



Cell Signaling and Regulation of Metabolism

Objectives

By the end of this lecture, students are expected to:

- Differentiate different steps in signaling pathways
- Describe the second messenger systems
- Recognize the function of signaling pathways for
 - Signal transmission
 - Amplification
- Discuss the role of signaling pathways in regulation and integration of metabolism

No cell lives in isolation

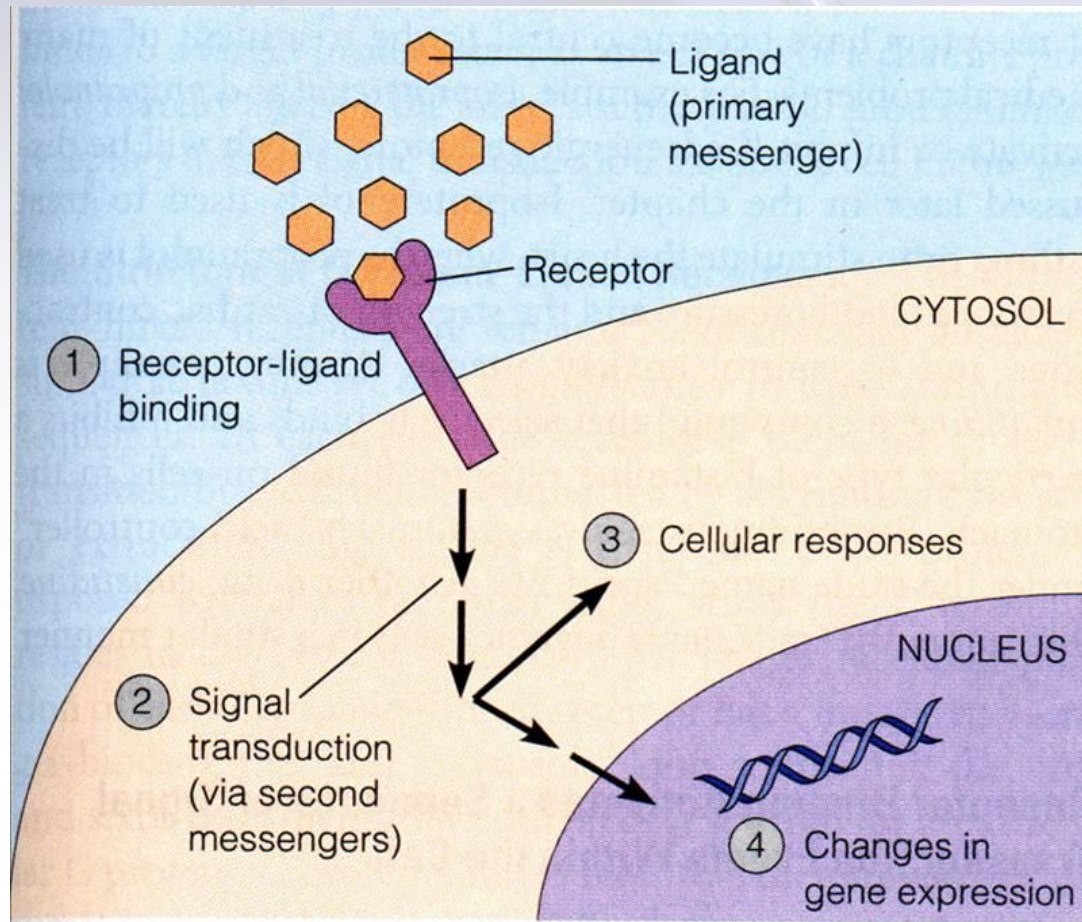
- Cells communicate with each other
- Cells send and receive information (signals)
- Information is relayed within cell to produce a response



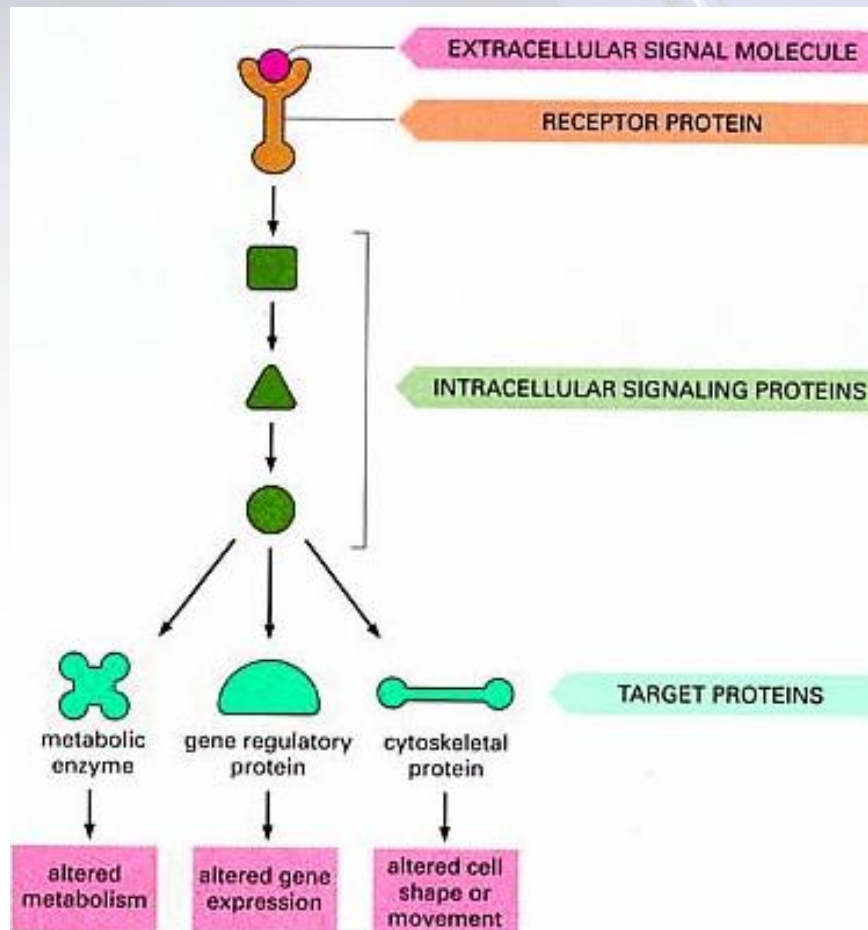
Signaling Process

- **Recognition** of signal
 - Receptors
- **Transduction**
 - Change of external signal into intracellular message with amplification and formation of second messenger
- **Effect**
 - Modification of cell metabolism and function

General Signaling Pathway



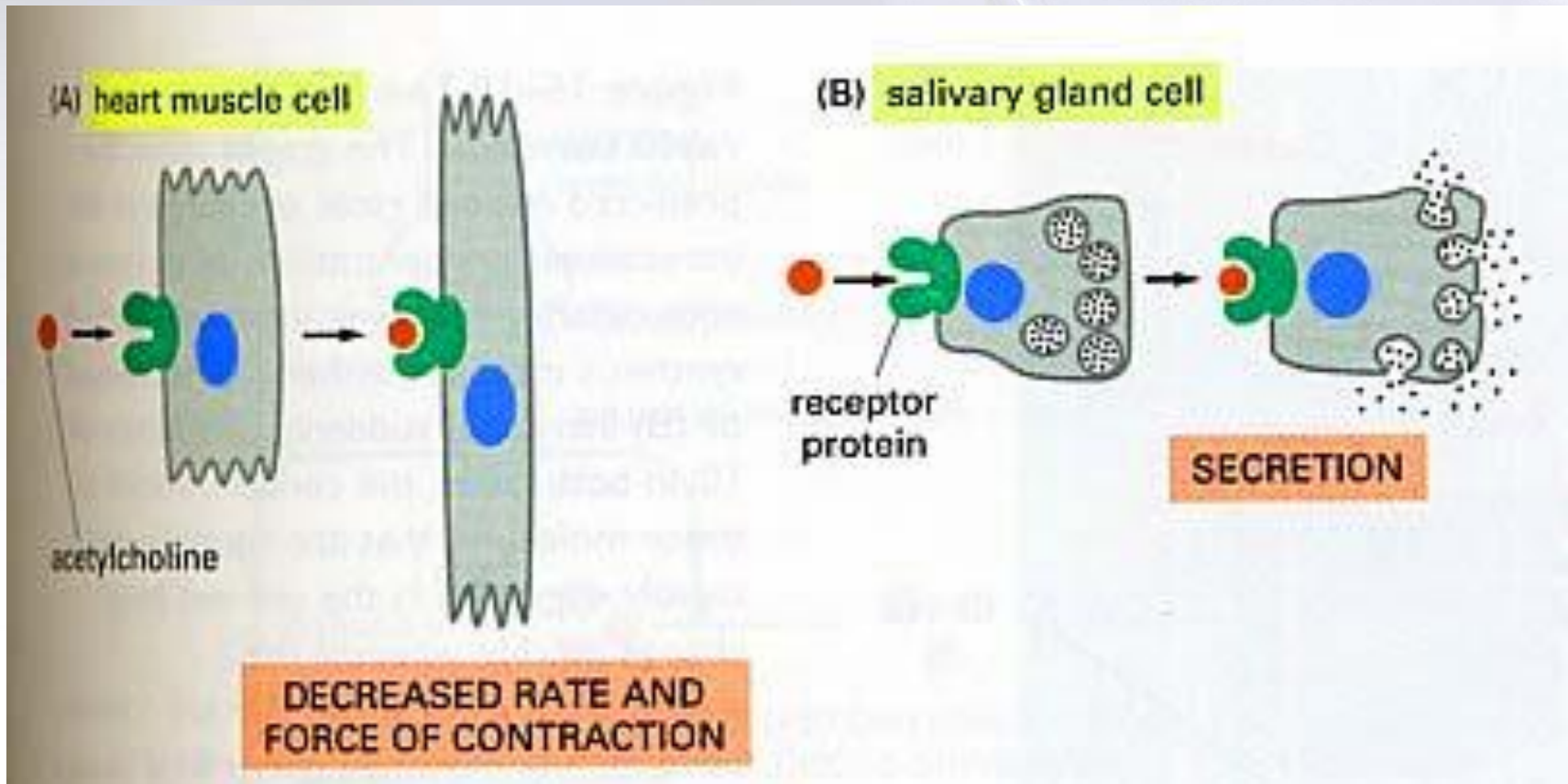
Signaling Cascades



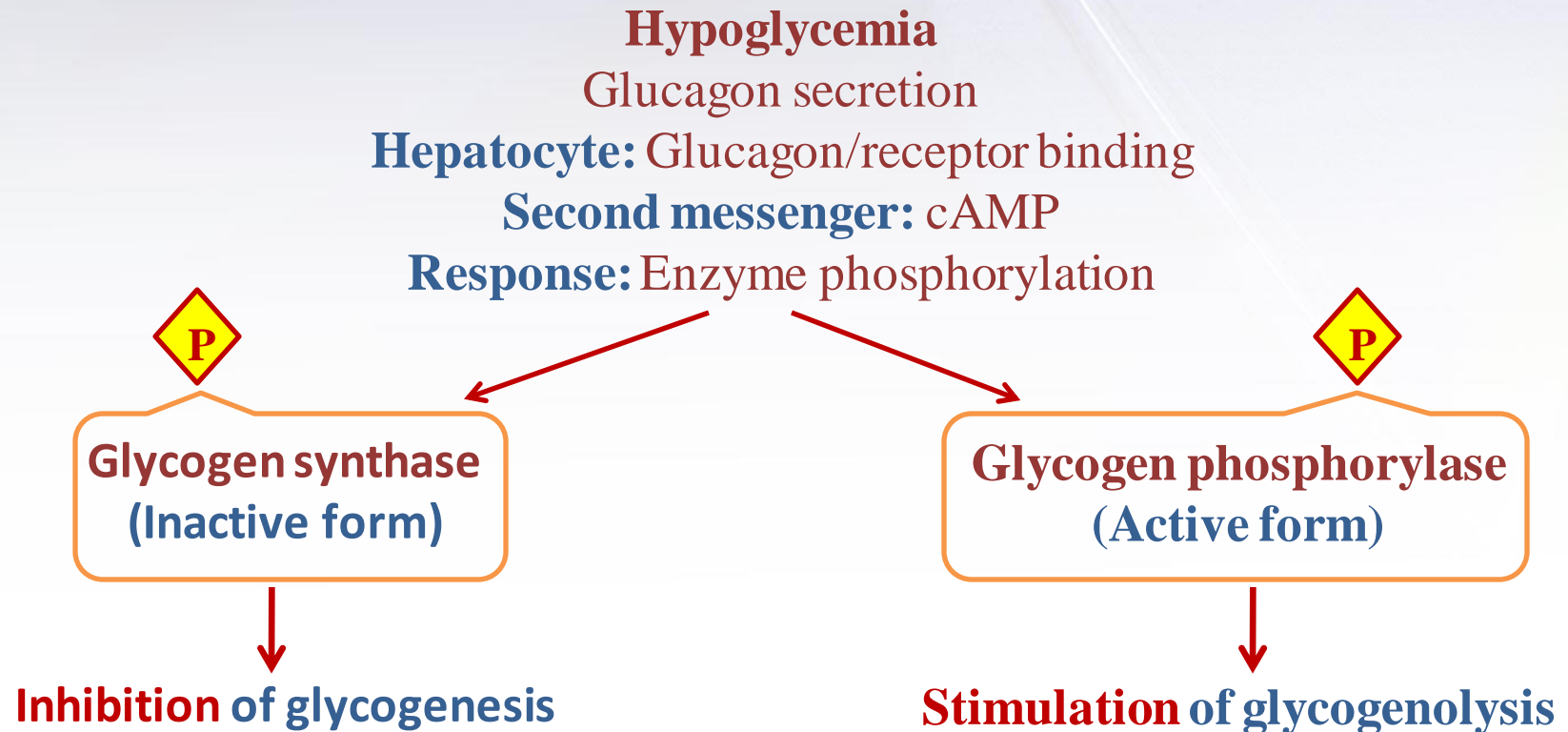
Recognition

- Performed by receptors
- Ligand will produce response only in cells that have receptors for this particular ligand
- Each cell has a specific set of receptors

Different Responses to the Same Signaling Molecule. (A) Different Cells



Different Responses to the Same Signaling Molecule. (B) One Cell but, Different Pathways



GTP-Dependant Regulatory Proteins (G-Proteins)

G-Proteins: Trimeric membrane proteins ($\alpha\beta\gamma$) G-stimulatory (G_s) and G-inhibitory (G_i) binds to GTP/GDP

Forms of G-Proteins



The α -subunit has **intrinsic GTPase activity**, resulting in hydrolysis of GTP into GDP and inactivation of G-proteins

Signaling Pathways for Regulation of Metabolism

Two important second messenger systems:

- ❑ Adenylyl cyclase system
- ❑ Calcium/phosphatidylinositol system

Adenylyl Cyclase System

Adenylyl cyclase: Membrane-bound enzyme, Converts ATP to cAMP

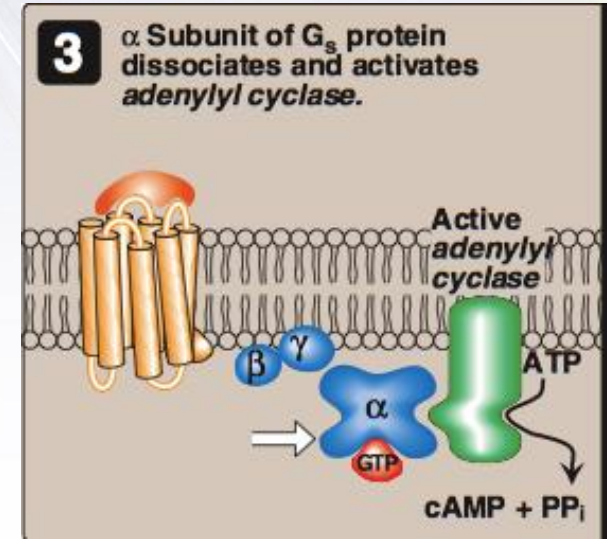
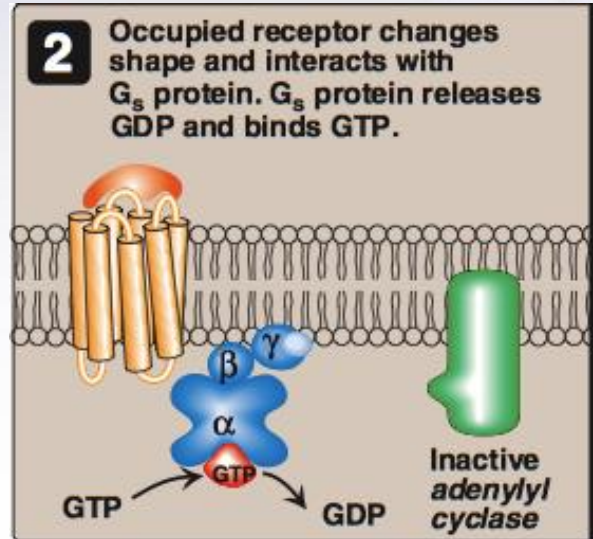
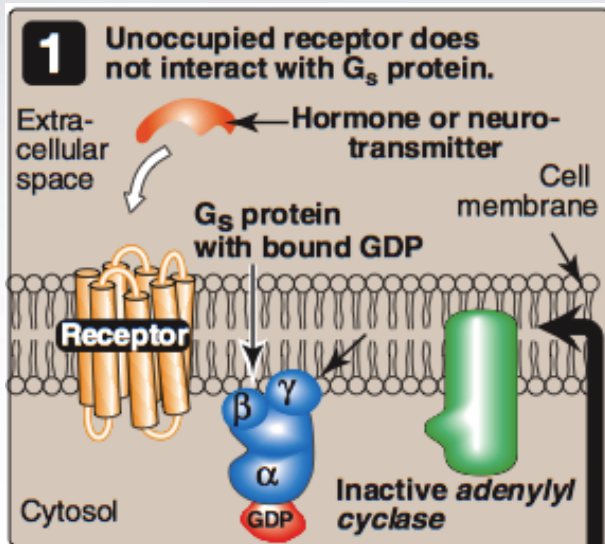
Activation/Inhibition:

Signal: Hormones or neurotransmitters (e.g., Glucagon and epinephrine)
or Toxins (e.g., Cholera and pertussis toxins)

Receptor: G-protein coupled receptor

Response: Activation/inhibition of protein kinase A (cAMP-dependent protein kinase)

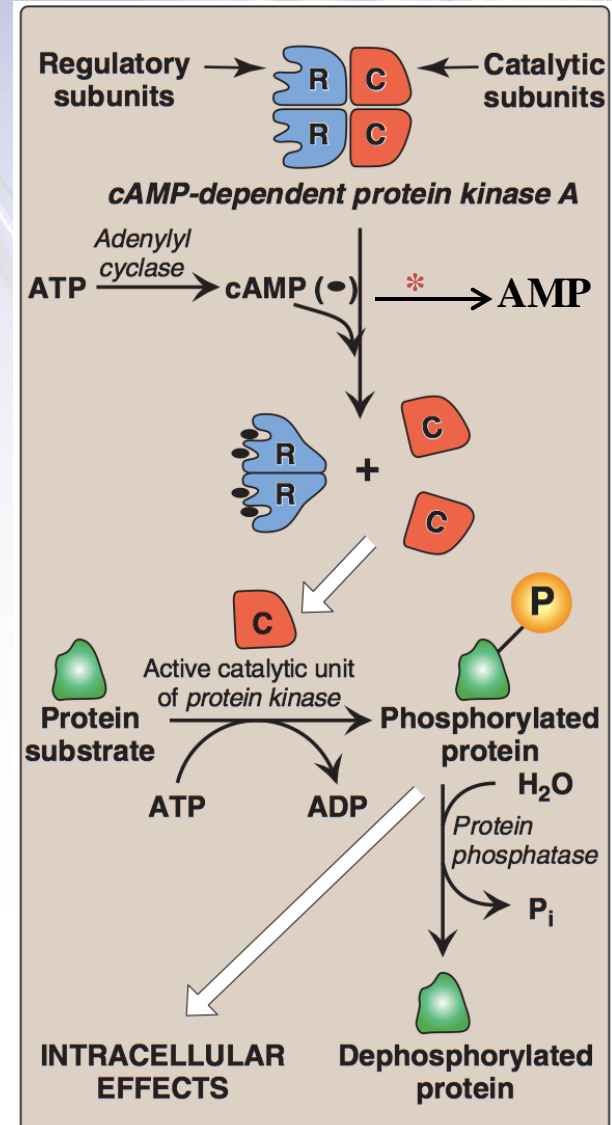
Signal Transduction: Adenylyl Cyclase System



Resting state: No Signal

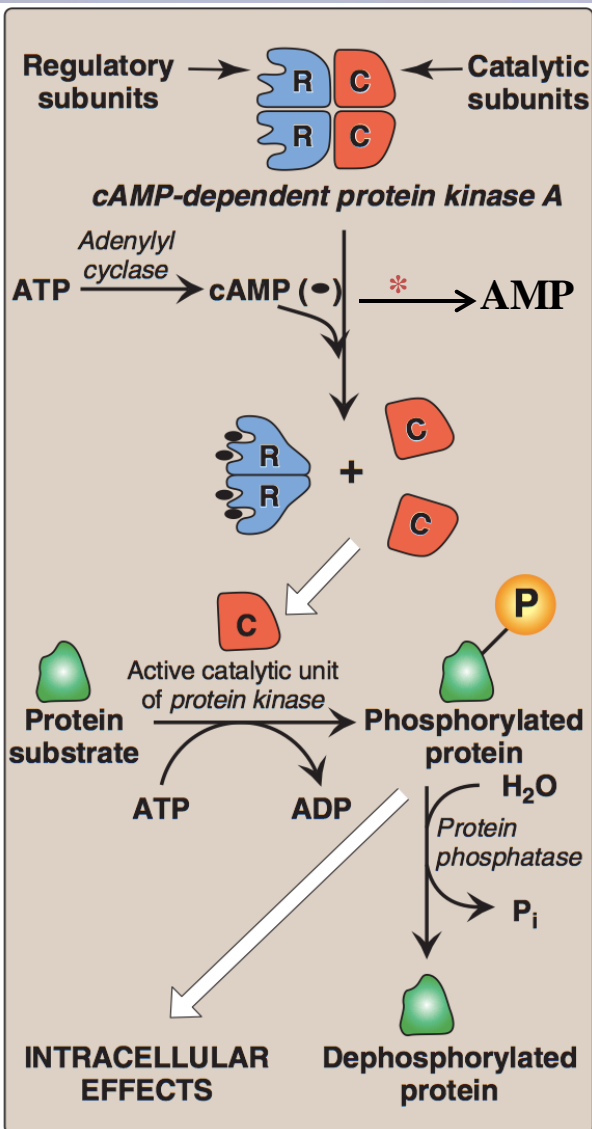
Ligand/Receptor Binding
Activation of G_s -protein
Activation of adenylyl cyclase

Actions of cAMP



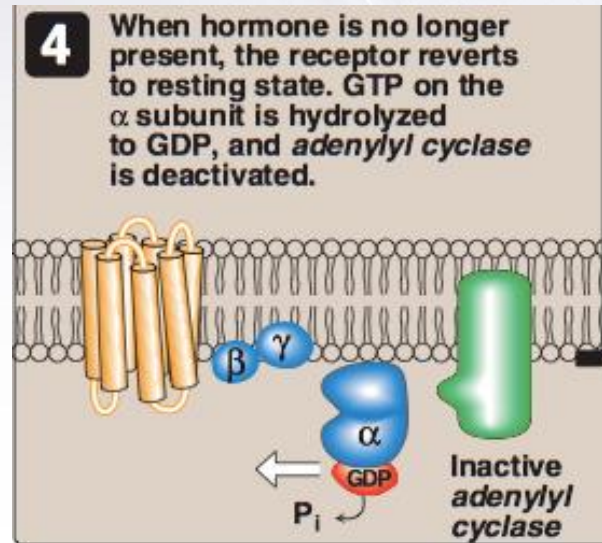
*Phosphodiesterase

Signal Termination

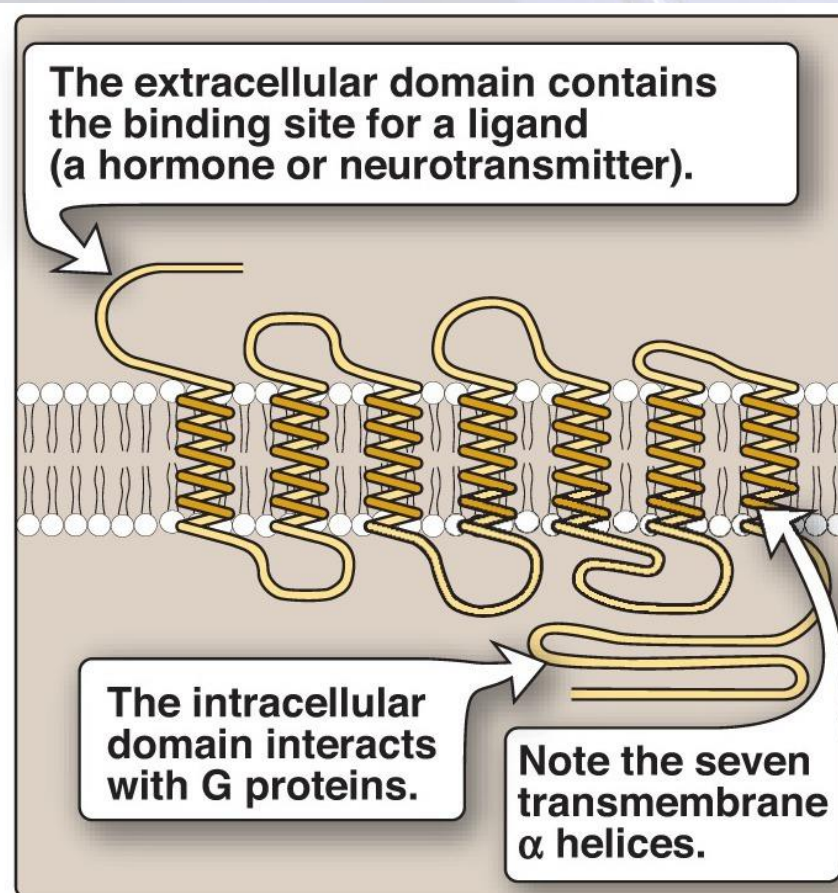


*Phosphodiesterase

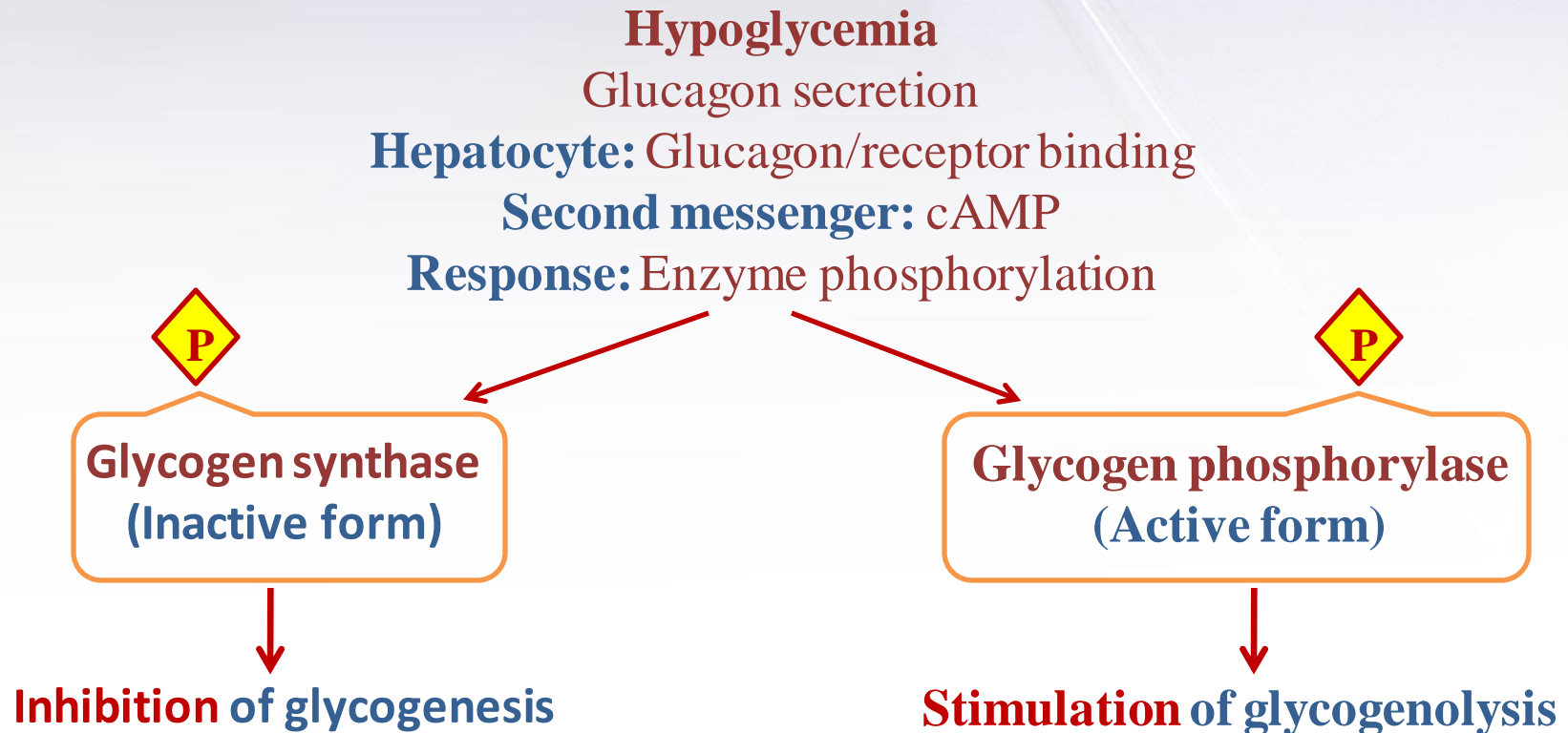
- Protein phosphatase
- Phosphodiesterase \rightarrow \downarrow cAMP \rightarrow Inactive protein kinase



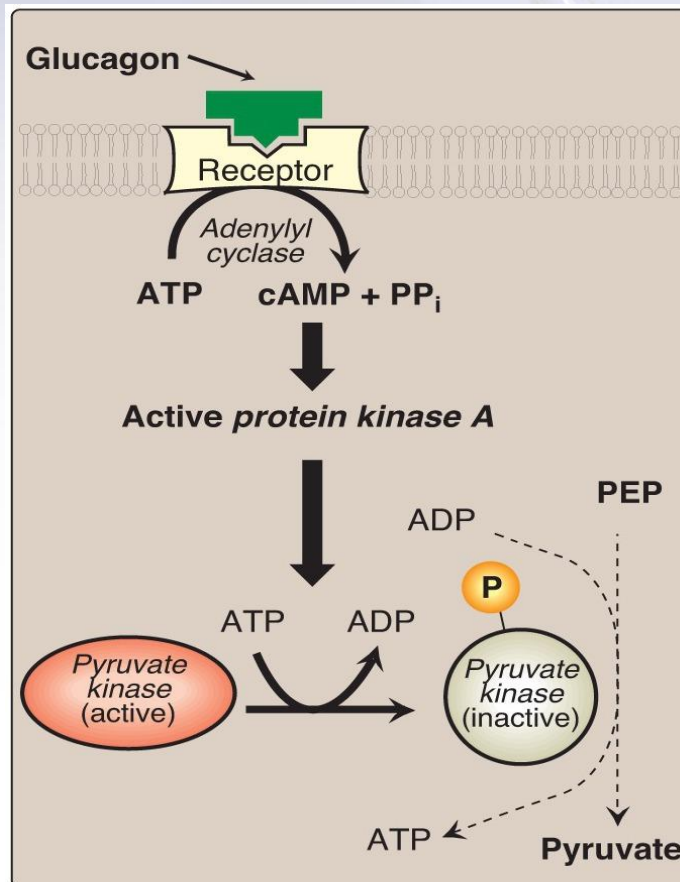
G-Protein Coupled Membrane Receptor



Regulation of Glycogen Metabolism by Glucagon: Effects on Glycogen Synthase and Phosphorylase



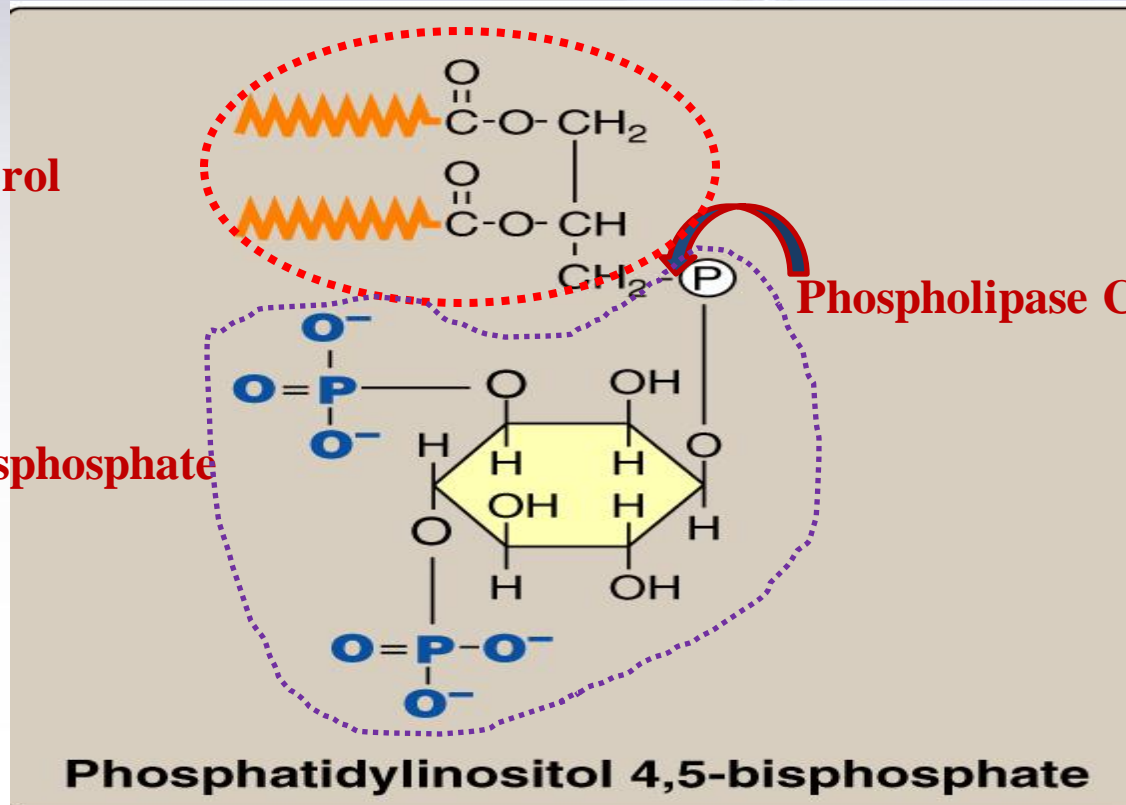
Pyruvate Kinase Regulation: Covalent Modification



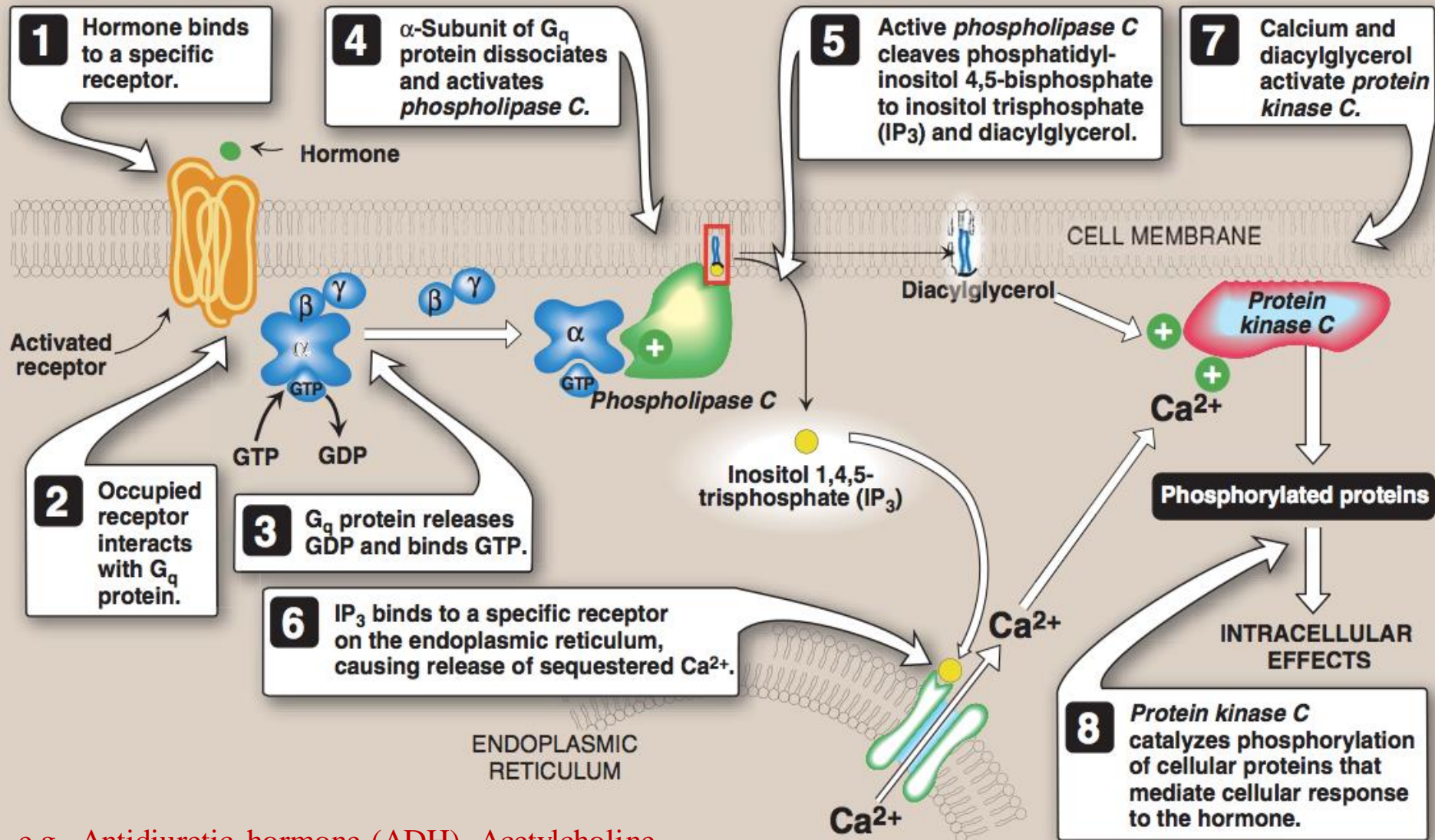
Calcium/Phosphatidylinositol System

**Diacylglycerol
(DAG)**

**Inositol Trisphosphate
(IP₃)**

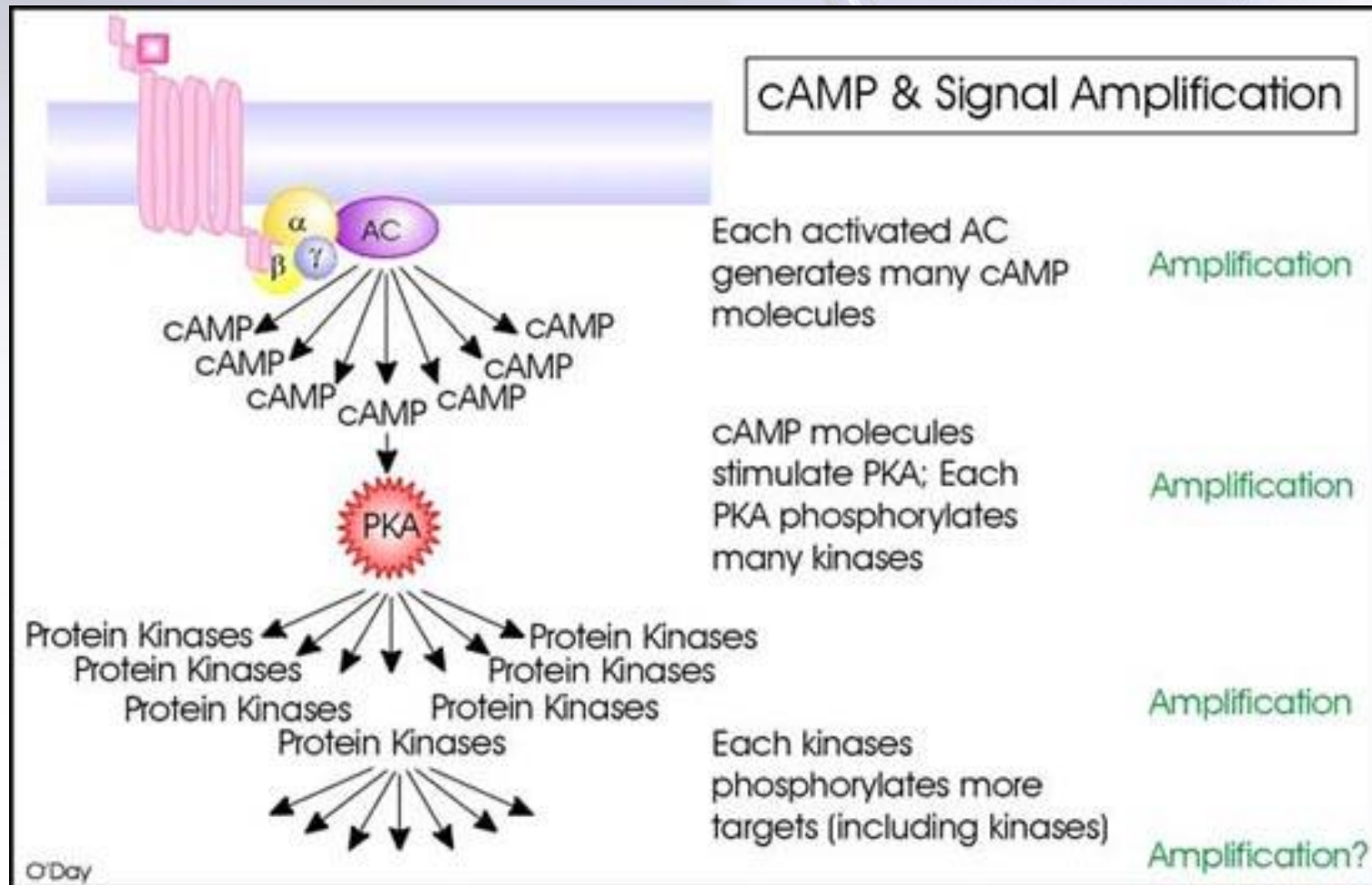


Intracellular Signaling by Inositol trisphosphate



e.g., Antidiuretic hormone (ADH), Acetylcholine

Signal Amplification



Take home messages

Cell signaling allows

- ❑ Signal transmission and amplification
- ❑ Regulation of metabolism
- ❑ Intercellular communications & coordination of complex biologic functions

Reference

Lippincott's Illustrated reviews: Biochemistry 6th edition, Unit 2, Chapter 8, Pages 91-107; and Chapter 17, Pages 204-205.