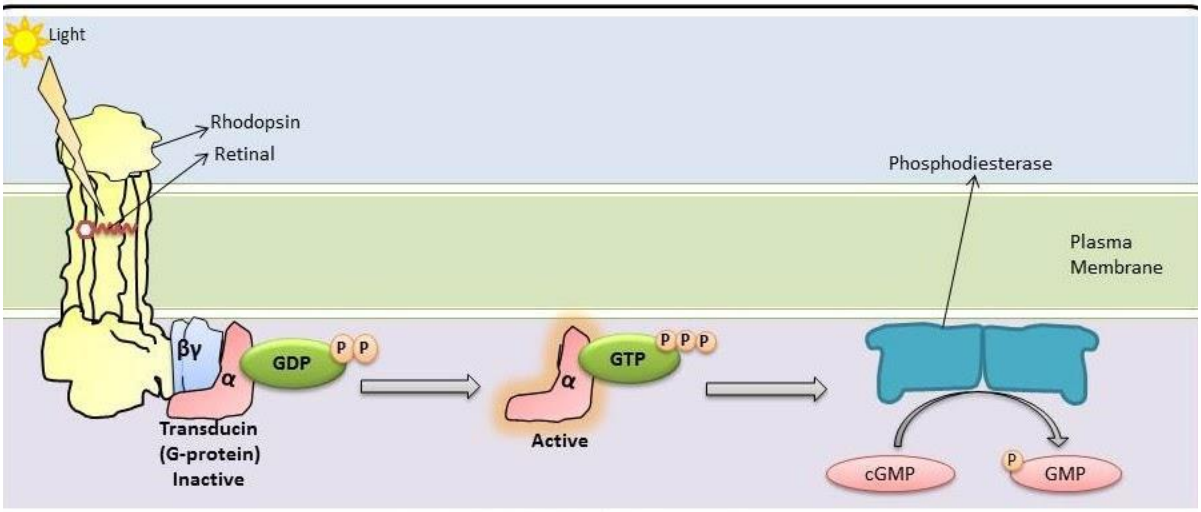
for Ca++. This enzyme then phosphorylates specific enzymes and other proteins in the cytosol to modulate their activities.



5. Role of calcium in hormone action: The action of most protein hormones is inhibited in the absence of calcium, even though the ability to increase or decrease c-AMP is comparatively unimpaired. ***Thus, calcium may be a more terminal signal for hormone action than c-AMP.*** It is suggested that ionized calcium in the cytosol is an important signal. ***The source of this calcium may be extracellular fluid, or it may arise from the mobilization of intracellular tissue-bound calcium.*** As mentioned, membrane-receptor binding may be responsible for this. The hormone receptor binding may directly inhibit the Ca++–ATPase. It may also directly open up voltage-independent Ca++ channels in the membrane to increase the diffusion of Ca++ into the cell down its inward concentration gradient, resulting in increased cytosolic Ca++ concentration, which then acts as a second messenger to affect cellular activities. The receptor-hormone complex may produce ITP, which in turn can increase cytosolic Ca++ concentration by enhancing the mobilization of Ca++ from mitochondrial and endoplasmic reticular pools. All these enzymes have special biochemical metabolic roles. Ca++ also changes membrane permeability. Many of its effects are mediated by its binding to Ca++–dependent regulatory proteins like calmodulin and troponin. (For calmodulin—refer to the chapter on Glycogen Metabolism).

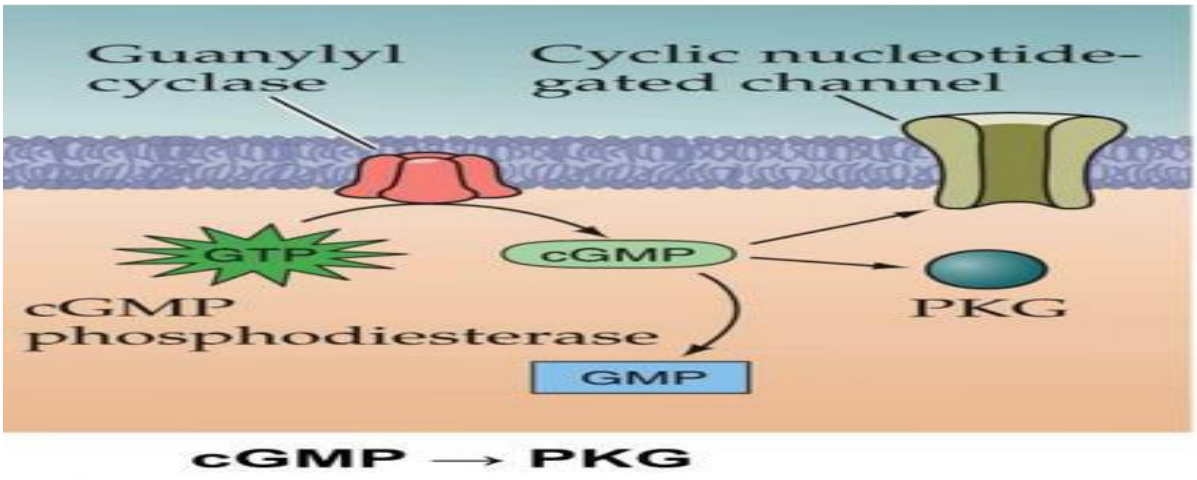
6. Role of c-GMP in hormone action: Hormones such as insulin and growth hormone affect the ***guanylate cyclase*** c-GMP system. This will increase the

intracellular conc. of c-GMP and activate c- GMP-dependent protein kinases. The active c-GMP-protein kinase would, in turn, bring about the phosphorylation of specific cellular proteins to change their activities, leading to the relaxation of smooth muscles, vasodilatation, and other effects. Ca++ may likely act as a second messenger to activate guanylate cyclase, thereby increasing the conc of c-GMP inside the cell.



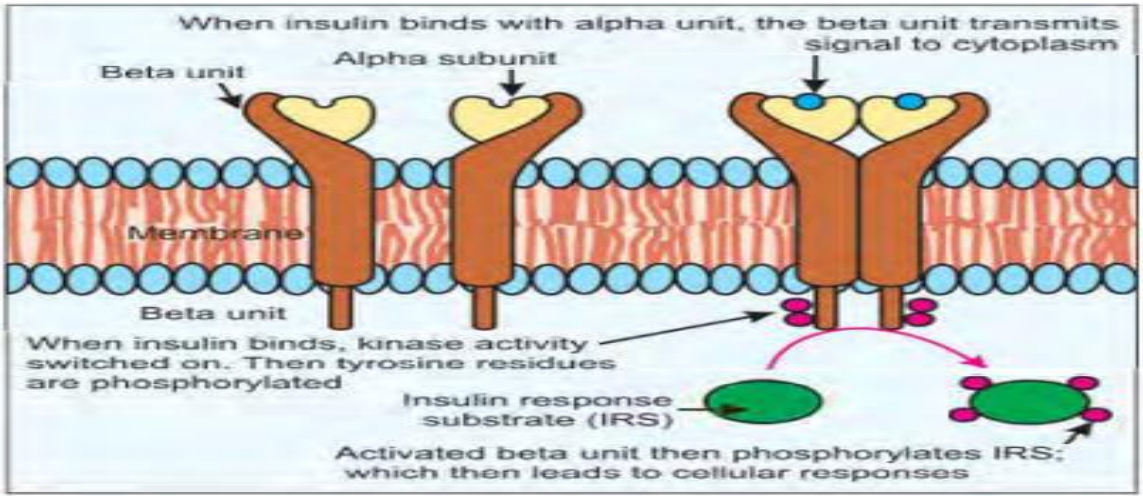
Role of cGMP in Photoreception

Namrata Heda



cGMP → PKG

7. Role of phosphorylation of tyrosine kinase: In fact, a second messenger for insulin, growth hormone, prolactin, oxytocin, etc., has not been identified so far. However, binding them to their respective membrane receptors activates a specific protein kinase called tyrosine kinase, which phosphorylates the tyrosine residue of specific proteins. This may bring about some metabolic Changes.



Hormone(s)	Origin	Major Function(s)
Group I. HORMONES THAT BIND TO INTRACELLULAR RECEPTORS		
Estrogens	Ovaries and adrenal cortex	Female sexual characteristics, menstrual cycle.
Progestins	Ovaries and placenta	Involved in menstrual cycle and maintenance of pregnancy.
Androgens	Testes and adrenal cortex	Male sexual characteristics, spermatogenesis.
Glucocorticoids	Adrenal cortex	Affect metabolisms, suppress immune system.
Mineralocorticoids	Adrenal cortex	Maintenance of salt and water balance.
Calcitriol (1, 25–DHCC)	Kidney (final form)	Promotes absorption of Ca^{2+} from intestine, kidney and bone.
Thyroid hormones (T_3, T_4)	Thyroid	Promote general metabolic rate.
Group II. HORMONES THAT BIND TO CELL SURFACE RECEPTORS		
A. The second messenger is cAMP		
Adrenocorticotropic hormone (ACTH)	Anterior pituitary	Stimulates the release of adrenocorticosteroids.
Follicle stimulating hormone (FSH)	Anterior pituitary	In females, stimulates ovulation and estrogen synthesis. In males, promotes spermatogenesis.
Luteinizing hormone (LH)	Anterior pituitary	Stimulates synthesis of estrogens and progesterone and causes ovulation. Promotes androgen synthesis by testes.
Chorionic gonadotropin (hCG)	Anterior pituitary	Stimulates progesterone release from placenta.
Thyroid stimulating hormone (TSH)	Anterior pituitary	Promotes the release of thyroid hormones (T_3, T_4).
β-Endorphins and enkephalins	Anterior pituitary	Natural endogenous analgesics (pain relievers).
Antidiuretic hormone (ADH)	Posterior pituitary (stored)	Promotes water reabsorption by kidneys.
Glucagon	Pancreas	Increases blood glucose level, stimulates glycogenolysis and lipolysis.
Parathyroid hormone (PTH)	Parathyroid	Increases serum calcium, promotes Ca^{2+} release from bone.
Calcitonin	Thyroid	Lowers serum calcium. Decreases Ca^{2+} uptake by bone and kidney.
Epinephrine	Adrenal medulla	Increases heart rate and blood pressure. Promotes glycogenolysis in liver and muscle and lipolysis in adipose tissue.
Norepinephrine	Adrenal medulla	Stimulates lipolysis in adipose tissue.
B. The second messenger is phosphatidyl inositol/calcium		
Thyrotropin-releasing hormone (TRH)	Hypothalamus	Promotes TSH release.
Gonadotropin-releasing hormone (GnRH)	Hypothalamus	Stimulates release of FSH and LH.
Gastrin	Stomach	Stimulates gastric HCl and pepsinogen secretion.
Cholecystokinin (CCK)	Intestine	Stimulates contraction of gall bladder and secretion of pancreatic enzymes.
C. The second messenger is unknown/unsettled		
Growth hormone (GH)	Anterior pituitary	Promotes growth of the body (bones and organs).
Prolactin (PRL)	Anterior pituitary	Growth of mammary glands and lactation.
Oxytocin	Posterior pituitary (stored)	Stimulates uterine contraction and milk ejection.
Insulin	Pancreas	Lowers blood glucose (hypoglycemic effect), promotes protein synthesis and lipogenesis.
Somatomedins (insulin-like growth factors, IGF-I, IGF-II)	Liver	Growth related functions of GH are mediated. Stimulates growth of cartilage.