Cell Signaling

1st Semester

Botany (Honours)

Biomolecule and cell biology (BSCHBOTC102)

Unit IV

By

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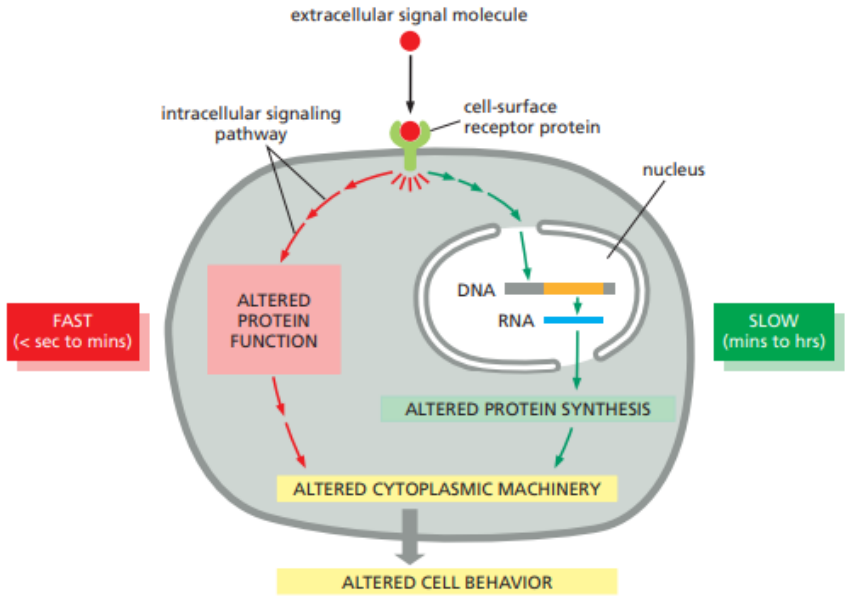
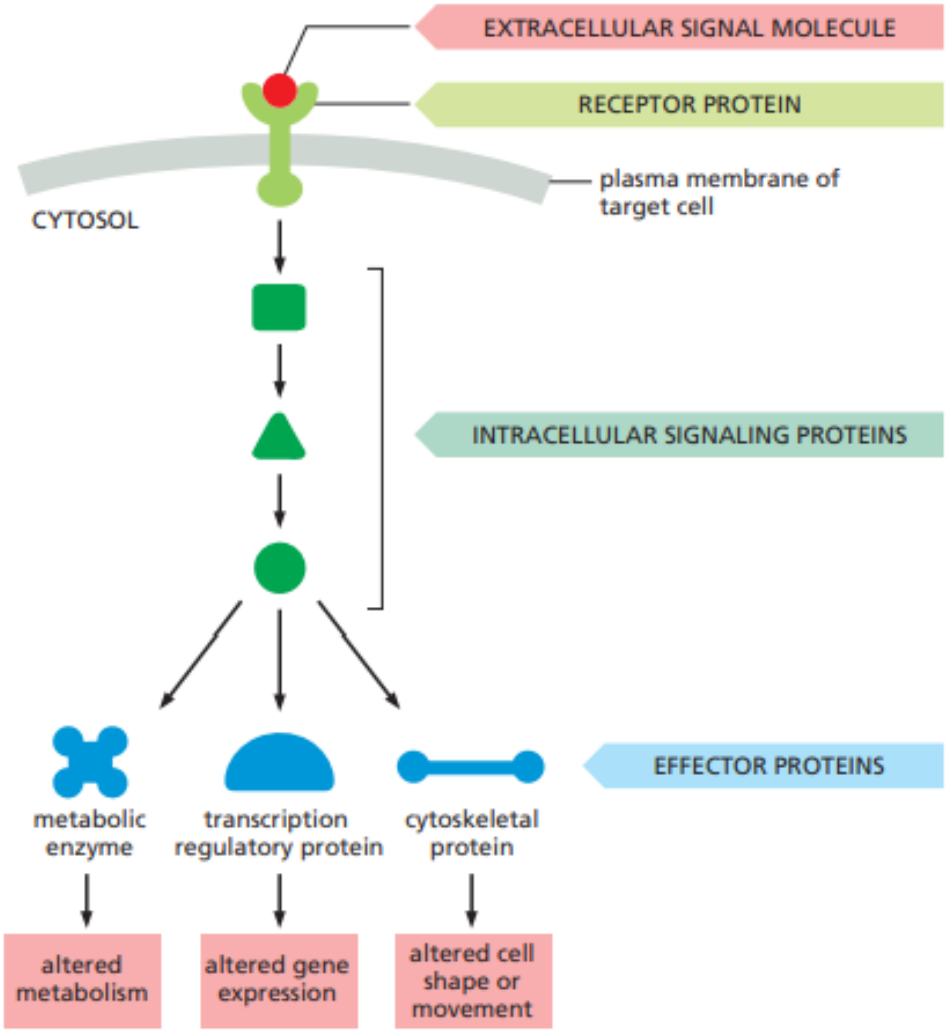
Introduction

- Cell always respond to change
- Every cell, from the most basic bacterial cell to the most complex eukaryotic cell, constantly scans its internal and external environments, analyses the data it learns, and adapts as necessary.
- For instance, unicellular organisms vary their behaviour in response to variations in the nutrients or poisons present in the environment.
- Numerous internal and external signals that regulate cellular growth, division, and differentiation throughout development as well as cellular activity in adult tissues are detected and acted upon by the cells of multicellular organisms.
- The regulatory proteins at the centre of all these communication systems generate chemical signals that are sent throughout the body or within a cell, typically being processed along the way and integrating with other signals to offer effective and unambiguous communication



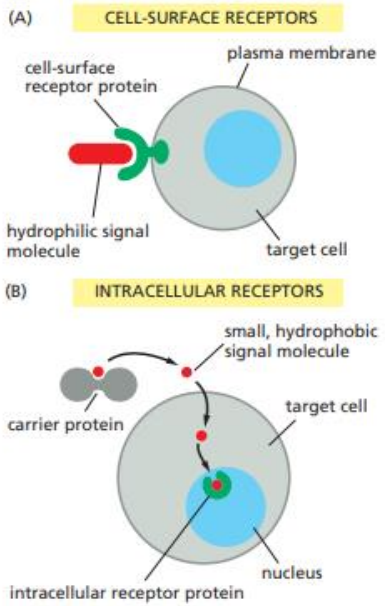
Types of molecules

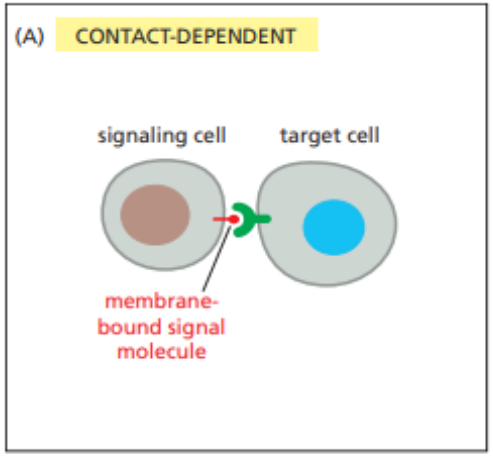
- **Extracellular signal molecules** mediates **c**ommunication between cells in multicellular organisms
- **Receptor proteins** helps in reception of the signals and depends on signal molecule that usually (but not always) binds to the cell surface
- **intracellular signaling pathways** is activated by the binding of signal molecules that activates the receptor
- These systems rely on intracellular signalling proteins, which interpret signals received from outside cells and channel them to the right intracellular destinations
- Effector proteins are the targets at the end of signalling pathways, which are modified in some manner by the incoming signal and carry out the necessary modification in cell activity
- These effectors might be transcription regulators, ion channels, metabolic pathway components, or cytoskeleton elements depending on the signal, the nature, and the condition of the receiving cell

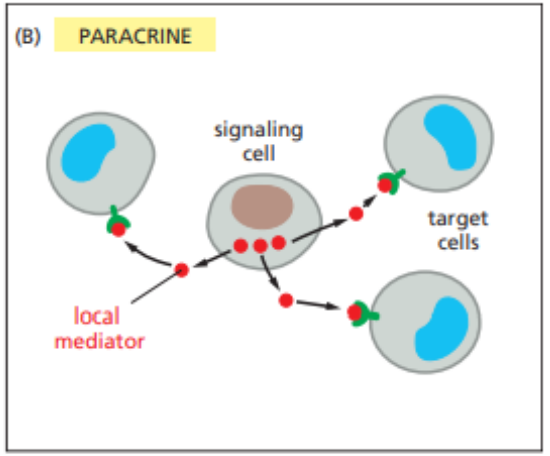


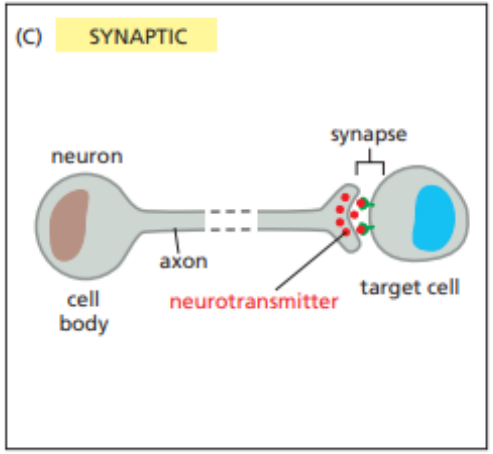
Extracellular Signals Can Act Over Short or Long Distances

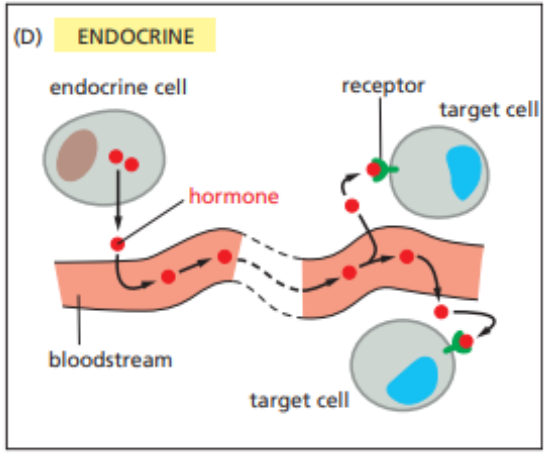
- **paracrine signaling** are locally mediated signal when the secreted molecules are local mediators, which act only on cells in the local environment
- In **paracrine signaling** the signaling and target cells are of different cell types
- When cells signals that they themselves respond to: this is referred to as **autocrine signaling**
- long-range signaling mechanisms is found in large multicellular organisms like human which need to coordinate the behavior of cells in remote parts of the body
- In **synaptic connection** neurotransmitter is delivered specifically to receptors on the postsynaptic target cell by the tightly organized structure of the synapse
- In **endocrine** the signal molecule called hormone secret from a distant cell and carried to the target by blood

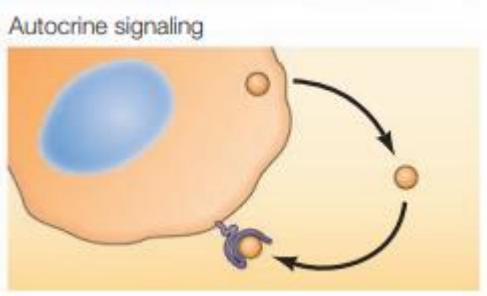












There Are Three Major Classes of Cell-Surface Receptor Proteins

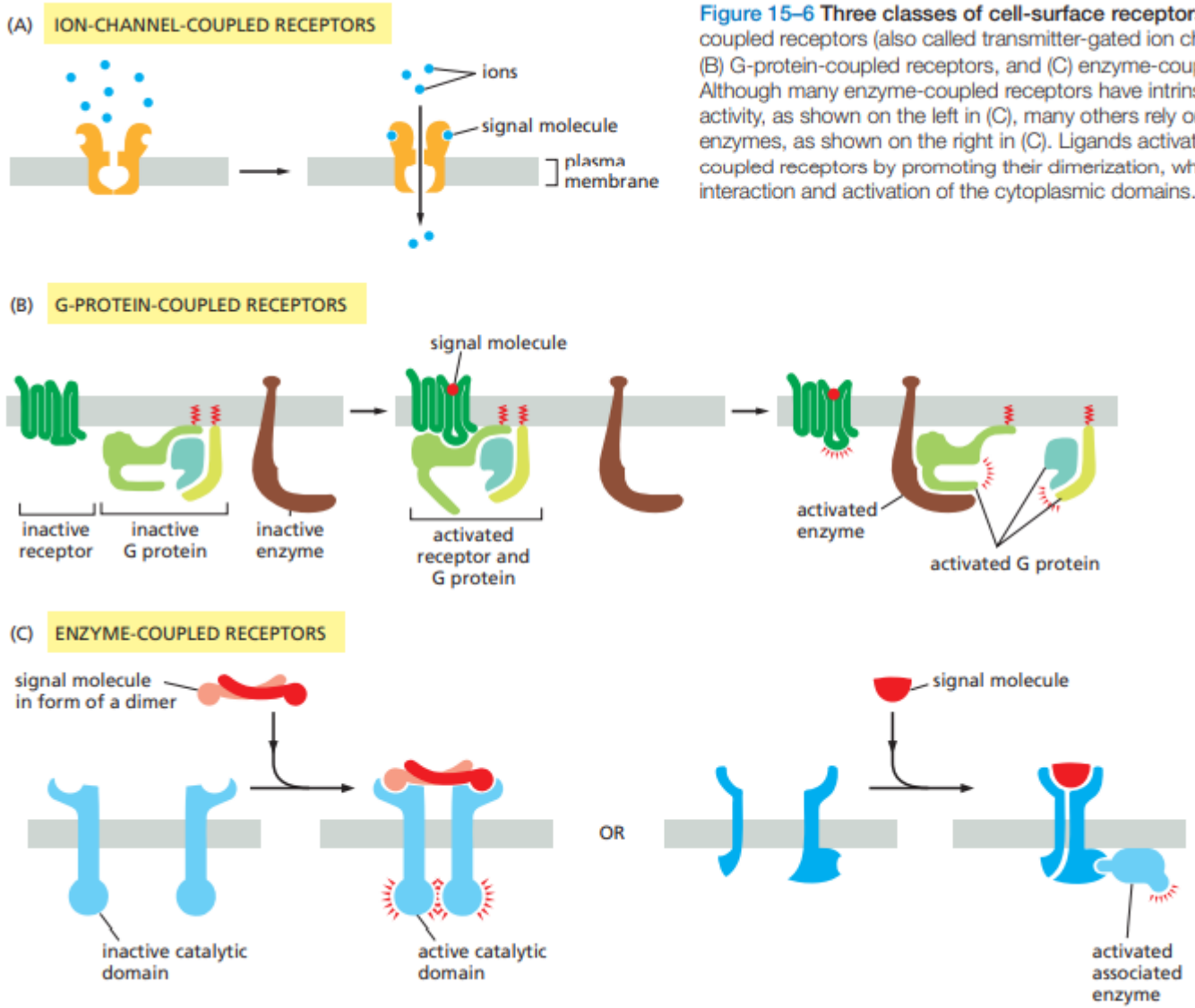
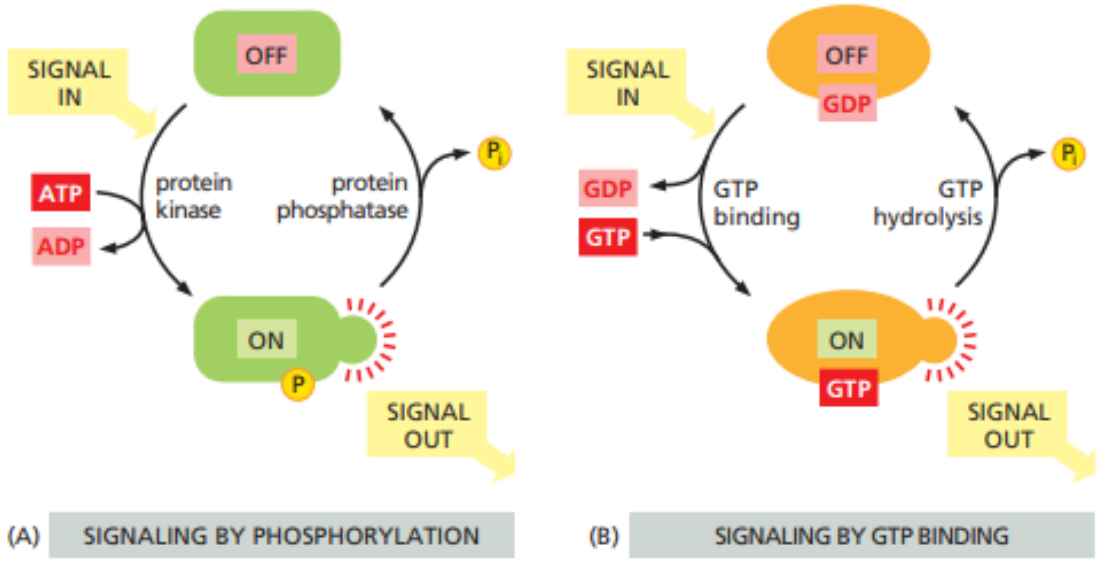


Figure 15–6 Three classes of cell-surface receptors. (A) Ion-channel-coupled receptors (also called transmitter-gated ion channels), (B) G-protein-coupled receptors, and (C) enzyme-coupled receptors. Although many enzyme-coupled receptors have intrinsic enzymatic activity, as shown on the left in (C), many others rely on associated enzymes, as shown on the right in (C). Ligands activate most enzyme-coupled receptors by promoting their dimerization, which results in the interaction and activation of the cytoplasmic domains.

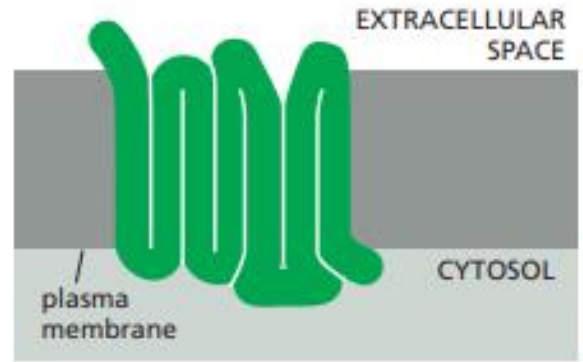
Cell-Surface Receptors Relay Signals Via Intracellular Signaling Molecules

- Numerous intracellular signalling molecules transmit messages that cell-surface receptors pick up to the inside of the cell
- Effector proteins that regulate cellular activity are altered as a result of the intracellular signalling processes that follow
- Small substances that function as some intracellular signalling molecules are frequently referred to as second messengers (the "first messengers" being the extracellular signals)
- When a receptor is activated, they are produced in huge quantities and diffuse out from the source, conveying the signal to other cell sections
- water-soluble molecules like cyclic AMP and Ca2+ diffuse in the cytosol, while lipid-soluble, such as diacylglycerol, are and diffuse in the plane of the plasma membrane



1. SIGNALING THROUGH G-PROTEIN-COUPLED RECEPTORS

- **RECEPTORS G-protein-coupled receptors (GPCRs)** The biggest class of cell-surface receptors, G-protein-coupled receptors (GPCRs), mediate the majority of responses to signals from the outside environment as well as signals from other cells, such as hormones, neurotransmitters, and local mediators
- They are essential to our ability to see, smell, and taste. In humans, there are more than 800 GPCRs

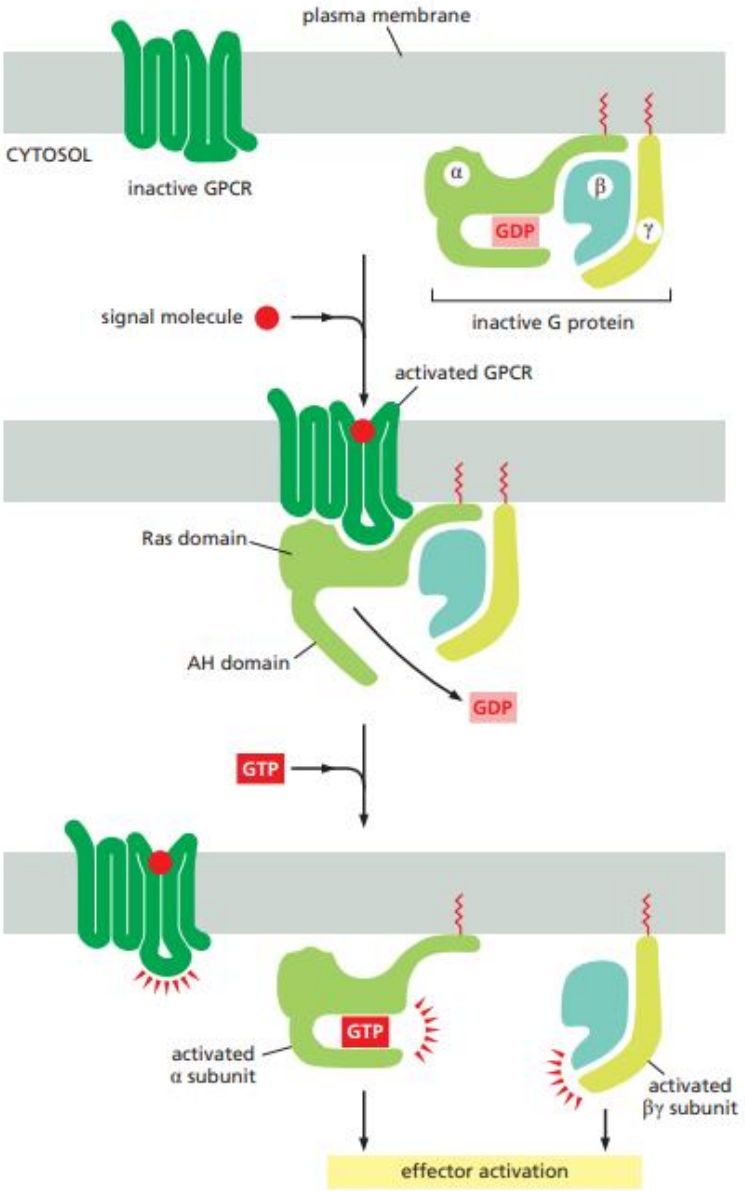


(A)

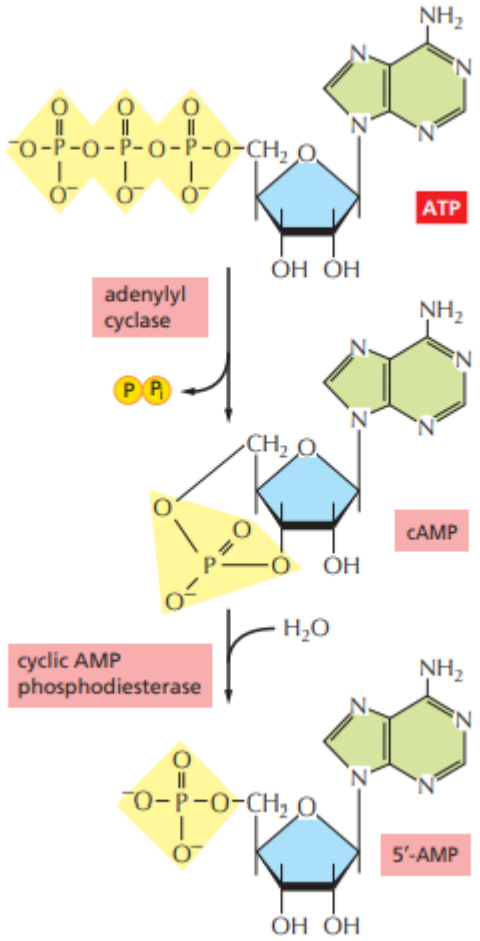

(B)

2. Trimeric G Proteins Relay Signals From GPCRs

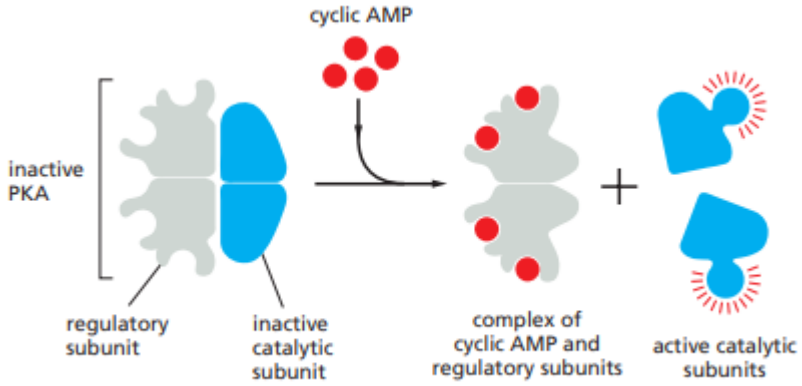
- A GPCR's conformation changes when an extracellular signal molecule binds to it, enabling the receptor to bind and modify the conformation of a trimeric G protein.
- The G protein AH domain of α subunit's moves outward to open the nucleotide-binding site, promoting the dissociation of GDP
- GTP binding, and then promotes closure of the nucleotide-binding site, causing conformational changes that result in the subunit's dissociation from the receptor and from the complex
- Each GTP-bound component of the complex controls how these downstream signalling molecules behave
- The receptor remains active while the extracellular signal molecule is attached to it, allowing it to facilitate the activation of several G-protein molecules

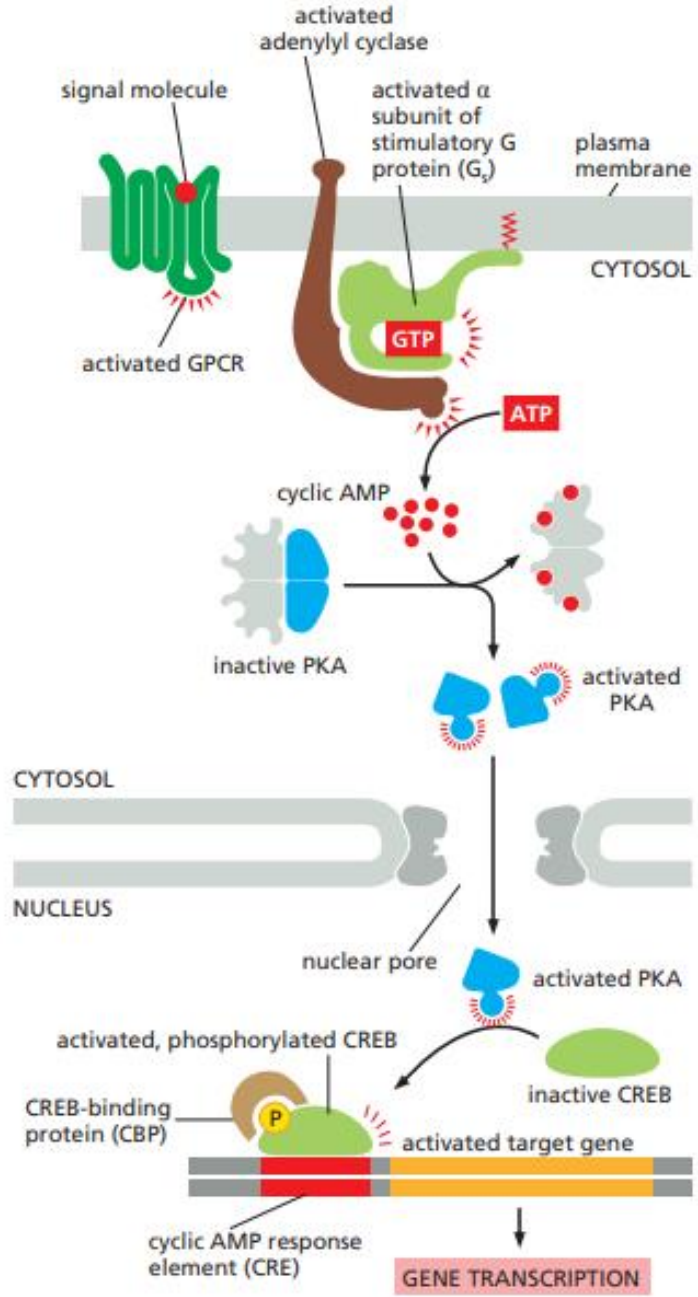


3. Some G Proteins Regulate the Production of Cyclic AMP



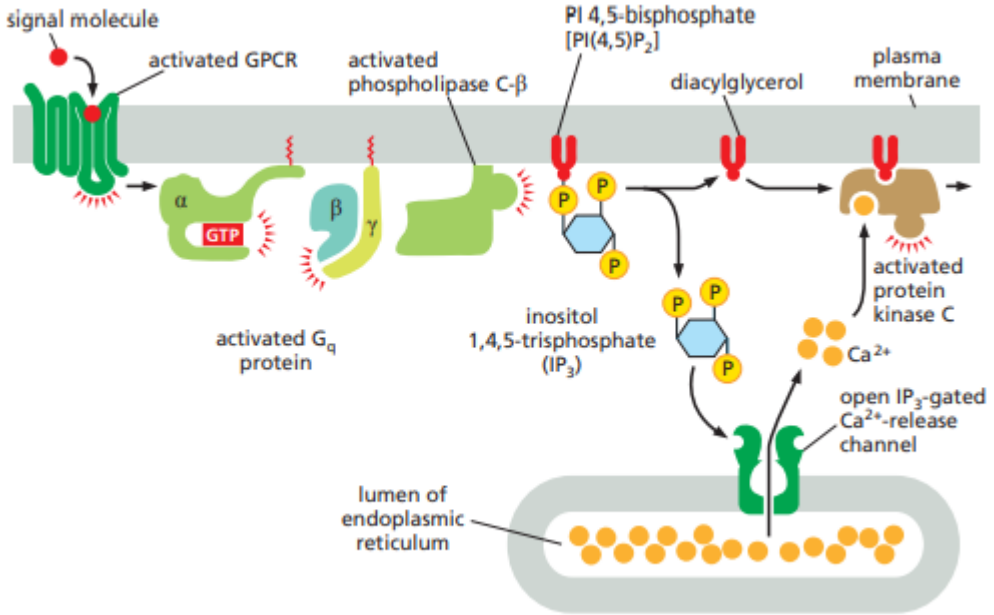
4. Cyclic-AMP-Dependent Protein Kinase (PKA) Mediates Most of the Effects of Cyclic AMP

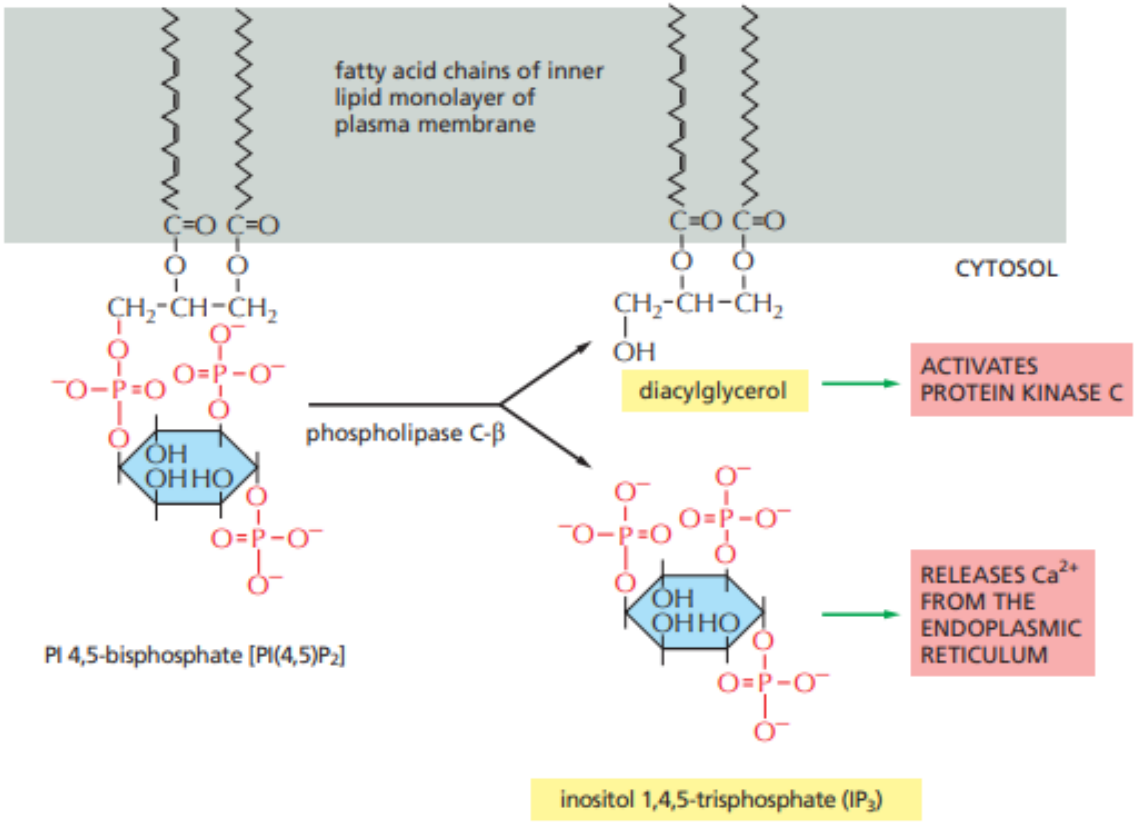



activated
adenylyl cyclase
signal molecule
activated α
subunit of
stimulatory G
protein (G_s)
plasma
membrane
CYTOSOL
GTP
activated GPCR
ATP
cyclic AMP
inactive PKA
activated
PKA
CYTOSOL
NUCLEUS
nuclear pore
activated PKA
activated, phosphorylated CREB
inactive CREB
CREB-binding
protein (CBP)
P
activated target gene
cyclic AMP response
element (CRE)
GENE TRANSCRIPTION

Some G Proteins Signal Via Phospholipids

- hydrolysis of PI(4,5)P2: inositol 1,4,5-trisphosphate (IP3) produce secondary molecules that convey the massage by diffusing through the cytosol and releases Ca2+ from the endoplasmic reticulum, and diacylglycerol, which remains in the membrane and helps to activate protein kinase C
- There are several classes of phospholipase C: these include the β class, which is activated by GPCRs; the γ class is activated by a class of enzymecoupled receptors called receptor tyrosine kinases (RTKs)





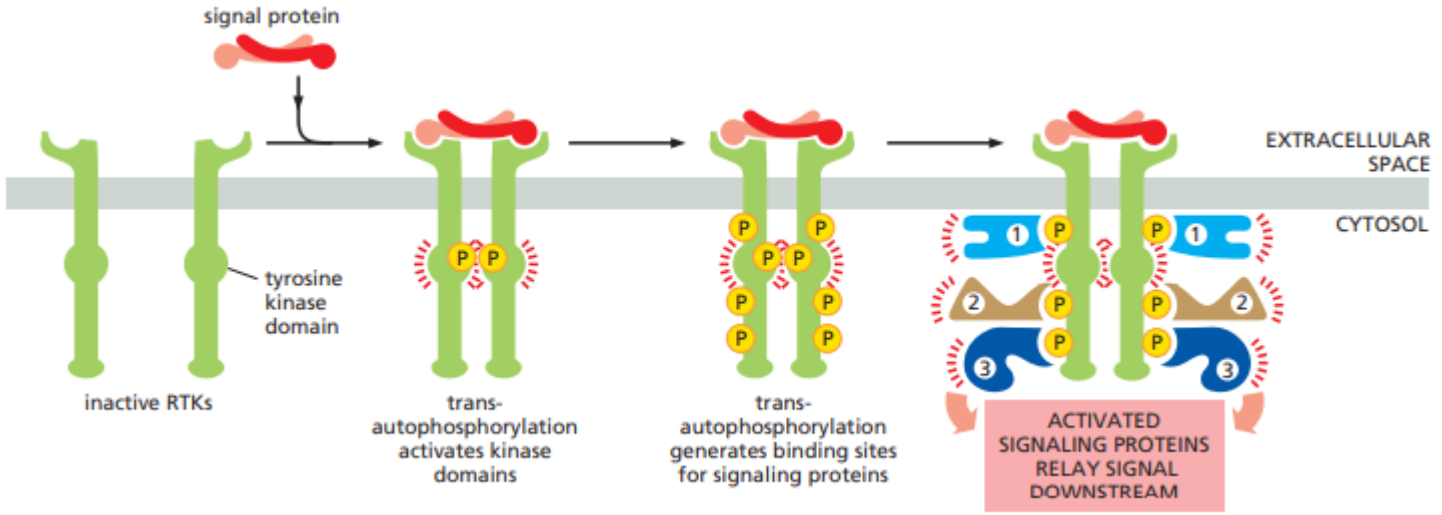
SIGNALING THROUGH ENZYME-COUPLED RECEPTORS

Enzyme-coupled receptors, like GPCRs, are transmembrane proteins with their ligand-binding domain on the plasma membrane's exterior. However, their cytosolic domain either possesses intrinsic enzyme activity or directly associates with an enzyme, as opposed to a cytosolic domain that connects with a trimeric G protein. A GPCR contains seven transmembrane segments, whereas an enzyme-coupled receptor normally only has one for each subunit

Activated Receptor Tyrosine Kinases (RTKs) Phosphorylate Themselves

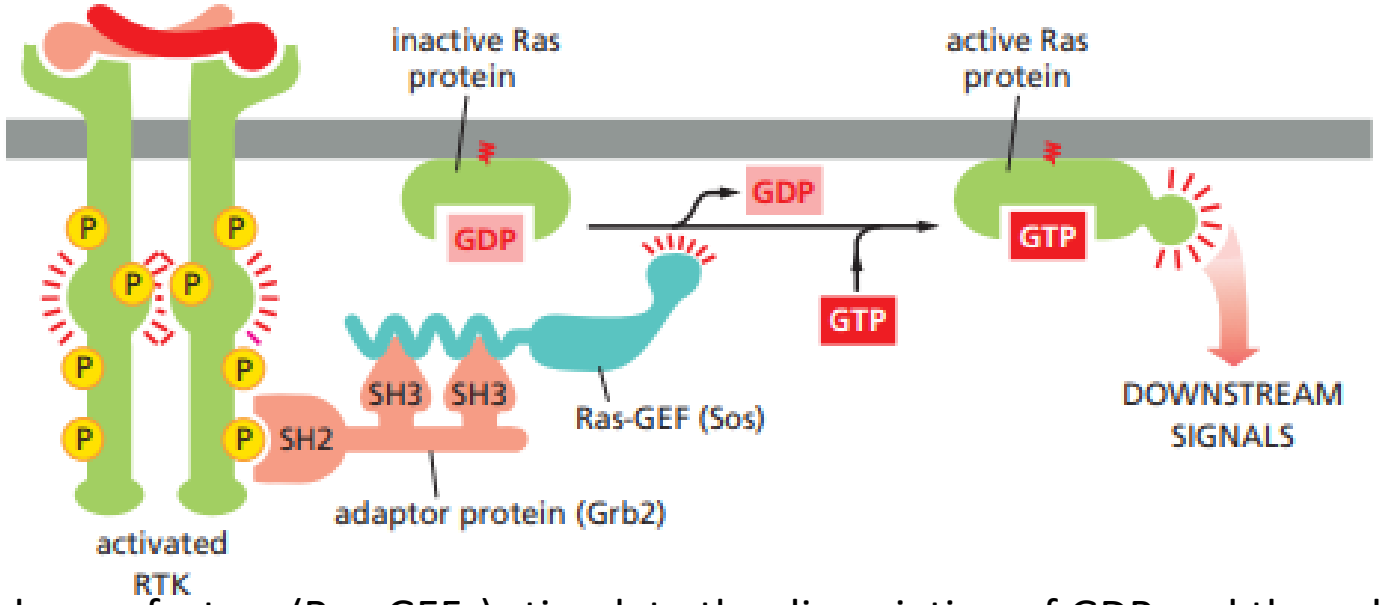
Many extracellular signal proteins act through receptor tyrosine kinases (RTKs)

- RTKs exist as monomers and internal kinase domain is inactive in the absence of extracellular signals
- two monomers comes together to form a dimer after binding of ligand
- two kinase domains phosphorylate each other in the close proximity in the dimer which has two effects
- First, the kinase domains promotes the complete activation of the domains by phosphorylation at some tyrosines
- Second, docking sites for intracellular signaling proteins is created by phosphorylation at tyrosines in other parts of the receptors resulting in the formation of large signaling complexes that can then broadcast signals along multiple signaling pathways



1. The GTPase Ras Mediates Signaling by Most RTK

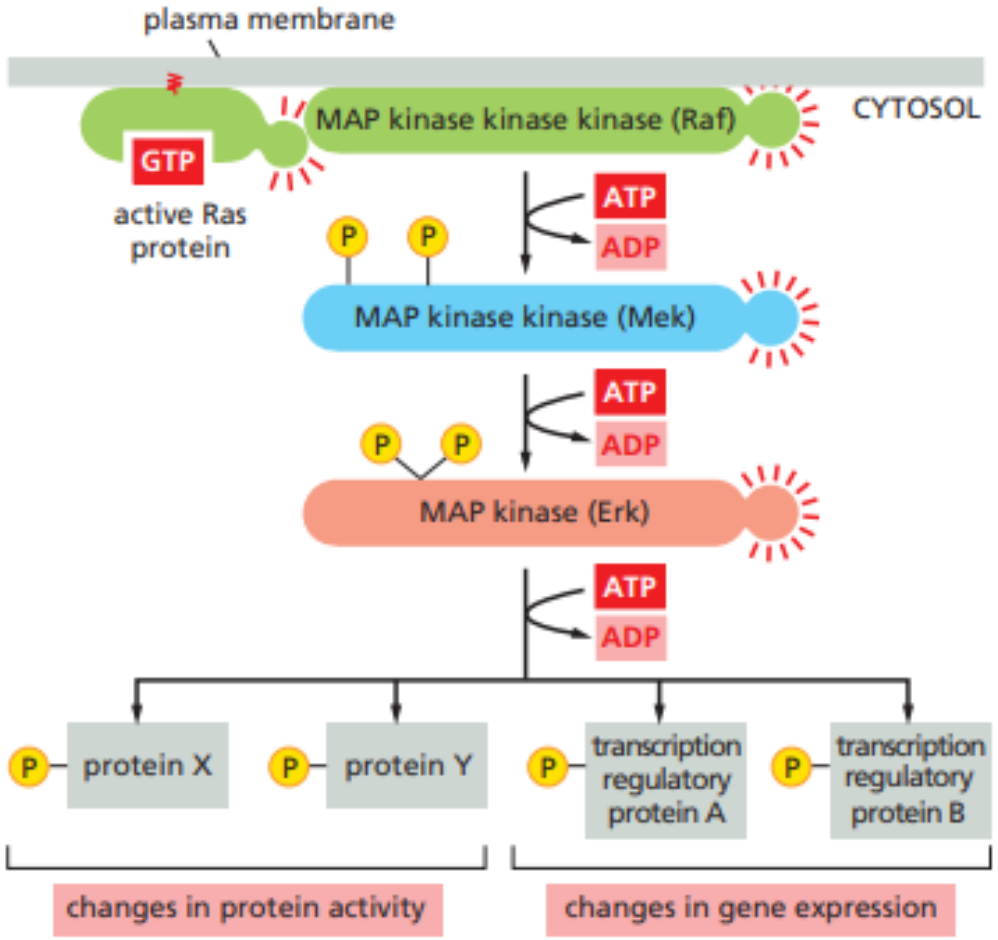
- various families of monomeric GTPases ane there in Ras superfamily
- only the Ras and Rho families relay signals from cell-surface receptors
- By interacting with different intracellular signaling proteins acting as a signaling hub



Ras guanine nucleotide exchange factors (Ras-GEFs) stimulate the dissociation of GDP and the subsequent uptake of GTP from the cytosol, thereby activating Ras

2. Ras Activates a MAP Kinase Signaling Module

- mitogen-activated protein kinase module (MAP kinase module) is one of the key mechanisms
- The three components of this system form a functional signaling module that has been remarkably well conserved during evolution and is used, with variations, in many different signaling contexts
- All the three components are protein kinases
- The final kinase is MAP kinase (MAPK)
- The next one upstream from this is MAP kinase kinase (MAPKK): it phosphorylates and thereby activates MAP kinase
- Next above that, receiving an activating signal directly from Ras, is MAP kinase kinase kinase (MAPKKK): it phosphorylates and thereby activates MAPKK
- In the mammalian Raf (= MAPKKK), Mek (= MAPKK), and Erk (=MAPK)



Thank you