A diagram of a cell membrane cross-section. The membrane is composed of a phospholipid bilayer with yellow heads and red tails. Several blue, Y-shaped receptors are embedded in the membrane, some with blue beaded chains extending from their extracellular domains. A green text label 'Cell Signaling PHYA-Sem-II-CC3' is positioned in the upper left. The main title 'G-Protein – Coupled Receptors' is written in large, bold, red letters across the center, with a subtitle '(Largest family of cell surface receptors)' in black below it. At the bottom, the author's name and affiliation are listed in blue text.

Cell Signaling
PHYA-Sem-II-CC3

G-Protein – Coupled Receptors

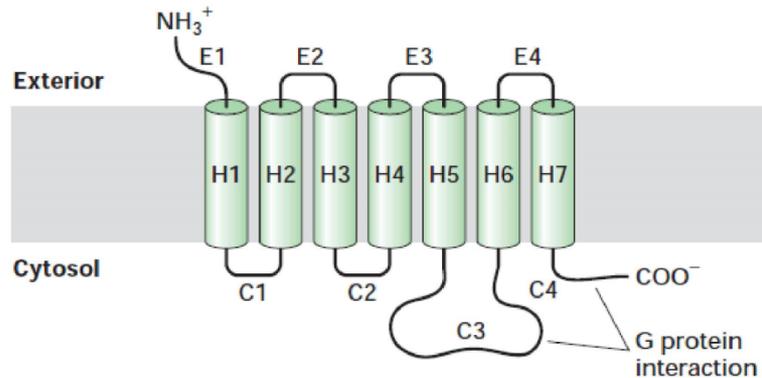
(Largest family of cell surface receptors)

Compiled and Prepared
by

Dr. Barnali Ray Basu
Department of Physiology
Surendranath College

Structure of G-Protein – Coupled Receptors

G Protein–Coupled Receptors That Activate or Inhibit Adenylyl Cyclase



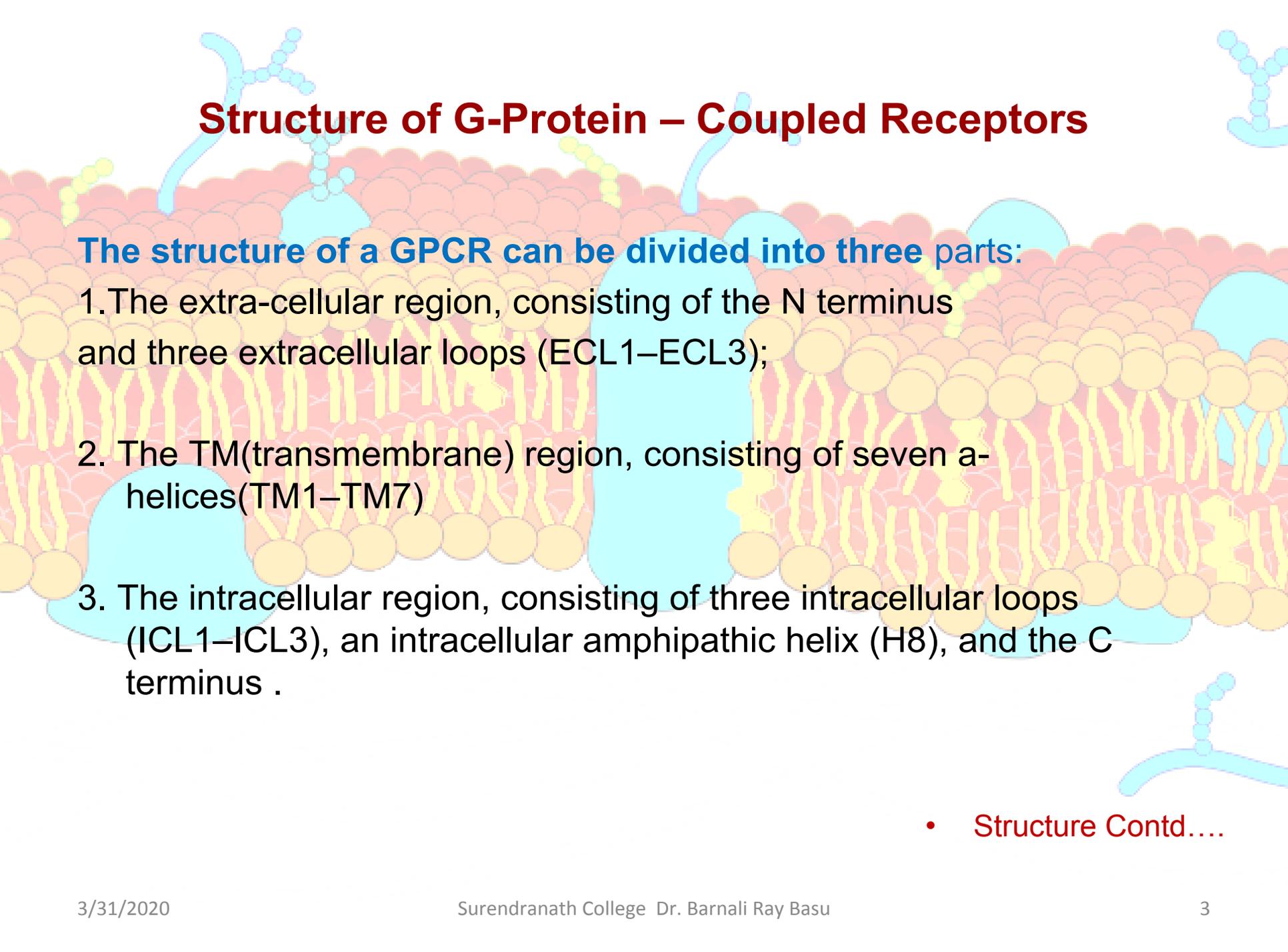
Schematic diagram of the general structure of G protein–coupled receptors

G protein–coupled receptors family referred to as seven –transmembrane receptor. The constitute the largest superfamily of proteins encoded by animal genomes.

Natural ligand that binds to these receptor are hormones, neurotransmitters, opium derivatives, chemoattractants, odorants and tastants

Structure Contd....

Structure of G-Protein – Coupled Receptors

A diagram of a G-protein coupled receptor (GPCR) embedded in a cell membrane. The membrane is shown as a phospholipid bilayer with yellow heads and red tails. The GPCR is a large blue structure with seven transmembrane helices. It has an N-terminus and three extracellular loops (ECL1-ECL3) on the top, and three intracellular loops (ICL1-ICL3), an intracellular amphipathic helix (H8), and a C-terminus on the bottom. A G-protein is shown as a blue Y-shaped structure on the right, with its alpha subunit bound to the GPCR and its beta-gamma complex bound to the membrane.

The structure of a GPCR can be divided into three parts:

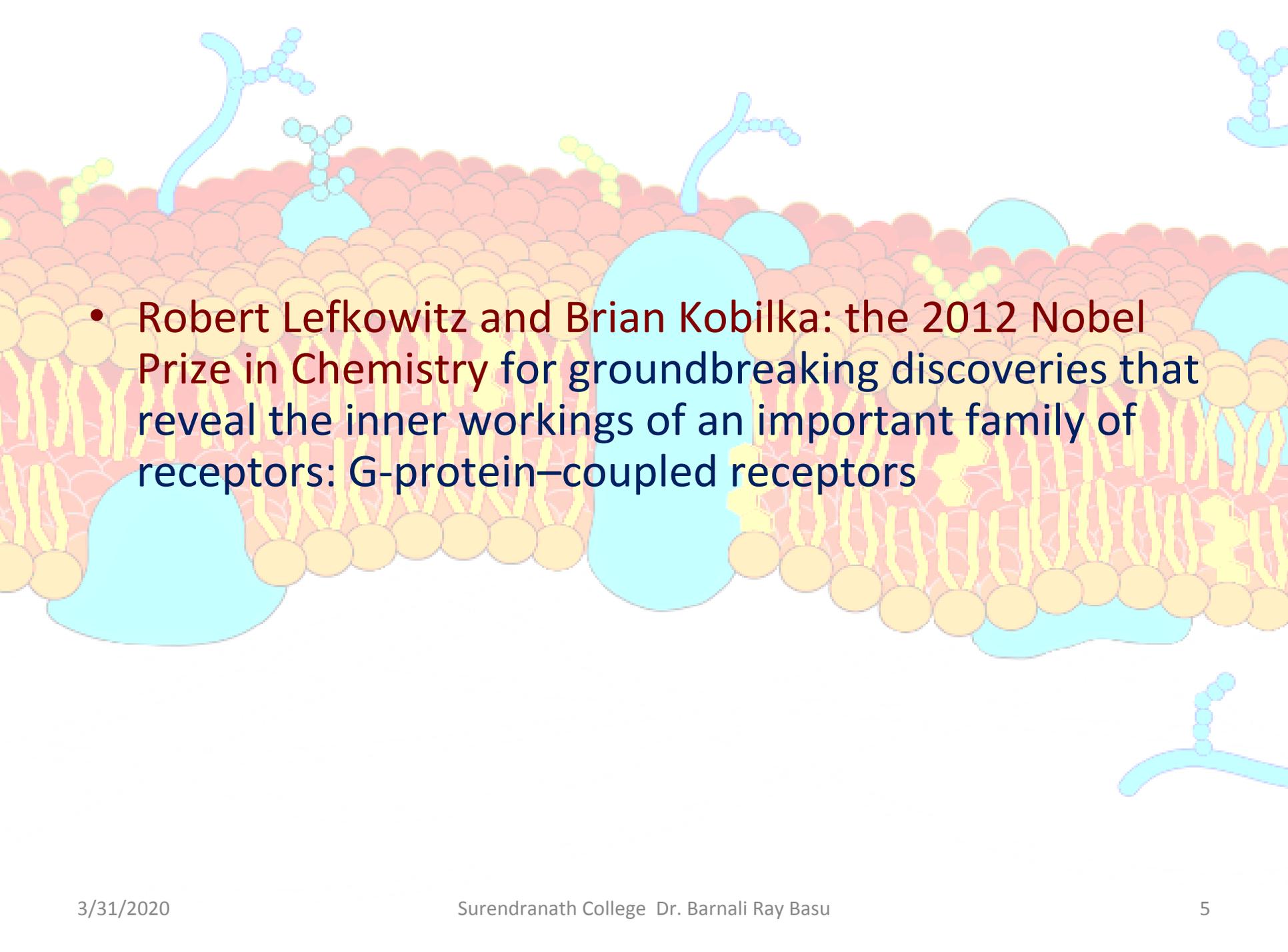
1. The extra-cellular region, consisting of the N terminus and three extracellular loops (ECL1–ECL3);
2. The TM(transmembrane) region, consisting of seven α -helices(TM1–TM7)
3. The intracellular region, consisting of three intracellular loops (ICL1–ICL3), an intracellular amphipathic helix (H8), and the C terminus .

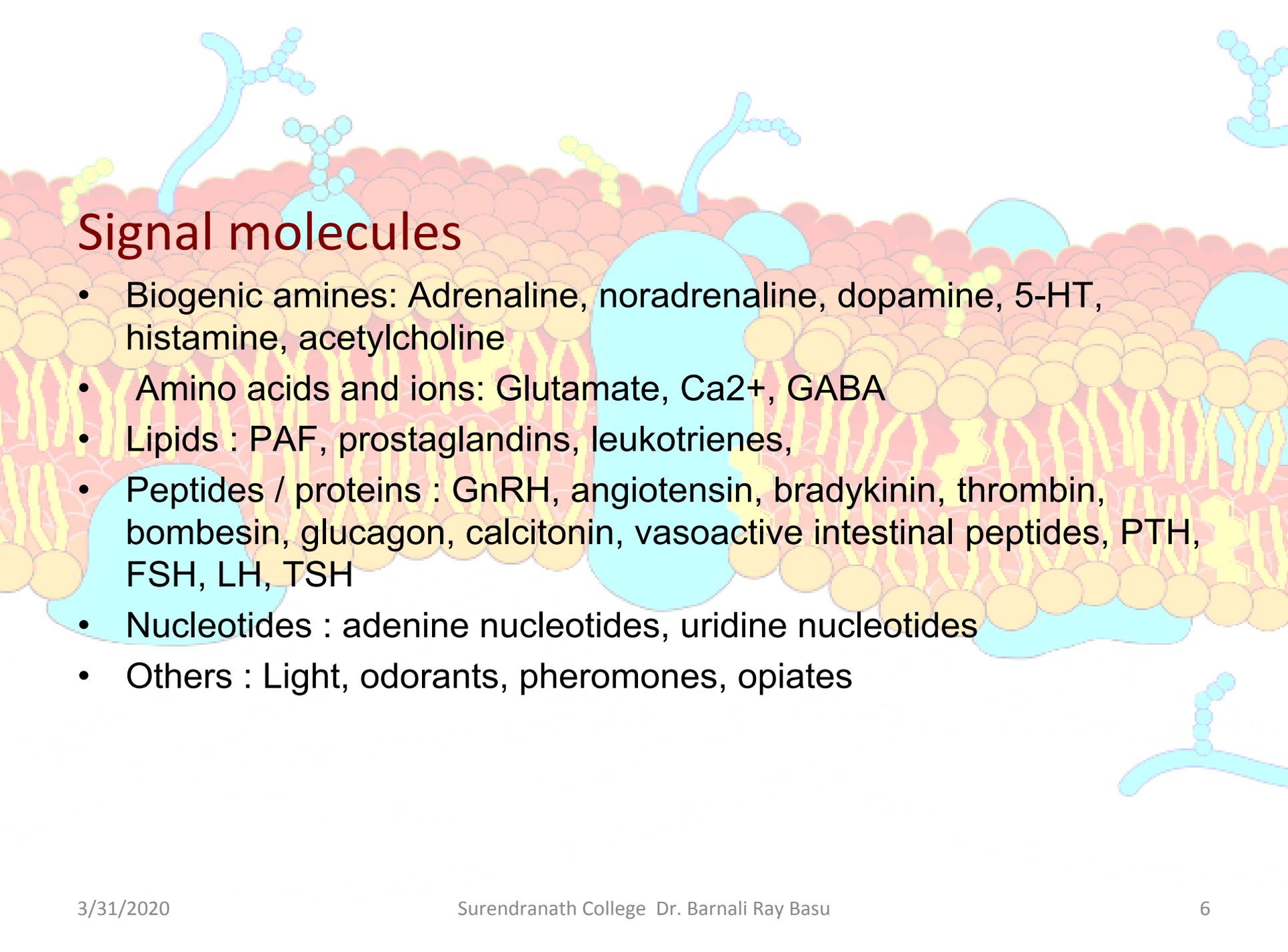
• Structure Contd....

Structure of G-Protein – Coupled Receptors

- G protein-coupled receptors are integral membrane proteins that possess seven membrane-spanning domains or transmembrane helices.
- These receptors activate a G protein ligand binding.
- G-protein is a trimeric protein. The 3 subunits are called α , β and γ .
- The α subunit can bind with guanosine diphosphate, GDP.
- This causes phosphorylation of the GDP to guanosine triphosphate, GTP, and activates the α subunit \longrightarrow which then dissociates from the β and γ subunits.
- The activated α subunit can further affect intracellular signaling proteins or target functional proteins directly.

• Structure Contd.....

- 
- **Robert Lefkowitz and Brian Kobilka: the 2012 Nobel Prize in Chemistry** for groundbreaking discoveries that reveal the inner workings of an important family of receptors: G-protein–coupled receptors



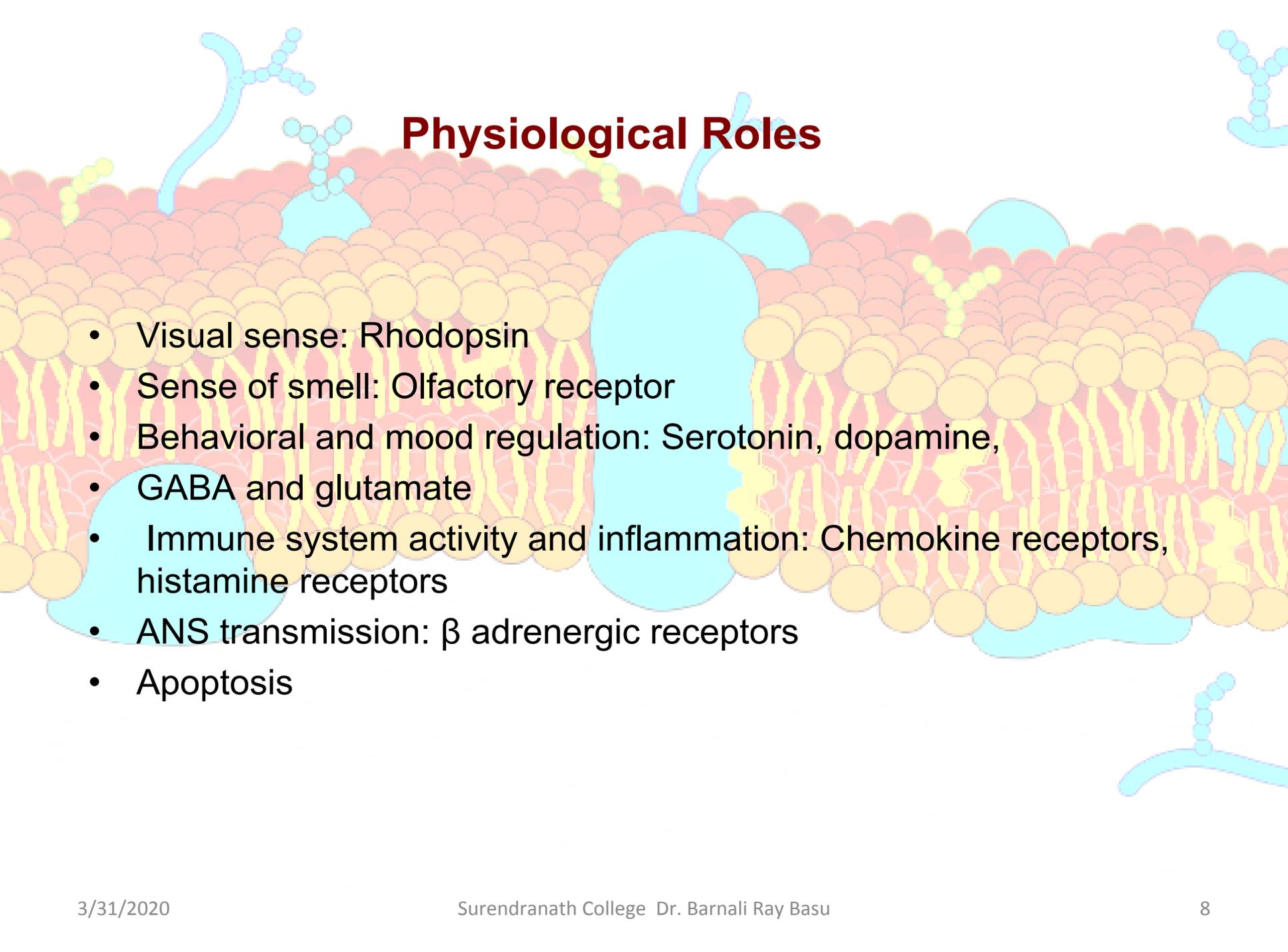
Signal molecules

- Biogenic amines: Adrenaline, noradrenaline, dopamine, 5-HT, histamine, acetylcholine
- Amino acids and ions: Glutamate, Ca^{2+} , GABA
- Lipids : PAF, prostaglandins, leukotrienes,
- Peptides / proteins : GnRH, angiotensin, bradykinin, thrombin, bombesin, glucagon, calcitonin, vasoactive intestinal peptides, PTH, FSH, LH, TSH
- Nucleotides : adenine nucleotides, uridine nucleotides
- Others : Light, odorants, pheromones, opiates

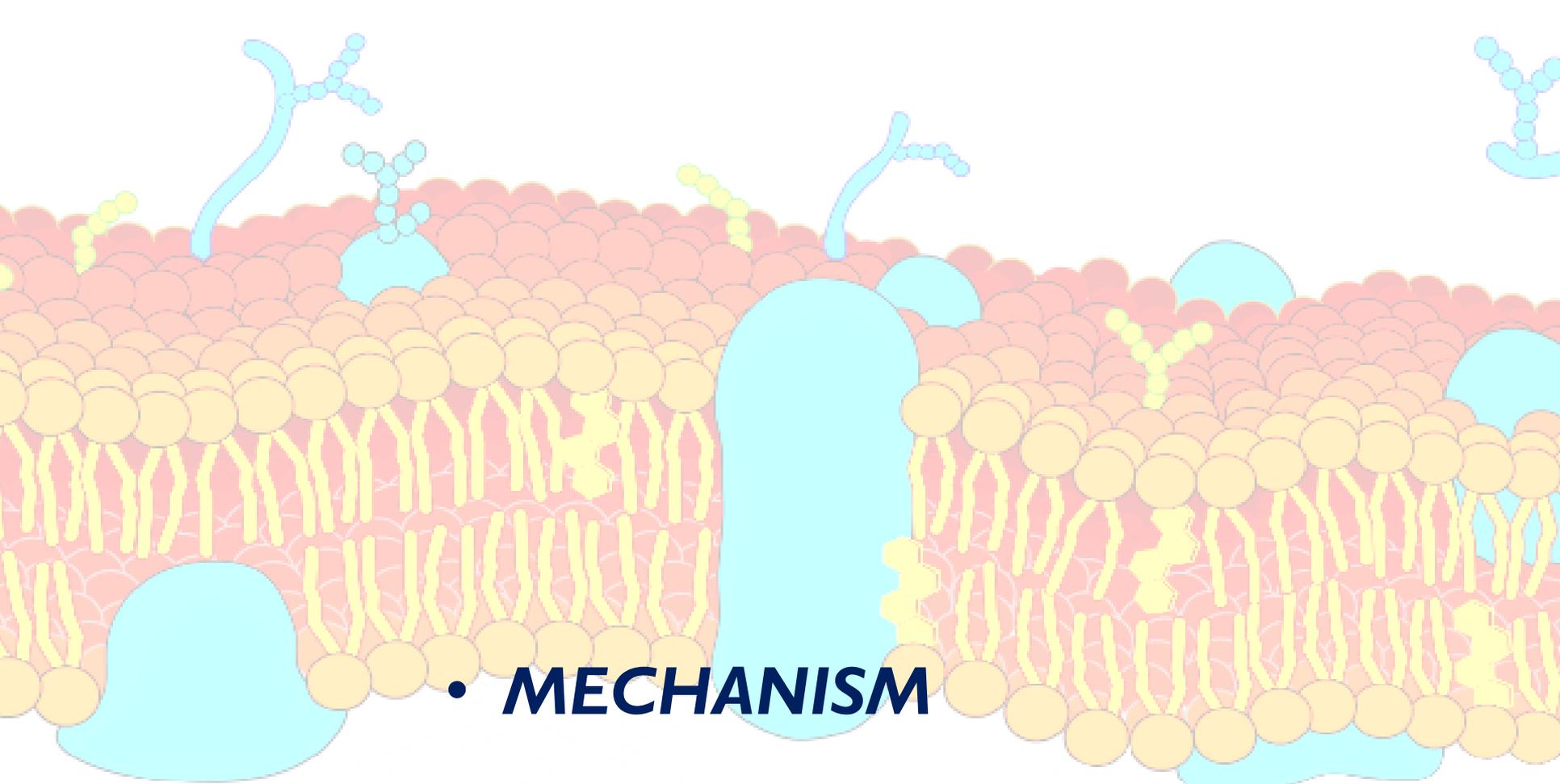
GPC Receptors

G Protein	Receptors	Signaling Pathway
G_s	Beta adrenergic receptors, glucagon, histamine, serotonin	Increase CAMP Excitatory effects
G_i	Alpha ₂ adrenergic receptors, mAChR, opioid, serotonin	Decrease CAMP Cardiac K ⁺ channel open- decrease heart rate
G_q	mAChR, H1, α1, Vasopressin type 1, 5HT _{1C}	PLC- IP ₃ , DAG Increase Cytoplasmic Ca
G_t	Rhodopsin and colour opsins in retinal rod and cone cells	Increase cGMP phosphodiesterase. Decrease cGMP

Physiological Roles



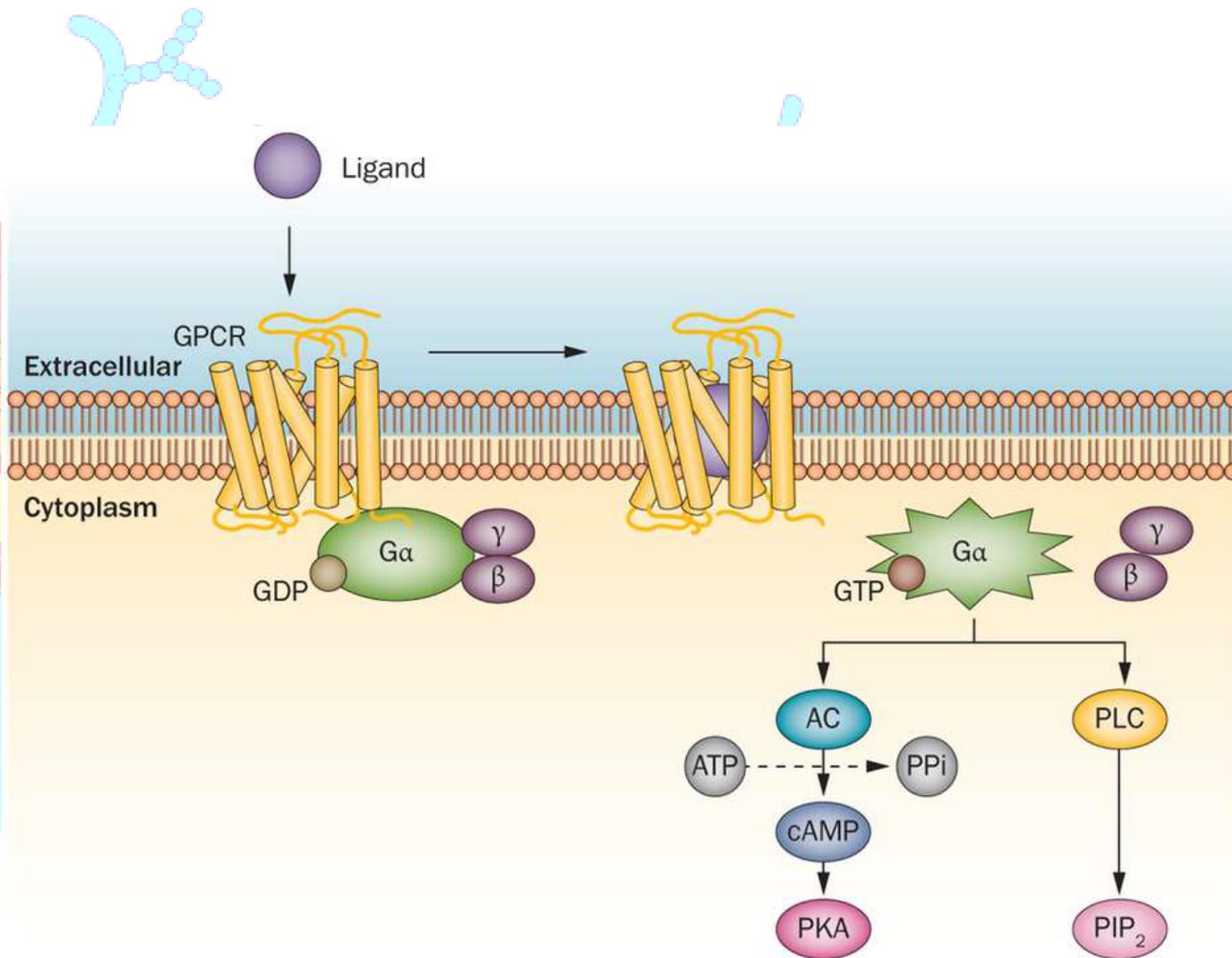
- Visual sense: Rhodopsin
- Sense of smell: Olfactory receptor
- Behavioral and mood regulation: Serotonin, dopamine, GABA and glutamate
- Immune system activity and inflammation: Chemokine receptors, histamine receptors
- ANS transmission: β adrenergic receptors
- Apoptosis



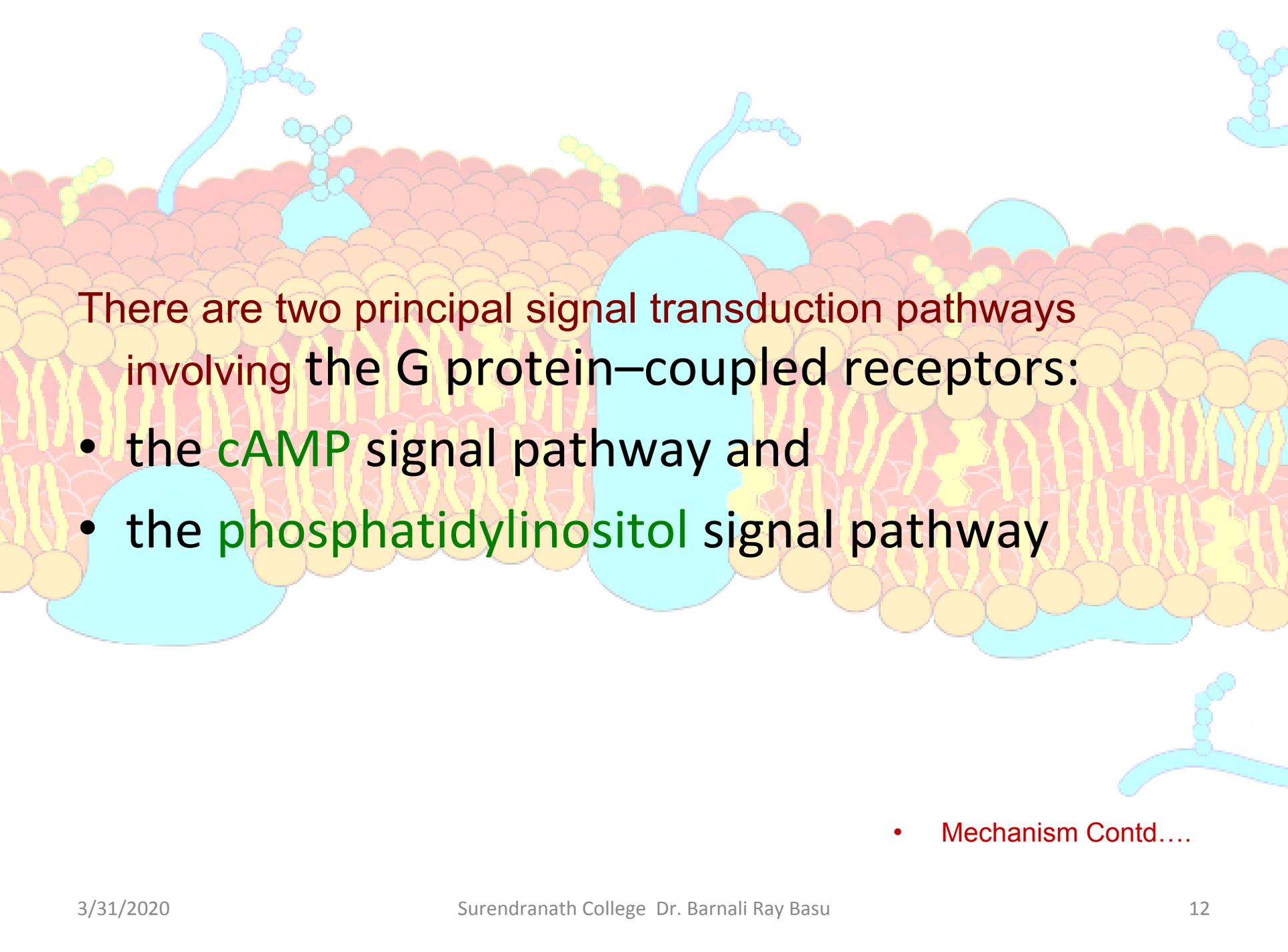
• **MECHANISM**

Steps:

- When an agonist binds to a GPCR, there is a conformational change in the receptor that is transmitted from the ligand-binding pocket to the second and third intracellular loops of the receptor which couple to the G protein heterotrimer.
- GPCR results in a conformational change in the receptor that is transmitted to the bound **G α subunit**.
- This conformational change causes the α subunit to exchange its bound GDP for GTP.
- Binding of GTP activates the α subunit and causes it to release both the $\beta\gamma$ dimer and the receptor, and active signaling molecules, both the GTP-bound α subunit and the $\beta\gamma$ heterodimer become and active signaling molecules.
- The interaction of the agonist-bound GPCR with the G protein is transient; following activation of one G protein,
- the receptor is freed to interact with other G proteins.
- **Mechanism Contd....**



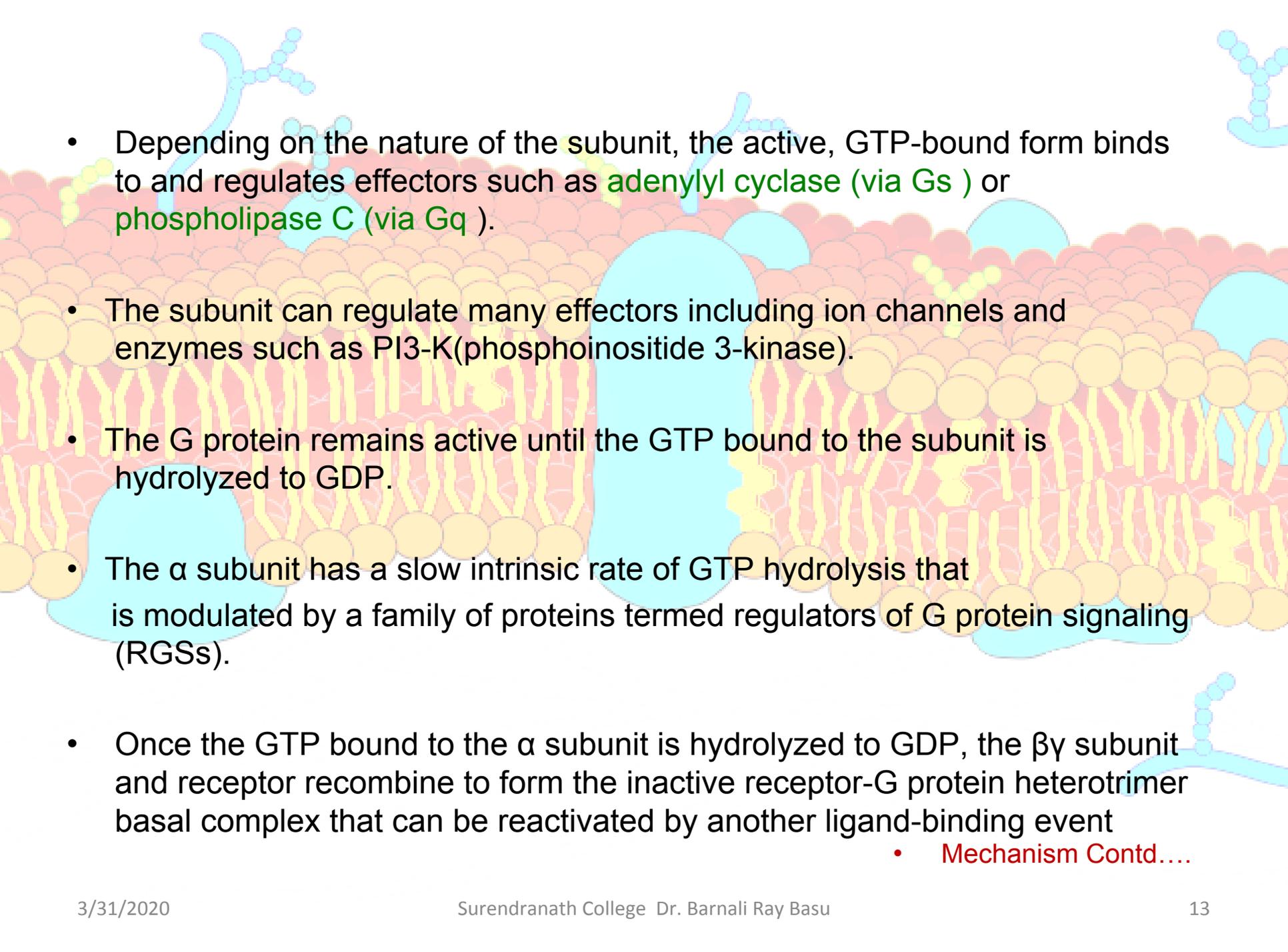
- Mechanism Contd....

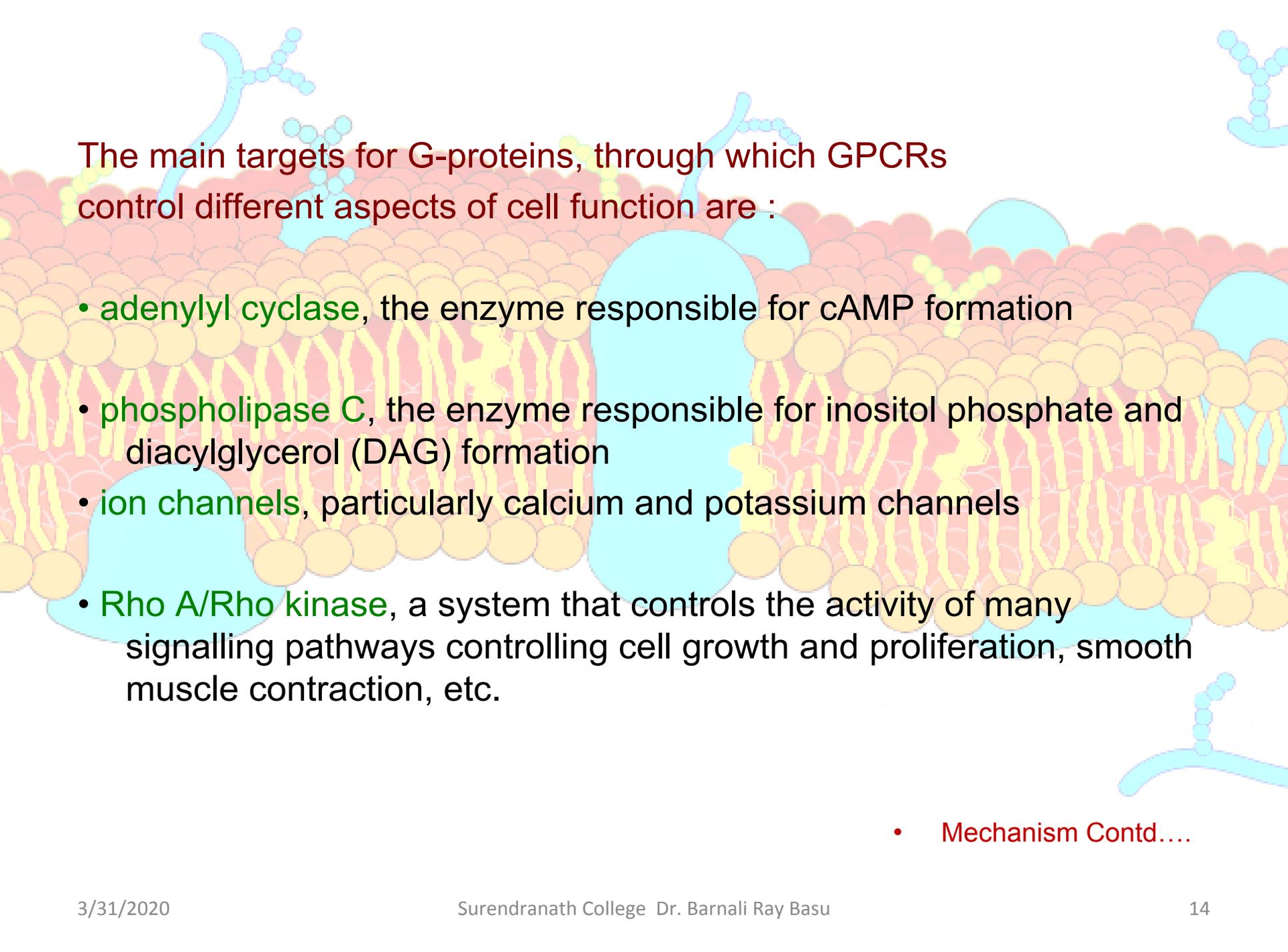
A diagram of a cell membrane cross-section. The membrane is composed of a phospholipid bilayer with yellow heads and red tails. Several blue Y-shaped receptors are embedded in the membrane, some with blue chains of spheres extending from them. Large cyan ovals are also embedded in the membrane. The text is overlaid on the central part of the diagram.

There are two principal signal transduction pathways involving the G protein–coupled receptors:

- the **cAMP** signal pathway and
- the **phosphatidylinositol** signal pathway

- Mechanism Contd....

- 
- The background of the slide features a stylized illustration of a cell membrane. It shows a phospholipid bilayer with yellow heads and red tails. Several blue, Y-shaped structures representing G protein-coupled receptors are embedded in the membrane. Some receptors are bound to yellow, branched structures representing ligands. The overall scene is set against a light blue background with faint, larger-scale versions of the membrane and receptor structures.
- Depending on the nature of the subunit, the active, GTP-bound form binds to and regulates effectors such as **adenylyl cyclase (via G_s)** or **phospholipase C (via G_q)**.
 - The subunit can regulate many effectors including ion channels and enzymes such as PI3-K(phosphoinositide 3-kinase).
 - The G protein remains active until the GTP bound to the subunit is hydrolyzed to GDP.
 - The α subunit has a slow intrinsic rate of GTP hydrolysis that is modulated by a family of proteins termed regulators of G protein signaling (RGSs).
 - Once the GTP bound to the α subunit is hydrolyzed to GDP, the $\beta\gamma$ subunit and receptor recombine to form the inactive receptor-G protein heterotrimer basal complex that can be reactivated by another ligand-binding event
 - **Mechanism Contd....**

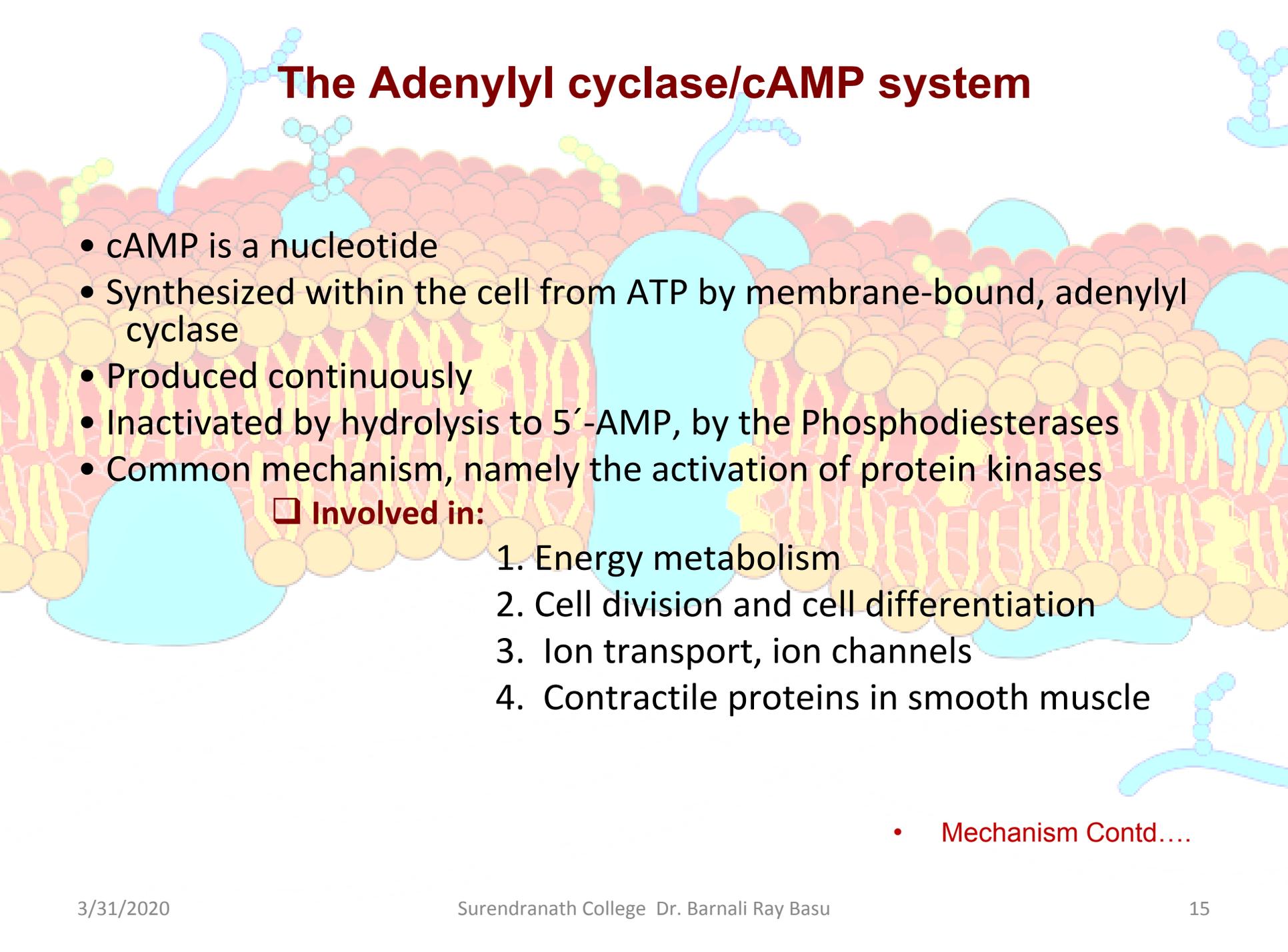


The main targets for G-proteins, through which GPCRs control different aspects of cell function are :

- **adenylyl cyclase**, the enzyme responsible for cAMP formation
- **phospholipase C**, the enzyme responsible for inositol phosphate and diacylglycerol (DAG) formation
- **ion channels**, particularly calcium and potassium channels
- **Rho A/Rho kinase**, a system that controls the activity of many signalling pathways controlling cell growth and proliferation, smooth muscle contraction, etc.

• Mechanism Contd....

The Adenylyl cyclase/cAMP system

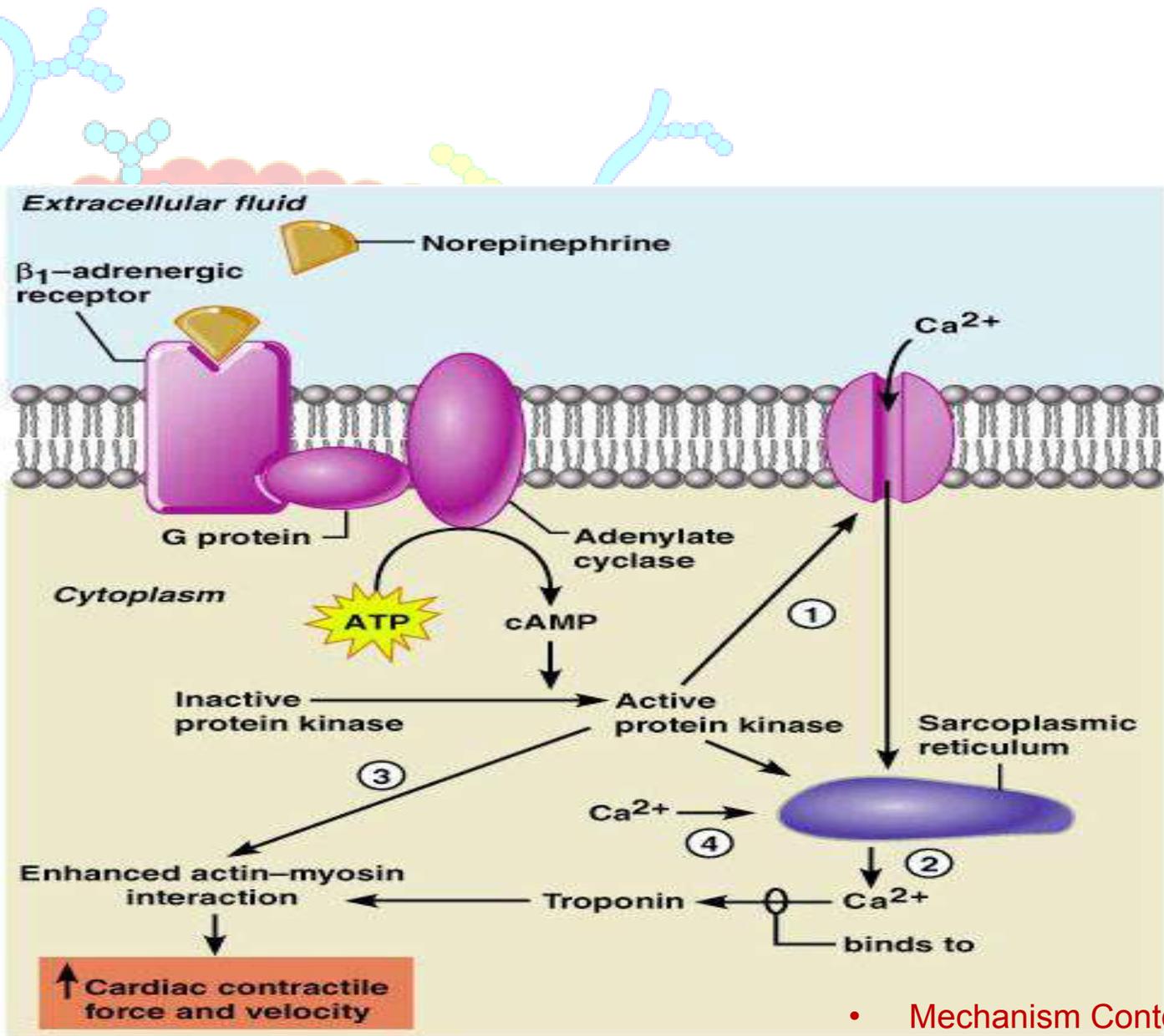


- cAMP is a nucleotide
- Synthesized within the cell from ATP by membrane-bound, adenylyl cyclase
- Produced continuously
- Inactivated by hydrolysis to 5'-AMP, by the Phosphodiesterases
- Common mechanism, namely the activation of protein kinases

Involved in:

1. Energy metabolism
2. Cell division and cell differentiation
3. Ion transport, ion channels
4. Contractile proteins in smooth muscle

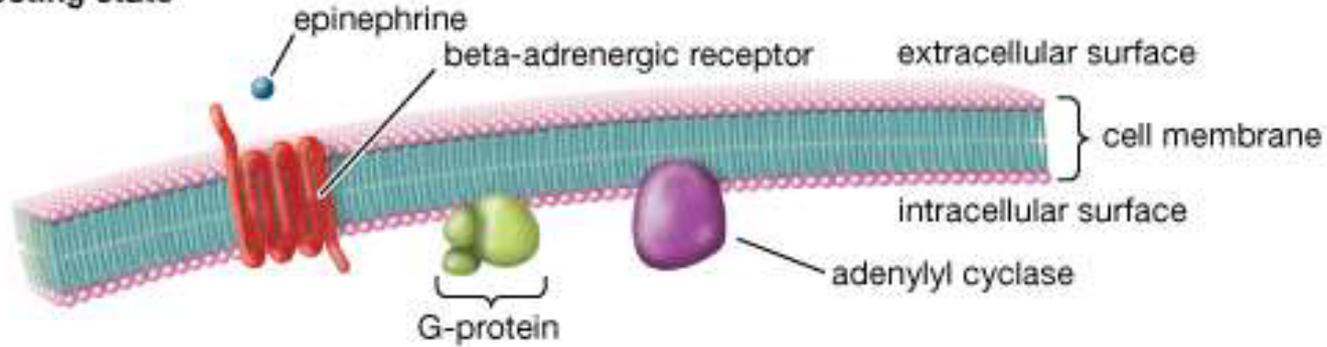
- Mechanism Contd....



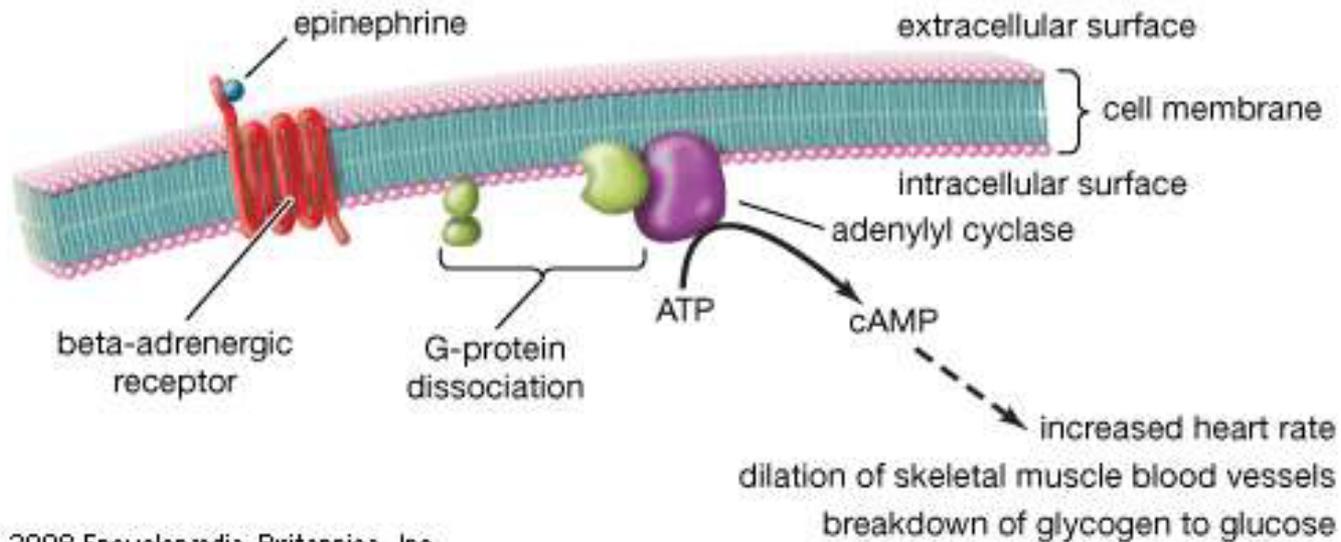
• Mechanism Contd....

Epinephrine-stimulated cAMP synthesis

resting state



stimulated state

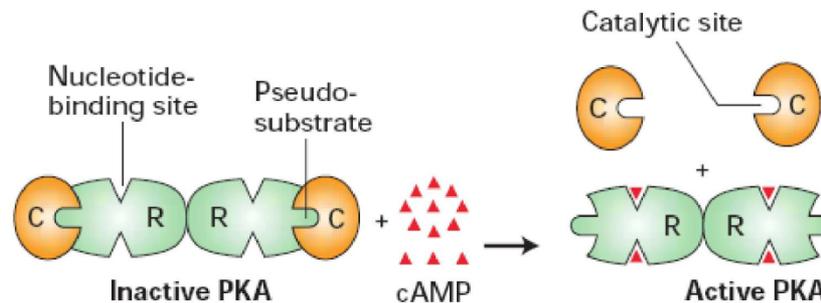


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- Mechanism Contd....

cAMP-Activate Protein Kinase A to Mediates Various Responses in Cells

Protein kinase A (cAMP dependent protein kinase) exist as an inactive tetrameric protein composed of two catalytic subunits and two regulatory subunit



Binding of cAMP by an R subunit occurs in a cooperative fashion; that is, binding of the first cAMP molecule lowers the K_d for binding of the second.

Thus small changes in the level of cytosolic cAMP can cause proportionately large changes in the amount of dissociated C subunits and, hence, in kinase activity.

- Mechanism Contd....

Glycogen Metabolism Is Regulated by Hormone-Induced Activation of PKA

The release of glucose from **glycogen**—occurs in muscle and liver cells stimulated by epinephrine or other hormones whose receptors are coupled to Gs protein

Glycogen synthase (GS)

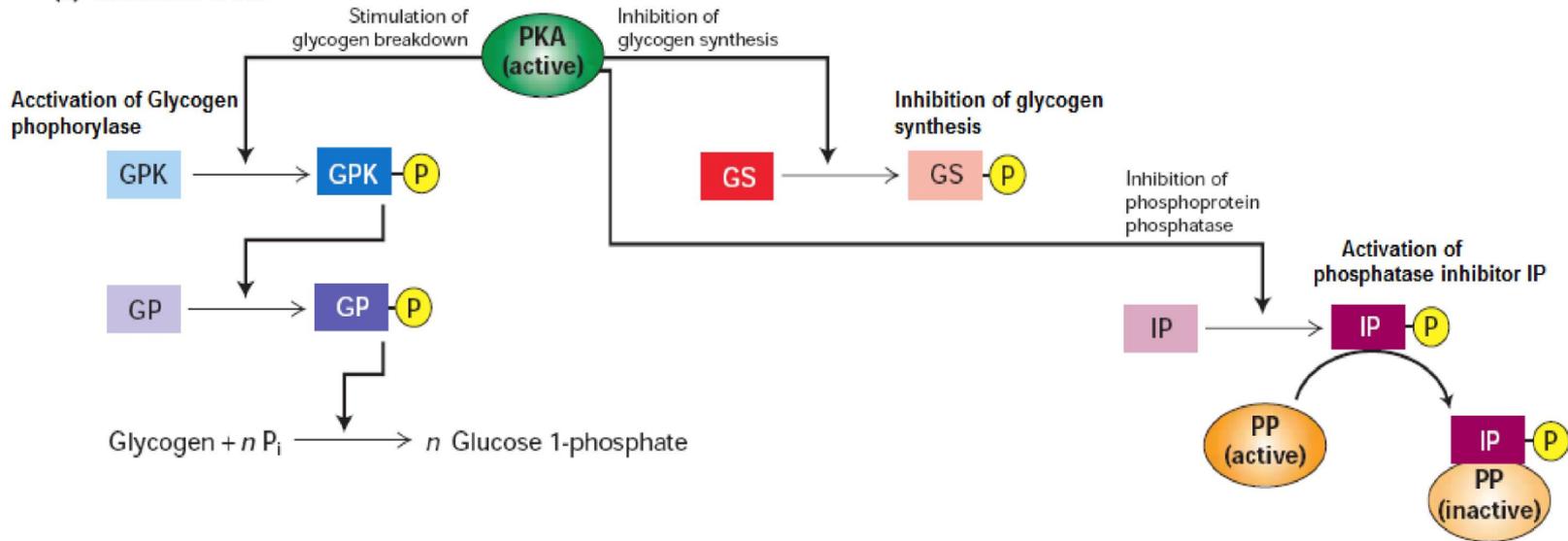


Glycogen phosphorylase (GP)



Glucose 6-P

(a) Increased cAMP



- Mechanism Contd....

Summary:

Ligand-induced activation of effector proteins associated with G protein-coupled receptors.

