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

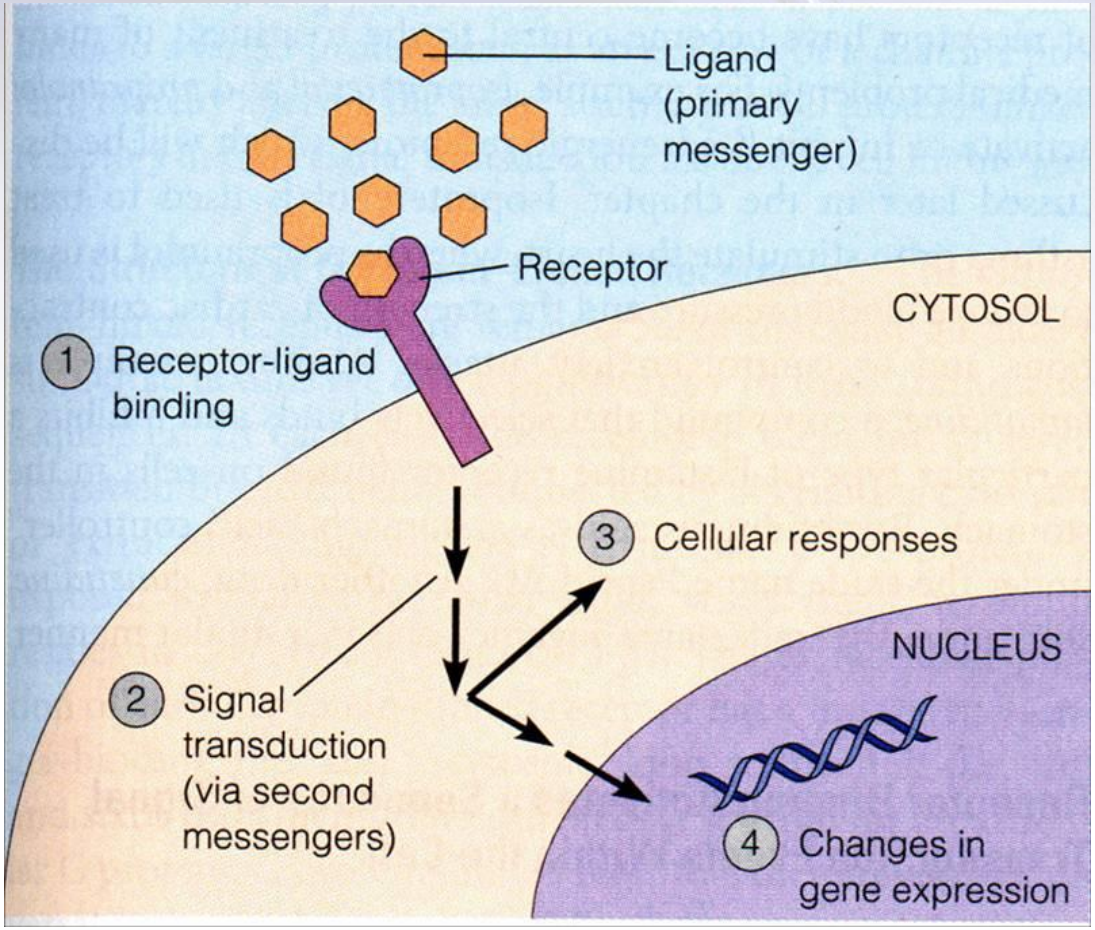
No cell lives in isolation

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

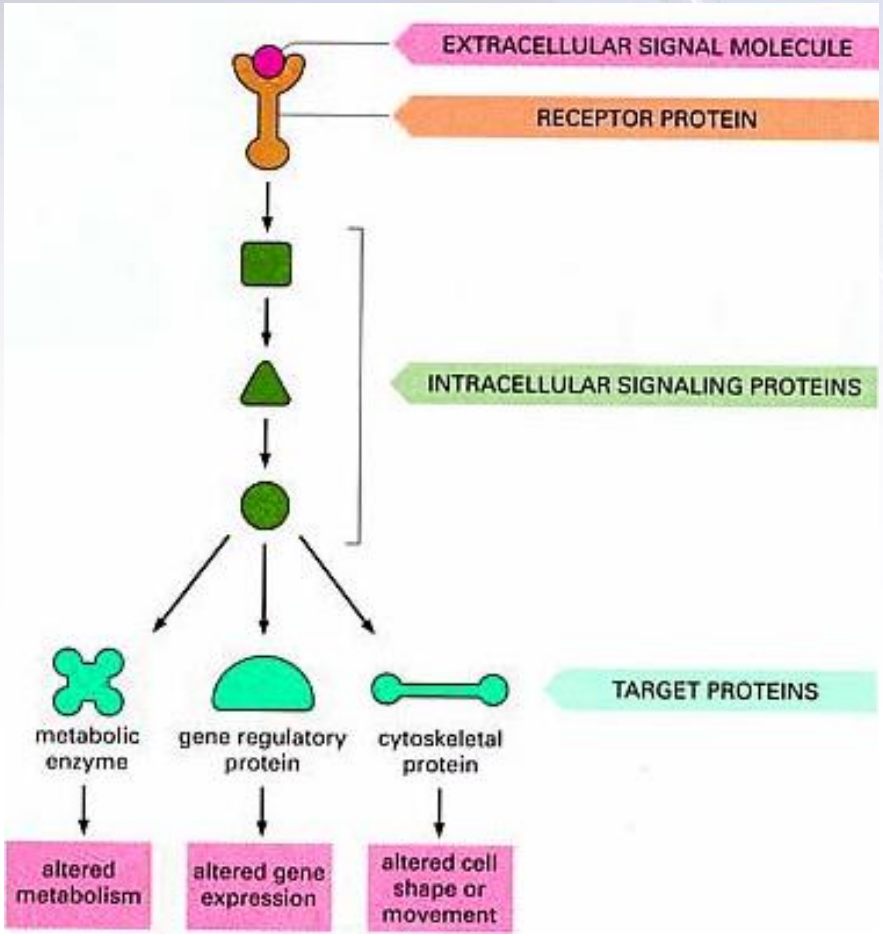
Signaling Process

- 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



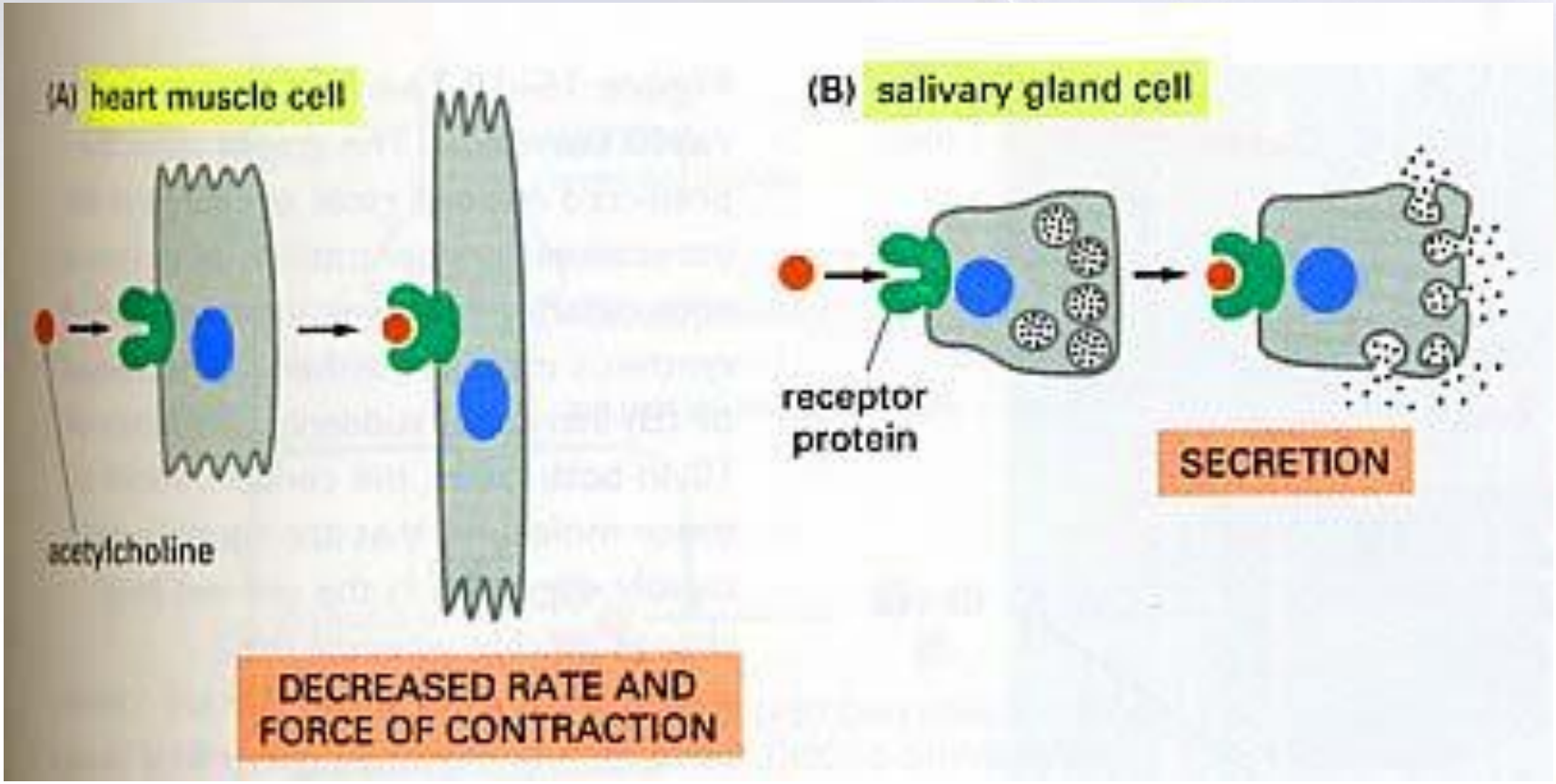
Signaling Cascades



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

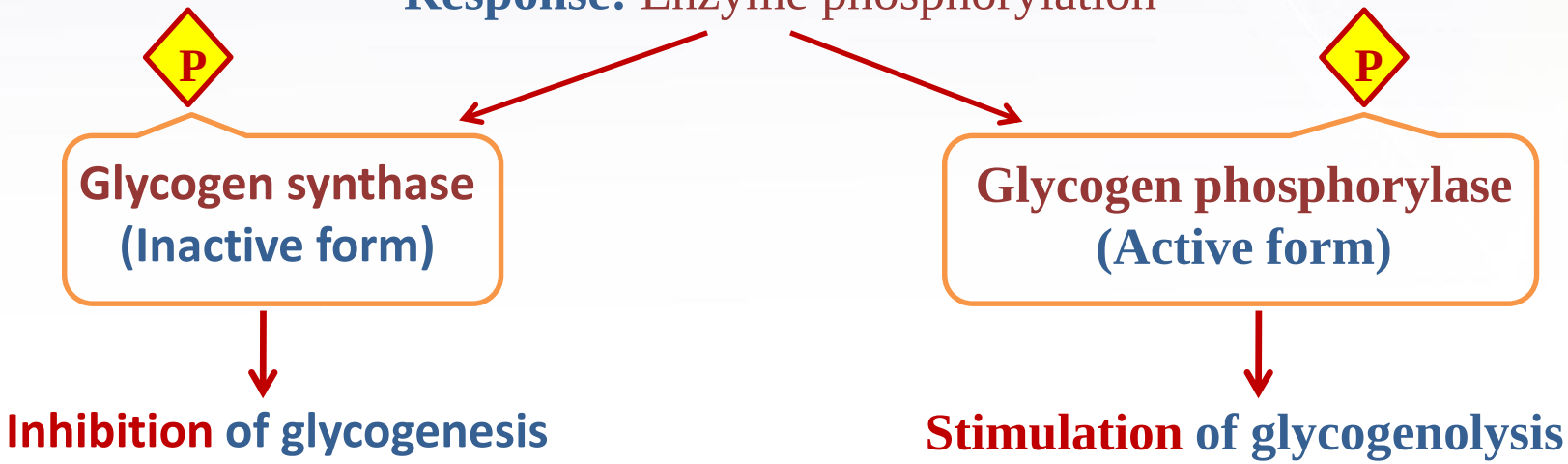
Hypoglycemia

Glucagon secretion

Hepatocyte: Glucagon/receptor binding

Second messenger: cAMP

Response: Enzyme phosphorylation



GTP-Dependant Regulatory Proteins (G-Proteins)

G-Proteins: Trimeric membrane proteins (αβγ) G-stimulatory (G_s) and G-inhibitory (G_i) binds to GTP/GDP

Forms of G-Proteins

Inactive form	Active form
Trimeric –bound GDP (αβγ/GDP)	α-bound GTP (α/GTP)

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

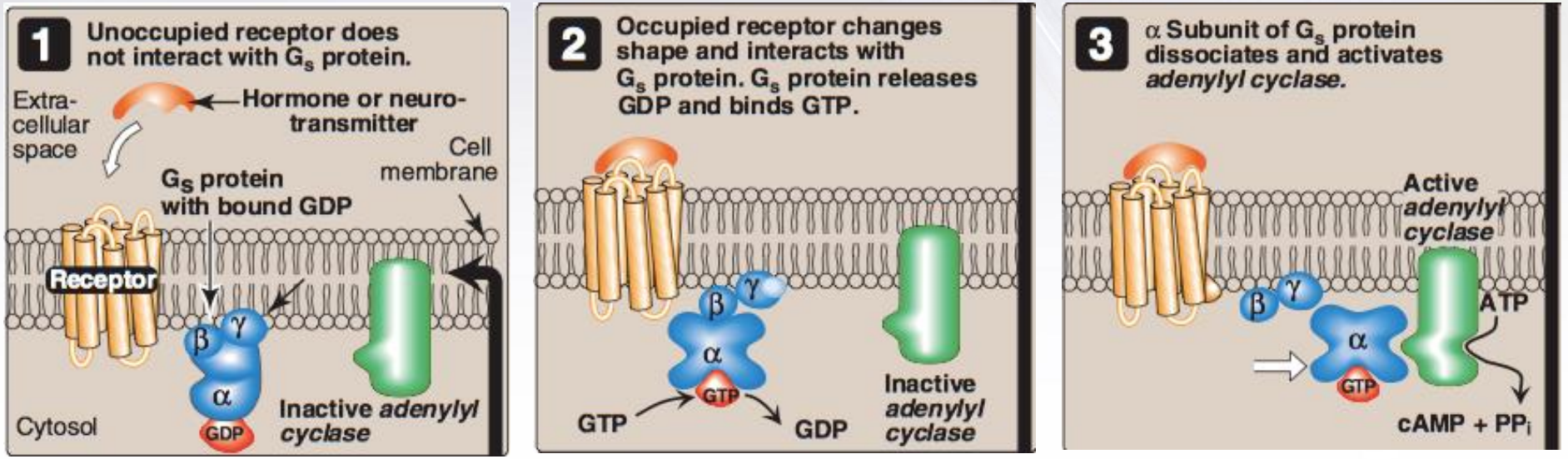
Activation/Inhibition:

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

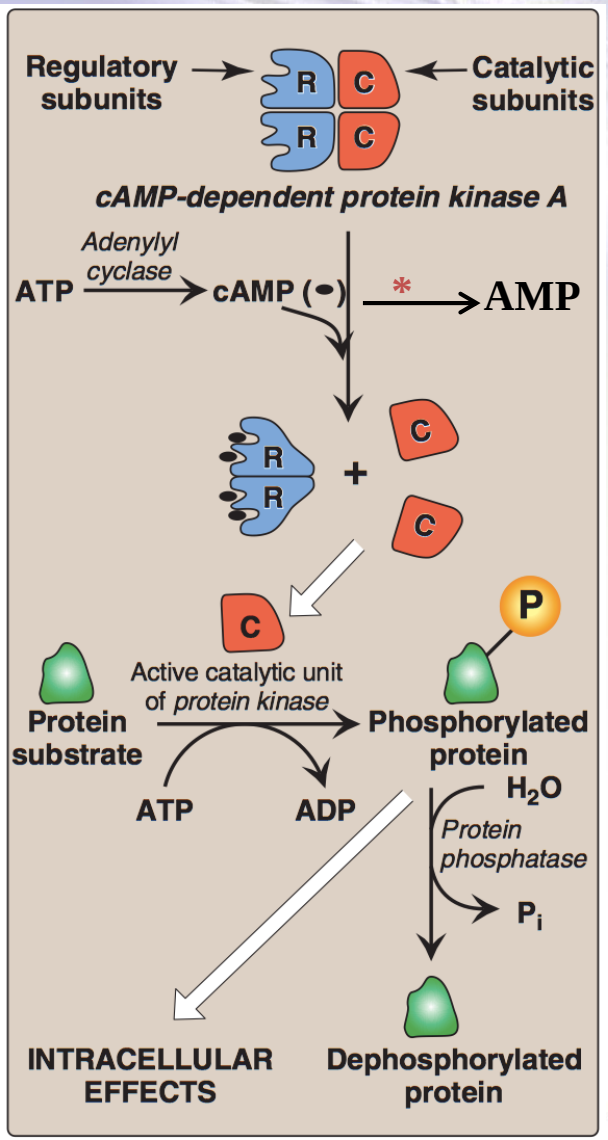


Resting state: No Signal

Ligand/Receptor Binding Activation of G_s-protein

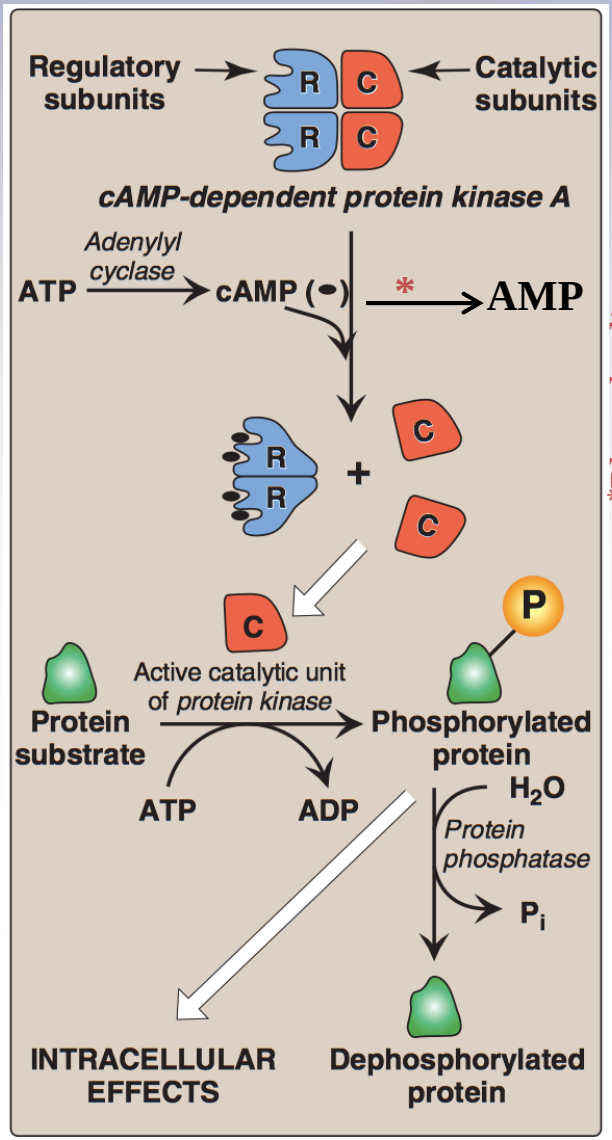
Activation of adenylyl cyclase

Actions of cAMP



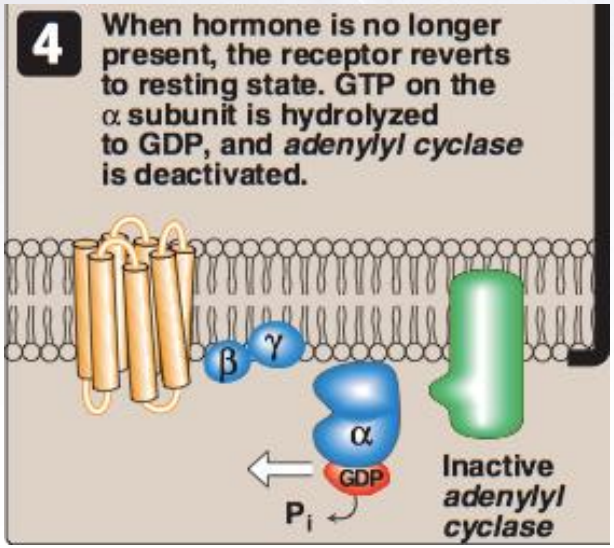
*Phosphodiesterase

Signal Termination

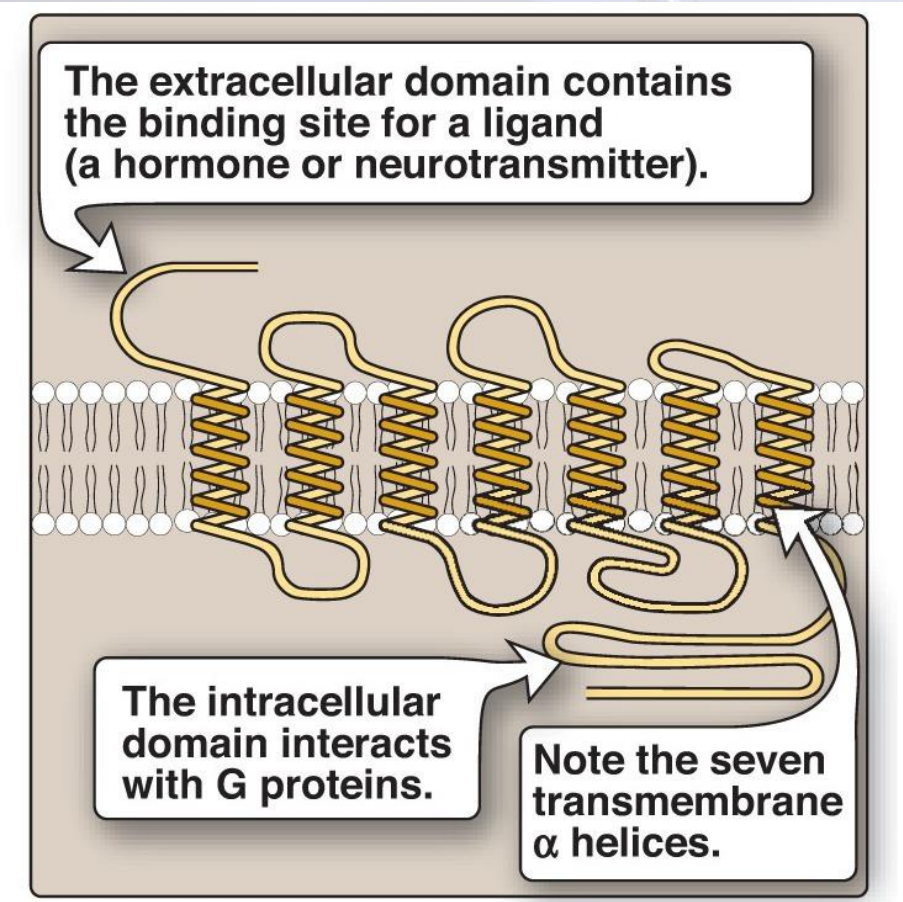


*Phosphodiesterase

- Protein phosphatase
- Phosphodiesterase → ↓cAMP → Inactive protein kinase



G-Protein Coupled Membrane Receptor



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

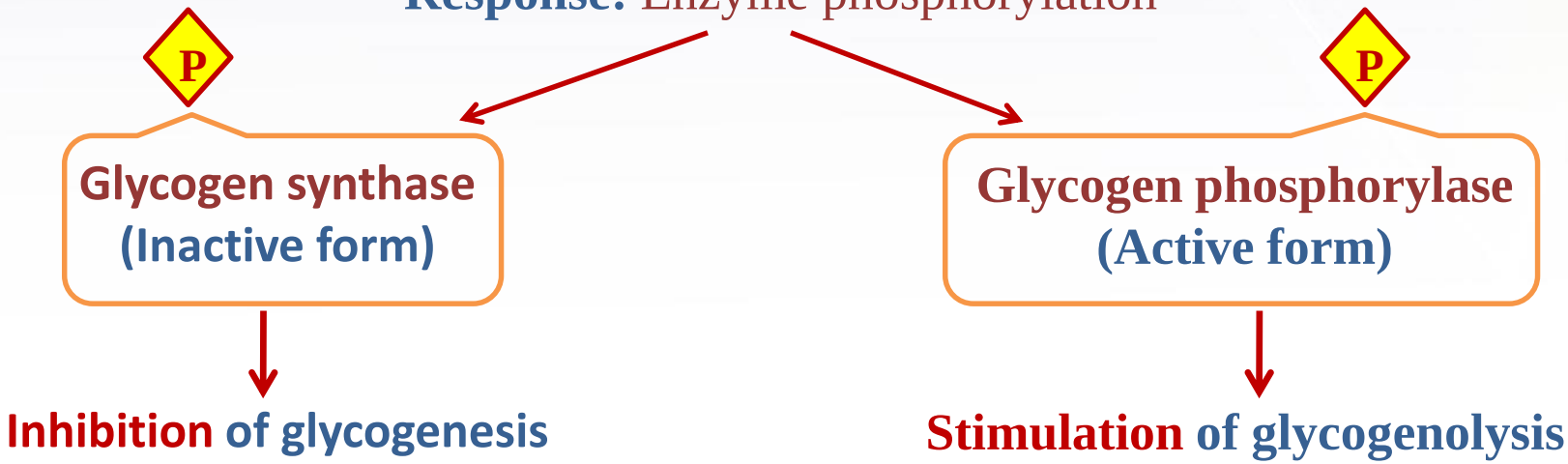
Hypoglycemia

Glucagon secretion

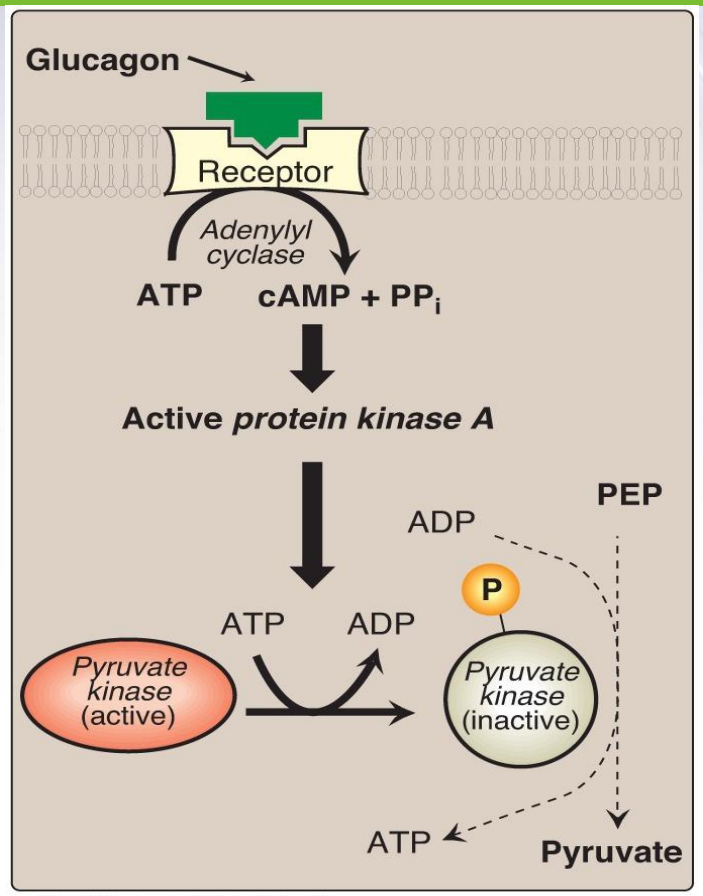
Hepatocyte: Glucagon/receptor binding

Second messenger: cAMP

Response: Enzyme phosphorylation



Pyruvate Kinase Regulation: Covalent Modification

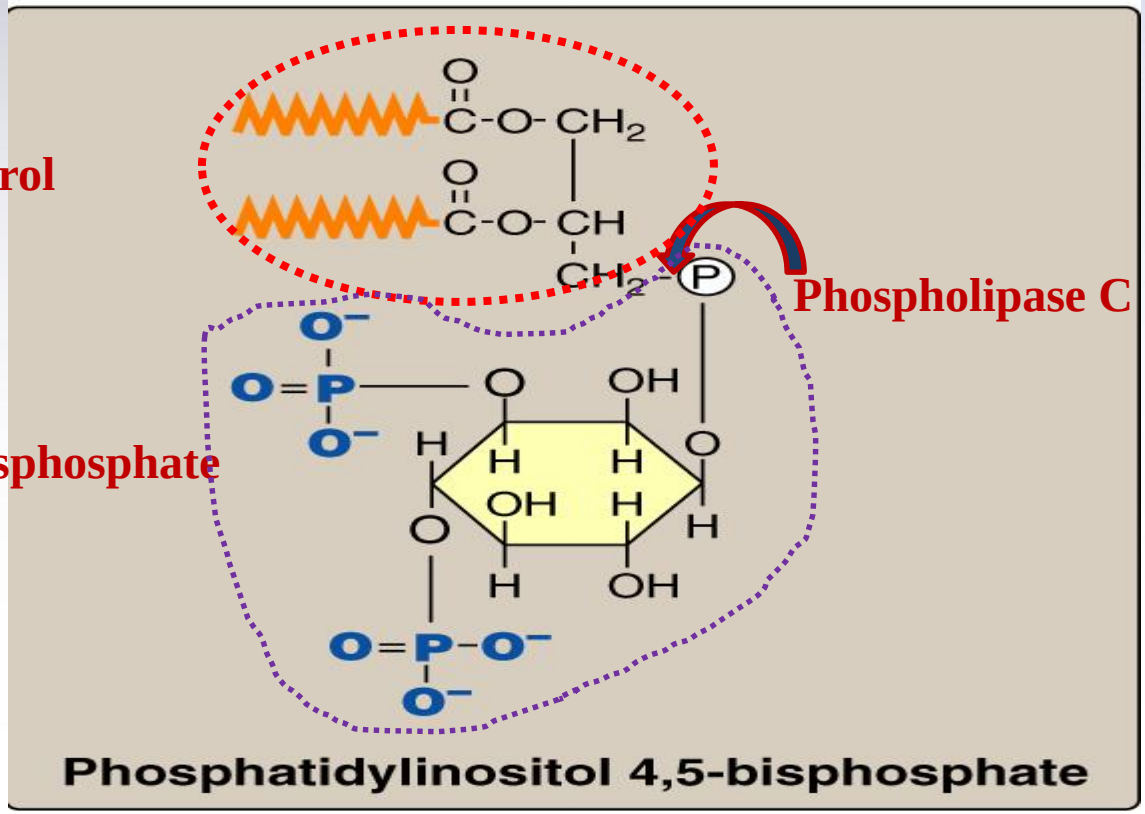


Phosphoenolpyruvate (PEP)

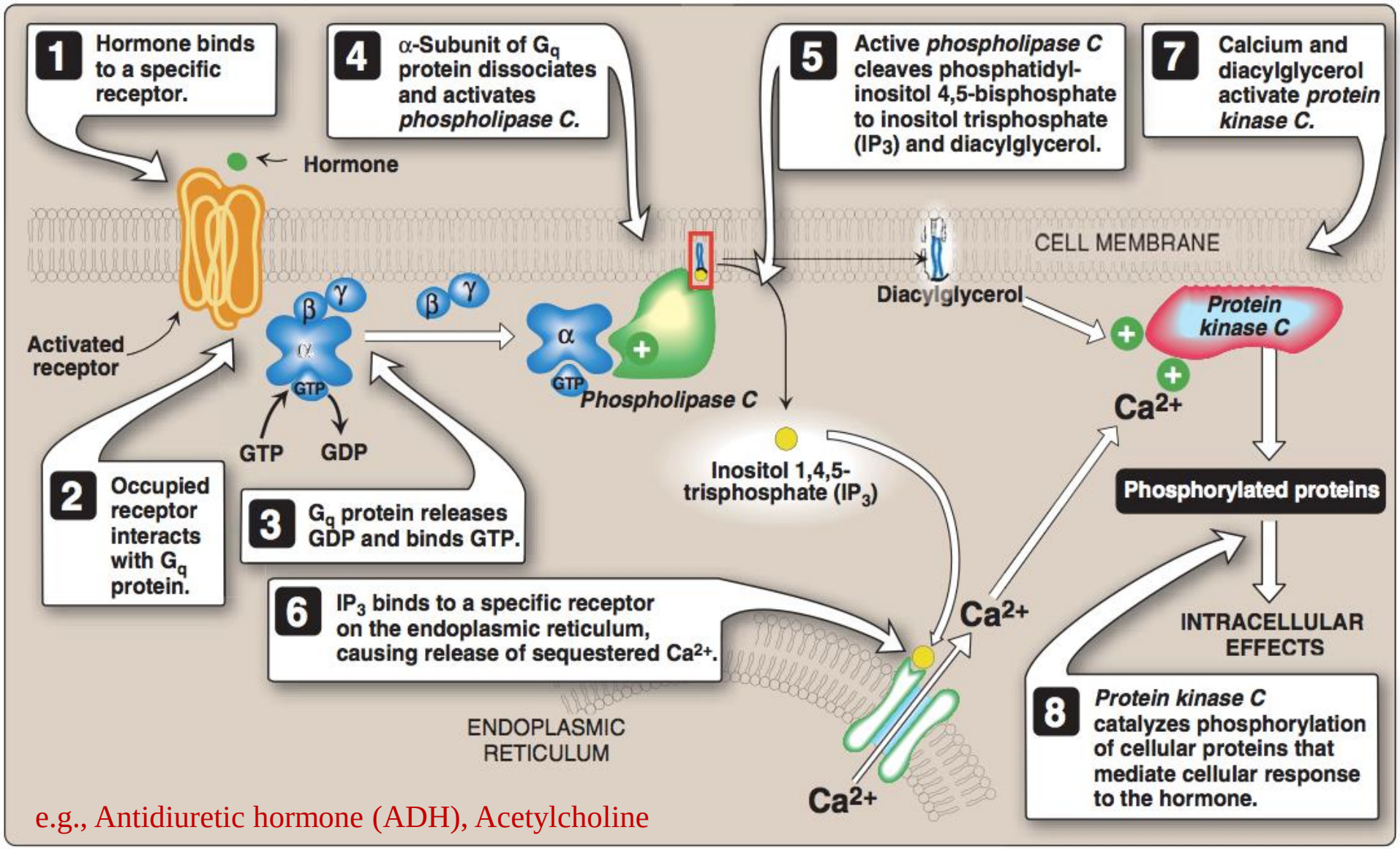
Calcium/Phosphatidylinositol System

Diacylglycerol (DAG)

Inositol Trisphosphate (IP_3)

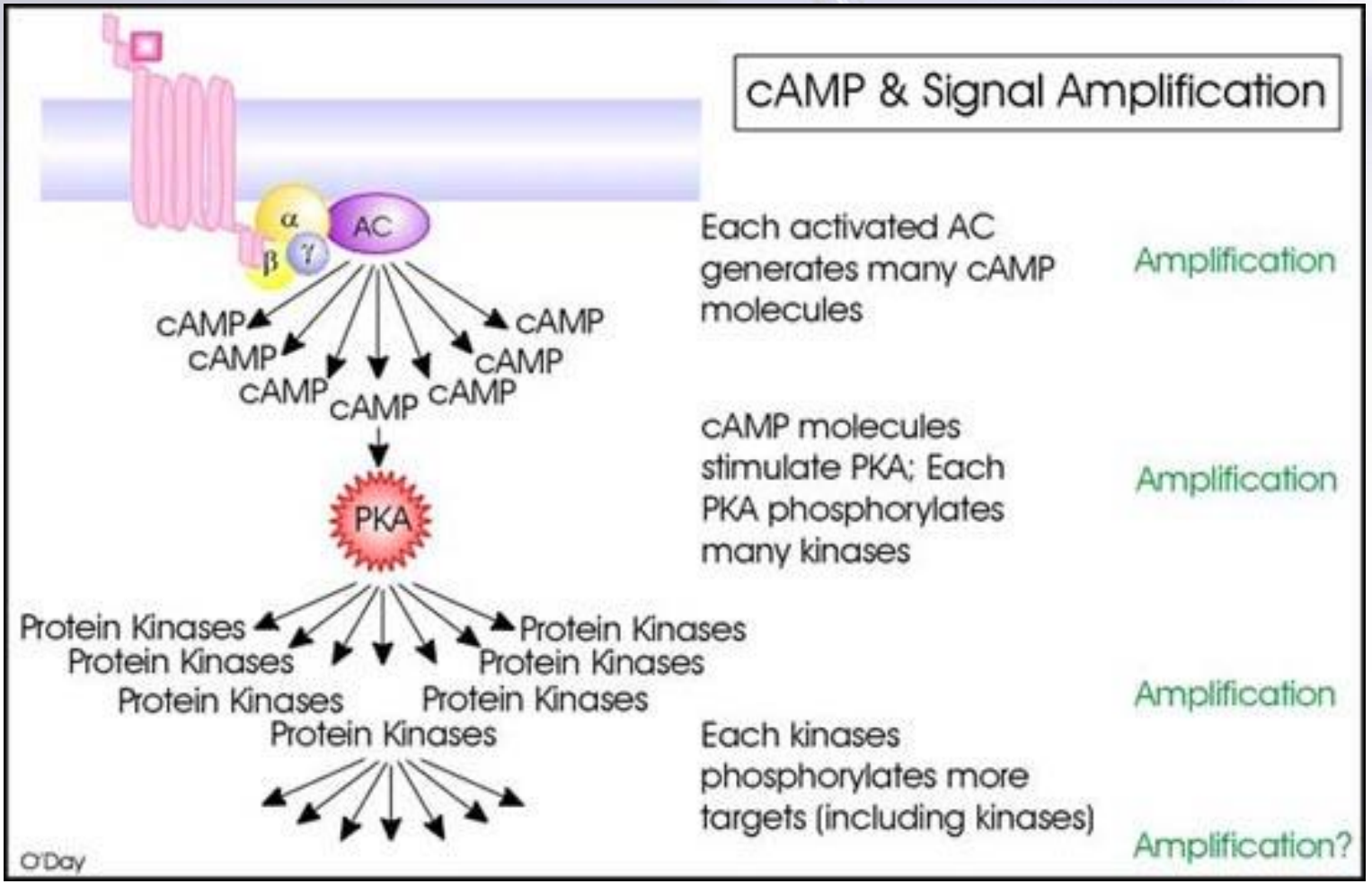


Intracellular Signaling by Inositol trisphosphate



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.