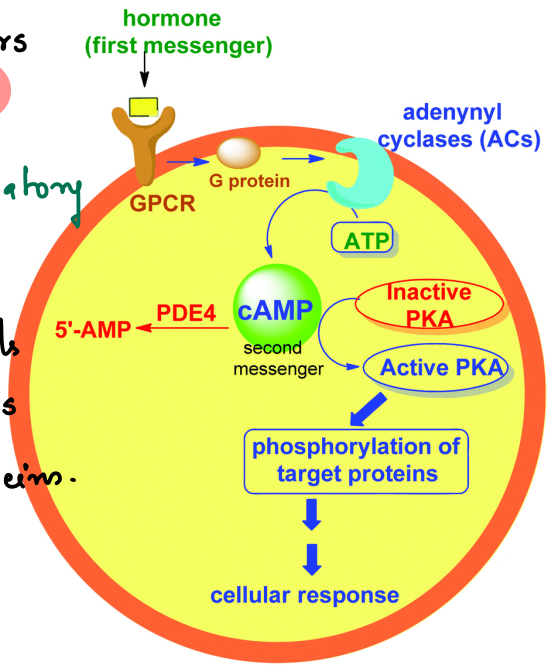
Hormone - Part 2

Hormones acting through cyclic AMP:

- Cyclic AMP (cAMP) was first discovered by Earl Sutherland in 1961.
- Action is through G-Protein coupled receptors (GPCRs)



(i) When any ligand binds, the GPCRs activate heterotrimeric GTP binding regulatory Proteins (G-Proteins)

- Different G-Proteins are present in the cells that are coupled with different receptors and activating different effector proteins.

(ii) G-protein activates Adenyl cyclase.

(iii) Adenyl cyclase converts ATP → cAMP (3,5-cyclic AMP) and phosphodiesterase hydrolyses cAMP → 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 cell increases several times.

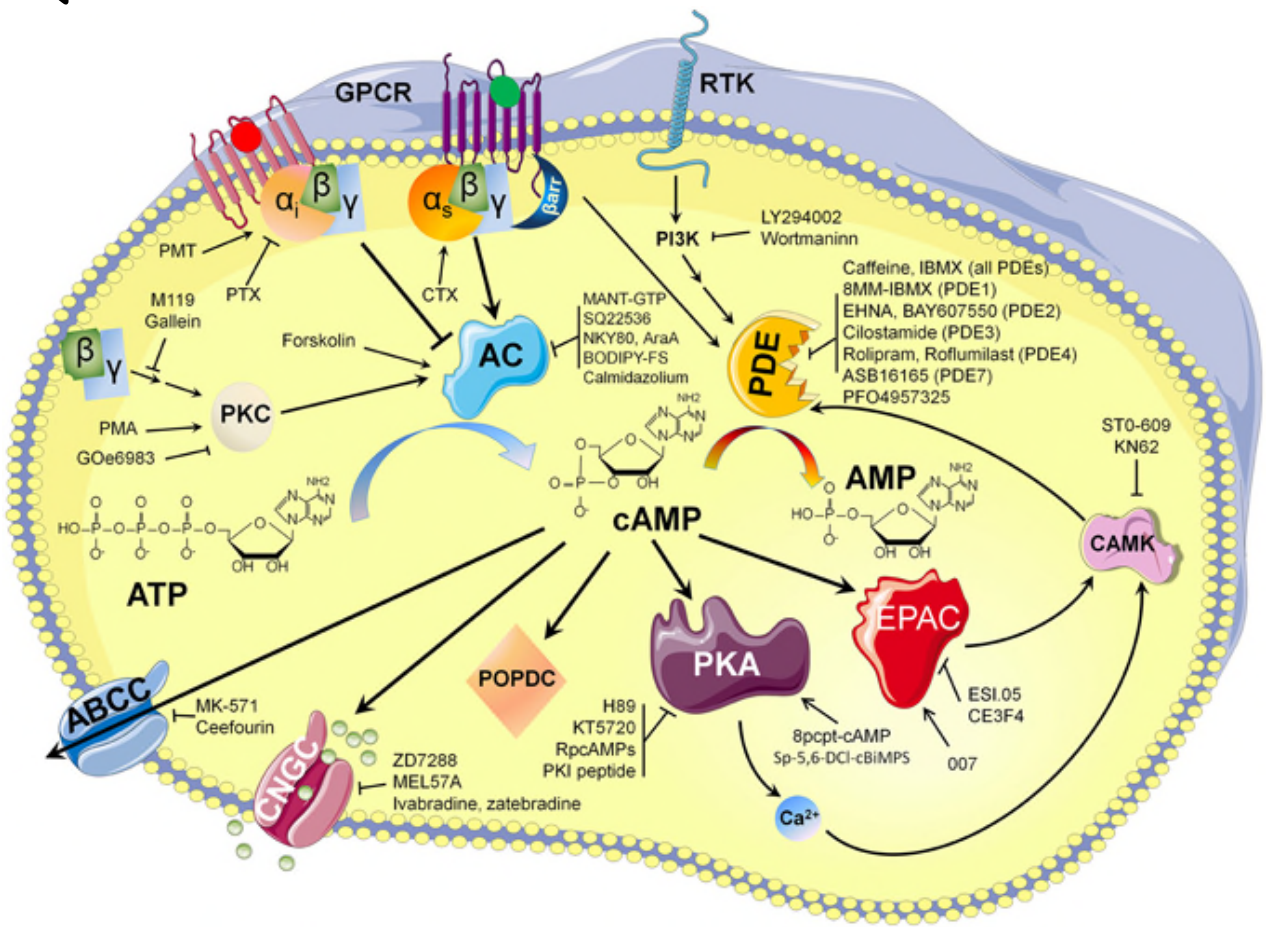
(iv) Second messenger activates PKA

- The cAMP activates the enzyme PKA (cyclic AMP dependent protein kinase)
- PKA is a tetrameric molecule having two regulatory (R) and two catalytic (C) subunits (R_2C_2)
- This complex has no activity. But cAMP binds to the regulatory subunit and dissociates the tetramer into regulatory and catalytic subunits. The catalytic subunit is now free to act.

(v) Kinase Phosphorylates the Enzyme.

- Catalytic subunit then transfers a phosphate group from ATP to different enzymes proteins.

- Phosphorylation usually takes place on OH groups of serine, threonine or tyrosine residues of substrates.
- Hence these kinase are called Ser / Thr Kinase. The enzymes may be activated or inactivated by this phosphorylation.
- This is an example of covalent modification.
- Glycogen phosphorylase & Hormone sensitive lipase are controlled by cyclic AMP.



G-Proteins :

- About 30 different G-proteins are identified, each being used for different signal transduction pathways.

Gα class	*Initiating signal*	*Downstream signal*
Gs (G-stimulatory)	β-adrenergic amines, glucagon, PTH, TSH, corticotrophin, many others	Stimulates adenylate cyclase
Gi (G-inhibitory)	Acetylcholine, α adrenergic amines, many neurotransmitters, chemokines	Inhibits adenylate cyclase
Gq	Acetylcholine, α adrenergic amines, many neurotransmitters, TRH	Increases IP3 and intracellular calcium
Gt (Transducin)	Photons	Stimulates cGMP phosphodiesterase

Wiki = Snippet

G-protein family	α-subunit	Gene	Signal transduction	Use/Receptors (examples)	Effects (examples)
G_i-family (InterPro : *IPR001408*)					
$G_{i/o}$	α_i, α_o	GNAO1 , GNAI1 , GNAI2 , GNAI3	Inhibition of adenylate cyclase, opens K^+-channels (via β/γ subunits), closes Ca^{2+}-channels	Muscarinic M_2 and M_4,[8] chemokine receptors, α_2-Adrenoreceptors, Serotonin 5-HT_1 receptors, Histamine H_3 and H_4, Dopamine D_2-like receptors, type 2 cannabinoid receptors (CB2) [9]	Smooth muscle contraction, depress neuronal activity, interleukin secretion by human leukocytes[9]
G_t	α_t (Transducin)	GNAT1 , GNAT2	Activation of phosphodiesterase 6	Rhodopsin	Vision
G_{gust}	α_{gust} (Gustducin)	GNAT3	Activation of phosphodiesterase 6	Taste receptors	Taste
G_z	α_z	GNAZ	Inhibition of adenylate cyclase	Platelets	Maintaining the ionic balance of perilymphatic and endolymphatic cochlear fluids.
G_s-family (InterPro : *IPR000367*)					
G_s	α_s	GNAS	Activation of adenylate cyclase	Beta-adrenoreceptors; Serotonin 5-HT_4, 5-HT_6 and 5-HT_7; Dopamine D_1-like receptors, Histamine H_2, type 2 cannabinoid receptors [9]	Increase heart rate, Smooth muscle relaxation, stimulate neuronal activity, interleukin secretion by human leukocytes [9]
G_{olf}	α_{olf}	GNAL	Activation of adenylate cyclase	olfactory receptors	Smell
G_q-family (InterPro : *IPR000654*)					
G_q	α_q, α_{11}, α_{14}, α_{15}, α_{16}	GNAQ , GNA11 , *GNA14*, *GNA15*	Activation of phospholipase C	α_1-Adrenoreceptors, Muscarinic M_1, M_3, and M_5,[8] Histamine H_1, Serotonin 5-HT_2 receptors	Smooth muscle contraction, Ca^{2+} flux
$G_{12/13}$-family (InterPro : *IPR000469*)					
$G_{12/13}$	α_{12}, α_{13}	GNA12 , GNA13	Activation of the Rho family of GTPases		Cytoskeletal functions, Smooth muscle contraction

Protein kinases :

- More than thousand protein kinases are now known.
- Some important are listed below :

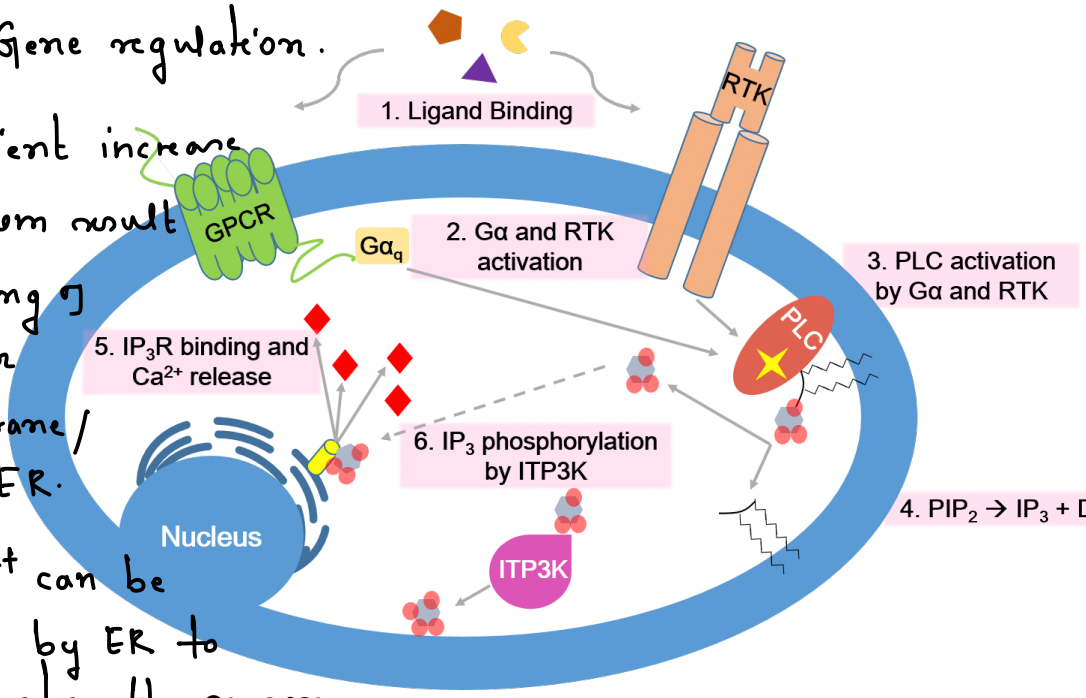
Signal molecule	*Second messenger*	*Protein kinase*	*Type*	*Substrates*
Hormones (glucagon, epinephrine, HSL, ADH, glycogen, ACTH, PTH, etc.	cAMP	Protein kinase A	Ser/Thr	Enzymes like phosphorylase, PFK2, CREBs, etc.
Nitric oxide, AMP	cGMP	Protein kinase G	Ser.Thr	Myosin, transducin
Serotonin, TRH	Calcium, IP3	Cam kinase	Ser/Thr	Exocytosis, smooth muscle contraction
Oxytocin, PDGF	DAG	Protein kinase C	Ser/Thr	Transcription factors, ion channel transporters
Growth factors, cytokines	PIP3	Protein kinase B	Ser/Thr	Glycogen metabolism, glucose transport, death signals like BAD
Insulin and insulin like growth factors	RTK in receptor	Tyrosine kinase	Tyr	IRS-1 (Insulin response substrate 1), IRS-2, MAP kinase, PDK
GH, prolactin, cytokines	RTK in receptor	Janus kinase (JAK)	Tyr	STAT (Signal transducers and activators of transcription

Calcium based Signal Transduction :

- Calcium is an important intracellular regulator of cell function like :

(i) contraction of muscles
(ii) secretion of hormones
(iii) secretion of Neurotransmitters
(iv) Cell division
(v) Regulation of Gene regulation.

- Rapid but transient increase in cytosolic calcium result from either opening of Ca^{2+} channels in the plasma membrane / Ca^{2+} channels in ER.
- The released Ca^{2+} can be rapidly taken up by ER to terminate the response.



Phospholipase C Pathway:

- Specific signals can trigger a sudden increase in cytoplasmic Ca^{2+} levels to 500-1000 nM by opening channels in ER or plasma memb
- The most common signaling pathway that increases cytoplasmic Ca^{2+} is **PLC pathway**.

(i) Many cell surface receptors, including G-Protein coupled receptors and receptor tyrosine kinases, activate **PLC enzyme**.

(ii) PLC mes hydrolysis of membrane phospholipid PIP_2 to form IP_3 and diacylglycerol (DAG), two classic 2° messenger.

(iii) DAG attaches to plasma memb and recruits Protein kinase C (PKC)

(iv) IP_3 diffuses to ER and is bound to IP3 receptor.

(v) The IP_3 receptor serves as a Ca^{2+} channel, and release Ca^{2+} from ER.

(vi) The Ca^{2+} bind to PKC and other proteins & activate them.